

Synthesis and Biological Activities of Substituted 1,2-Diazole Derivatives

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The synthesis and biological activities (antiinflammatory and antimicrobial) of a number of 1,2-diazole derivatives are described. N¹-nicotinoyl-3-methyl-5-phenyl-4-sulpha/substituted phenylazo-1,2-diazoles have been synthesised by the condensation of sulpha/ substituted phenylazo-1-phenyl-1,3-butanedione with nicotinic acid hydrazide, using glacial acetic acid as condensing agent. Pharmacological profile of the compounds synthesised is described.

INTRODUCTION

In the past years considerable evidence has been accumulated to demonstrate the efficacy of substituted 1,2-diazole derivatives in potential antituberculous¹, antineoplastic², antidiabetic³, antifertility⁴, antirheumatic, analgesic, antipyretic, adrenolytic, necrosis-potentiating⁵ and antitumour^{6,7}, muscle relaxant, hypnotic, anticonvulsant⁸⁻¹¹ activities, etc. Nicotinic acid hydrazide is used as an antipellagic¹² and antitumour¹³ agent. To further assess the potential of such a class of compounds and because of the highly acidic nature of non-steroidal antiinflammatory agents under current clinical usage, causing gastrointestinal toxicity, it is imperative to develop a non-acidic, non-steroidal, antiinflammatory agent, and for this the present work was undertaken.

The present communication describes the synthesis of N¹-nicotinoyl-3-methyl-5-phenyl-4-(sulpha/substituted phenylazo)-1,2-diazoles of type (A) by the condensation of (sulpha/substituted phenylazo)-1-phenyl-1,3-butanediones with nicotinic acid hydrazide using glacial acetic acid as the condensing agent, and the study of the biological activity of the products (Scheme-1). The homogeneity and purity of the compounds were checked by TLC and their structures established by IR, NMR spectral studies and elemental analysis.

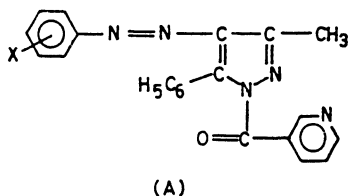
EXPERIMENTAL

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

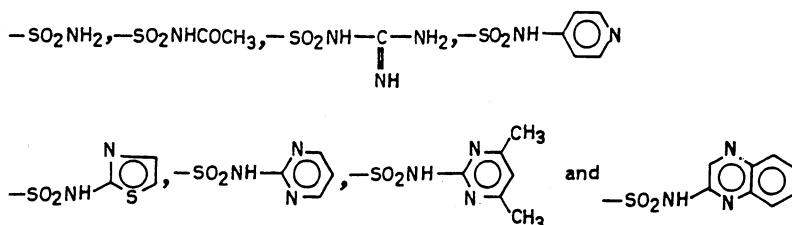
The melting points of the synthesised compounds were determined in open capillaries in a Ganson electrical melting point apparatus and are uncorrected. The homogeneity and purity of the compounds was routinely checked over thin layer chromatoplates coated with silica gel G (thickness 0.5 mm), developing solvent acetone/DMF (3 : 1), non-saturated chambers at room temperature (20 ± 1°C). IR spectra (ν_{\max} in cm⁻¹) were determined in KBr on a Perkin-Elmer

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577 spectrophotometer and $^1\text{H NMR}$ spectra on Bruker AC 300F spectrophotometer at 300 MHz in CDCl_3 or $\text{CDCl}_3 + \text{DMSO-d}_6$ using TMS as in internal reference (chemical shift δ , ppm).



Where: $-\text{X} = -\text{Cl}, -\text{Br}, -\text{NO}_2, -\text{CH}_3, -\text{OH}, -\text{CO}_2\text{H}, -\text{OCH}_3, -\text{NHCOCH}_3, -\text{C}_6\text{H}_4-\text{NH}_2$



Scheme-1

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

A mixture of the appropriate sulpha/substituted phenylazo-1-phenyl-1,3-butanedione (0.1 g) and nicotinic acid hydrazide (0.05 g) in glacial acetic acid was refluxed on an oil bath at $120\text{--}130^\circ\text{C}$ for 4 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 75 and 85%.

The IR spectra had characteristic peaks at 780 cm^{-1} (aromatic ring); 1580 cm^{-1} ($\text{N}=\text{N}$); 1638 cm^{-1} ($\text{C}=\text{N}$); 1750 cm^{-1} ($\text{C}=\text{O}$ 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. The following δ (ppm) values were obtained: 2.46 (2s, 3, CH_3); 6.9 (dd, 2, ArH, *ortho* to X, $J = 10$ and 2 Hz); 7.18–7.40 (m, 4,4-pyridine carbonyl, *meta* to $\text{C}=\text{O}$); 7.46 (bs, 5, ArH, $\text{C}_1\text{--C}_6\text{H}_5$); 7.70–7.79 (2dd, 2,4-pyridine-carbonyl, *ortho* to $\text{C}=\text{O}$, $J = 8$ and 3 Hz) (X denotes the substituent group).

