STUDIES IN SULPHONAMIDES—PART X

Synthesis and antibacterial study of some substituted sulphonamidobenzeneazo propane-1, 3-diones

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The present paper describes the synthesis of four differently substituted dibenzoylmethanes, viz., 1-(*m*-nitrophenyl)-3-(*p*-chlorophenyl)-, 1-(*m*-nitrophenyl)-3-(*p*-bromophenyl)-, 1, 3-di (*p*-methoxyphenyl) and 1-(*p*-ethoxyphenyl)-3-phenyl propane-1, 3-diones and study of their coupling reactions with different diazotised sulphonamide bases. The resulting 2-sulphonamidobenzeneazo derivatives were subjected to biological assay *in vitro* against *S. aureus* and *E. coli* and some of these were found to possess considerable activity.

In view of the encouraging results obtained during the course of our earlier work[1], it was thought worthwhile to extend this by synthesising some new propane-1, 3-diones having either electron—attracting or repelling groups present in both the phenyl rings and couple these with different diazotised sulphonamide bases in order to study the effect of the various substituents on the rate of coupling reactions as well as on the antibacterial properties of the azo compounds and thus compare the results with those obtained earlier.

The study of the coupling reactions revealed that the presence of an electron repelling group (e.g., ethoxyl) in any of the phenyl rings of β-diketone causes a decrease in the rate of coupling reaction thereby giving lower yields as compared to those where electron withdrawing groups were present. The rate of coupling is further suppressed by the presence of electron repelling groups in both the phenyl rings of the β-diketone. On the other hand if one phenyl ring contains the nitro group and the other a halogen atom then the rate of the coupling reaction increases in comparison to those where one phenyl ring contains the electron attracting and the other an electron repelling group but the rate is less as compared to those where only nitro group is present.

The yields of the azo compounds ranged between 65 to 85%.

EXPERIMENTAL PROCEDURE

Different 1, 3-diaryl propane-1, 3-diones required for this work were prepared by employing the method of Barnes and Dodson[2].

1-(m-Nitrophenyl)-3-(p-chlorophenyl) propane-1, 3-dione

p-Chloroacetophenone (0.05 mol) and *m*-nitrobenzaldehyde (0.05 mol) were condensed in presence of sodium hydroxide to yield *m-nitrobenzylidene p-chloroacetophenone* (ethanol), m.p. 156°.

The above chalkone on bromination yielded a dibromide, m.p. 172°, which on dehydrobromination and hydrolysis furnished the required propane-1, 3-dione (glacial acetic acid), m.p. 180°. (Yield : 12.0 gm; 73%).

(Found : C, 59.0; H, 3.1. $C_{15}H_{10}O_4NCl$ requires C, 59.3; H, 3.3%).

The alcoholic solution of the β-diketone gave an intense reddish-violet colouration with aqueous ferric chloride.

1-(m-Nitrophenyl)-3-(p-bromophenyl) propane-1, 3-dione

Condensation of *m*-nitrobenzaldehyde and *p*-bromoacetophenone in equimolecular proportions in presence of aqueous sodium hydroxide furnished *m-nitrobenzylidene p-bromoacetophenone* (ethanol), m.p. 157°.

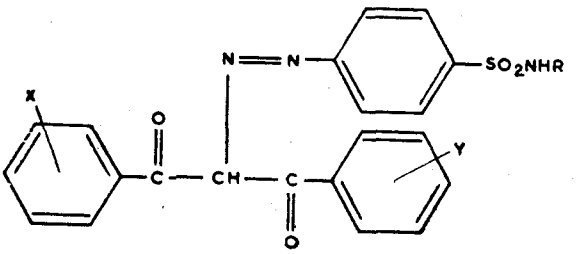
Its dibromide, m.p. 162° on dehydrobromination and hydrolysis furnished the β-diketone (ethanol-glacial acetic acid), m.p. 184°. (Yield : 13.5 g; 81%).

(Found : C, 51.9; H, 3.0. $C_{15}H_{10}O_4NBr$ requires C, 51.7; H, 2.9%).

Its alcoholic solution gave a violet colouration with aqueous ferric chloride.

1, 3-Di (p-methoxyphenyl) propane-1, 3-dione

A mixture of *p*-methoxyacetophenone (0.05 mol) and anisaldehyde (0.05 mol) in methanol was condensed in presence of sodium hydroxide to furnish *anisylidene p-methoxyacetophenone* (ethanol), m.p. 125°.



