STUDIES IN SULPHONAMIDES—PART XI

Synthesis and study of the antibacterial properties of 1-methyl-3-aryl-2-(N-substituted p-sul-phamylbenzeneazo) propane-1, 3-diones

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In this paper four 1-methyl-3-arylpropane-1, 3-diones, 1-methyl-3- (3′ 4′-dichlorophenyl)-, 1-methyl-3-(2′-chloro-5′-methylphenyl)-,1-methyl-3-(α-naphthyl)-, 1-methyl-3-(5′ 6′ 7′ 8′-tetrahydro-naphth-2′-yl) propane-1, 3-diones have been synthesised and coupled with different diazotised sulphonamide bases in presence of sodium acetate to give the corresponding 1-methyl-3-aryl-2- (N-substituted p-sulphamylbenzeneazo) propane-1, 3-diones. These azo-compounds have been tested *in vitro* for their antibacterial properties against *S. aureus, E. coli* and *p. pyocyanea* and were found to possess considerable activity.

In continuation of the earlier work[1] on the study of coupling reactions of 1-methyl-3-arylpropane-1, 3-diones and antibacterial properties of the azo-compounds, four 1-methyl-3-arylpropane-1, 3-diones were prepared and later coupled with differently substituted diazotised sulphonamide bases. The main object of taking up this work was to study the effect of (*i*) the introduction of one more chlorine atom and replacement of the methyl group by a chlorine atom in the phenyl ring at position-3 of the propanedione and (*ii*) saturation of one of the phenyl rings of the naphthalene moiety attached at position-3 of the propane-1, 3-dione on the rate of coupling and on the pharmacological properties of the azo-compounds obtained after coupling.

During the course of coupling reaction it was observed that the rate of coupling reaction increased if an electron donating group like methyl was replaced by chlorine atom in the phenyl ring of 1-methyl-3-aryl-propane-1, 3-dione thereby giving higher yields. On comparing these results with those obtained earlier with the azo-compounds from 1-methyl-3-(p-chlorophenyl) propane-1, 3-dione[1], it became clear that introduction of an additional chlorine atom in the phenyl ring caused an increase in the rate of coupling. It was also observed that saturation of one of the phenyl rings of the naphthalene moiety caused an increase in the rate of coupling reaction.

The yields of the azo-compounds ranged between 70 to 88%

EXPERIMENTAL PROCEDURE

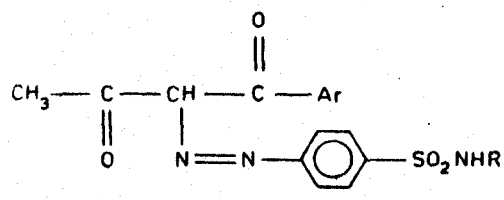
Out of the four β-diketones, three, 1-methyl-3-(3′,4′-dichlorophenyl)-, 1-methyl-3-(2′-chloro-5′-methylphenyl),—1-methyl-3-(α-naphthyl) propane-1, 3-diones were prepared according to the standard methods[2,3] and the preparation of the fourth is given below.

Synthesis of 1-*methyl*-3-(5′,6′,7′,8′-*tetrahydronaphth*-2′-*yl*) *propane*-1, 3-*dione*.

A mixture of 5, 6, 7, 8-tetrahydronaphth-2-yl methyl ketone (17.4 g; 0.1 mol) and ethyl acetate (70.4g ; 0.8 mol) was gradually added to sodium (5.75 g; 0.25 mol) in dry ether (100 ml) contained in a R. B. flask (500 ml) fitted with a double walled reflux condenser carrying a guard tube, with cooling and shaking during two hours. The contents were refluxed for 6-7 hours, cooled, poured into ice-cold water, acidified with glacial acetic acid and extracted with ether. The ethereal layer was shaken with a saturated solution of cupric acetate, the copper complex which separated out was filtered, washed with ether, finally with water and then decomposed with dilute sulphuric acid. The separated oil was poured over ice, taken up in ether, the ethereal layer washed with water, dried over anhydrous sodium sulphate and ether removed. The residual liquid was distilled and *pure* 1-*methyl*-3-(5′,6′,7′,8′-*tetrahydronaphth*-2′-*yl*) *propane*-1, 3-*dione* was collected at 185-8° /11 mm (Yield : 15.4 g; 71.3%).

(Found : *C*, 77.6; *H*, 7.2, C_{14} H_{16} O_2 requires *C*, 77.8; *H*, 7.4%).

