J. Indian Chem. Soc.,
Vol. LI, February 1974 pp. 354-357

Studies in Heterocyclic Compounds, Part II. Synthesis of ethyl (arylsulphonamidobenzeneazo) aceto-and benzoyl-acetates, 1, 3-disubstituted-4-(substituted sulphonamido-benzeneazo) pyrazol-5-ones and evaluation of their antibacterial properties.

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Manuscript received 20 July 1973 , accepted 19 September 1973

Ethyl acetoacetate and ethylbenzoylacetate are coupled with diazotised N^1-4-nitrophenyl-, N^1-2-methoxyphenyl-, N^1-4-bromophenyl-, N^1-guanidyl-, N^1-2,4-dichlorophenyl-and N^1-3,4-dimethylphenyl sulphanilamides to give ethyl (arylsulphonamidobenzeneazo) aceto-and benzoylacetates. These on reaction with four different carbonyl reagents, furnished 1, 3-disubstituted-4-substituted sulphonamido-benzeneazo) pyrazole-5-ones. All the azo compounds and the pyrazol-5-ones have been screened *in vitro* by the cup-plate agar diffusion method for their antibacterial properties.

CONSIDERABLE importance is being attached to the chemistry of pyrazolone nucleus as pyrazolone or its derivatives have been claimed to be effective as germicides[1], antimicrobial agents[2], antiactinics[3], antidiuretics[4], analgesics and antipyretics[5], antifungals[6], antihistaminics[7], anti-M-tuberculosis[8] and antirheumatics[9] besides its use in influenza.[10]

β-keto esters, like β-diketones[11] react with aryldiazonium chlorides to yield arylazo derivatives[12] which on condensation with carbonyl reagents furnished pyrazole-5-ones[13,14].

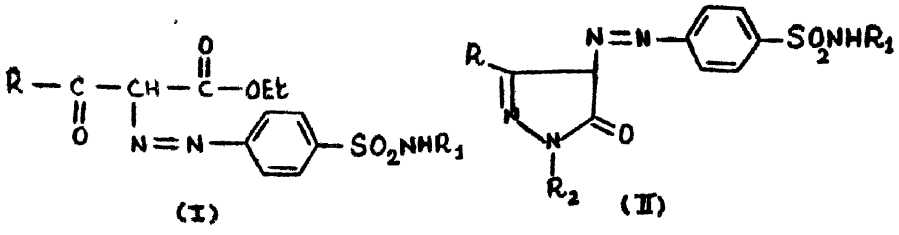
Perusal of literature revealed that very meagre amount of work has been carried out on the synthesis of pyrazol-5-ones having a sulphonamide moiety; the only report in this respect has been the preparation and study of the antibacterial properties of 3-benzene sulphonamidopyrazol-5-ones[15]. It was, therefore, thought of interest to synthesize some compounds having a sulphonamide moiety attached to position-4 through an azo-linkage in the pyrazol-5-one ring and screen these for their antibacterial properties.

Substituted sulphonamidobenzeneazo derivatives of ethyl acetoacetate and ethyl benzoylacetate of the type(I) have been prepared by coupling the two β-keto-esters with diazotised sulphonamide bases ; the former on reaction with the four carbonyl reagents, hydrazine hydrate (100%), phenylhydrazine, p-toluylhydrazine and p-nitrophenylhydrazine furnished the corresponding substituted sulphonamidobenzeneazo pyrazol-5-ones of the type (II). The purity of all these compounds was checked by T. L. C. and the structure by independent synthesis and elemental analysis.

The unambiguous synthesis of the substituted pyrazol-5-one was carried out by condensing the β-keto ester with a carbonyl reagent and subseqent coupling with a diazotised sulphonamide base. This compound had identical structure with the product prepared by first coupling the β-keto ester with a diazotised sulphonamide base and cyclising with a carbonyl reagent as the mixed m. p. was undepressed.

All the azo-compounds and pyrazol-5-ones were screened by the cup-plateagar diffusion method against S. aureus and E. coli *in vitro* for their antibacterial properties. The results of biological assay indicate that azo compounds prepared from ethylacetoacetate and ethylbenzoylacetate showed greater activity against S. aureus except compound number 3 in Table 2. Of all the 4-substituted sulphonamidobenzeneazo pyrazol-5-ones, some were found to be highly active, while others showed considerable activity against E. coli, except the compounds, number 4 in Tables 4, 5 and 6 and number 1 in Table 10, which exhibited very meagre activity against E. coli. When tested against S. aureus, only compound 3 in Table 9 exhibited considera ble activity and the rest were found inactive.

