SYNTHESIS OF SOME SULPHONAMIDE DERIVATIVES OF ISOXAZOLES AND ISOXAZOLIN-5-ONES AS POSSIBLE ANTIBACTERIALS

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ABSTRACT

A wide range of isoxazoles and isoxazoline-5-ones properly substituted with sulphonamide moiety were prepared as possible antibacterial compounds. Their structures have been confirmed on the basis of elemental analysis, IR, NMR and mass spectral data.

INTRODUCTION

A WIDE range of physiological properties are found to be associated with isoxazoles[1–3] and isoxazolines[4–7]. As sulphonamides have also been reported to exhibit significant antibacterial activity, it was considered interesting to synthesize some isoxazoles and isoxazoline correctly substituted with sulphonamide moiety at position four. In the present paper several such compounds have been synthesized by incorporating sulphonamide moiety at position 4, of the isoxazole or isoxazoline rings. It is expected that introduction of such a moiety will turn these compounds into competitive antagonists of *p*-aminobenzoic acid[8].

EXPERIMENTAL

Melting points of the synthesized compounds were determined using a Kofler hot stage apparatus and are uncorrected. IR spectra were obtained on an infrared spectrophotometer (Beckman IR-20) and λ_{max} were determined on a UV–VIS Specord-spectrophotometer (C. Zeiss, Jena). C, H or N analysis gave satisfactory results. The mass spectra of some selected samples were scanned on a Hewlett Packard (5985B) instrument. NMR spectra were recorded on an IBM NR-80 spectrometer.

The sulphadrugs used in these studies were sulphanilamide, sulphacetamide, sulphamethoxypyridazine, sulphadiazine, sulphamerazine, sulphaguanidine, sulphadimidine, sulphapyridine, sulphaphenazole and sulphathiazole were obtained from Sigma Chemical Company, USA. The reactive methylene compounds, pentane-2,4-dione, 1-phenyl-1,3-butanedione, 1,3-diphenylpropane-1, 3-dione and ethyl 2,3-dioxobutyrate were BDH products. The diazotization of the appropriate sulphadrug and their coupling with reactive methylene compounds was carried out by the method reported in the literature[9].

1,3-Diphenyl-2(p-sulphamoylphenylhydrazone) propane–1,3–dione

Sulphanilamide (0.0125 M) was dissolved in a mixture of concentrated hydrochloric acid (6.3 ml) and water (6.3 ml), and cooled to 0°C. Sodium nitrite was gradually added to this cooled mixture and vigorously stirred. The diazotized sulphanilamide solution thus obtained was filtered into a well-cooled solution of 1,3-diphenylpropane 1,3-dione (0.0125 M) dissolved in ethanol (25 ml) and sodium acetate (8.0 g). A precipitate began to separate almost immediately. This was allowed to stand overnight, filtered, dried and recrystallized from ethanol m.p. 130°C. [Found: C = 61.7%, H = 4.10%, N = 10.10% Calc. for $C_{21}H_{17}N_3O_4S$, C = 61.9, H = 4.17%, N = 10.31%].

Preparation of the isoxazole

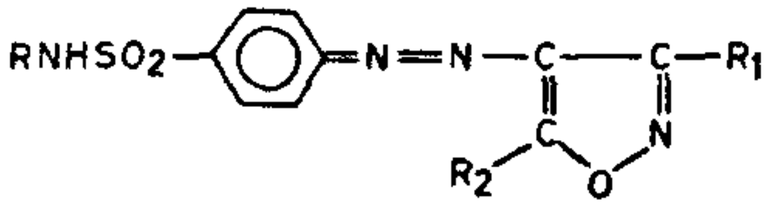
1,3-Diphenyl–2–(*p*-sulphamoylphenylhydrazone) propane-1, 3–dione was dissolved in ethyl alcohol (40 ml) on heating and to this an aqueous solution of hydroxylamine hydrochloride (0.34 g) containing sodium acetate (1 g) was added. The mixture was refluxed for 5 hr and cooled to room temperature. Shining crystals thus separated, were filtered, dried and crystallized from ethanol. It had a m.p. 178°C. [C = 62.01%, H = 3.83%, N = 13.73% Calcd. for $C_{21}H_{16}N_4O_3S$, C = 62.37%, H = 3.96%, N = 13.86%].