The anisylidene *p*-methoxyacetophenone on bromination furnished a dibromide, m.p. 135°, which on dehydrobromination and hydrolysis yielded the required β-diketone (ethanol), m.p. 118°. (Yield : 12.8 g; 80.8%).

(Found : C, 70.9; H, 5.7. $C_{17}H_{16}O_4$ requires C, 71.8; H, 5.6%).

It gave a violet colouration with aqueous ferric chloride and formed copper chelate with cupric acetate.

The other β-diketone viz., 1-(*p*-ethoxyphenyl)-3-phenyl propane-1, 3-dione was prepared using the standard method[3].

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

To an ice-cold, well stirred solution of 1, 3-diaryl propane-1, 3-dione (0.002 mol) in acetone or acetone-alcohol mixture, containing sodium acetate was gradually added a well cooled diazotised solution of the sulphonamide (0.002 mol) at 0–5°. Stirring was continued for further 5–10 minutes and the yellow coloured azo compound was precipitated by adding cold water. The solid which separated out was filtered, washed well with water, dried and pure *1, 3-diaryl-2-(substituted sulphonamidobenzeneazo) propane-1, 3-dione* was crystallised from ethanol or glacial acetic acid or ethanol-glacial acetic acid/ DMF mixture.

TABLE 1

1-(*p*-Ethoxyphenyl)-3-phenyl-2-(substituted sulphonamidobenzeneazo) propane-1, 3-diones

(I : X= *p*-OC_2H_5 ; Y=H)

S. No.	R	M.P. (°C)	Colour	Yield (%)	Molecular formula	C (Found) (%)	H (Found) (%)	C (Requires) (%)	H (Requires) (%)	Antibacterial activity *S. aureus*	Antibacterial activity *E. coli*
1.	H	162	SYN	77	$C_{23}H_{21}O_5N_3S$	61·1	4·8	61·2	4·6	+	+
2.	Acetyl	152	BY	72	$C_{25}H_{23}O_6N_3S$	61·0	4·8	60·8	4·7	++	+
3.	Phenyl	110	YO	75	$C_{29}H_{25}O_5N_3S$	66·0	4·6	66·0	4·7	+	—
4.	*o*-Methylphenyl	152	SO	71	$C_{30}H_{27}O_5N_3S$	66·3	5·0	66·5	5·0	++	—
5.	*o*-Methoxyphenyl	164	SYO	74	$C_{30}H_{27}O_6N_3S$	65·0	4·8	64·6	4·8	+	—
6.	*p*-Methoxyphenyl	141	BYN	72	$C_{30}H_{27}O_6N_3S$	64·6	4·8	64·6	4·8	+	—
7.	Guanidyl	225	SBY	68	$C_{24}H_{23}O_5N_5S$	58·3	4·9	58·4	4·7	++	—
8.	α-Pyridyl	202	Y	75	$C_{28}H_{24}O_5N_4S$	63·5	4·5	63·6	4·5	+	+
9.	Pyrimidyl	271	SPY	78	$C_{27}H_{23}O_5N_5S$	60·9	4·0	61·2	4·3	+	—
10.	4,6-Dimethylpyrimidyl	202	Y	77	$C_{29}H_{27}O_5N_5S$	62·4	4·8	62·5	4·8	+	—
11.	2,6-Dimethylpyrimidyl	250	Y	72	$C_{29}H_{27}O_5N_5S$	62·6	4·8	62·5	4·8	++	—
12.	2,6-Dimethoxypyrimidyl	115	YO	70.	$C_{29}H_{27}O_7N_5S$	59·0	4·7	59·1	4·6	—	—
13.	5-Methyl-1,3,4-thiadiazolyl	222	Y	72	$C_{26}H_{23}O_5N_5S_2$	56·7	4·0	56·8	4·2	+++	—

B– Bright ; Br– Brownish ; D– Dark ; F–Flakes ; N–Needles ; O– Orange ; P– Pale; R–Red ; S– Shining ; Y–Yellow

Table 2

1-(*m*-Nitrophenyl)-3-(*p*-chlorophenyl)-2-(substituted sulphonamidobenzeneazo) propane-1, 3-diones

(I : X=*m*-NO_2; Y=*p*-Cl)

