STUDIES IN SULPHONAMIDES—PART V

Synthesis of some 1 : 3-diaryl-2-(substituted sulphonamidobenzeneazo) propane-1 : 3-diones and evaluation of their antibacterial properties

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Five substituted dibenzoylmethanes, 1-(p-chlorophenyl)-1-(p-bromophenyl)-, 1-(p-methylphenyl)-, 1-(p-methoxyphenyl)-, and 1-(p-biphenyl)-3-phenyl propane-1 : 3-diones are coupled with diazotised sulphanilamide, sulphacetamide, N^1-phenyl-, N^1-p-chlorophenyl-, N^1-p-methylphenyl-, N^1-p-methoxyphenyl-, N^1-pyrimidyl-, N^1-guanidyl-, N^1-4 : 6-dimethylpyrimidyl-and N^1-α-pyridyl sulphanilamides in presence of sodium acetate. All these forty one substituted sulphonamidobenzeneazo 1 : 3-diketones are crystallised and screened *in vitro* for their antibacterial properties and some of these are found to be highly active against *S. aureus* and *E. coli*.

Azo-compounds gained early recognition as potential therapeutics and the azo-dyestuffs first tested against trypanosomal infections in animals were Trypan Red, Trypan Blue and Afridol Violet, which were found to be highly active[1-3]. Further work, however established the relationship between the fastness of the dyes for cotton and trypanocidal activity[4].

Compounds having reactive methylene groups, such as β-diketones and β-keto esters couple with diazotised bases to give azo-compounds[5-7], and some of these, besides acting as dyestuffs, were found to be therapeutically active[8,9].

A major and important development in chemotherapy has been the discovery of the antibacterial properties of prontosil, which on metabolic degradation furnished the active component, p-aminobenzene sulphonamide[10-14]. Since then quite a large number of p-aminobenzenesulphonamides having different substituents in the benzene ring, at N^1 and N^4 positions were synthesised and on subjecting these to *in vitro* tests, only products having substituents at N^1 were found to be highly active while those substituted at N^4 hardly showed any activity[15].

Recently the synthesis of naphthalene analogues of sulphanilamides have been reported and some of these were found to possess antibacterial properties against *E. coli* and *S. aureus* when subjected to *in vitro* tests[16,17].

Since β-diketones[18], azo-compounds[19], and sulphonamides separately exhibit antibacterial properties, it was thought of interest to synthesise compounds which may contain all the above mentioned moieties and to screen these compounds *in vitro* for their biological activity.

Perusal of literature indicated that only meagre amount of work on the coupling reactions of dibenzoyl methanes with diazotised sulphonamides has been reported. With this object in view, the work presented in this and subsequent papers was taken up and the present paper describes the synthesis of substituted 1 : 3-diphenyl propane-1 : 3-diones, their coupling with diazotised sulphonamide bases, the effect of the various substituents present in the phenyl rings on the rate of coupling and a study of the pharmacological properties of these substituted sulphonamidobenzeneazo compounds. The pharmacological study of all these compounds was carried out by the usual cup-plate[20] method against *S. aureus* and *E. coli*.

EXPERIMENTAL PROCEDURE

Different 1 : 3-diaryl propane-1 : 3-diones [21-24] and sulphonamides [15, 25-29] required for this work, were prepared by us.

Synthesis of 1 : 3-diaryl-2-(substituted sulphonamidobenzeneazo) propane-1 : 3-diones.

To an ice-cold well stirred solution of 1 : 3-dione (0·002 mole) in acetone containing sodium acetate was gradually added a diazotised solution of the sulphonamide (0·002 mole) at 0–5°. The azo-compound was precipitated by adding ice-cold water and after stirring for further 10 minutes, the solid product was filtered, washed well with water, dried and pure 1 : 3-diaryl-2-(substituted sulphonamidobenzeneazo) propane-1 : 3-dione was crystallised from glacial acetic acid or ethanol or acetone or from a mixture of glacial acetic acid and ethanol. Some azo-compounds were obtained after adding ice-cold water to the reaction mixture and keeping it overnight. The general structure is given in Fig. 1.

Pharmacological Evaluations

All the compounds synthesised have been screened for their antibacterial activities against *S. aureus* and *E. coli* at two different concentrations, 500 μg/ml and 1000 μg/ml. However, considerable activity was exhibited when tests were carried out in concentrations of 500 μg/ml and these results are entered in Tables 1–5. Test solutions were prepared in a mixture of dimethylformamide and water (3 : 7) which was used as a control. The zones of inhibition were measured by vernier callipers and the activities of the compounds are represented by (+), (++) and (+++) depending upon the diameter and clarity of the zones of inhibition; where no zones of inhibition were obtained, the results have been shown in the Tables 1–5 by (—).

The various compounds and the results of biological assay are entered in Tables 1–5.

