STUDIES IN SULPHONAMIDES—PART XII

Synthesis of 1, 3-diaryl-2-(N-substituted p-sulphamylbenzeneazo) propane-1, 3-diones and evaluation of their antibacterial properties

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Four new 1, 3-diarylpropane-1, 3-diones, 1-(*m*/*p*-nitrophenyl)-3-(*p*-ethylphenyl)- and 1-(*m*/*p*-nitrophenyl)-3-(*p*-ethoxyphenyl)- propane-1, 3-diones have been synthesised and coupled with a number of diazotised sulphonamide bases to yield the corresponding 1, 3-diaryl-2-(N-substituted *p*-sulphamylbenzeneazo) propane-1, 3-diones. These azo-compounds have been screened *in vitro* for their antibacterial properties against *S. aureus*, *E. coli* and *P. pyocyanea*.

In earlier papers the effect of chloro, bromo, methyl and methoxyl groups and the effect of exchanging the nitro group from meta to para positions when present in the phenyl rings of propane-1, 3-diones has been described[1,2]. As an extension of this work, the present communication deals with the synthesis of four new β-diketones. With a view to compare the rates of coupling reactions, these β-diketones were made to react with differently substituted diazotised sulphonamide bases to give the corresponding 1,3-diaryl-2-(N-substituted *p*-sulphamylbenzeneazo) propane-1, 3-diones. These azo-compounds were later subjected to *in vitro* screening against three micro-organisms.

During the course of this work it was observed that the rate of coupling reaction increased when the ethyl group present in the phenyl ring at the position-3 of the propane-1, 3-dione was replaced by an ethoxyl group thereby giving higher yields. The other observation was that the shifting of the nitro group from meta to the para position in the phenyl ring attached at position-1 of the propane-1, 3-dione caused an overall increase in the yields of the azo-compounds.

The yields of the azo-compounds ranged between 71 to 85%.

EXPERIMENTAL PROCEDURE

The following four new β-diketones were prepared by employing the standard method[3].

1-(*m-Nitrophenyl*)-3-(*p-ethylphenyl*) *propane*-1, 3-*dione*

m-Nitrobenzaldehyde (0.06 mol) and *p*-ethylacetophenone (0.06 mol) were condensed in presence of aqueous sodium hydroxide to give *m-nitrobenzylidene p-ethylacetophenone* which was crystallised from ethanol as a light yellow solid, m. p. 120°.

(Found : *C*, 72.6; *H*, 5.4. $C_{17}H_{15}O_3N$ requires *C*, 72.8; *H*, 5.3%).

This styryl ketone on bromination gave the dibromide, m.p. 120°, subsequent dehydrobromination and hydrolysis yielded 1-(*m-nitrophenyl*)-3-(*p-ethylphenyl*) *propane*-1, 3-*dione*, which on crystallisation from ethanol-glacial acetic acid mixture in light yellow needles had m.p. 127°.

(Found : *C*, 68.5; *H*, 5.2. $C_{17}H_{15}O_4N$ requires *C*, 68.7; *H*, 5.0%).

The ethanolic solution of this β-diketone gave a violet red colouration with aqueous ferric chloride-

1-(*p-Nitrophenyl*)-3-(*p-ethylphenyl*) *propane*-1, 3-*dione*

p-Nitrobenzaldehyde and p-ethylacetophenone were condensed in equimolecular quantities in presence of aqueous sodium hydroxide to give *p-nitrobenzylidene p-ethylacetophenone* which was crystallised from ethanol as a light yellow solid, m.p. 134°.

(Found : *C*, 72.5; *H*, 5.4. $C_{17}H_{15}O_3N$ requires *C*, 72.8; *H*, 5.3%).

This chalcone on bromination gave the corresponding dibromide, m.p. 118° and this dibromide on dehydrobromination and subsequent hydrolysis gave the required β-diketone, which on crystallisation from glacial acetic acid as a yellow solid had m.p. 169°.

(Found : *C*, 68.6; *H*, 5.2. $C_{17}H_{15}O_4N$ requires *C*, 68.7; *H*, 5.1%).

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

1-(*m-Nitrophenyl*)-3-(*p-ethoxyphenyl*) *propane*-1, 3-*dione*

m-Nitrobenzaldehyde (0.02 mol) and *p*-ethoxyacetophenone (0.02 mol) were condensed in presence of aqueous sodium hydroxide to furnish *m-nitrobenzylidene p-ethoxyacetophenone* which was crystallised from ethanol as a cream coloured solid, m.p. 113°.