Its alcoholic solution gave violet colouration with aqueous ferric chloride.



(I)

The sulphonamides required for this work were prepared by standard methods.[4-18]

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

To an ice-cold solution of 1-methyl-3-arylpropane-1, 3-dione (0.002 mol) in acetone containing sodium acetate was gradually added a diazotised solution of the sulphonamide (0.002 mol) with stirring at 0-5°. The azo-compound obtained by the addition of ice-cold water and stirring for ten minutes, was filtered, washed with water and dried. *Pure* 1-*methyl*-3-*aryl*-2-(*N-substituted p-sulphamyl-benzeneazo*) *propane*-1, 3-*dione* (I) were crystallised from ethanol or glacial acetic acid or DMF or from a mixture of any of the above two solvents. These azo-compounds are recorded in Tables 1 to 4.

TABLE 1

1-METHYL-3-(3′,4′-DICHLOROPHENYL)-2-(N-SUBSTITUTED *p*-SULPHAMYLBENZENEAZO) PROPANE-1, 3-DIONES

(I. : Ar=3, 4-Dichlorophenyl)

S. No.	R	M.P. °C	Colour	Yield %	Molecular formula	Percentage Found C	Percentage Found H	Percentage Requires C	Percentage Requires H	Antibacterial activity S. *aureus*	Antibacterial activity E. *coli*	Antibacterial activity P. *pyocyanea*
1.	*H*	185	YSF	78	$C_{16}H_{13}O_4N_3Cl_2S$	46.2	3.2	46.4	3.1	(—)	(—)	(+)
2.	Acetyl	192	Y	82	$C_{18}H_{15}O_5N_3Cl_2S$	47.5	3.1	47.3	3.3	(—)	(—)	(—)
3.	Phenyl	201	B	76	$C_{22}H_{17}O_4N_3Cl_2S$	54.0	3.5	53.9	3.5	(+)	(—)	(—)
4.	*o*-Methylphenyl	195	YSN	82	$C_{23}H_{19}O_4N_3Cl_2S$	54.9	4.0	54.8	3.8	(—)	(+)	(+)
5.	*m*-Methylphenyl	169	Y	80	$C_{23}H_{19}O_4N_3Cl_2S$	54.8	3.9	54.8	3.8	(—)	(+)	(—)
6.	*p*-Methylphenyl	178	Y	77	$C_{23}H_{19}O_4N_3Cl_2S$	55.0	3.9	54.8	3.8	(—)	(—)	(—)
7.	*o*-Chlorophenyl	183	BSN	74	$C_{22}H_{16}O_4N_3Cl_3S$	50.2	3.1	50.4	3.1	(—)	(++)	(+)
8.	*m*-Chlorophenyl	182	YOS	78	$C_{22}H_{16}O_4N_3Cl_3S$	50.5	3.0	50.4	3.1	(+)	(++)	(—)
9.	*p*-Chlorophenyl	186	RB	76	$C_{22}H_{26}O_4N_3Cl_3S$	50.4	3.3	50.4	3.1	(+)	(++)	(++)
10.	*p*-Bromophenyl	190	OSF	74	$C_{22}H_{16}O_4N_3Cl_2BrS$	46.6	3.0	46.4	2.8	(++)	(+++)	(—)
11.	Guanidyl	245	YSN	72	$C_{17}H_{16}O_4N_5Cl_2S$	44.7	3.5	44.7	3.3	(+)	(—)	(—)
12.	α-Pyridyl	226	YSN	77	$C_{21}H_{16}O_4N_4Cl_2S$	51.3	3.4	51.3	3.3	(—)	(—)	(—)
13.	2-Pyrimidinyl	263	Y	82	$C_{20}H_{15}O_4N_5Cl_2S$	49.0	3.2	48.8	3.1	(+)	(+)	(+)
14.	2, 6-Dimethyl-4-pyrimidinyl	250	Y	78	$C_{22}H_{19}O_4N_5Cl_2S$	50.7	3.8	50.8	3.7	(—)	(+)	(+)
15.	4, 6-Dimethyl-2-pyrimidinyl	245	BS	80	$C_{22}H_{19}O_4N_5Cl_2S$	50.9	3.4	50.8	3.7	(—)	(+)	(+)
16.	2, 6-Dimethoxy-4-pyrimidinyl	199	Y	82	$C_{22}H_{19}O_6N_5Cl_2S$	47.7	3.6	47.8	3.4	(+)	(+)	(+)
17.	5-Methyl-1, 3, 4-thiadiazol-2-yl	201	OF	80	$C_{19}H_{15}O_4N_5Cl_2S_2$	44.5	3.0	44.5	2.9	(—)	(—)	(—)

