STUDIES IN SULPHONAMIDES—PART VIII

Synthesis of 1-aryl-3-methyl-2-(substituted sulphonamidobenzeneazo) propane-1, 3-diones and evaluation of their antibacterial properties

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1-Aryl-3-methylpropane-1, 3-diones, viz., 1-(4¹ chlorophenyl) ,1 -(4'-bromophenyl)-1-(4'-chloro-3'-methyl-phenyl)- and 1-biphenyl-3-methylPropane-1, 3-dions have been synthesised and coupled with different diazotised sulphonamied, bases in presence of sodium acetate to furnish the respective 1-aryl-3-methyl-2-(subsituted sulphonamidobenzeneazo propane-1, 3-diones. All these azo compounds have been tested *in vitro* for their antibacterial properties aginst *S. aureus* and *E. coli* and majority of these are found active against *S. aureus*.

Some β-diketones are reported to exhibit phenol coefficients against B. *typhosus* and also found to be active against *Staphylococcus aureus*[1]. Again simple azo compounds and those derived from sulphonamides show a wide divergence of activity upto 100 fold than the parent compounds [2,3].

β-Diketones readily couple with diazotised sulphonamide bases to furnish the azo compounds which are reported to be biologically active[4]. In view of the encouraging results obtained in respect of their biological properties, the work was undertaken to prepare 1-aryl-3-methylpropane-1, 3-diones and then couple them with a wide variety of diazotised sulphonamide bases. The main objective of taking up this work was to study the effect of (i) replacing one of the phenyl rings of the dibenzoylmethanes by a methyl group, (ii) the presence of electron attracting groups in the phenyl ring of the various benzoylacetones on the rate of the coupling reactions and make a comparison amongst these and with those prepared from dibenzoylmethanes [4,5]. The second object was to study their pharmacological properties as the azo dyes in general have been widely used as valuable therapeutics.

Besides their uses in medicine and dye industry, the pyrazole derivatives have of late been reported to be potential high explosives.[6] The bacteriological study of all these compounds was carried out using the cup-plate agar diffusion method against two organisms, *S. aureus* and *E. coli*.

EXPERIMENTAL PROCEDURE

Preparation of 1-(4'-Chloro-3'-methylphenyl)-3-methyl propane-1, 3-dione

To a R. B. flask (1 lit) fitted with a double-walled reflux condenser and a guard tube, containing dry ether (300 ml) was added sodium (2·3 g; 0·1 mol) followed by a mixture of ethyl acetate (26·4 g ; 0·3 mol) and 4-chloro-3-methylacetophenone (16·9 g ; 0·1 mol) with frequent shaking and cooling. The contents were refluxed for 5-6 hrs, cooled, added to ice-cold water, extracted with ether, and the ethereal layer rejected. The aqueous layer was acidified with acetic acid and extracted with ether, the ethereal layer shaken with a saturated solution of cupric acetate and copper salt of the β-diketone which separated out was filtered, washed with ether, finally with water and then decomposed with dilute sulphuric acid. Pure *1-(4'-chloro-3'-methylphenyl)-3-methylpropane-1,-3,-dione* was crystallised from ethanol as a light brown solid, m.p. 59°, (Yield : 10·1 g ; 48%).

(Found : C-62·6; H- 5·1% C_{11} H_{11} O_2 Cl requires C-62·7; H-5·2%).

Its alcoholic solution gave violet colouration with ferric chloride solution.

All the other 1-aryl-3-methylpropane-1, 3-diones [7–9] and sulphonamides[10–23] required for this work were prepared by the standard methods.

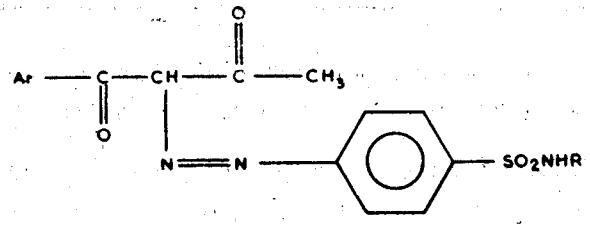

Fig. 1- General structure of azo-compound of benzoylacetones

Synthesis of 1-aryl-3-methyl-2-(substituted sulphonamidonbenzeneazo) propane-1, 3-diones