The various compounds synthesised and the resulst of their antibacterial properties are entered in Tables 1 to 10



Experimental

The sulphonamides required for our work were prepared by the standard methods. [16-19]

Synthesis of 1-substituted-3-methyl-4-(substituted sulphonamidobenzeneazo) pyrazol-5-ones.

Ethyl (aryl sulphonamidobenzeneazo) acetoacetates.

To an ice-cold solution of ethyl acetoacetate (0.005 mol) in acetone, containing sodium acetate, was gradually added a diazotised solution of the sulphonamide (0.005 mol.) during stirring and cooling. The reaction mixture was further stirred for 10 min and the yellow coloured azo compound precipitated by the addition of ice-cold water; it was filtered, washed well with water, and dried. The pure azo compound was crystallised from ethanol or glacial acetic acid or from a mixture of the above two solvents.

3-Methy-4-(substituted sulphonamidobenzeneazo) pyrazol-5-ones.

A solution of ethyl (substituted sulphonamidobenzeneazo) acetoacetate (0.00022 mol) in glacial acetic acid and hydrazine hydrate (100%; 0.0016 mol) was refluxed in an oil bath at 160°-70° for 5-6 hr and left overnight. The orange coloured compound which separated out was filtered, washed well with water, dried and crystallised from glacial acetic acid.

Pyrazol-5-ones from p-toluylhydrazine were prepared by employing the same procedure.

Cyclisation with phenylhydrazine, and *p*-nitrophenyl hydrazine were carried out by refluxing in glacial acetic acid-ethanol mixture but in the later case addition of a drop of conc. sulphuric acid was found essential.

Similar series of reactions were carried out with ethyl benzoylacetate and all the results are entered in Tables I to 10.

TABLE 1—ETHYL (SUBSTITUTED SULPHONAMIDOBENZENEAZO) ACETOACETATES

(I ; R = CH_3)

S. No.	R_1	M. P. °C	Colour	Yield %	Mol. formula	% Found C	H	% Reqd. C	H	Antibacterial activity against S. aureus	E. coi
1.	*p*-Bromophenyl	159- 0	YW	85	$C_{18}H_{18}O_5N_3SBr$	46.2	3.7	46.1	3.8	(−)	(+++)
2.	*p*-Nitrophenyl	180	SBY	82	$C_{18}H_{18}O_7N_4S$	49.7	4.3	49.8	4.1	(+)	(+++)
3.	o-Ethoxyphenyl	134-5	SY	75	$C_{20}H_{23}O_6N_3S$	55.5	5.1	55.4	5.3	(+)	(++)
4.	Guanidyl	171-2	GYF	70	$C_{13}H_{17}O_5N_5S$	43.8	4.8	43.9	4.8	(+)	(++)
5.	3,4-Dimethylphenyl	162	SORF	78	$C_{20}H_{23}O_5N_3S$	57.7	5.5	57.5	5.5	(+)	(+++)

TABLE 2—ETHYL (SUBSIITUTED SULPHONAMIDOBENZENEAZO) BENZOYLACETATES

(I ; R = C_6H_5)

S. No.	R_1	M. P. °C	Colour	Yield %	Mol. formula	% Found C	H	Reqd. C	H	Antibacterial activity against S. aureus	E. coli
1.	*p*-Nitrophenyl	168	LBY	82	$C_{23}H_{20}O_7N_4S$	55.8	4.1	55.6	4.0	(−)	(+++)
2.	o-Ethoxyphenyl	138	SGYF	76	$C_{25}H_{25}O_6N_3S$	60.5	4.9	60.6	5.0	(+)	(+++)
3.	Guanidyl	174-5	Y	70	$C_{18}H_{19}O_5N_5S$	51.7	4.4	51.8	4.5	(++)	(+++)
4.	3,4-Dimethylphenyl	122	SGYF	75	$C_{25}H_{25}O_5N_3S$	62.9	5.0	62.6	5.2	(−)	(+)
5.	2,4-Dichorophenyl	130-1	SYF	80	$C_{23}H_{19}O_5N_3SCl_2$	53.0	3.8	53.1	3.6	(−)	(+)

TABLE 3—3-METHYL-4-(SUBSTITUTED SULPHONAMIDOBENZENEAZO) PYRAZOL-5-ONES

(II ; R_2 = H, R = CH_3)