(Found : C, 68.9; *H*, 5.0. $C_{17}H_{15}O_4N$ requires *C*, 68.7; *H*, 5.0%).

Its dibromide, m.p. 126° was dehydrobrominated and hydrolysed to give 1-(*m-nitrophenyl*)-3-(*p-ethoxyphenyl*) *propane*-1, 3-*dione* which was crysfallised from ethanol-glacial acetic acid mixture and had m.p-143°.

(Found : *C*, 65.0, *H*, 4.7. $C_{17}H_{15}O_5N$ requires *C*, 65.2; *H*, 4.8%).

The alcoholic solution of this β-diketone gave a violet red colouration with aqueous ferric chloride.

1-(*p-Nitrophenyl*)-3-(*p-ethoxyphenyl*) *propane*-1, 3-*dione*

Condensation of *p*-nitrobenzaldehyde and *p*-ethoxyacetophenone in equimolecular quantities in presence of aqueous sodium hydroxide gave *p-nitrobenzylidene p-ethoxyacetophenone*; on crystallisation from ethanol it had m.p. 159°.

(Found : *C*, 68.5; *H*, 5.0. $C_{17}H_{15}O_4N$ requires *C*, 68.7; *H*, 5.0%).

The dibromide of the above styrylketone having m.p. 148°, was dehydrobrominated and hydrolysed to give the corresponding β-diketone, which was crystallised from glacial acetic acid in yellow needles, m.p. 159°.

(Found : *C*, 65.3; *H*, 4.6. $C_{17}H_{15}O_4N$ requires *C*, 65.2; *H*, 4.8%).

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

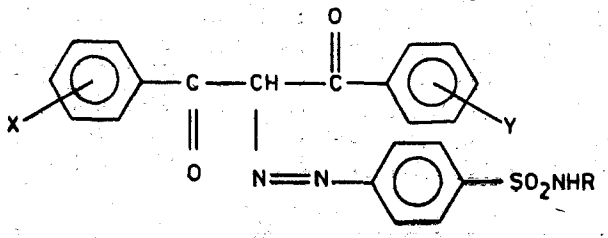
All the N±-substituted sulphanilamides required for this work were prepared by the standard methods[4-18].

Synthesis of 1, 3-*diaryl*-2-(*N-substituted p-sulphamylbenzeneazo*) *propane*-1, 3-*diones*

An ice cold solution of 1, 3-diarylpropane-1, 3-dione (0.002 mol) in acetone containing sodium acetate was mechanically stirred and a diazotised solution of the sulphonamide (0.002 mol) was added during stirring at 0-5°. The reaction mixture was further stirred and the azo-compound obtained by the addition of ice-cold water was filtered, washed with water, and dried. *Pure* 1, 3-*diaryl*-2-(*N-substituted p-sulphamyl-benzeneazo*) *propane*-1, 3-*dione* (I) was crystallised from ethanol or glacial acetic acid or DMF or a mixture of any two of these solvents. These azo-compounds are entered in Tables 1 to 4.

EVALUATION OF THE ANTIBACTERIAL PROPERTIES

These azo-compounds have been tested *in vitro* against three micro-organisms *S. aureus*, *E. coli* and *P. pyocyanea* at two different concentrations of 250 μg/ml and 500 μg/ml using the cup-plate agar diffusion method and the results with the concentrations of 250 μg/ml are also entered in Tables 1=4.



(I)

TABLE 1

1-(*m*-NITROPHENYL)-3-(*p*-ETHYLPHENYL)-2-(N-SUBSTITUTED (*p*-SULPHAMYLBENZENEAZO) PROPANE-1, 3-DIONES

(A : X=*m*-NO_2; Y=*p*-C_2H_5)