TABLE 2

1-METHYL-3-(2′-CHLORO-5′-METHYLHENYL)-2-(N-SUBSTITUTED *p*-SULPHAMYLBENZENEAZO) PROPANE-1, 3-DIONES

(I : Ar = 2-Chloro-5-methylphenyl)

S. No.	R	M.P. °C	Colour	Yield %	Molecular formula	Percentage Found C	Found H	Requires C	Requires H	Antibacterial activity *S. aureus*	*E. coli*	*P. pyocyanea*
1.	H	164	YN	73	$C_{17}H_{16}O_4N_3ClS$	52.2	3.9	51.9	4.1	(—)	(—)	(—)
2.	Acetyl	208	Y	77	$C_{19}H_{18}O_5N_3ClS$	52.4	4.0	52.4	4.1	(—)	(++)	(+)
3.	Phenyl	181	YSN	73	$C_{23}H_{23}O_4N_3ClS$	56.9	4.5	56.8	4.3	(—)	(+)	(—)
4.	*o*-Methylphenyl	203	YSN	79	$C_{24}H_{22}O_4N_3ClS$	59.5	4.7	59.6	4.6	(++)	(+++)	(+)
5.	*m*-Methylphenyl	142	Y	76	$C_{24}H_{22}O_4N_3ClS$	59.9	4.6	59.6	4.6	(++)	(+++)	(—)
6.	*p*-Methylphenyl	177	SY	74	$C_{24}H_{22}O_4N_3ClS$	59.8	4.5	59.6	4.6	(—)	(—)	(+)
7.	*o*-Chlorophenyl	184	YN	74	$C_{23}H_{19}O_4N_3Cl_2S$	55.0	3.7	54.9	3.8	(—)	(+)	(+)
8.	*m*-Chlorophenyl	186	YSN	76	$C_{23}H_{19}O_4N_3Cl_2S$	54.6	4.0	54.9	3.8	(—)	(+)	(+)
9.	*p*-Chlorophenyl	183	SY	75	$C_{23}H_{18}O_4N_3Cl_2S$	54.7	3.7	54.9	3.8	(—)	(—)	(—)
10.	*p*-Bromophenyl	175	Y	79	$C_{23}H_{19}O_4N_3ClBrS$	50.2	3.6	50.4	3.5	(—)	(—)	(—)
11.	Guanidyl	249	Y	70	$C_{18}H_{18}O_4N_5ClS$	49.7	4.0	49.7	4.1	(—)	(—)	(—)
12.	α-Pyridyl	233	Y	74	$C_{22}H_{18}O_4N_4ClS$	56.1	4.3	56.2	4.0	(—)	(+)	(+)
13.	2-Pyrimidinyl	260	Y	81	$C_{21}H_{18}O_4N_5ClS$	53.2	4.0	53.5	3.8	(+)	(++)	(+)
14.	2, 6-Dimethyl-4-pyrimidinyl	195	Y	76	$C_{23}H_{22}O_4N_5ClS$	55.3	4.6	55.3	4.4	(—)	(+)	(—)
15.	4, 6-Dimethyl-2-pyrimidinyl	172	Y	78	$C_{23}H_{22}O_4N_5ClS$	55.5	4.4	55.3	4.4	(—)	(—)	(—)
16.	2, 6-Dimethoxy-4-pyrimidinyl	225	Y	84	$C_{23}H_{22}O_6N_5ClS$	51.9	4.1	52.0	4.1	(+)	(+)	(+)
17.	5-Methyl-1, 3, 4-thiadiazol-2-yl	191	Y	78	$C_{20}H_{18}O_4N_5ClS_2$	49.0	3.9	48.9	3.7	(—)	(+)	(—)

TABLE 3

1-METHYL-3-(α-NAPHTHYL)-2-(N-SUBSTITUTED *p*-SULPHAMYLBENZENEAZO) PROPANE-1, 3-DIONES

(I : Ar= α-Naphthyl)