S. No.	R	M.P. (°C)	Colour	Yield (%)	Molecular formula	C (Found) (%)	H (Found) (%)	C (Required) (%)	H (Required) (%)	Antibacterial activity *S. aureus*	Antibacterial activity *E. coli*
1.	H	172	YN	82	$C_{21}H_{15}O_6N_4SCl$	52·0	3·0	51·8	3·1	+	—
2.	Acetyl	220	SY	77	$C_{23}H_{17}O_7N_4SCl$	52·5	3·1	52·2	3·2	++	+
3.	Phenyl	236	YN	78	$C_{27}H_{19}O_6N_4SCl$	57·6	3·4	57·6	3·4	+	+
4.	*o*-Methylphenyl	201	BrY	76	$C_{28}H_{21}O_6N_4SCl$	58·4	3·8	58·3	3·6	+	+
5.	*o*-Methoxyphenyl	204	YO	77	$C_{28}H_{21}O_7N_4SCl$	56·7	3·3	56·7	3·5	+	—
6.	*p*-Methoxyphenyl	207	DY	76	$C_{28}H_{21}O_7N_4SCl$	56·9	3·4	56·7	3·5	+	+
7.	Guanidyl	252	BY	75	$C_{22}H_{17}O_6N_6SCl$	50·1	3·0	49·9	3·2	—	—
8.	α-Pyridyl	232	Y	78	$C_{26}H_{18}O_6N_5SCl$	55·3	3·2	55·4	3·2	+	—
9.	Pyrimidyl	280	SO	82	$C_{25}H_{17}G_6N_6SCl$	53·0	3·0	53·1	3·0	—	+
10.	4,6-Dimethylpyrimidyl	223	Y	79	$C_{27}H_{21}O_6N_6SCl$	54·9	3·3	54·7	3·5	+	+
11.	2,6-Dimethylpyrimidyl	266	PY	76	$C_{27}H_{21}O_6N_6SCl$	54·6	3·6	54·7	3·5	+	+
12.	2,6-Dimethoxypyrimidyl	193	Y	79	$C_{27}H_{21}O_8N_6SCl$	52·1	3·3	51·9	3·4	+	+

Table 3

1-(*m*-Nitrophenyl)-3-(*p*-bromophenyl)-2-(substituted sulphonamidobenzeneazo) propane-1, 3-diones

(I : X=*m*-NO_2; Y=*p*-Br)

S. No.	R	M.P. (°C)	Colour	Yield (%)	Molecular formula	C (Found) (%)	H (Found) (%)	C (Required) (%)	H (Required) (%)	Antibacterial activity *S. aureus*	Antibacterial activity *E. coli.*
1.	H	224	DY	84	$C_{21}H_{15}O_6N_4SBr$	47·4	2·8	47·4	2·8	—	+
2.	Acetyl	200	BY	80	$C_{23}H_{17}O_7N_4SBr$	48·1	3·2	48·2	3·0	—	—
3.	Phenyl	246	BY	80	$C_{27}H_{19}O_6N_4SBr$	53·4	3·0	53·4	3·1	—	++
4.	*o*-Methylphenyl	209	BY	77	$C_{28}H_{21}O_6N_4SBr$	54·0	3·5	54·1	3·4	+	+
5.	*o*-Methoxyphenyl	216	SYO	78	$C_{28}H_{21}O_7N_4SBr$	52·9	3·3	52·7	3·3	+	+
6.	*p*-Methoxyphenyl	211	YO	79	$C_{28}H_{21}O_7N_4SBr$	52·7	3·1	52·7	3·3	—	+
7.	Guanidyl	248	BrY	76	$C_{22}H_{17}O_6N_6SBr$	46·0	3·2	46·1	3·0	+	++
8.	α-Pyridyl	257	SY	79	$C_{26}H_{18}O_6N_5SBr$	51·3	3·1	51·3	3·0	+	++
9.	Pyrimidyl	270	SY	85	$C_{25}H_{17}O_6N_6SBr$	49·5	3·0	49·3	2·8	—	++
10.	4,6-Dimethylpyrimidyl	165	Y	80	$C_{27}H_{21}O_6N_6SBr$	51·0	3·2	50·9	3·3	—	+
11.	2,6-Dimethylpyrimidyl	268	Y	78	$C_{27}H_{21}O_6N_6SBr$	51·2	3·3	50·9	3·3	—	++
12.	5-Methyl-1, 3, 4-thiadiazolyl	240	BY	82	$C_{24}H_{17}O_6N_6S_2Br$	46·0	2·5	45·8	2·7	+++	+

The different azo compounds thus prepared and the results of the antibacterial tests, carried out by employing the usual cup-plate agar diffusion method against *S. aureus* and *E. coli* at 500 ug/ml are given in Tables 1 to 4.