S. No.	R	M.P. (°C)	Colour	Yield (%)	Molecular formula	C (Found) (%)	H (Found) (%)	C (Requires) (%)	H (Requires) (%)	Antibacterial properties: *S. aureus.*	*E. coli*	*P. pyocyanea*
1.	H	206	Y	75	$C_{23}H_{20}O_6N_4S$	57.4	4.0	57.5	4.2	(+)	(—)	(+)
2.	Acetyl	165	Y	72	$C_{25}H_{22}O_7N_4S$	57.5	4.4	57.5	4.2	(—)	(—)	(—)
3.	Phenyl	204	Y	72	$C_{29}H_{24}O_6N_4S$	62.3	4.3	62.6	4.3	(—)	(—)	(++)
4.	*o*-Methylphenyl	199	Y	71	$C_{30}H_{26}O_6N_4S$	63.0	4.5	63.2	4.6	(++)	(—)	(++++)
5.	*m*-Methylphenyl	198	Y	74	$C_{30}H_{26}O_6N_4S$	63.2	4.5	63.2	4.6	(—)	(—)	(+)
6.	*p*-Methylphenyl	205	Y	77	$C_{30}H_{26}O_6N_4S$	63.5	4.8	63.2	4.6	(+)	(—)	(++)
7.	*o*-Chlorophenyl	216	Y	79	$C_{24}H_{23}O_6N_4ClS$	59.1	4.0	59.0	3.9	(++)	(+)	(—)
8.	*m*-Chlorophenyl	215	Y	78	$C_{29}H_{23}O_6N_4ClS$	59.3	4.0	59.0	3.9	(+)	(+)	(++)
9.	*p*-Chlorophenyl	218	Y	80	$C_{29}H_{23}O_6N_4ClS$	58.9	3.7	59.0	3.9	(+)	(++)	(+)
10.	*p*-Bromophenyl	226	Y	82	$C_{29}H_{23}O_6N_4BrS$	55.0	3.6	54.8	3.6	(+)	(+)	(+)
11.	Guanidyl	185	Y	76	$C_{24}H_{22}O_6N_5S$	55.4	4.1	55.2	4.2	(+)	(+)	(++)
12.	α—Pyridyl	237	Y	76	$C_{28}H_{23}O_6N_6S$	60.0	4.0	60.3	4.1	(++)	(+)	(—)
13.	2-Pyrimidinyl	245	YR	80	$C_{27}H_{22}O_6N_5S$	58.1	4.2	58.3	3.9	(+)	(+)	(+)
14.	2,6-Dimethyl-4-pyrimidinyl	249	Y	76	$C_{29}H_{22}O_6N_6S$	59.5	4.5	59.4	4.4	(—)	(+++)	(++)
15.	4,6-Dimethyl-2-pyrimidinyl	233	Y	78	$C_{29}H_{26}O_6N_6S$	59.2	4.4	59.4	4.4	(—)	(+)	(+)
16.	2,6-Dimethoxy-4-pyrimidinyl	135	Y	75	$C_{29}H_{26}O_8N_6S$	56.1	4.3	56.3	4.2	(++)	(++)	(+)
17.	5-Methyl-1,3,4-thiadiazol-2-yl	207	Y	77	$C_{26}H_{22}O_6N_6S_2$	54.3	3.6	54.0	3.6	(++)	(++)	(+)

TABLE 2

1-(*p*-NITROPHENYL)-3-(*p*-ETHYLPHENYL)-2-(N-SUBSTITUTED *p*-SULPHAMYLBENZENEAZO)=PROPANE-1, 3,DIONES

(A : X=*p*-NO_2, Y=*p*-C_2H_5)

S. No.		M.P. (°C)	Colour	Yield (%)	Molecular formula	C (Found) (%)	H (Found) (%)	C (Requires) (%)	H (Requires) (%)	Antibacterial properties: *S. aureus*	*E. coli*	*P. pyocyanea*
1.	H	234	YSN	74	$C_{23}H_{20}O_6N_4S$	57.6	4.2	57.5	4.2	(++++)	(+)	(++)
2.	Acetyl	228	Y	76	$C_{25}H_{22}O_7N_4S$	57.8	4.1	57.5	4.2	(+)	(+)	(+)
3.	Phenyl	221	Y	78	$C_{29}H_{24}O_6N_4S$	62.4	4.1	62.6	4.3	(+++)	(+)	(+++)
4.	*p*-Methylphenyl	222	Y	80	$C_{30}H_{26}O_6N_4S$	63.0	4.8	63.2	4.6	(++++)	(+)	(+++)
5.	*o*-Chlorophenyl	190	Y	82	$C_{29}H_{23}O_6N_4ClS$	59.2	4.0	59.0	3.9	(+++)	(+++)	(+)
6.	*m*-Chlorophenyl	187	YBN	77	$C_{29}H_{23}O_6N_4ClS$	59.1	4.2	59.0	3.9	(++)	(+++)	(—)
7.	*p*-Chlorophenyl	245	Y	83	$C_{29}H_{23}O_6N_4ClS$	58.9	3.9	59.0	3.9	(+++)	(++)	(+)
8.	*p*-Bromophenyl	248	Y	84	$C_{29}H_{23}O_6N_4BrS$	55.0	3.7	54.8	3.6	(++++)	(+)	(—)
9.	Guanidyl	253	YB	77	$C_{27}H_{22}O_6N_6S$	55.2	4.1	55.2	4.2	(+)	(+)	(+)
10.	2-Pyriimidinyl	248	Y	81	$C_{27}H_{22}O_6N_6S$	58.0	4.0	58.1	3.9	(+)	(+)	(+)
11.	2,6-Dimethyl-4-pyrimidinyl.	204	Y	78	$C_{29}H_{26}O_6N_6S$	59.5	4.3	59.4	4.4	(+)	(—)	(+++)
12.	4,6-Dimethyl-2-pyrimidinyl	215	Y	81	$C_{29}H_{26}O_6N_6S$	59.3	4.4	59.4	4.4	(++)	(+)	(+)
13.	2,6-Dimethoxy-4-pyrimidinyl .	233	Y	75	$C_{29}H_{26}O_8N_6S$	56.3	4.1	56.3	4.2	(+)	(++)	(+)

