Asian Journal of Chemistry Vol. 11, No. 1 (1999) 207–212

Synthesis and Antifungal Activity of N^1-Nicotinoyl-3-Methyl-4-(substituted Azo)-1,2-Pyrazoline-5-One

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A novel series of N^1-nicotinoyl-3-methyl-4-(sulpha/substitued phynyl azo)-1,2-pyrazoline-5-one have been synthesised by the condensation of sulpha/substituted phenyl azo ethyl-3-oxobutyrate with nicotinic acid hydrazide, using glacial acetic acid as condensing agent. Some of the products showed significant antifungal activity against *C. albicans*, *C. neoformans*, *S. schenikii*, *T. mentagrophytes* and *A. fumigatus*.

INTRODUCTION

A survey of the literature reveals that pyrazoline-5-one derivatives possess various types of biological activities, *viz.*, potential antiinflammatory[1, 2], tranquillizing[3], muscle relaxant[4], psychoanaleptic[5], hypnotics[6], anticonvulsant[7] antitubercuious[8], antineoplastic[9], antidiabetic[10], antifertility[11], antiepileptic[12], proteolytic[13], antiobesity anticholinergic[14], antitumour[15, 16], action, etc, while nicotinic acid hydrazide is used as antipellagric[17] and antitumour agent[18].

The method of preparation of pyrazoline-5-one was first reported by Ludwig Knorr[19] in 1883. Since then many new methods of synthesising the substituted pyrazoline-5-one and their derivatives have been developed[20].

The present paper deals with that when diazotised sulphadrugs, aromatic amines, are condensed at reactive methylene position of β-keto ester, sulpha/substituted phenyl azo ethyl-3-oxobutyrate are obtained. The condensed products on cyclisation with nicotinic acid hydrazide gives N^1-nicotinoyl-3-methyl-4-(sulpha/substituted phenylazo)-1,2-pyrazoline-5-one and their antifungal activity was studied.

EXPERIMENTAL

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), on saturated chambers at room temp. (20 ± 1°C). IR spectra (ν_{max} in cm^{-1}) were determined in KBr on a Perkin-Elmer 577

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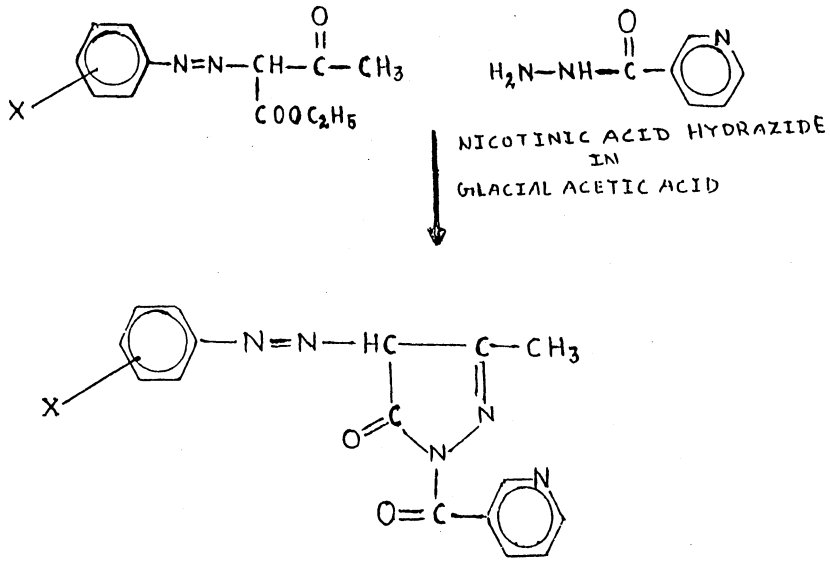
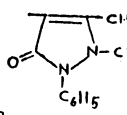
spectrophotometer; ^1H NMR spectra on Bruker Ac 300F Spectrophotometer at 300 MHz in $CDCl_3$ or $CDCl_3$ + DMSO-d_6 using TMS as an internal reference (chemical shift δ, ppm).

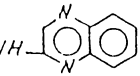


Where;

X= $-Br$, $-Cl$, $-NO_2$, $-OCH_3$, $-CH_3$, $-OH$, $-COOH$,

$-SO_2NH_2$, $-SO_2NH-$  , $-SO_2NH-$  ,  ,

$-SO_2NH-C(=NH)-NH_2$, $-SO_2NH-$  , $-SO_2NH-$  ,

$-SO_2NHCOCH_3$ and $-SO_2NH-$  etc.