An ice-cold solution of 1-aryl-3-methylpropane-1, 3-dione (0·002 mol) in ethanol or acetone containing sodium acetate was mechanically stirred, a diazotised solution of sulphonamide (0·002 mol) was gradually added during stirring and cooling (0–5°). The yellow coloured azo compound was precipitated by the addition of ice-cold water and after stirring for further 10 minutes, the solid product was filtered, washed well with water, and dried. Pure *1-aryl-3-methyl-2- (substituted sulphonamidobenzeneazo) propane-1, 3-dione* of the type as shown in Fig. 1 was crystallised from ethanol or glacial acetic acid or DMF or from a mixture of any of the above two solvents. All the azo compounds synthesised in the above manner are included in Tables 1 to 4.

The yields of the azo compounds ranged between 68 and 81% and the rate of coupling reaction increased when electron attracting groups were present in the phenyl ring of benzoylacetones thereby giving higher yields. The replacement of one of the phenyl rings of dibenzoylmethanes by the methyl group as in the case of benzoylacetones caused a decrease in the rate of coupling reaction when lower yields were obtained as compared with the yields with the analogous dibenzoylmethanes.

TABLE 1

1-(4′ CHLOROPHENYL)—3-METHYL-2-(SUBSTITUTED SULPHONAMIDOBENZENEAZO) PROPANE-1, 3-DIONES

(A; Ar = 4′—CHLOROPHENYL)

R	M.P. °C	Colour	Yield %	Molecular formula	Percentage Found C	Found H	Requires C	Requires H	Antibacterial activity S. aureus	E. coli
H	204	Y	75	$C_{16}H_{14}O_4N_3SCl$	50·8	3·7	50·6	3·7	++	+
Acetyl	206	Y	77	$C_{18}H_{16}O_5N_3SCl$	51·0	3·9	51·2	3·8	+	—
Phenyl	147	Y	74	$C_{22}H_{18}O_4N_3SCl$	58·0	4·1	57·9	3·9	+	—
O-Methylphenyl	164	Y	70	$C_{23}H_{20}O_4N_3SCl$	58·6	4·2	58·8	4·3	+	—
O-Methoxyphenyl	125	Y	77	$C_{23}H_{20}O_5N_3SCl$	57·0	4·0	56·8	4·1	+	—
p-Methoxyphenyl	157	Y	75	$C_{23}H_{20}O_5N_3SCl$	56·8	4·4	56·8	4·1	+	—
Guanidyl	240	Y	71	$C_{17}H_{16}O_4N_5SCl$	48·7	4·0	48·9	3·8	++	+
α-Pyridyl	131	Y	72	$C_{21}H_{17}O_4N_4SCl$	55·1	3·9	55·2	3·7	++	+
Pyrimidyl	237	Y	85	$C_{20}H_{16}O_4N_5SCl$	52·4	3·5	52·4	3·5	+	—
4,6-Dimethylpyrimidyl	198	Y	78	$C_{22}H_{20}O_4N_5SCl$	54·5	4·0	54·3	4·1	+	+
2,6-Dimethylpyrimidyl	230	Y	78	$C_{22}H_{20}O_4N_5SCl$	54·1	4·3	54·3	4·1	++	—
2,6-Dimethoxypyrimidyl	170	Y	82	$C_{22}H_{20}O_6N_5SCl$	51·3	4·0	51·0	3·9	++	—
5-Methyl-1, 3, 4-thiadiazolyl	213	Y	80	$C_{19}H_{16}O_4N_5S_2Cl$	47·7	3·6	47·7	3·3	++	+
n-Butylcarbamide	161	Y	81	$C_{21}H_{23}O_5N_4SCl$	52·5	4·7	52·7	4·8	+	—

Y = Yellow, OY = Orange yellow; O = Orange; YB = Yellowish brown; R = Red; YO = Yellowish Orange

TABLE 2

1-(4'-BROMOPHENYL)-3-METHYL-2-(SUBSTITUTED SULPHONAMIDOBENZENEAZO) PROPANE-1, 3-DIONES
(A ; Ar = 4 ' BROMOPHENYL)