TABLE 3

1-(*m*-NITROPHENYL)-3-(*p*-ETHOXYPHENYL)-2-(N-SUBSTITUTED *p*-SULPHAMYLBENZENEAZO) PROPANE-1, 3-DIONES

(A : X=*m*-NO_2 ; Y=*p*-OC_2H_5)

S. No.	*R*	M.P. (°C)	Colour	Yield (%)	Molecular formula	C Found (%)	H Found (%)	C Requires (%)	H Requires (%)	Antibacterial Properties: *S. aureus*	*E. coli*	*P. pyocyanea*
1.	H	199	YO	77	$C_{23}H_{20}O_7N_4S$	55.1	3.9	55.6	4.0	(+)	(—)	(+)
2.	Acetyl	156	Y	74	$C_{25}H_{22}O_8N_4S$	55.6	4.1	55.7	4.1	(—)	(—)	(+)
3.	Phenyl	200	YS	76	$C_{29}H_{24}O_7N_4S$	61.0	4.2	60.8	4.2	(—)	(—)	(—)
4.	*o*-Methylphenyl	187	YOS	74	$C_{30}H_{26}O_7N_4S$	61.4	4.5	61.4	4.4	(—)	(—)	(+)
5.	*m*-Methylphenyl	190	YO	77	$C_{30}H_{26}O_7N_4S$	61.3	4.4	61.4	4.4	(+++)	(—)	(+)
6.	*p*-Methylphenyl	222	O	79	$C_{30}H_{26}O_7N_4S$	61.1	4.6	61.4	4.4	(—)	(—)	(—)
7.	*o*-Chlorophenyl	199	SO	77	$C_{29}H_{23}O_7N_4S$	57.4	4.0	57.4	3.8	(+)	(+)	(++)
8.	*m*-Chlorophenyl	196	SY	79	$C_{29}H_{23}O_7N_4ClS$	57.3	3.9	57.4	3.8	(—)	(+)	(—)
9.	*p*-Chlorophenyl	242	YO	80	$C_{29}H_{23}O_7N_4ClS$	57.3	3.7	57.4	3.8	(+++)	(+)	(+)
10.	*p*-Bromophenyl	239	Y	84	$C_{29}H_{23}O_7N_4BrS$	54.0	3.5	53.9	3.5	(++)	(+)	(++)
11.	Guanidyl	251	YO	76	$C_{24}H_{22}O_7N_6S$	53.2	4.0	53.4	4.1	(++++)	(+)	(+++)
12.	α-Pyridyl	170	Y	75	$C_{28}H_{23}O_7N_5S$	58.4	4.2	58.4	4.0	(++)	(++)	(+)
13.	2-Pyrimidinyl	218	YO	81	$C_{27}H_{22}O_7N_6S$	56.4	4.0	56.5	3.9	(+)	(+)	(—)
14.	2,6-Diimethyl-4-pyrimidinyl	220	Y	78	$C_{29}H_{26}O_7N_6S$	57.8	4.4	57.8	4.3	(—)	(—)	(—)
15.	4,6-Dimethyl-2-pyrimidinyl	215	Y	80	$C_{29}H_{26}O_7N_6S$	57.7	4.3	57.8	4.3	(—)	(+)	(—)
16.	2,6-Dimethoxy-4-pyrimidinyl	138	Y	77	$C_{29}H_{26}O_9N_6S$	60.0	4.0	59.9	4.1	(—)	(+)	(+)
17.	5-Methyl-1,3,4-thiadiazol-2-yl	167	Y	78	$C_{26}H_{22}O_7N_6S_2$	52.4	3.8	52.5	3.7	(++)	(—)	(—)