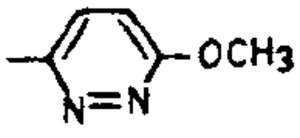
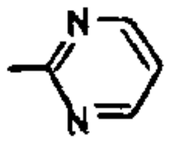
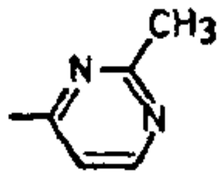
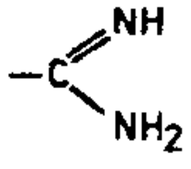
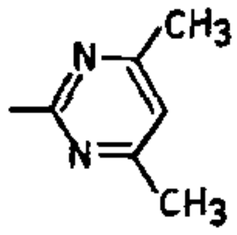
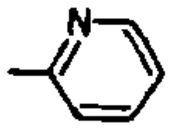
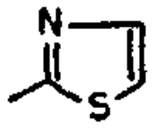
The characteristics of isoxazoles prepared by this method using different sulphadrugs and reactive methylene compounds are summarized in table 1.

Isoxazilin-5-ones were similarly prepared by using the hydrazone (0.005 M) obtained from sulphonamides and ethyl-2,3-dioxobutyrate. Their characteristics are given in table 2.

The compounds were characterized on the basis of their elemental analysis for C,H and N. The presence of characteristic absorption bands at 1600–1630 cm^{-1} for –N = N-linkage, 1150–1170 cm^{-1}

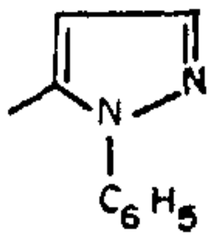
Table 1 *Characteristics of 4-(p-sulphamoylphenyl azo)–3,5–dimethyl/phenyl isoxazole*



Sl No.	R	R_1	R_2	Mol. formula	Colour	Yield %	M P. (°C)	λ_{max}
1.	H	CH_3	CH_3	$C_{11}H_{12}N_4O_3S$	Y	60	274–6	379
2		CH_3	C_6H_5	$C_{16}H_{14}N_4O_3S$	O	65	260–2	383
3.		C_6H_5	C_6H_5	$C_{21}H_{16}N_4O_3S$	Y	70	278–0	380
4.	$-COCH_3$	CH_3	CH_3	$C_{13}H_{14}N_4O_4S$	Y	65	276–8	380
5.		CH_3	C_6H_5	$C_{18}H_{16}N_4O_4S$	O	68	210–2	382
6.		C_6H_5	C_6H_5	$C_{23}H_{18}N_4O_4S$	R	60	222–4	380
7.		CH_3	CH_3	$C_{10}H_{16}N_6O_4S$	DY	65	315–6	377
8.		CH_3	C_6H_5	$C_{21}H_{18}N_6O_4S$	O	65	235–7	381
9.		C_6H_5	C_6H_5	$C_{26}H_{20}N_6O_4S$	R	60	291–3	380
10.		CH_3	CH_3	$C_{14}H_{14}N_6O_3S$	Y	60	280–2	376
11.		CH_3	C_6H_5	$C_{19}H_{16}N_6O_3S$	B	65	237–9	380
12.		C_6H_5	C_6H_5	$C_{24}H_{18}N_6O_3S$	R	60	290–2	378
13.		CH_3	CH_3	$C_{15}H_{16}N_6O_3S$	B	60	341–2	380
14.		CH_3	C_6H_5	$C_{20}H_{18}N_6O_3S$	Y	65	240–2	382
15.		C_6H_5	C_6H_5	$C_{25}H_{20}N_6O_3S$	R	65	271–3	382
16.		CH_3	CH_3	$C_{12}H_{14}N_6O_3S$	Y	65	320–2	375
17.		CH_3	C_6H_5	$C_{17}H_{16}N_6O_3S$	O	55	272–4	377
18.		C_6H_5	C_6H_5	$C_{19}H_{16}N_6O_4S$	B	70	256–8	378
19.		CH_3	CH_3	$C_{17}H_{18}N_6O_3S$	Y	70	257–9	370
20.		CH_3	C_6H_5	$C_{22}H_{20}N_6O_3S$	O	70	268–9	376
21.		C_6H_5	C_6H_5	$C_{27}H_{22}N_6O_3S$	R	60	283–5	376
22.		CH_3	CH_3	$C_{16}H_{15}N_5O_3S$	Y	60	296–7	372
23.		CH_3	C_6H_5	$C_{21}H_{17}N_5O_3S$	B	70	237–9	378
24.		C_6H_5	C_6H_5	$C_{26}H_{19}N_5O_3S$	R	60	272–4	380
25.		CH_3	CH_3	$C_{14}H_{13}N_5O_3S_2$	B	65	262–4	380
26.		CH_3	C_6H_5	$C_{19}H_{15}N_5O_3S_2$	O	60	252–4	382