Synthesis of N^1-nicotinoyl-3-methyl-4-(sulpha/substituted phenyl azo)-1,2-pyrazoline-5-one

A solution of sulpha/substituted phenylazo ethyl-3-oxobutyrate and nicotinic acid hydrazide was condensed on a water bath for about 3 h. It was kept overnight to give a yellow solid mass which was filtered, washed well with water, dried and recrystallised from ethanol and DMF mixture to give shining coloured powder of N^1-nictotinoyl-3-methyl-4-(sulpha/substituted phenyl azo)-1,2-pyrazoline-5-one. The spectra had characteristic peak IR (KBr)(cm^{-1}): 750 ν(C—Cl), 1590 ν(N=N), 1680 ν(C=O pyridyl), 1710 ν(C=O cyclic) and 1650 ν(C=N). The structures of compounds were also confirmed by ^1H NMR spectral studies: NMR ($CDCl_3$ + DMSO-d_6) : [δ] 2.1 (S, 3H, CH_3); 7.30–7.90 (m, 8H, ArH); 15.0 (δ, 1H, CH ⇌ C–CH) ppm.

Their characteristics are recorded in Table-I. The yields vary from 75 to 85%.

TABLE-1
CHARACTERISTICS OF N^1-NICOTINOYL-3-METHYL-4-(SUBSTITUTED AZO)-1,2-PYRAZOLIN-5-ONE

Substituted (z) (Colour)	m.p. (°C)	Crystallisation solvent	Molecular formula	Nitrogen % Found (Calcd.)	R_f value
Phenylazo (SBrRF)	195	Ethanol/ Acetic acid	$C_{16}H_{13}N_5O_2$	22.92 (22.80)	0.9262
2-Chlorophenylazo (OPr)	200	"	$C_{16}H_{12}N_5O_2Cl$	20.46 (20.52)	0.9376
3-Chlorophenylazo (SCF)	216	"	$C_{16}H_{12}N_5O_2Cl$	20.56 (20.52)	0.9324
4-Chlorophenylazo (SGYN)	215	"	$C_{16}H_{12}N_5O_2Cl$	20.48 (20.52)	0.9309
2-Nitrophenylazo (LOPr)	180	"	$C_{16}H_{12}N_6O_4$	23.76 (23.86)	0.8919
3-Nitrophenylazo (YPr)	238	"	$C_{16}H_{12}N_6O_4$	23.79 (23.86)	0.7218
4-Nitrophenylazo (SDYN)	255	"	$C_{16}H_{12}N_6O_4$	23.92 (23.86)	0.7379
4-Bromophenylazo (SGYN)	220	"	$C_{16}H_{12}N_5O_2Br$	18.23 (18.13)	0.9241
2-Methylphenylazo (SBrRN)	218	"	$C_{17}H_{15}N_5O_2$	21.74 (21.80)	0.9219
4-Methylphenylazo (SGYPr)	175	"	$C_{17}H_{15}N_5O_2$	21.75 (21.80)	0.7357
3-Methoxyphenylazo (LBPr)	168	"	$C_{17}H_{15}N_5O_3$	20.68 (20.77)	0.9601
4-Methoxyphenylazo (OPr)	176	"	$C_{17}H_{15}N_5O_3$	20.83 (20.77)	0.9298
2-Carboxyphenylazo (DYF)	292	Ethanol/DMF	$C_{17}H_{13}N_5O_4$	19.86 (19.94)	0.3907
4-Carboxyphenylazo (YPr)	315	"	$C_{17}H_{13}N_5O_4$	19.86 (19.94)	0.4965
4-Hydroxyphenylazo (SLBPr)	215	"	$C_{16}H_{13}N_5O_3$	21.73 (21.67)	0.9069
1, Naphthylazo (SDBN)	220	"	$C_{20}H_{15}N_5O_2$	19.66 (19.60)	0.9436
4-Aminodiphenylazo (SDBPr)	282d	"	$C_{22}H_{18}N_6O_2$	21.06 (21.10)	0.7805

