STUDIES IN SULPHONAMIDES—PART IX

Synthesis and antibacterial study of some substituted sulphonamidobenzeneazo benzoylacetones

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Four differently substituted benzoylacetones, viz., 1-(4′-methylphenyl)-, 1-(4′-ethylphenyl)-, 1-(4′-methoxyphenyl)-, and 1-(4′-ethoxyphenyl)-3-methyl propane-1, 3-diones have been synthesised and coupled with fourteen different diazotised sulphonamide bases. All the resulting sulphonamidobenzeneazo derivatives when subjected to their screening *in vitro* against *S. aureus* and *E. coli* were found to possess considerable activity.

In continuation of our earlier work[1] on the synthesis and antibacterial study of 1-aryl-3-methyl-2-(substituted sulphonamidobenzeneazo) propane-1, 3-diones having electron attracting groups in the phenyl ring, the present communication describes the coupling reactions of some new benzoylacetones having electron donating groups in the phenyl ring with differently substituted diazotised sulphonamide bases. The object of carrying out this work was to study the effect of the various substituents and their positions on the rate of coupling reaction and also on the antibacterial properties of the azo compounds. This piece of work will also provide us an opportunity to compare the effects of electron attracting and electron repelling groups on the rate of coupling as well as on the antibacterial properties.

During the course of this reaction it has been observed that the presence of electron repelling groups causes the rate of coupling to decrease thereby giving lower yields as compared to the electron attracting groups. This is in confirmation of the earlier observations[2] and there seems to be a regular gradation in the yields of the azo compounds according to the electronegativity of the group present in the phenyl ring of the benzoylacetones.

The yield of the azo compounds ranged between 68 to 81%.

EXPERIMENTAL PROCEDURE

Synthesis of 1-(4′-ethoxyphenyl)-3-methyl propane-1, 3-dione

In a dry R.B. flask (1 L) fitted with a double-walled reflux condenser and a guard tube, were placed sodium (2·3 g; 0.1 mol) and dry ether (300 ml); a mixture of ethyl acetate (26.4 g; 0.3 mol) and p-ethoxyacetophenone (16.4 g; 0.1 mol) was added during 30 minutes 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 was rejected. The aqueous layer was acidified with glacial acetic acid and extracted with ether, the ethereal layer shaken with a saturated solution of cupric acetate when the copper salt of the β-diketone separated out. This was filtered, washed with ether and finally with water and then decomposed with dilute sulphuric acid; *pure 1-(4′-ethoxyphenyl)-3-methyl propane-1, 3-dione* was crystallised from ethanol as a light pale yellow solid, m.p. 46°. (Yield : 8.7 g; 42%)

(Found : C, 69.5; H, 6.6. $C_{12}H_{14}O_3$ requires C, 69.9; H, 6.8%).

Its alcoholic solution gave violet colouration with aqueous ferric chloride.

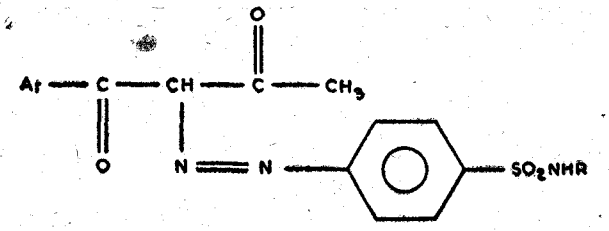
Synthesis of 1-(4′-ethylphenyl)-3-methyl propane-1, 3-dione

In a R.B. flask (1 L) fitted with a double-walled reflux condenser and a guard tube, were placed sodium (11.5 g ; 0.5 mol) and ethyl acetate (123.2 g; 1.4 mol), the contents kept in a freezing mixture and p-ethyl acetophenone (74.5 g; 0.5 mol) was gradually added with shaking during two hr. The reaction mixture after keeping in refrigerator for 18 hr. deposited the sodium salt, which was filtered, washed well with ether and dried; this was dissolved in water, acidified with dilute acetic acid (30%) and extracted with ether. The ethereal solution was worked up in the usual manner through the copper chelate and had b.p. 150°/10 mm (Yield : 34 g; 45.1%)

(Found : C, 75.7; H, 7.1. $C_{12}H_{14}O_2$ requires C, 75.9; H, 7.4%).