TABLE 4

1, 3-Di(*p*-Methoxyphenyl)-2-(substituted sulphonamidobenzeneazo) propane-1, 3-diones

(I : X=Y=*p*-OCH_3)

S. No.	R	M.P. (°C)	Colour	Yield (%)	Molecular formula	C (Found) (%)	H (Found) (%)	C (Required) (%)	H (Required) (%)	Antibacterial Activity *S. aureus*	Antibacterial Activity *E. coli*
1.	H	180	Y	75	$C_{23}H_{21}O_6N_3S$	59·0	4·6	59·1	4·5	—	—
2.	Acetyl	175	BY	68	$C_{25}H_{23}O_7N_3S$	59·0	4·6	58·9	4·5	+	+
3.	Phenyl	214	OR	69	$C_{29}H_{25}O_6N_3S$	64·2	4·3	64·1	4·6	–	–
4.	*o*-Methylphenyl	120	SO	67	$C_{30}H_{27}O_6N_3S$	64·5	4·9	64·6	4·8	+	–
5.	*o*-Methoxyphenyl	191	BON	68	$C_{30}H_{27}O_7N_3S$	63·0	4·7	62·8	4·7	–	–
6.	*p*-Methoxyphenyl	176	Y	68	$C_{30}H_{27}O_7N_3S$	62·7	4·8	62·8	4·7	+	–
7.	Guanidyl	280	BY	65	$C_{24}H_{23}O_6N_5S$	56·7	4·6	56·6	4·5	+	–
8.	α-Pyridyl	209	SY	70	$C_{28}H_{24}O_6N_4S$	61·6	4·3	61·8	4·4	+	–
9.	Pyrimidyl	275	SPY	77	$C_{27}H_{23}O_6N_5S$	59·4	4·1	59·4	4·2	+	–
10.	4, 6-Dimethylpyrimidyl	155	BYN	76	$C_{29}H_{27}O_6N_5S$	60·9	4·6	60·7	4·7	–	–
11.	2, 6-Dimethylpyrimidyl	215	PY	70	$C_{29}H_{27}O_6N_5S$	61·0	4·6	60·7	4·7	+	—
12.	2, 6-Dimethoxypyrimidyl	153	YG	72	$C_{29}H_{27}O_8N_5S$	57·4	4·5	57·5	4·5	—	+
13.	5-Methyl-1,3,4-thiadiazolyl	240	SY	74	$C_{26}H_{23}O_6N_5S_2$	55·0	4·1	55·2	4·1	++	—

The inference drawn from the screening work indicated that if an electron attracting group (e.g., ethoxyl) is present in one of the phenyl rings of β-diketones, the synthesised azo compound show activity against *S. aureus* and no activity against *E. coli* except compounds No. 1, 2 and 8 (Table 1) which show very meagre activity against *E. coli*.

In the case of azo compounds synthesised from β-diketones having the substituents of the same type, the antibacterial activity varies with the electronegativity of the groups present e.g., azo compounds synthesised from β-diketones having nitro group in one phenyl ring and chlorine in the other were found to be more active against *S. aureus* as compared to *E. coli* but the activity is of the reversed order when chlorine atom is replaced by bromine. In the case of azo compounds having methoxyl group in both the phenyl rings the activity is even less than those in which only one methoxyl or ethoxyl is present.

Another important conclusion drawn is that the azo compounds having heterocyclic ring containing three hetero atoms attached to the nitrogen of the sulphonamide were found to be most active against *S. aureus* out of all the compounds synthesised. These results are in accordance with those obtained earlier[1].

REFERENCES

1. MRS. KABRA, A., SAHARIA, G. S. & SHARMA, H. R., *Def. Sci. J.*, 25 (1975), 25.

2. BARNES, R. P. & DODSON, L. B., *J. Amer. Chem. Soc.*, 65 (1943), 1585.

3. BRADLEY, W. & ROBINSON, R., *J. Chem. Soc.*, 1926, 2356.