

Synthesis and Studies of Possible Pharmacologically Active Heterocyclic Compounds

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A series of N¹-nicotinoyl-3,5-diphenyl-4-(sulfamoylphenylazo)-1,2-diazoles have been synthesised by the condensation of sulfamoyl phenylazo-1,3-diphenyl-1,3-propanedione with nicotinic acid hydrazide, using glacial acetic acid as the condensing agent. Some of the products showed significant antifungal activity against *A. Niger*, *P. oryzae*, *F. oxysporum*, *C. sachari* and antibacterial activity against *E. coli*, *S. typhi* and *B. aureus*.

INTRODUCTION

Pyrazole derivatives have been studied extensively because of their ready accessibility, diverse chemical reactivity, broad spectrum of biological activity and variety of industrial applications¹⁻³. Recently pyrazole derivatives were reported to show antiinflammatory, antimicrobial and pesticidal activities, etc.⁴⁻⁹ Nicotine acid hydrazide is used as antipellagic and antitumour agent^{10, 11}. In view of these observations, it was thought desirable to synthesise some new diazole derivatives having the sulfonamide moiety attached through an azo linkage at position 4 and a nicotinoyl moiety at position 1 in the hope that the resulting compounds may prove to possess valuable pharmacological properties.

The present communication describes that when diazotised sulphadrag aromatic amines are condensed at reactive methylene position of 1,3-diketone, sulfamoylphenylazo-1,3-diphenyl-1,3-propanediones are obtained. The condensed products on cyclisation with nicotinic acid hydrazide give N¹-nicotinoyl-3,5-diphenyl-4-(sulfamoylphenylazo)-1,2-diazoles and their antimicrobial activity was studied.

EXPERIMENTAL

All the chemicals used are either BDH or E. Merck and A.R. grade.

The melting points of the synthesised compounds were determined in open capillaries in a Ganson electrical melting point apparatus and uncorrected. The homogeneity and purity of the compounds was routinely checked over thin layer

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chromatoplates coated with silica gel G. (thickness 0.5 mm), developing solvent acetone/DMF (3 : 1) nonsaturated chambers at room temperature ($20 \pm 1^\circ$). IR spectra (λ_{\max} in cm^{-1}) were determined in KBr on a Perkin-Elmer 577 spectrophotometer; $^1\text{H-NMR}$ spectra were taken on Bruker Ac 300 F spectrophotometer at 300 MHz in $\text{CDCl}_3 + \text{DMSO-d}_6$ using TMS as in internal reference (chemical shift δ ppm).

Synthesis of N^1 -nicotinoyl-3,5-diphenyl-4-(X)-azo-1,2-diazoles

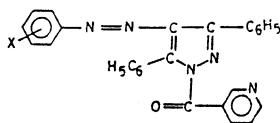
A mixture of the appropriate sulfamoylphenylazo-1,3-diphenyl-1,3-propanedione (0.1 g) and nicotinic acid hydrazide (0.5 g) in glacial acetic acid was refluxed on an oil bath at $160\text{--}170^\circ\text{C}$ for 6 h and then allowed to stand overnight. The coloured compound which separated was filtered off, washed well with water, dried and recrystallized from a mixture of glacial acetic acid and DMF.

By analogous procedures, several substituted 1,2-diazoles have been synthesised, their characteristics are recorded in Table-1. The yields were between 70 and 80% (Scheme-1).