Substituted (z) (Colour)	m.p. (°C)	Crystallisation solvent	Molecular formula	Nitrogen % Found (Calcd.)	R_f value
2-Chloro-4-nitrophenylazo (SBrRGe)	232	Ethanol/DMF	$C_{16}H_{11}N_6O_4Cl$	21.72 (21.76)	0.7523
3-Nitro-4-methylphenylazo (YPr)	171	"	$C_{17}H_{14}N_6O_4$	23.00 (22.95)	0.6944
2,4,6-Tribromophenylazo (SBN)	232	"	$C_{16}H_{10}N_5O_2Br_3$	12.79 (12.86)	0.9383
2,3-Dimethyl-1-phenylpyrazoloneazo (LBPr)	213	"	$C_{21}H_{19}N_7O_3$	23.44 (23.50)	0.1754
2-Sulphanilamido-benzeneazo (LYPr)	185	"	$C_{16}H_{14}N_6O_4S$	21.79 (21.76)	0.9082
N^1-2-pyrimidyl sulphanilamidobenzeneazo (GYPr)	268	"	$C_{20}H_{16}N_8O_4S$	24.18 (24.13)	0.9082
N^1-2 (4,6-dimethyl)-sulphanilamidobenzeneazo (BPr)	204	"	$C_{22}H_{20}N_8O_4S$	22.70 (22.76)	0.9552
N^1-2-guanyl sulphanil-amidobenzeneazo (DYPr)	235	"	$C_{17}H_{16}N_8O_4S$	26.20 (26.16)	0.9541
N^1-2-pyridyl sulphanil-amidobenzeneazo (YPr)	255	"	$C_{21}H_{17}N_7O_4S$	21.12 (21.16)	0.9324
N^1-2-thiazolyl sulphanil amidobenzeneazo (GYPr)	262	"	$C_{19}H_{15}N_7O_4S_2$	20.83 (20.89)	0.9758
N^1-2-acetyl sulphanil-amidobenzeneazo (SYPr)	206	"	$C_{18}H_{16}N_6O_5S$	19.55 (19.62)	0.9484
N^1-2-quinoxalyl sulpha-nilamidobenzeneazo (SWN)	166	"	$C_{24}H_{18}N_8O_4S$	21.84 (21.78)	0.8828

The values for all the compounds were determined on silica Gel-G plates (Thickness 0.5–0.6 mm) with developer acetone/dimethyl formamides) (3 : 1) in saturated chamber at room temp. (20 ± 1°C)

*B = Brown, Br = Brick, C = cream, D = Dark, F = Flakes, G = Golden, Ge = Granules, L = Light, N = needles, O = orange, Pr = Powder, R = Red. S = Shining, W = White Y = Yellow.

Biological Assay: The newly synthesised compounds were screened against *C. albicans, C. neoformans, S. schenikii, T. mentagrophytes* and *A. Fumigatus.* The antifungal activities were assayed following filter paper disc plate method.

Filter paper discs (8 mm diameter) were separately dipped in each solution and subsequently placed on Sabouraud's dextrose agar medium plates[21] (90 mm diameter). Thereafter freshly treated petridishes were incubated at 27 ± 1°C for *ca.* 70 h. Filter paper discs soaked in griseofulvin (1000 ppm) were used to serve as control. The antifungal activities were measured as the average of maximum dimension of zones of inhibition around the filter paper discs. The observations and results are recorded in Table-2. A critical examination of data recorded in table revealed that few compounds are associated with adequate antifungal activity, whereas no inhibition zones were noticed with pure solvent.

TABLE-2
ANTIFUNGAL ACTIVITY DATA

Name of compounds	Name of pathogens				
	C. albicans	*C. neoformans*	*S. schenikii*	*T. mentagrophytes*	*A. Fumigatus*
N^1-nicotinyl-3-methyl-4-(4-methylphenylazo)-1,2-pyrazoline-5-one	+++	+++	+	–	++
N^1-nicotinyl-3-methyl-4-(4-Bromophenylazo)-1,2-pyrazoline-5-one	–	++	–	+	+++
N^1-nicotinyl-3-methyl-4-(N^1-2-acetyl-sulphanilamidobenzeneazo)-1,2-pyrazoline-5-one	+	–	++	+	–
N^1-nicotinyl-3-methyl-4-(N^1-2-guanylsulphanilamidobenzeneazo)-1,2-pyrazoline-5-one	–	++	++	–	+++
N^1-nicotinyl-3-methyl-4-(N^1-2-quinoxalylsulphanilamidobenzeneazo)-1,2-pyrazoline-5-one	+++	+	+	–	++
N^1-nicotinyl-3-methyl-4-[N^1-2,4,6-dimethyl)sulphanilamidobenzene]-1,2-pyrazolin-5-one	++	–	–	++	+++
N^1-nicotinyl-3-methyl-4-(2,4,6-tribromophyenylazo)-1,2-pyrazolin-5-one	+	++	+	–	+++
N^1-nicotinyl-3-methyl-4-(2-methyl-phenylazo)-1,2-pyrazolin-5-one	–	+++	+	+++	–

– = No inhibition, + = Zone size 5–6 mm, ++ = Zone size 6–8 mm
+++ = Zone size greater than 8 mm.

ACKNOWLEDGEMENTS

The authors wish to express their sincere thanks to prof. A.N. Singh, Sahu Jain College, Najiababad, for ncecessary laboratory facilities. The authors also indebted to Dr. T.R. Sweeny, Director, W.A.R.I., Washington (D.C.) for testing the compounds as antifungal agents.

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(*Received*: 4 September 1998; *Accepted*: 3 November 1998) AJC-1594