Its alcoholic solution gave violet colouration with ferric chloride solution.

The other two 1-aryl-3-methyl propane-1, 3-diones[3—5] and fourteen sulphonamides[1] required for this work were prepared by the standard methods.



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

A diazotised solution of the sulphonamide (0.002 mol) was gradually added to an ice cold solution of 1-aryl-3-methyl propane-1, 3-dione (0.002 mol) in ethanol containing sodium acetate during stirring and cooling (0—5°) and the contents further stirred for 10 minutes. Excess of ice cold water was then added and the yellow coloured solid so obtained was filtered, washed well with water, dried and *pure 1-aryl-3-methyl-2-(substituted sulphonamidobenzeneazo) propane-1, 3-diones* were crystallised from ethanol or glacial acetic acid or DMF or a mixture of any two of the above solvents.

Antibacterial properties were studied by the method described in the earlier paper and the results with dilutions of 500 ug/ml have been entered as (+), (++), (+++) and (—) in Tables 1—4.

The results of the antibacterial tests indicate that the azo compounds synthesised by coupling 1-aryl-3-methylpropane-1, 3-diones having the electron donating groups such as ethoxyl or methoxyl with diazotised sulphanilamide or sulphacetamide are inactive against both the organisms except the compounds synthesised from 1-(4′-ethoxyphenyl)- 3-methyl propane-1, 3-dione which show meagre activity against *E. coli*. The introduction of the alkyl group in the phenyl ring of the 1, 3-dione does not improve the activity, but the compounds synthesised from 1-(4′-ethyl phenyl)-3-methyl propane-1, 3-dione are found to be feebly active against *S. aureus*. Replacement of the hydrogen atom at N^1 by phenyl or substituted phenyl has no marked effect on the activity; however, the introduction of the heterocycic ring causes an overall increase in the activity against *S. aureus* only except a few compounds. These results are in conformation with the conclusions drawn on the basis of our earlier work[1].

TABLE 1

1-(4′-METHOXYPHENYL)-3-METHYL-2-(SUBSTITUTED SULPHONAMIDOBENZENEAZO) PROPANE-1, 3-DIONES
(Fig. 1. Ar=4′-methoxyphenyl)

R	M.P. °C	Colour	Yield %	Molecular formula	Percentage				Antibacterial activity	
					Found		Requires			
					C	H	C	H	*S. aureus*	*E. coli*
H	186	Y	73	$C_{17}H_{17}O_5N_3S$	54·4	4·1	54·4	4·3	—	—
Acetyl	185	Y	75	$C_{19}H_{19}O_6N_3S$	54·6	4·6	54·7	4·6	—	—
Phenyl	200	Y	71	$C_{23}H_{21}O_5N_3S$	61·0	4·8	61·2	4·7	—	—
o-Methylphenyl	179	Y	71	$C_{24}H_{23}O_5N_3S$	62·0	5·1	61·9	4·9	+	—
o-Methoxyphenyl	146	Y	75	$C_{24}H_{23}O_6N_3S$	60·2	4·7	59·9	4·8	—	—
p-Methoxyphenyl	173	Y	78	$C_{24}H_{23}O_6N_6S$	60·1	4·7	59·9	4·8	+	+
Guanidyl	210	Y	69	$C_{18}H_{19}O_5N_5S$	51·8	4·8	51·8	4·6	+	—
a-Pyridyl	197	Y	70	$C_{22}H_{20}O_5N_4S$	58·4	4·4	58·4	4·4	+	—
Pyrimidyl	227	Y	80	$C_{21}H_{19}O_5N_3S$	55·4	4·3	55·6	4·2	+	+
4, 6-Dimethylpyrimidyl	163	Y	80	$C_{23}H_{23}O_5N_5S$	57·5	4·9	57·4	4·8	(++)	—
2, 6-Dimethylpyrimidyl	200	Y	72	$C_{23}H_{23}O_5N_5S$	57·6	5·0	57·4	4·8	+	—
2, 6-Dimethoxypyrimidyl	162	Y	78	$C_{23}H_{23}O_7N_5S$	53·7	4·5	53·8	4·5	+	—
5-Methyl-1, 3, 4-thiadiazolyl	205	Y	75	$C_{20}H_{19}O_5N_5S_2$	50·8	4·1	50·7	4·0	+	—
n-Butylcarbamido	172	Y	77	$C_{22}H_{26}O_6N_4S$	55·7	5·3	55·7	5·5	++	+