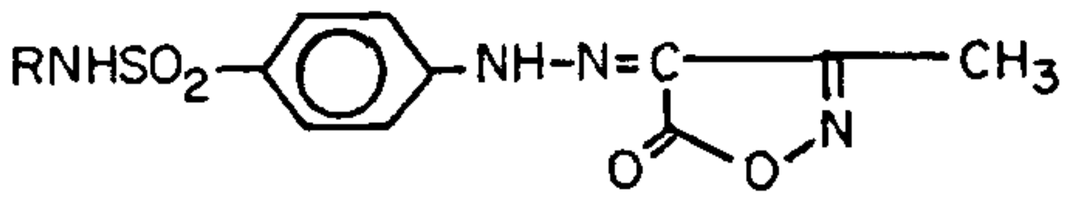
(*Contd.*)

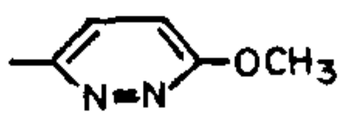
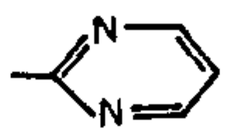
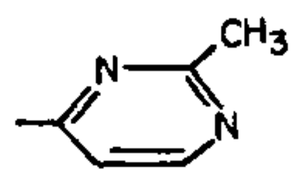
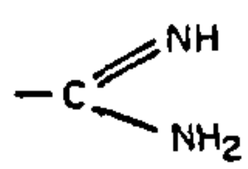
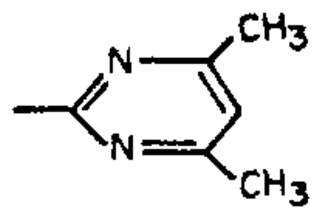
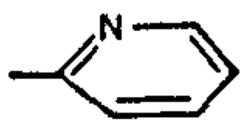
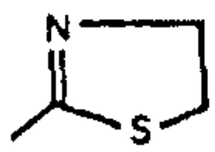
Table 1 (*Contd.*)

Sl. No.	R	R_1	R_2	Mol. formula	Colour	Yield %	M.P. (°C)	λ_{max}
27.		C_6H_5	C_6H_5	$C_{24}H_{17}N_5O_3S_2$	R	60	268–0	378
28.		CH_3	CH_3	$C_{20}H_{18}N_6O_3S$	Y	60	276–8	382
29.		CH_3	C_6H_5	$C_{25}H_{20}N_6O_3S$	Y	60	293–5	378
30.		C_6H_5	C_6H_5	$C_{30}H_{22}N_6O_3S$	B	65	310–2	382

Colour: DY = Dark Yellow, Y = Yellow, B = Brown, O = Orange and R = Red.

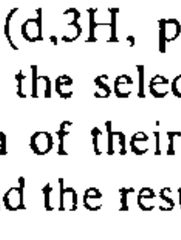
Table 2 *Characteristics of 4-(p-sulphomoyl phenylhydrazono)-3-methylisoxazolin-5-ones*



R	Mol. Formula	Colour	Yield (%)	M.P.(°C)
H	$C_{10}H_{10}N_4O_4S$	Y	60	262–4
— $COCH_3$	$C_{12}H_{12}N_4O_5S$	Y	70	256–8
	$C_{15}H_{14}N_6O_5S$	Y	60	279–0
	$C_{14}H_{12}N_6O_4S$	O	60	272–4
	$C_{15}H_{14}N_6O_4S$	Y	65	268–0
	$C_{11}H_{12}N_6O_4S$	Y	65	276–8
	$C_{16}H_{16}N_6O_4S$	Y	60	281–3
	$C_{15}H_{13}N_5O_4S$	Y	62	264–6
	$C_{13}H_{12}N_5O_4S_2$	B	60	258–9

(*Contd.*)

Table 2 (*Contd*)

R	Mol Formula	Colour	Yield (%)	M P (°C)
	$C_{19}H_{16}N_6O_4S_2$	Y	60	280–2

and 1330–1350 cm^{-1} for cyclic $-C=C-$ and 740–760 cm^{-1} for substituted phenyl ring[10,11] further supported the proposed structure. The mass spectral studies of the selected samples (1,4,10,16 and 22) also provided evidence for molecular ion peak. The observed λ_{max} in the visible region clearly indicated that π chromophore system has been extended. The NMR spectra of compound 10 (table 1) exhibited δ value: 2.814 (d,6H,2CH_3), 6.51 (t,1H,NH_2), 7.81 (m,4H,ArH) and 8.611 (d,3H, protons on the pyrimidine ring). Some of the selected samples have been sent for evaluation of their antibacterial and antineoplastic activity and the results will be reported later.

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NEWS

NOBEL PRIZE IN MEDICINE

Dr. Susumu Tonegawa, a Japanese Professor at the US Massachusetts Institute of Technology (MIT) is the winner of the 1987 Nobel Prize for Physiology and Medicine for his discovery of "the genetic principle for generation of antibody diversity". Dr. Tonegawa is the seventh Japanese Nobel Prize winner, but the first for Physiology and Medicine.