TABLE 4

1-(*p*-NITROPHENYL)-3-(*p*-ETHOXYPHENYL)-2-(N-SUBSTITUTED *p*-SULPHAMYLBENZENEAZO) PROPANE-1, 3-DIONES

(A : X=*p*-NO_2 ; Y=*p*-OC_2H_5)

S. No.	R	M.P. (°C)	Colour	Yield (%)	Molecular formula	C Found (%)	H Found (%)	C Requires (%)	H Requires (%)	Antibacterial properties: *S. aureus*	*E. coli*	*P. pyocyanea*
1.	H	221	YO	78	$C_{23}H_{20}O_7N_4S$	55.5	4.1	55.6	4.0	(+)	(—)	(+)
2.	Acetyl	127	Y	76	$C_{25}H_{22}O_8N_4S$	55.3	4.1	55.7	4.1	(—)	(—)	(—)
3.	Phenyl	203	Y	79	$C_{29}H_{24}O_7N_4S$	61.0	4.1	60.8	4.2	(+)	(—)	(+)
4.	*o*-Methylphenyl	208	YO	75	$C_{30}H_{26}O_7N_4S$	61.4	4.5	61.4	4.4	(—)	(+)	(—)
5.	*m*-Methylphenyl	215	Y	77	$C_{30}H_{26}O_7N_4S$	61.6	4.5	61.4	4.4	(—)	(+)	(—)
6.	*p*-Methylphenyl	213	Y	80	$C_{30}H_{26}O_7N_4S$	61.3	4.4	61.4	4.4	(—)	(—)	(+)
7.	*o*-Chlorophenyl	186	Y	79	$C_{29}H_{23}O_7N_4ClS$	57.5	4.0	57.4	3.8	(+)	(+)	(+)
8.	*m*-Chlorophenyl	188	Y	79	$C_{29}H_{23}O_7N_4ClS$	57.4	3.9	57.4	3.8	(+)	(+)	(++)
9.	*p*-Chlorophenyl	246	Y	82	$C_{29}H_{23}O_7N_4ClS$	57.3	4.0	57.4	3.8	(++)	(+)	(+)
10.	*p*-Bromophenyl	240	Y	85	$C_{29}H_{23}O_7N_4BrS$	53.7	3.6	53.9	3.5	(++)	(+)	(—)
11.	Guanidyl	275-6	O	78	$C_{24}H_{22}O_7N_6S$	53.4	4.4	53.7	4.1	(++++)	(+)	(+)
12.	*y*-pyridyl	233	Y	76	$C_{28}H_{23}O_7N_5S$	58.5	4.2	58.4	4.0	(++)	(+)	(++)
13.	2-Pyrimidinyl	233	Y	82	$C_{27}H_{22}O_7N_6S$	56.4	4.0	56.5	3.9	(+)	(+)	(+)
14.	2,6-Dimethyl-4-pyrimidinyl	148	Y	79	$C_{29}H_{26}O_7N_6S$	57.9	4.1	57.8	4.3	(—)	(—)	(+++)
15.	5-Methyl-1,3,4-thiadiazol-2-yl	201	YO	77	$C_{26}H_{22}O_7N_6S_2$	52.5	3.8	52.5	3.7	(++)	(++)	(+++)

B='Brown'; F='Flakes'; N='Needles'; O='Orange'; R='Red'; S='Shining'; Y='Yellow'.

1, 3-Diaryl-2-(N-substituted *p*-sulphamylbenzeneazo) propane-1, 3-diones in general exhibited activity against all the three micro-organisms. If these results were compared among themselves it became evident that the replacement of an ethyl group by an ethoxyl group in the phenyl ring attached at position-3 of the propane-1, 3-dione, caused a decrease in the activity except in a few cases. However, if a nitro group was changed from the meta to the para position, the azo-compounds by and large showed considerable increase in activity especially against *S. aureus* and *E. coli* which is in confirmation of earlier inferences[1].

Again, if the results were compared on the basis of changes made in the substitution pattern of the sulphonamide moiety, keeping the substituents in the phenyl rings attached at positions-1 and 3 unaltered, it was observed that the replacement of the methyl group by a halogen atom in the phenyl ring attached at N^1 of the sulphonamides, the activity against *S. aureus* and *E. coli* increased. However, the replacement of the phenyl ring of the sulphonamide residue attached at position N^1 by a heterocyclic ring caused an increase in activity against *S. aureus* and *E. coli.*

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