S. No.	R	M.P. °C	Colour	Yield %	Molecular formula	Percentage Found C	Found H	Requires C	Requires H	Antibacterial activity *S. aureus*	*E. coli*	*P. pyocyanea*
1.	*H*	186	Y	76	$C_{20}H_{17}O_4N_3S$	61.0	4.3	60.8	4.3	(—)	(—)	(+)
2.	Acetyl	216	Y	82	$C_{22}H_{19}O_5N_3S$	60.4	4.4	60.4	4.4	(—)	(—)	(+)
3.	Phenyl	199	Y	78	$C_{26}H_{21}O_4N_3S$	66.2	4.8	66.2	4.5	(—)	(—)	(—)
4.	*o*-Methylphenyl	205	YO	74	$C_{27}H_{23}O_4N_3S$	66.7	4.4	66.8	4.7	(—)	(—)	(+)
5.	*m*-Methylphenyl	196	YO	76	$C_{27}H_{23}O_4N_3S$	66.9	4.8	66.8	4.7	(—)	(—)	(—)
6.	*p*-Methylphenyl	185	Y	80	$C_{27}H_{23}O_4N_3S$	66.7	4.6	66.8	4.7	(—)	(—)	(—)
7.	*o*-Chlorophenyl	177	Y	82	$C_{26}H_{20}O_4N_3ClS$	62.1	4.0	61.8	4.0	(+)	(+)	(—)
8.	*m*-Chlorophenyl	173	Y	80	$C_{26}H_{20}O_4N_3ClS$	61.8	4.0	61.8	4.0	(+)	(+)	(+)
9.	*p*-Chlorophenyl	177	Y	83	$C_{26}H_{20}O_4N_3ClS$	61.7	4.1	61.8	4.0	(+)	(—)	(+)
10.	*p*-Bromophenyl	175	Y	84	$C_{26}H_{20}O_4N_3BrS$	56.9	3.5	56.9	3.6	(+)	(+)	(—)
11.	Guanidyl	275	Y	75	$C_{21}H_{19}O_4N_5S$	57.4	4.2	57.7	4.3	(—)	(+)	(—)
12.	α-Pyridyl	207	Y	77	$C_{25}H_{20}O_4N_4S$	63.7	4.2	63.6	4.2	(+)	(+)	(—)
13.	2-Pyrimidinyl	232	Y	80	$C_{24}H_{19}O_4N_5S$	60.5	4.1	60.9	4.0	(+)	(+)	(+)
14.	2, 6-Dimethyl-4-pyrimidinyl	251	Y	85	$C_{26}H_{23}O_4N_5S$	62.1	4.8	62.3	4.6	(+)	(—)	(++)
15.	4,6-Dimethyl-2-pyrimidinyl	185	Y	82	$C_{26}H_{23}O_4N_5S$	62.2	4.4	62.3	4.6	(+)	(—)	(++)
16.	2,6-Dimethoxy-4-pyrimidinyl	223	Y	84	$C_{26}H_{23}O_6N_5S$	58.6	4.2	58.5	4.3	(—)	(—)	(++)
17.	5-Methyl-1, 3, 4-thiadiazol-2-yl	235	Y	86	$C_{23}H_{19}O_4N_5S_2$	56.3	4.0	56.0	3.9	(++)	(—)	(+)

TABLE 4

1-METHYL-3-(5′, 6′, 7′,8′-TETRAHYDRONAPHTH-2 -yl)-2-(N-SUBSTITUTED *p*-SULPHAMYLBENZENEAZO) PROANE-1, 3-DIONES

(I : Ar=5, 6, 7, 8-Tetrahydronaphth-2-yl)