Biological Studies: The substituted diazoles were tested *in vivo* for their antiinflammatory activity and *in vitro* for their antimicrobial activity.

TABLE-I
CHARACTERISTICS OF N¹-NICOTINOYL-3-METHYL-5-PHENYL-
4-(X)-AZO-1,2-DIAZOLES

S. No.	'X' (colour)	m.p. (°C)	Molecular formula	Yield (%)	N% found (calcd.)	R _f value
1.	Phenyl (Pale yellow)	115	C ₂₂ H ₁₇ N ₅ O	77	19.01 (19.07)	0.61
2.	2-Chlorophenyl (Shining pale yellow)	130	C ₂₂ H ₁₆ N ₅ OCl	79	17.40 (17.46)	0.91
3.	3-Chlorophenyl (Shining yellow orange)	126	C ₂₂ H ₁₆ N ₅ OCl	76	17.42 (17.46)	0.54
4.	4-Chlorophenyl (Pale yellow)	199	C ₂₂ H ₁₆ N ₅ OCl	80	17.41 (17.46)	0.76
5.	2,4,6-Tribromophenyl (Light yellow)	285	C ₂₂ H ₁₄ N ₅ OBr ₃	81	11.51 (11.59)	0.69
6.	3-Fluorophenyl (Shining pale yellow)	295	C ₂₂ H ₁₆ N ₅ OF	79	18.12 (18.18)	0.79
7.	2-Chloro-4-nitrophenyl (Light brown)	240	C ₂₂ H ₁₅ N ₆ O ₃ Cl	74	18.69 (18.84)	0.65
8.	2-Nitrophenyl (Shining orange yellow)	138	C ₂₂ H ₁₆ N ₆ O ₃	82	20.29 (20.39)	0.88
9.	3-Nitrophenyl (Dirty yellow)	120	C ₂₂ H ₁₆ N ₆ O ₃	76	20.30 (20.39)	0.67
10.	4-Nitrophenyl (Yellow)	117	C ₂₂ H ₁₆ N ₆ O ₃	77	20.30 (20.39)	0.86
11.	3-Nitro-4-methylphenyl (Orange)	190	C ₂₃ H ₁₈ N ₆ O ₃	78	19.62 (19.72)	0.71
12.	2-Methylphenyl (Shining dark yellow needles)	178	C ₂₃ H ₁₉ N ₅ O	81	18.30 (18.38)	0.81
13.	4-Methylphenyl (Dark yellow)	115	C ₂₃ H ₁₉ N ₅ O	82	18.32 (18.38)	0.90
14.	2-Methoxyphenyl (Pale yellow)	181	C ₂₃ H ₁₉ N ₅ O ₂	75	17.60 (17.63)	0.54
15.	4-Methoxyphenyl (Yellow)	189	C ₂₃ H ₁₉ N ₅ O ₂	75	17.60 (17.63)	0.96
16.	4-Aminodiphenyl (Red)	175	C ₂₈ H ₂₂ N ₆ O	77	18.31 (18.34)	0.85
17.	1-Naphthyl (Brown)	110	C ₂₆ H ₁₉ N ₅ O	80	16.76 (16.79)	0.93
18.	2-Naphthyl (Dirty yellow)	105	C ₂₆ H ₁₉ N ₅ O	81	16.74 (16.79)	0.91
19.	4-Carboxyphenyl (Yellow)	185	C ₂₃ H ₁₇ N ₅ O ₃	82	17.01 (17.03)	0.78
20.	4-Hydroxyphenyl (Yellow needles)	163	C ₂₂ H ₁₇ N ₅ O ₂	76	18.21 (18.28)	0.95
21.	2,3-Dimethyl-1-phenylpyrazolone (Shining brown)	213	C ₂₇ H ₂₃ N ₇ O ₂	75	20.51 (20.54)	0.49
22.	2-Sulfonamidobenzene (Pale yellow)	225	C ₂₂ H ₁₈ N ₆ O ₃ S	78	18.80 (18.84)	0.90

S. No.	'X' (colour)	m.p. (°C)	Molecular formula	Yield (%)	N% found (calcd.)	R _f value
23.	N ¹ -2-pyridylsulfonamidobenzene (Dark yellow)	256	C ₂₇ H ₂₁ N ₇ O ₃ S	81	18.72 (18.74)	0.60
24.	N ¹ -2-pyrimidylsulfonamidobenzene (Yellow)	245	C ₂₆ H ₂₀ N ₈ O ₃ S	82	21.30 (21.37)	0.50
25.	N ¹ -2-thiazolylsulfonamidobenzene (Shining yellow)	213	C ₂₅ H ₁₉ N ₇ O ₃ S ₂	85	18.48 (18.52)	0.85
26.	N ¹ -2-guanylsulfonamidobenzene (Light orange)	276	C ₂₃ H ₂₀ N ₈ O ₃ S	77	22.91 (22.95)	0.73
27.	N ¹ -2-(4,6-dimethyl)-pyrimidylsulfonamidobenzene (Dirty yellow)	261	C ₂₈ H ₂₄ N ₈ O ₃ S	76	20.24 (20.29)	0.82
28.	N ¹ -2-acetylsulfonamidobenzene (Pale yellow)	249	C ₂₄ H ₂₀ N ₆ O ₄ S	80	17.19 (17.22)	0.99
29.	N ¹ -2-quinoxalylsulfonamidobenzene (Shining yellow flakes)	289	C ₃₀ H ₂₂ N ₈ O ₃ S	82	19.42 (19.51)	0.79