Y=Yellow; OY=Orange yellow; YO=Yellowish orange ; O=Orange

TABLE 2

1-(4′-ETHOXYPHENYL)-3-METHYL-2-(SUBSTITUTED SULPHONAMIDOBENZENEAZO) PROPANE-1, 3-DIONES
(Fig. 1. Ar = 4′- thoxyphenyl)

R	M.P. °C	Colour	Yield %	Molecular formula	Percentage Found C	Found H	Requires C	Requires H	Antibacterial activity *S. aureus*	*E. coli*
H	202	Y	72	$C_{18}H_{19}O_5N_3S$	55·5	5·0	55·5	4·9	—	+
Acetyl	195	Y	74	$C_{20}H_{21}O_6N_3S$	56·0	5·1	55·7	4·9	—	+
Phenyl	205	OY	68	$C_{24}H_{23}O_5N_3S$	61·7	4·9	61·9	4·9	—	+
o-Methylphenyl	205	Y	69	$C_{25}H_{25}O_5N_3S$	62·8	5·2	62·6	5·2	—	—
o-Methoxyphenyl	162	Y	74	$C_{25}H_{25}O_6N_3S$	60·8	5·0	60·6	6·1	—	—
p-Methoxyphenyl	150	Y	74	$C_{25}H_{25}O_6N_3S$	60·6	5·1	60·6	5·1	+	+
Guanidyl	253	Y	67	$C_{19}H_{21}O_5N_5S$	52·7	4·7	52·9	4·9	—	+
α-Pyridyl	196	Y	68	$C_{23}H_{22}O_5N_4S$	59·0	4·8	59·2	4·7	—	—
Pyrimidyl	257	Y	79	$C_{22}H_{21}O_5N_5S$	56·4	4·5	56·5	4·5	+	—
4, 6-Dimethylpyrimidyl	183	Y	81	$C_{24}H_{25}O_5N_5S$	58·3	5·0	58·2	5·1	+	—
2, 6-Dimethylpyrimidyl	145	Y	71	$C_{24}H_{25}O_5N_5S$	58·3	5·1	58·2	5·1	+	—
2, 6-Dimethoxypyrimidyl	165	Y	73	$C_{24}H_{25}O_7N_5S$	54·3	4·9	54·6	4·7	—	—
5-Methyl-1, 3, 4-thiadiazolyl	180	Y	75	$C_{21}H_{21}O_5N_5S_2$	51·9	4·2	51·7	4·3	+	—
n-Butylcarbamido	185	Y	77	$C_{23}H_{28}O_6N_4S$	56·6	6·0	56·6	5·7	+	+