S. No.	R	M.P. °C	Colour	Yield %	Molecular formula	Percentage Found C	Percentage Found H	Percentage Requires C	Percentage Requires H	Antibacterial activity *S. aureus*	Antibacterial activity *E. coli*	Antibacterial activity *P. pyocyanea*
1.	H	233	Y	81	$C_{20}H_{21}O_4N_3S$	60.2	5.6	60.2	5.3	(+)	(—)	(—)
2.	Acetyl	241	Y	85	$C_{22}H_{23}O_5N_3S$	60.1	5.3	59.9	5.2	(—)	(+)	(—)
3.	Phenyl	165	Y	80	$C_{26}H_{25}O_4N_3S$	65.9	5.1	65.7	5.3	(—)	(—)	(+)
4.	*o*-Methylphenyl	141	SO	82	$C_{27}H_{27}O_4N_3S$	66.4	5.5	66.3	5.5	(+)	(+)	(+)
5.	*m*-Methylphenyl	148	Y	85	$C_{27}H_{27}O_4N_3S$	66.1	5.6	66.3	5.5	(—)	(—)	(—)
6.	*p*-Methylphenyl	169	B	81	$C_{27}H_{27}O_4N_3S$	66.4	5.2	66.3	5.5	(—)	(+)	(—)
7.	*o*-Chlorophenyl	160	Y	77	$C_{26}H_{24}O_4N_3ClS$	61.2	4.4	61.3	4.7	(++)	(+)	(—)
8.	*m*-Chlorophenyl	158	Y	80	$C_{26}H_{24}O_4N_3ClS$	61.3	4.7	61.3	4.7	(+)	(+)	(+)
9.	*p*-Chlorophenyl	171	O	80	$C_{26}H_{24}O_4N_3ClS$	61.1	4.9	61.3	4.7	(+)	(+)	(—)
10.	*p*-Bromophenyl	181	O	86	$C_{26}H_{24}O_4N_3BrS$	56.0	4.2	56.3	4.3	(+)	(+)	(—)
11.	α-Pyridyl	204	SY	78	$C_{25}H_{24}O_4N_4S$	63.2	5.1	63.0	5.0	(++)	(+)	(—)
12.	2-Pyrimidinyl	216	YO	83	$C_{24}H_{23}O_4N_5S$	60.4	4.8	60.4	4.8	(+++)	(+)	(—)
13.	2, 6-Dimethyl-4-pyrimidinyl	130	Y	88	$C_{26}H_{27}O_4N_5S$	61.9	5.1	61.8	5.3	(++)	(+)	(—)
14.	4, 6-Dimethyl-2-pyrimidinyl	141	Y	87	$C_{26}H_{27}O_4N_5S$	61.8	5.6	61.8	5.3	(+)	(—)	(—)
15.	2, 6-Dimethoxy-4-pyrimidinyl	218	O	84	$C_{26}H_{27}O_6N_5S$	58.0	5.2	58.1	5.0	(+)	(—)	(—)
16.	5-Methyl-1, 3, 4-thiadiazol-2-yl	215	YB	86	$C_{23}H_{23}O_4N_5S_2$	55.2	4.7	55.5	4.6	(++)	(+)	(—)

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

EVALUATION OF THE ANTIBACTERIAL PROPERTIES

All the synthesised azo-compounds have been tested *in vitro*[19] 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 concentration of 250 μg/ml are entered in the Tables 1-4.

These azo-compounds were found to exhibit mixed activity against the three micro-organisms. Most of the compounds of the series of 1-methyl-3-(3′, 4′-dichlorophenyl)-and 1-methyl-3-(2′-chloro-5′-methyl-phenyl)-2-(*N*-substituted *p*-sulphamylbenzeneazo) propane-1, 3-diones were active against *E. coli* and less active against *S. aureus* and *P. pyocyanea*. When the results of these two series were compared among themselves, it was observed that when the chlorine atom was replaced by a methyl group, the activity against all the three micro-organisms decreased in general with only few exceptions. However, when the results of the screening of 1-methyl-3-(3′, 4′-dichlorophenyl)-2-(*N*-substituted *p*-sulphamyl benzeneazo) propane-1, 3. diones were compared with those of 1-methyl-3-(4′-chloro-3′-methylphenyl)-and 1-methyl-3-(*p*-chlorophenyl) -2-(*N*-substituted *p*-sulphamylbenzeneazo) propane-1, 3-diones[1], it became clear that the introduction of one more chlorine atom as well as the replacement of the methyl group by a chlorine atom causes an increase in the activity against *E. Coli.*

On comparing the results of screening of 1-methyl-3-(α-naphthyl)- and 1-methyl-3-(5′, 6′, 7′, 8′-tetrahydronaphth-2′-yl)-2-(*N*-substituted *p*-sulphamylbenzeneazo) propane-1, 3-diones, it was inferred that saturation of one of the phenyl rings of naphthalene moiety made these compounds more active against *E. coli* and *S. aureus* and less active against *P. pyocyanea* wih only few exceptions.

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 except in the case of 1-methyl-3-(2′-chloro-5′-methylphenyl)-2-(*N*-substituted *p*-sulphamylbenzeneazo) propane-1, 3-diones. However, the replacement of the phenyl ring of sulphonamide residue attached at N^1 by a heterocyclic ring such as simple α-pyridyl or 2-pyrimidinyl causes an increase in activity against *S. aureus* and *E. coli* except the compound No. 12 in Table 1.

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