R	M.P. °C	Colour	Yield %	Molecular formula	Percentage Found C	Found H	Requires C	Requires H	Antibacterial activity S aureus	E. coli
H	217	Y	75	$C_{16}H_{14}O_4N_3SBr$	45·5	3·3	45·3	3·3	+	—
Acetyl	218	Y	76	$C_{18}H_{16}O_5N_3SBr$	46·3	3·5	46·3	3·4	—	—
Phenyl	164	Y	73	$C_{22}H_{18}O_4N_3SBr$	53·0	3·6	52·8	3·6	+	+
o-Methylphenyl	158	Y	71	$C_{23}H_{20}O_4N_3SBr$	53·4	4·0	53·7	3·9	—	—
o-Methoxyphenyl	175	Y	76	$C_{23}H_{20}O_5N_3SBr$	52·0	4·0	52·0	3·8	+	—
p-Methoxyphenyl	170	Y	75	$C_{23}H_{20}O_5N_3SBr$	52·1	4·1	52·0	3·8	—	—
Guanidyl	212	Y	70	$C_{17}H_{16}O_4N_5SBr$	44·0	3·7	43·8	3·4	+	—
a-Pyridyl	187	Y	70	$C_{21}H_{17}O_4N_4SBr$	50·3	3·4	50·3	3·4	—	—
Pyrimidyl	242	Y	83	$C_{20}H_{16}O_4N_5SBr$	48·0	3·1	47·8	3·2	—	+
4,6-Dimethylpyrimidyl	192	Y	77	$C_{22}H_{20}O_4N_5SBr$	49·8	3·7	49·8	3·6	—	—
2, 6 -Dimethylpyrimidyl	237	Y	76	$C_{20}H_{20}O_4N_5SBr$	49·6	3·5	49·8	3·6	+	—
2, 6 -Dimethoxypyrmidyl	142	Y	80	$C_{22}H_{20}O_6N_5S^2Br$	47·1	4·1	47·0	3·8	+	+
5-Methyl-1, 3, 4-thiadiazolyl	216	Y	78	$C_{19}H_{16}O_4N_5S_2Br$	43·9	3·5	43·7	3·6	++	—
n-Butylcarbamido	167	Y	79	$C_{21}H_{23}O_5N_4SBr$	48·2	4·7	48·2	4·4	—	—

TABLE 3

1-(4'-CHLORO-3/'-METHYLPHENYL)-3-METHYL-2-(SUBSTITUTED SULPHONAMIDOBENZENEAZO) PROPANE-1, 3-DIONES
(A ; Ar = 4'-CHLORO-3'-METHYLPHENYL)

R	M.P. °C	Colour	Yield %	Molecular formula	Percentage Found C	Found H	Requires C	Requires H	Antibacterial activity S. aureus	E. coli
H	212	Y	72	$C_{17}H_{16}O_4N_3SCl$	52·0	4·3	51·8	4·0	—	—
Acetyl	212	Y	75	$C_{19}H_{18}O_5N_3SCl$	52·4	4·1	52·3	4·1	+	—
Phenyl	180	OY	72	$C_{23}H_{20}O_4N_3SCl$	58·8	4·5	58·8	4·3	+	+
o-Methylphenyl	189	Y	70	$C_{24}H_{22}O_4N_3SCl$	59·6	4·8	59·6	4·6	+	—
o-Methoxyphenyl	112	OY	79	$C_{24}H_{22}O_5N_3SCl$	57·5	4·5	57·7	4·4	+	+
p-Methoxyphenyl	188	O	74	$C_{24}H_{22}O_5N_3SCl$	57·9	4·5	57·7	4·4	+	—
Guanidyl	240	Y	72	$C_{18}H_{18}O_4N_5SCl$	50·0	4·2	49·6	4·1	—	—
a-Pyridyl	220	Y	71	$C_{22}H_{19}O_4N_4SCl$	56·0	4·2	56·1	4·0	—	—
Pyrimidyl	232	Y	79	$C_{21}H_{18}O_4N_5SCl$	53·5	3·8	53·4	3·8	—	+
4, 6-Dimethylpyrimidyl	218	Y	78	$C_{23}H_{22}O_4N_5SCl$	55·5	4·2	55·3	4·4	+	—
2, 6-Dimethylpyrimidyl	234	Y	70	$C_{23}H_{22}O_4N_5SCl$	55·1	4·6	55·3	4·4	+	—
2, 6-Dimethoxypyrimidyl	190	Y	77	$C_{23}H_{22}O_6N_5SCl$	52·0	4·0	51·9	4·1	+	+
5-Methyl-1, 3, 4-thiadiazolyl	218	Y	78	$C_{20}H_{18}O_4N_5S_2Cl$	61·5	4·5	61·3	4·6	—	—
n-Butylcarbamide	182	Y	74	$C_{22}H_{25}O_5N_4SCl$	53·8	5·0	53·6	5·1	—	—