S. No.	R_1	M. P. °C	Colour	Yield %	Mol. formula	% Found C	H	Reqd. C	H	Antibacterial activity against S. aureus	E. coli
1.	*p*-Bromophenyl	229-30	SYF	80	$C_{16}H_{14}O_3N_5S$ Br	44.3	3.0	44.0	3.2	(++)	(+++)
2.	*p*-Nitrophenyl	279	YF	82	$C_{16}H_{14}O_5N_6S$	47.8	3.6	47.8	3.5	(−)	(++)
3.	o-Ethoxyphenyl	251	BYR	75	$C_{18}H_{19}O_4N_5S$	53.7	4.7	53.9	4.7	(−)	(++)
4.	Guanidyl	283	Y	73	$C_{11}H_{13}O_3N_7S$	40.9	4.2	40.9	4.0	(−)	(++)
5.	3,4-Dimethylphenyl	256	DYF	74	$C_{18}H_{19}O_3N_5S$	56.0	5.1	56.1	4.9	(−)	(++)

TABLE 4—1-PHENYL-3-METHYL-4-(SUBSTITUTED SULPHONAMIDOBENZENEAZO) PYRAZOL-5-ONES

(II ; R_2 = C_6H_5, R = CH_3)

S. No.	R_1	M. P. °C	Colour	Yield %	Mol. formula	% Found C	H	Reqd. C	H	Antibacterial activity against S. aureus	E. coli
1.	*p*-Bromophenyl	268-9	SROF	84	$C_{22}H_{18}O_3N_5SBr$	51.3	3.6	51.6	3.5	(−)	(++)
2.	*p*-Nitrophenyl	285	SR	85	$C_{22}H_{18}O_5N_6S$	55.3	3.6	55.2	3.7	(−)	(++)
3.	o-Ethoxyphenyl	178	SYOF	73	$C_{24}H_{23}O_4N_5S$	60.5	4.6	60.4	4.8	(−)	(++)
4.	Guanidyl	258	YOF	75	$C_{17}H_{17}O_3N_7S$	50.9	4.3	51.1	4.3	(−)	(+)
5.	3,4-Dimethylphenyl	246	SRON	71	$C_{24}H_{23}O_3N_5S$	62.5	4.8	62.5	5.0	(−)	(++)

TABLE 5—1(-pMETHYLPHENYL)-3-METHYL-4-(SUBSTITUTED SULPHONAMIDOBENZENEAZO) PYRAZOL-5-ONES.

(II ; $R_2 = p\text{-}CH_3C_6H_4$, $R = CH_3$)

S. No.	R_1	M. P. °C	Colour	Yield %	Mol. formula	% Found C	% Found H	% Reqd. C	% Reqd. H	Antibacterial activity against S. aureus	Antibacterial activity against E. coli
1.	*p*-Bromophenyl	242	SRF	80	$C_{23}H_{20}O_3N_5SBr$	52.5	3.8	52.5	3.8	(–)	(++)
2.	*p*-Nitrophenyl	239	BrR	81	$C_{23}H_{20}O_5N_6S$	56.3	4.1	56.1	4.1	(–)	(++)
3.	o-Ethoxyphenyl	167	BOF	73	$C_{25}H_{25}O_4N_5S$	61.0	5.2	61.1	5.1	(–)	(++)
4.	Guanidyl	273	O	72	$C_{18}H_{19}O_3N_7S$	52.4	4.6	52.3	4.6	(–)	(+)
5.	3,4-Dimethylphenyl	222-3	SRN	71	$C_{25}H_{25}O_3N_5S$	63.3	5.1	63.2	5.3	(–)	(+++)

TABLE 6—1-(p-NITROPHENYL)-3-METHYL-4-(SUBSTITUTED SULPHONAMIDOBENZENEAZO) PYRAZOL-5-ONES

(II ; $R_2 = p\text{-}NO_2.C_6H_4$, $R = CH_3$)