TABLE-1
CHARACTERISTICS OF N^1 -NICOTINOYL-3,5-DIPHENYL-4-(X) AZO-1,2-DIAZOLES

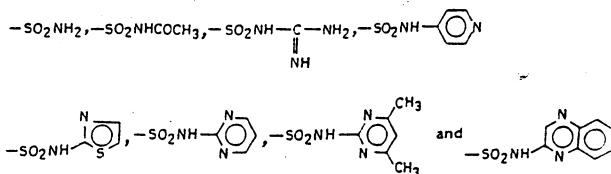
X	m.p. ($^\circ\text{C}$)	Colour	m.f.	Nitrogen		R_f value
				Found	Calcd.	
Phenyl	146	dark yellow	$\text{C}_{27}\text{H}_{19}\text{N}_5\text{O}$	16.29	16.31	0.8457
2-Chlorophenyl	165	pale yellow	$\text{C}_{27}\text{H}_{18}\text{N}_5\text{OCl}$	15.10	15.12	0.7079
3-Chlorophenyl	203	light brown	$\text{C}_{27}\text{H}_{18}\text{N}_5\text{OCl}$	15.10	15.12	0.6954
4-Chlorophenyl	156	brown	$\text{C}_{27}\text{H}_{18}\text{N}_5\text{OCl}$	15.09	15.12	0.7234
4-Bromophenyl	245	dark yellow	$\text{C}_{27}\text{H}_{18}\text{N}_5\text{OBr}$	13.76	13.78	0.7534
2,4,6-Tribromophenyl	249	yellow	$\text{C}_{27}\text{H}_{16}\text{N}_5\text{OBr}_3$	10.47	10.51	0.9856
3-Fluorophenyl	289	pale yellow	$\text{C}_{27}\text{H}_{18}\text{N}_5\text{OF}$	15.63	15.66	0.8499
2-Chloro-4-nitrophenyl	211	pale yellow	$\text{C}_{27}\text{H}_{17}\text{N}_6\text{O}_3\text{Cl}$	16.51	16.54	0.5683
2-Nitrophenyl	274	light yellow	$\text{C}_{27}\text{H}_{18}\text{N}_6\text{O}_3$	17.63	17.72	0.7943
3-Nitrophenyl	267	brown	$\text{C}_{27}\text{H}_{18}\text{N}_6\text{O}_3$	17.69	17.72	0.8682

X	m.p. (°C)	Colour	m.f.	Nitrogen		R _f value
				Found	Calcd.	
2-Methylphenyl	133	pale yellow	C ₂₈ H ₂₁ N ₅ O	15.78	15.81	0.9160
4-Methylphenyl	173	white	C ₂₈ H ₂₁ N ₅ O	15.79	15.81	0.9237
2-Methoxyphenyl	221	pale yellow	C ₂₈ H ₂₁ N ₅ O ₂	15.21	15.25	0.8386
4-Methoxyphenyl	188	dark brown	C ₂₈ H ₂₁ N ₅ O ₂	15.21	15.25	0.8860
4-Aminodiphenyl	265	dark yellow	C ₂₃ H ₂₄ N ₆ O	16.14	16.15	0.8239
1-Naphthyl	240	red	C ₃₁ H ₂₁ N ₅ O	14.59	14.62	0.5909
2-Naphthyl	235	yellow	C ₃₁ H ₂₁ N ₅ O	14.56	14.62	0.5448
4-Carboxyphenyl	275	dark yellow	C ₂₈ H ₁₉ N ₅ O ₃	14.78	14.80	0.7665
4-Hydroxyphenyl	199	pale yellow	C ₂₇ H ₁₉ N ₇ O ₂	15.69	15.73	0.7099
2,3-dimethyl-1-phenyl- pyrazolone	282	brown	C ₃₂ H ₂₅ N ₆ O ₂	18.15	18.18	0.8091
2-Sulfonamidobenzene	191	dark yellow	C ₂₇ H ₂₀ N ₇ O ₃ S	16.52	16.54	0.5023
N ¹ -2-pyridylsulfonamido- benzene	285	dark yellow	C ₃₂ H ₂₃ N ₈ O ₃ S	16.70	16.75	0.6988
N ¹ -2-pyrimidylsulfonamido benzene	262	red	C ₃₁ H ₂₂ N ₇ O ₃ S	19.07	19.11	0.5838
N ¹ -2-thiazoylsulfonamido-b enzene	215	pale yellow	C ₃₀ H ₂₁ N ₈ O ₃ S ₂	16.51	16.58	0.9084
N ¹ -2-guanylsulfonamido- benzene	295	pale yellow	C ₂₈ H ₂₂ N ₈ O ₃ S	20.31	20.36	0.6284
N ¹ -2-(4,6-dimethyl) pyridi- dylsulfonamidobenzene	321	pale yellow	C ₃₃ H ₂₆ N ₆ O ₃ S	18.21	18.24	0.4511
N ¹ -2-acetylsulfonamido- benzene	278	brown	C ₂₉ H ₂₂ N ₅ O ₄ S	15.21	15.27	0.6924