EVALUATION OF THE ANTIBACTERIAL PROPERTIES

All the azo compounds have been tested *in vitro*[5] against two organisms *S. aureus* and *E. coli* at two different concentrations of 500 μg/ml and 1000 μg/ml and the results with the concentrations of 500 μg/ml have been entered in Tables 1-4.

The conclusion drawn on the basis of the results of the antibacterial tests is that if the phenyl ring of the benzoylacetone contains electron withdrawing group or atoms, the azo compounds synthesised by coupling with diazotised sulphanilamide or sulphacetamide exhibit activity against *S. aureus* but not against *E.coli*. On stepping down the series of electronegativity, the activity against *S. aureus* also vanishes out. The introduction of the phenyl or substituted phenyl groups at the N^1 atom of the sulphonamide has no effect on the activity; however, the introduction of a heterocyclic ring and particularly those having more than one hetero

TABLE 4

1-BIPHENYL-3-METHYL-2-(SUBSTITUTED SULPHONAMIDOBENZENEAZO) PROPANE-1, 3DIONES

(A ; Ar = BIPHENYL)

R	M.P. °C	Colour	Yield %	Molecular formula	Percentage Found C	Found H	Requires C	Requires H	Antibacterial activity S. aureus	E. coli
H	237	Y	73	$C_{22}H_{19}O_4N_3S$	62·7	4·3	62·7	4·5	—	—
Acetyl	235	Y	76	$C_{24}H_{21}O_5N_3S$	62·0	4·6	62·2	4·5	—	—
Phenyl	189	Y	72	$C_{28}H_{23}O_4N_3S$	67·5	4·8	67·6	4·6	—	—
o-Methylphenyl	188	R	69	$C_{29}H_{25}O_4N_3S$	68·0	5·0	68·1	4·9	—	+
o-Methoxyphenyl	165	YB	78	$C_{29}H_{25}O_5N_3S$	66·2	4·6	66·0	4·7	—	—
p-Methoxyphenyl	178	YO	74	$C_{29}H_{25}O_5N_3S$	66·1	4·7	66·0	4·7	—	+
Guanidyl	264	Y	72	$C_{23}H_{21}O_4N_5S$	60·0	4·5	59·6	4·5	—	++
α-Pyridyl	246	Y	70	$C_{27}H_{22}O_4N_4S$	65·0	4·5	65·0	4·4	—	—
Pyrimidyl	265	YO	81	$C_{26}H_{21}O_4N_5S$	62·6	4·0	62·5	4·2	+	+
4, 6-Dimethylpyrimidyl	220	OY	77	$C_{28}H_{25}O_4N_5S$	64·1	4·6	63·8	4·7	+	+
2, 6-Dimethylpyrimidyl	187	Y	72	$C_{28}H_{25}O_4N_5S$	63·8	4·7	63·8	4·7	—	—
2, 6-Dimethoxypyrimidyl	174	Y	80	$C_{28}H_{25}O_6N_5S$	60·1	4·5	60·1	4·5	—	—
5-Methyl-1, 3, 4-thiadiazolyl	196	Y	80	$C_{25}H_{21}O_4N_5S_2$	58·0	3·9	57·8	4·0	+++	—
n-Butylcarbamido	192	Y	77	$C_{27}H_{28}O_5N_4S$	62·4	5·6	62·3	5·4	+	+

atom have a definite effect on the antibacterial activity. The azo compounds synthesised by coupling diazotised N′—5-methyl-1, 3, 4-thiadiazol-2-yl sulphanilamide with all the benzoylacetones studied were found to possess a high degree of activity against *S. aureus* and either no or very feeble activity against *E. coli* except the compound 5-methyl-1, 3, 4-thiadiazolyl in Table 3 which has no activity against either of the organisms.

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