S. No.	R_1	M. P °C	Colour	Yield %	Mol. formula	% Found C	% Found H	% Reqd. C	% Reqd. H	Antibacterial activity against S. aureus	Antibacterial activity against E. coli
1.	*p*-Bromophenyl	280	SYF	82	$C_{22}H_{17}O_5N_6SBr$	47.7	3.2	47.4	3.0	(–)	(++)
2.	*p*-Nitrophenyl	291	SYF	85	$C_{22}H_{17}O_7N_7S$	50.5	3.2	50.5	3.2	(–)	(++)
3.	o-Ethoxyphenyl	237	Y	76	$C_{24}H_{22}O_6N_6S$	55.0	4.2	55.2	4.2	(–)	(+)
4.	Guanidyl	300	Y	73	$C_{17}H_{16}O_5N_8S$	46.0	3.6	45.9	3.6	(–)	(+)
5.	3,4-Dimethylphenyl	255	SBrY	73	$C_{24}H_{22}O_5N_6S$	57.0	4.4	56.9	4.3	(–)	(++)

TABLE 7—3-PHENYL-4-(SUBSTITUTED SULPHONAMIDOBENZENEAZO) PYRAZOL-5-ONES

(II ; $R_2 = H$, $R = C_6H_5$)

S. No.	R_1	M. P °C	Colour	Yield %	Mol. formula	% Found C	% Found H	% Reqd. C	% Reqd. H	Antibacterial activity against S. aureus	Antibacterial activity against E. coli
1.	*p*-Nitrophenyl	291	O	75	$C_{21}H_{16}O_5N_6S$	54.2	3.5	54.3	3.4	(–)	(++)
2.	o-Ethoxyphenyl	192	O	70	$C_{23}H_{21}O_4N_5S$	59.5	4.4	59.6	4.5	(–)	(++)
3.	Guanidyl	274	RO	68	$C_{16}H_{15}O_3N_7S$	50.0	3.9	49.9	3.9	(–)	(++)
4.	3,4-Dimethylphenyl	281	SLR	68	$C_{23}H_{21}O_3N_5S$	61.7	4.8	61.7	4.7	(–)	(+++)
5.	2,4-Dichlorophenyl	242	SON	72	$C_{21}H_{15}O_3N_5SCl_2$	51.9	3.1	51.6	3.1	(–)	(++)

TABLE 8—1,3-DIPHENYL-4-(SUBSTITUTED SULPHONAMIDOBENZENEAZO) PYRAZOL-5-ONES

(II ; $R_2 = R = C_6H_5$)

S. No.	R_1	M. P °C	Colour	Yield %	Mol. formula	% Found C	% Found H	% Reqd. C	% Reqd. H	Antibacterial activity against S. aureus	Antibacterial activity against E. coli
1.	*p*-Nitrophenyl	283	BrR	80	$C_{27}H_{20}O_5N_6S$	60.1	3.7	60.0	3.7	(–)	(++)
2.	o-Ethoxyphenyl	182-3	OR	74	$C_{29}H_{25}O_4N_5S$	64.7	4.5	64.6	4.6	(–)	(++)
3.	Guanidyl	289-9	OR	73	$C_{22}H_{19}O_3N_7S$	57.4	4.2	57.3	4.1	(–)	(++)
4.	3,4-Dimethylphenyl	216-7	SOR	72	$C_{29}H_{25}O_3N_5S$	66.4	4.8	66.5	4.8	(–)	(++)
5.	2,4-Dichlorophenyl	219	SRF	78	$C_{27}H_{19}O_3N_5SCl_2$	57.4	3.5	57.4	3.4	(–)	(++)

TABLE 9—1-(p-METHYLPHENYL)-3-PHENYL-4-(SUBSTITUTED SULPHONAMIDOBENZENEAZO) PYRAZOL-5-ONES

(II : $R_2 = p - CH_3.C_6H_4$, $R = C_6H_5$)

S. No.	R_1	M. P °C	Colour	Yield %	Mol. formula	% Found C	% Found H	% Reqd. C	% Reqd. H	Antibacterial activity against S. aureus	Antibacterial activity against E. coli
1.	*p*-Nitrophenyl	286	BRF	76	$C_{28}H_{22}O_5N_6S$	60.8	4.0	60.6	3.9	(–)	(++)
2.	o-Ethoxyphenyl	174	SR	72	$C_{30}H_{27}O_4N_5S$	65.2	4.7	65.1	4.9	(–)	(++)
3.	Guanidyl	298	RB	69	$C_{23}H_{21}O_3N_7S$	58.3	4.4	58.1	4.4	(+++)	(++)
4.	3,4-Dimethyl phenyl	242	DR	70	$C_{30}H_{27}O_3N_5S$	66.8	5.1	67.0	5.0	(+)	(+++)
5.	2,4-Dichlorophenyl	223	BrR	73	$C_{28}H_{21}O_3N_5SCl_2$	58.1	3.8	58.1	3.6	(–)	(++)