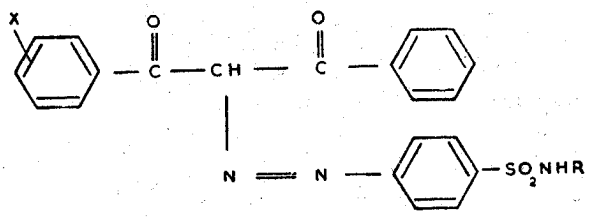

Fig. 1—General structure of azo-compounds.

It has been observed that the rate of the coupling reaction increases giving higher yields, when electron withdrawing groups (e.g., chlorine or bromine atoms) are present in para position in either of the phenyl rings of 1 : 3-diphenyl propane-1 : 3-diones ; other groups such as methyl or methoxyl decrease the rate of reaction thereby giving lower yields.

On the basis of the work of biological assay, it appears that sulphonamidobenzeneazo derivatives of β-diketones were active *in vitro* against *E. coli* and *S. aureus*. Some of these compounds, No. 4, 5, 6 in Table 1 ; No. 5 in Table 2; No. 3, 4, 5, 6 in Table 3 ; No. 5, 6 in Table 4 and No. 4, 5 in Table 5 showed quite significant activity against *E. coli* while compound No. 1 in Table 2 and No. 1, 2 in Table 4 exhibited strong activity against *S. aureus*.

TABLE 1

1-(p-CHLOROPHENYL)-3-PHENYL-2-(SUBSTITUTED SULPHONAMIDOBENZENE AZO) PROPANE-1 : 3-DIONES
(X = p-Chloro)

S. No.	R	M. P. (°C)	Colour	Yield (%)	Mol. formula	Percentage Found C	Found H	Reqd. C	Reqd. H	Antibacterial activity *S. aureus*	*E. coli*
1	H	195	Y	82	$C_{21}H_{15}O_4N_3SCl$	57·2	3·5	57·0	3·6	(++)	(++)
2	acetyl	198	Y	80	$C_{23}H_{17}O_5N_3SCl$	57·3	3·8	57·1	3·7	(++)	(++)
3	phenyl	179-80	SYF	72	$C_{27}H_{19}O_4N_3SCl$	62·4	3·7	62·6	3·8	(—)	(—)
4	p-chlorophenyl	228	LYF	75	$C_{27}H_{18}O_4N_3SCl$	58·8	3·5	58·7	3·4	(—)	(+++)
5	p-methylphenyl	220	BLYF	68	$C_{28}H_{22}O_4N_3SCl$	63·3	4·2	63·2	4·1	(—)	(+++)
6	p-methoxyphenyl	216	Y	68	$C_{28}H_{22}O_5N_3SCl$	61·5	4·1	61·3	4·0	(—)	(+++)
7	pyrimidyl	230	BYF	78	$C_{25}H_{16}O_4N_5SCl$	57·8	3·5	57·7	3·4	(+)	(+)
8	guanidyl	252	BY	75	$C_{22}H_{18}O_4N_5SCl$	54·5	3·5	54·6	3·7	(—)	(+)
9	4′ : 6′-dimethyl pyrimidyl	175	SY	75	$C_{27}H_{22}O_4N_5SCl$	58·9	4·1	59·1	4·0	(++)	(+)
10	α-pyridyl	222	Y	74	$C_{26}H_{19}O_4N_4SCl$	59·9	3·5	60·1	3·6	(++)	(++)

TABLE 2

1-(p-BROMOPHENYL)-3-PHENYL-2-(SUBSTITUTED SULPHONAMIDOBENZENEAZO) PROPANE-1 : 3-DIONES
(X = p-Bromo)

S. No.	R	M. P. (°C)	Colour	Yield (%)	Mol. formula	Percentage Found C	Found H	Reqd. C	Reqd. H	Antibacterial activity *S. aureus*	*E. coli*
1	H	185	BYN	89	$C_{21}H_{16}O_4N_3SBr$	52·0	3·3	51·8	3·3	(+++)	(++)
2	acetyl	181	BYN	81	$C_{23}H_{18}O_5N_3SBr$	52·4	3·4	52·2	3·4	(—)	(+)
3	phenyl	184	Y	74	$C_{27}H_{20}O_4N_3SBr$	57·5	3·6	57·6	3·5	(—)	(++)
4	p-chlorophenyl	217	PY	76	$C_{27}H_{19}O_4N_3SBrCl$	54·1	3·3	54·3	3·2	(—)	(—)
5	p-methylphenyl	212	Y	70	$C_{28}H_{22}O_4N_3SBr$	58·4	3·7	58·5	3·8	(—)	(+++)
6	p-methoxyphenyl	215	Y	71	$C_{28}H_{22}O_5N_3SBr$	56·9	3·8	56·7	3·7	(—)	(+)
7	pyrimidyl	240	SYF	80	$C_{25}H_{16}O_4N_5SBr$	53·0	3·1	53·1	3·1	(—)	(+)

TABLE 3

(p-METHYLPHENYL)-3-PHENYL-2-(SUBSTITUTED SULPHONAMIDOBENZENEAZO) PROPANE-1 : 3-DIONES
(X=p-Methyl)