The R_f values for all the compounds: on silica gel plates (thickness 0.5 mm), developing solvent acetone/dimethylformamide (3 : 1), non-saturated chambers at room temperature (20 ± 1°C)

***In-vivo* studies: Antiinflammatory activity**

Compounds belonging to the series were subjected to preliminary screening for antiinflammatory activity by carrageenan induced rat paw edema method.

The test compounds suspended in 10% ethanol in 50 mg/kg dose and standard ibuprofen were administered. Edema was induced by injecting 0.1 mL of 1% carrageenan suspension in normal saline. Some of the products showed significant antiinflammatory activity as they exhibited inhibition ranging from 75 to 85%, while ibuprofen at the same dose produced an inhibition 83% at 50 mg/kg dose. Their activity data are recorded in Table-2.

TABLE-2
EFFECT OF COMPOUNDS SYNTHESISED ON CARRAGEENAN INDUCED PAW EDEMA IN RATS
(Dose 50 Mg/Kg; Number of Animals Used, 5)

Compound	Av. body weight (g)	Mean paw swelling (±SE)	Suppression (%)
Ibuprofen	234	0.770	82.6
7	166	0.640	77.5
8	190	0.704	88.0
9	158	0.550	67.7
18	194	0.700	79.6
19	212.6	0.536	49.6
20	236	0.662	83.8
23	231	0.400	42.6

***In vitro* studies: Antimicrobial activity**

The activity was determined using cup-plate, agar diffusion method¹⁴ by measuring the inhibition zones in mm. All the compounds were screened *in vitro* for their antimicrobial activity against a variety of bacterial strains as *B. subtilis*, *S. pyogens*, *E. coli*, *K. pneumoniae* and fungi such as *A. Niger* and *S. cerevisiae* at a concentration of 50 µg/mL.

Under identical conditions the standard antibiotics Chloramphenicol showed a zone of inhibition of 21 to 27 mm, norfloxacin of 22 to 27 mm against bacterial strain and griseofulvin showed a zone of inhibition of 24–26 mm against fungal strain. Most of the compounds showed moderate activity. Maximum activity 21–30 mm was shown by compounds 2, 9, against *B. subtilis*, 3, 4, 14 against *S. pyogens*, 15, 16 against *K. pneumoniae*, 11, 12 against *A. niger* and 5, 7 against *S. cerevisiae*.

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REFERENCES

1. R. Behnisch, F. Mietzch and H. Schmidt, *Am. Rev. Tuberc.*, **61**, 1 (1950).
2. H.G. Garg and R.A. Sharma, *J. Pharm. Sci.*, **59**, 350 (1970).
3. H.G. Garg and P.P. Singh, *J. Med. Chem.*, **13**, 1250 (1970).
4. S.S. Tiwari and A. Sharma, *J. Indian Chem. Soc.*, **52**, 153 (1975).
5. E. Jucker, A.J. Lindemann and F. Rissi, U.S. Pat., 342, 3041 (1962).
6. W. Wilson and N. Bottigliere, *Cancer Chemotherapy*, **21**, 137 (1962).
7. C.W. Noell and C.C. Cheng, *J. Med. Chem.*, **12**, 545 (1969).
8. L.G. Polevoi, Tr. Nauchn. Konf. Aspir. i Ord. 1-yi (Pervyi) Mosk, Med. Inst., Moscow, 159 (1964); *Chem. Abstr.*, **65**, 19147 (1966).
9. V.M. Avakumov and Yu. M. Batulin, *Farmakol. Toksikol.*, **31**, 402 (1968); *Chem. Abstr.*, **69**, 75439 (1938).
10. L.G. Polevoi, A.N. Kudrin, I.I. Grandberg and A.N. Kost, *Izv. Timiryazev. Sel'skokhoz. Akad.*, 192 (1968); *Chem. Abstr.*, **69**, 1557 (1968).
11. Y.M. Batulin, *Farmakol. Toksikol.*, **31**, 533 (1968); *Chem. Abstr.*, **70**, 2236 (1969).
12. T.S. Osdene, P.B. Russell and L. Rane, *J. Med. Chem.*, **10**, 431 (1976).
13. G.L. Jenkins, W.H. Haatung and J.B. Data, *The Chemistry of Organic Medicinal Products* (1957).
14. A.L. Barry, *The Antimicrobial Susceptibility Test: Principle and Practice*, Lea and Febiger, Philadelphia, pp. 180–93 (1976).