TABLE 10—(p-NITROPHENYL)-3-PHENYL-4-(SUBSTITUTED SULPHONAMIDOBEZENEAZO) PYRAZOL-5-ONES

(II : $R_2 = p\text{-}NO_2C_6H_4$; $R = C_6H_5$)

S. No.	R_1	M. P °C	Colour	Yield %	Mol. formula	% Found C	% Found H	% Reqd. C	% Reqd. H	Antibacterial activity against S. aureus	Antibacterial activity against E. coli
1.	*p*-Nitrophenyl	296	SR	78	$C_{27}H_{19}O_7N_7S$	55.5	3.3	55.4	3.2	(–)	(++)
2.	o-Ethoxyphenyl	256	SRF	74	$C_{29}H_{24}O_6N_6S$	59.4	4.0	59.6	4.1	(+)	(+)
3.	Guanidyl	303	Y	71	$C_{22}H_{18}O_5N_8S$	52.1	3.6	52.2	3.5	(–)	(++)
4.	3,4-Dimethylphenyl	249	SBrYF	72	$C_{29}H_{24}O_5N_6S$	61.4	4.3	61.3	4.2	(–)	(++)
5.	2,4-Dichlorophenyl	275-6	O	76	$C_{27}H_{18}O_5N_6SCl_2$	53.0	3.0	53.2	3.0	(–)	(++)

B—Bright ; Br - Brownish ; D - Dark ; F - Flakes ; G - Golden ; L - Light ; N - Needles ; O - Orange ; P - Pale ; R - Red ; S - Shining ; Y - Yellow.

Reference

1. C. N. ANDERSON, U. S. PAT., 1938. 2, 107, 321,
2. A. GIRARD, U. S. PAT., 1941. 2, 256, 261.
3. M. I. QUIROGA and P. H. MAGNIN, Excerpta, *Med., Sect.* XIII, 1954, **8**, 135; *Chem Abs.*, 1955, **49**, 13593.
4. V. PACOVSKY and V. HOLECEK, *Casopis Lekaru Ceskych.*, 1956, **95**, 300; *Chem Abs.*, 1956, **50**, 7306.
5. J. MAJ, E. PRZEGALINSKI and H. SZURSKA, *Diss. Pharm. Pharmacol.* 1966, **18**, 345; *Chem Abs*, 1967, 1444r.
6. Y. USUI and C. MATSMURA, *Yakugaku Zasshi.*, 1967, **87**, 38; *Chem. Abs.*, 1967, **67**, 11452h.
7. J. E. ALBERTY, J. HUKKI, P. LAITINEV and J. MYRY, *Arzneim. Forsch.*, 1967,**17**, 214; *Chem Abs* 1967. **67**, 43734 .
8. M. R. PATEL, R. A. PALLARE and C.V. DELIWALA, *Indian J. Microbiol.*, 1966, **6** 35; *Chem Abs* 1968, *68*, 37917j.
9. O. DANEK and S. NOUZOVA, *Collect.Czech.Chem. Commun.*, 1968, **33**, 425.
10. M. DOHRN and P. DIEDRICH, U. S. PAT., 1944. 2, 345, 384.
11. G. S. SAHARIA and H. R. SHARMA, *Def. Sci. J.*, 1972, **22**, 135, 139.
12. F. D.CHATTAWAY and D. R. ASHWORTH, *J. Chem. Soc.*, 1933, **475**, 1143; 1934, **476**, 1985.
13. H. G. GARG and C. PRAKASH, *J. Med. Chem.*, 1971, **14** 175.
14. H. G. GARG and C. PRAKASH, *J. Pharm Sci.*, 1971, **60**, 323.
15. W. SCHINDLER, *Z. Chem.*, 1965,**5**, 382 *Chem Abs.*, 1966, **64**, 3517b.
16. G. L. WEBSTER and L. D. POWERS, *J. Amer. Chem. Soc.*, 1938, **60**, 1553.
17. H. BAUER, *J. Amer Chem. Soc.*, 1939, **61**, 613.
18. R. O. ROBLIN, JR., J. H. WILLIAMS, P.S. WINNEK and J. P. ENGLISH, *J. Amer. Chem. Soc.*, 19 40, **62**, 1999.
19. C. MARCHANT, C. C. LUCAS, L. MECLELL, and P. H. GREEY, CANAD. *J. Res.*, 1942, **208**, 5.