S. No.	R	M. P. (°C)	Colour	Yield (%)	Mol. formula	Percentage Found C	Found H	Reqd. C	Reqd. H	Antibacterial activity *S. aureus*	*E. coli*
1	H	181	PY	75	$C_{22}H_{19}O_4N_3S$	61·5	4·7	61·3	4·5	(—)	(—)
2	acetyl	199	BY	72	$C_{24}H_{21}O_5N_3S$	62·3	4·6	62·2	4·5	(—)	(+)
3	phenyl	198-9	GYF	65	$C_{28}H_{23}O_4N_3S$	67·5	4·8	67·5	4·6	(++)	(+++)
4	p-chlorophenyl	208	GYF	70	$C_{28}H_{22}O_4N_3SCl$	63·1	4·6	63·2	4·3	(+)	(+++)
5	p-methylphenyl	217	PY	61	$C_{29}H_{25}O_4N_3S$	68·0	5·0	68·1	4·8	(+)	(+++)
6	p-methoxyphenyl	208	GYF	61	$C_{29}H_{25}O_5N_3S$	66·2	4·5	66·0	4·7	(++)	(+++)
7	pyrimidyl	217	BY	70	$C_{26}H_{21}O_4N_5S$	62·6	4·2	62·5	4·2	(—)	(—)
8	guanidyl	238	PY	63	$C_{25}H_{21}O_4N_5S$	59·3	4·6	59·1	4·5	(+)	(+)
9	4′ : 6′-dimethyl pyrimidyl	208	SPY	65	$C_{28}H_{25}O_4N_5S$	63·5	4·5	63·7	4·7	(—)	(—)

TABLE 4

1-(p-METHOXYPHENYL)-3-PHENYL-2-(SUBSTITUTED SULPHONAMIDOBENZENEAZO) PROPANE-1 : 3-DIONES
(X=p-Methoxy)

S. No.	R	M. P. (°C)	Colour	Yield (%)	Mol. formula	Percentage Found C	Found H	Reqd. C	Reqd. H	Antibacterial activity *S. aureus*	*E. coli*
1	H	184	PY	78	$C_{22}H_{19}O_5N_3S$	60·2	4·2	60·4	4·3	(+++)	(—)
2	acetyl	184	Y	74	$C_{24}H_{21}O_6N_3S$	60·3	4·2	60·1	4·4	(+++)	(+)
3	phenyl	179	BY	65	$C_{28}H_{23}O_5N_3S$	65·5	4·2	65·5	4·5	(—)	(++)
4	p-chlorophenyl	194	SYF	65	$C_{28}H_{22}O_5N_3SCl$	61·4	4·1	61·3	4·0	(—)	(+)
5	p-methylphenyl	194	Y	62·6	$C_{29}H_{25}O_5N_3S$	66·2	4·5	66·0	4·7	(—)	(+++)
6	p-methoxyphenyl	192	BY	65·5	$C_{29}H_{25}O_6N_3S$	64·1	4·4	64·1	4·6	(—)	(+++)
7	pyrimidyl	210	Y	73	$C_{26}H_{21}O_5N_5S$	60·7	4·1	60·6	4·1	(—)	(++)
8	guanidyl	240	BY	70	$C_{25}H_{21}O_5N_5S$	57·6	4·2	57·6	4·3	(—)	(+)
9	4′ : 6′-dimethyl pyrimidyl	164	BY	71	$C_{28}H_{25}O_5N_5S$	61·7	4·7	61·8	4·6	(—)	(+)

TABLE 5

1 (p-BIPHENYL)-3-PHENYL-2-(SUBSTITUTED SULPHONAMIDOBENZENEAZO) PROPANE-1 : 3-DIONES
(X=p-Phenyl)

S. No.	R	M. P. (°C)	Colour	Yield (%)	Mol. formula	Percentage Found C	Found H	Reqd. C	Reqd. H	Antibacterial activity *S. aureus*	Antibacterial activity *E. coli*
1	H	236	Y	65	$C_{27}H_{21}O_4N_3S$	67·3	4·8	67·3	4·9	(—)	(+)
2	acetyl	229	Y	62	$C_{29}H_{23}O_5N_3S$	66·2	4·3	66·3	4·4	(++)	(+)
3	phenyl	141	Y	58	$C_{33}H_{25}O_4N_3S$	70·8	4·6	70·8	4·5	(—)	(++)
4	p-chlorophenyl	210	PY	60	$C_{33}H_{24}O_4N_3SCl$	66·5	4·2	66·7	4·0	(—)	(+++)
5	p-methylphenyl	196	PY	56	$C_{34}H_{27}O_5N_3S$	70·9	4·5	71·2	4·7	(—)	(+++)
6	p-methoxyphenyl	158	BYF	58	$C_{34}H_{27}O_5N_3S$	69·4	4·6	69·3	4·7	(—)	(++)

B—Bright; F—Flakes; N—Needles; G—Golden; P—Pale; Y—Yellow; S—Shining.

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