(A)

Where: $-X = -Cl, -Br, -NO_2, -CH_3, -OH, -CO_2H, -OCH_3, -NHCOCH_3, -C_6H_4-NH_2$



Scheme-1

IR spectra in KBr were recorded on a Perkin-Elmer grating IR spectrophotometer. The spectra had characteristic peaks at 780 cm^{-1} (aromatic ring), 1580 cm^{-1} $\nu(-N=N-)$, 1600 cm^{-1} $\nu(C=N)$; 1740 cm^{-1} $\nu(C=O)$ of tert. amide having N in diazole ring) which helped in establishing the structures of the compounds.

The structures of the substituted diazoles were also confirmed by $^1\text{H-NMR}$ spectral studies. In CDCl_3 solution, the following δ (ppm) values were obtained: 7.47–7.50 (2s, 10, $-\text{C}(\text{C}_6\text{H}_5)_2$); 7.35 (dd, 2, *meta* to $-\text{N}=\text{N}-\text{C}_6\text{H}_4\text{X}$, $J = 6\text{ Hz}$); 7.12 (dd, 2,4-pyridinecarbonyl, *ortho* to $\text{C} = \text{O}$, $J = 9$ and 2 Hz); 7.93 (dd, 2, *ortho* to X, $J = 9$ and 3 Hz); 8.04 (dd, 2,4-pyridinecarbonyl, *meta* to $\text{C} = \text{O}$, $J = 9$ and 2 Hz), where X = substituent group.

Antifungal screening: The antifungal activity of the compounds was determined against *Aspergillus niger*, *Pyricularia oryzae*, *Fusarium oxysporum* and *cephalosporum sachari* at 100 ppm concentration by Agar growth technique¹². The results were compared with standard fungicide carbendazim tested under similar conditions (Table-2).

Antibacterial screening: The antibacterial activity of the compounds were tested against *Escherichia coli*, *Salmonella typhi* and *Bacillus aureus* by filter paper disc method¹³ with necessary modifications. All the test compounds were dissolved in DMF and filter paper discs of 0.6 mm diameter containing 100 μg per disc were prepared, dried and placed on the surface of bacteria seeded agar plates. These were incubated at 37°C for 24 h.

The antibacterial activity was determined by the following formula.

$$\text{Activity} = \frac{Y - 0.6}{X - 0.6} \times 100$$

where X (mm) is the diameter of the inhibition zone by tetracycline and Y (mm) is the diameter of the inhibition zone by the sample. The diameter of paper disc was 0.6 mm (Table-2).

TABLE-2
ANTIMICROBIAL ACTIVITY OF COMPOUNDS

Compound	Fungicidal activity at 100 ppm				Antibacterial activity at 100 µg/disc		
	<i>A. niger</i>	<i>P. oryzae</i>	<i>F. oxysporum</i>	<i>C. sachari</i>	<i>E. coli</i>	<i>S. typhi</i>	<i>B. aureus</i>
2	45	52	44	44	25	43	20
3	61	74	73	65	65	74	31
4	55	55	54	47	60	69	25
7	61	73	73	66	42	51	18
9	36	37	37	42	11	18	—
10	49	54	52	48	18	25	13
13	70	83	80	68	71	59	21
14	66	56	58	50	69	70	19
15	67	80	76	54	28	49	32
16	43	40	42	44	13	19	—
17	52	66	59	54	20	24	18
18	57	73	72	70	44	59	7
19	52	67	64	55	38	52	15
20	57	70	69	66	22	24	23
21	43	48	48	45	7	11	—
22	68	70	66	61	18	24	10
23	78	85	83	69	54	42	28
24	70	70	66	62	49	40	31
25	70	84	81	69	43	37	37
26	48	53	52	47	11	7	—
Carbendazim	86	89	89	87	—	—	—
Tetracycline	—	—	—	—	100	100	100

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