TABLE 3

1-(4′-METHYLPHENYL)-3-METHYL-2-(SUBSTITUTED SULPHONAMIDOBENZENEAZO) PROPANE-1, 3-DIONES
(Fig. 1; Ar=4′-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	180	Y	72	$C_{17}H_{17}O_4N_3S$	56·7	4·7	56·8	4·7	—	—
Acetyl	192	Y	74	$C_{19}H_{19}O_5N_3S$	57·0	4·8	56·9	4·7	—	—
Phenyl	165	Y	71	$C_{23}H_{21}O_4N_3S$	63·3	5·0	63·4	4·8	—	—
o-Methylphenyl	162	Y	68	$C_{24}H_{23}O_4N_3S$	64·0	5·0	64·1	5·1	—	—
o-Methoxyphenyl	146	YO	73	$C_{24}H_{23}O_5N_3S$	62·1	4·6	61·9	4·9	—	+
p-Methoxyphenyl	139	OY	73	$C_{24}H_{23}O_5N_3S$	61·6	4·9	61·9	4·9	—	+
Guanidyl	226	Y	73	$C_{18}H_{19}O_4N_5S$	54·0	5·1	53·9	4·7	+	+
α-Pyridyl	167	OY	69	$C_{22}H_{20}O_4N_4S$	60·5	4·6	60·6	4·6	+	+
Pyrimidyl	208	OY	79	$C_{21}H_{19}O_4N_5S$	57·7	4·3	57·7	4·3	+	—
4, 6-Dimethylpyrimidyl	185	Y	74	$C_{23}H_{23}O_4N_5S$	59·5	5·0	59·4	4·9	+	+
2, 6-Dimethylpyrimidyl	197	OY	74	$C_{23}H_{23}O_4N_5S$	59·7	5·0	59·4	4·9	+	—
2, 6-Dimethoxypyrimidyl	191	O	78	$C_{23}H_{23}O_6N_5S$	55·4	4·6	55·5	4·6	+	—
5-Methyl-1, 3, 4-thiadiazolyl	222	O	76	$C_{20}H_{19}O_4N_5S_2$	52·5	4·2	52·5	4·1	+	—
n-Butylcarbamido	150	Y	76	$C_{22}H_{26}O_6N_4S$	57·7	5·7	57·6	5·9	+	+

TABLE 4

1-(4′-ETHYLPHENYL)-3-METHYL-2-(SUBSTITUTED SULPHONAMIDOBENZENEAZO) PROPANE-1, 3-DIONES
(Fig. 1; Ar=4′-ethylphenyl)

R	M.P. °C	Colour	Yield %	Molecular formula	Percentage				Antibacterial activity	
					Found		Requires			
					C	H	C	H	*S. aureus*	*E. coli*
H	188	Y	70	$C_{18}H_{19}O_4N_3S$	58·1	5·1	57·9	5·1	+	—
Acetyl	182	Y	74	$C_{20}H_{21}O_5N_3S$	57·8	5·0	57·8	5·1	+	—
Phenyl	145	Y	70	$C_{24}H_{23}O_4N_3S$	64·0	5·3	64·1	5·1	+	—
o-Methylphenyl	169	Y	69	$C_{25}H_{25}O_4N_3S$	65·1	5·4	64·8	5·4	—	—
o-Methoxyphenyl	147	Y	71	$C_{25}H_{25}O_5N_3S$	62·7	5·0	62·6	5·2	+	—
p-Methoxyphenyl	199	Y	72	$C_{25}H_{25}O_5N_3S$	62·8	5·2	62·6	5·2	+	—
Guanidyl	249	Y	72	$C_{19}H_{21}O_4N_5S$	55·1	4·9	54·9	5·1	+	—
α-Pyridyl	160	Y	68	$C_{23}H_{22}O_4N_4S$	61·3	4·7	61·3	4·9	+	—
Pyrimidyl	260	Y	76	$C_{22}H_{21}O_4N_5S$	58·8	4·8	58·5	4·7	+	+
4, 6-Dimethylpyrimidyl	140	Y	73	$C_{24}H_{25}O_4N_5S$	60·0	5·2	60·1	5·2	+	+
2, 6-Dimethylpyrimidyl	178	Y	73	$C_{24}H_{25}O_4N_5S$	60·3	5·0	60·1	5·2	+	—
2, 6-Dimethoxypyrimidyl	178	OY	75	$C_{24}H_{25}O_6N_5S$	56·5	5·0	56·4	4·9	+	—
5-Methyl-1, 3, 4-thiadiazolyl	212	Y	74	$C_{21}H_{21}O_4N_5S_2$	53·4	4·1	53·5	4·5	++	—
n-Butylcarbamido	170	Y	75	$C_{23}H_{29}O_5N_4S$	58·7	5·9	58·5	5·9	—	—

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