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Synthesis and Anti-Inflammatory activity of Sulpha/substituted 1,2-Diazoles

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ABSTRACT
A Novel compound namely N^1(3 Nicotinoyl) 3,5 dimethyl-4-(N-4-sulfamoyl-azo)-1,2-diazoles has been synthesized by two step processes. Synthesis of N^1-4-sulfamoylphenylhydrazono-3,5-dimethyl propane-1,3-dione and sulfonamide, which interacting with 3-Nicotinoyl hydrazine to form final compound. The newly synthesized compound N^1-(3-Nicotinoyl)-3,5-dimethyl 4-(N^1-4-sulfamoyl phenyl azo) 1,2-diazoles was screened for anti-inflammatory activity.
Keywords: *synthesis, anti-inflammatory activity, sulfonamide 1,3-diketone,3-Nicotinoyl hydrazine.*

I. INTRODUCTION

The organic chemists employing the art of synthesis have been responsible for the development of vast majority of drug used in modern system of medicine. Many founding fathers of medicinal chemists were interested not only in natural products but also on the effect of synthetic compounds in living system.

A heterocyclic compound is one which possess cyclic structures with at least one hetero atom in the ring. Nitrogen,oxygen and sulfur are the most common hetero atoms. Heterocyclic compounds are very widely distributed in nature and essential to the life in various ways. Vitamin C exists in the form of five membered(furan) or six membered(pyron) rings containing one oxygen atom.Most member of Vitamin B group possess heterocyclic ring containing nitrogen. One example is Vitamin B_6 (Pyridoxime),which derivative of pyridine essential in amino acid metabolism.

1,2-diazole is a heterocyclic compound having varied biological activity and still of great scientific now adays. They are widely found in bioorganic and medicinal chemistry application in drug discovery. Nitrogen based heterocyclic compounds are very important in the field of medicinal chemistry. The present diazoles were prepared because of its good biological activity. Compounds including a 1,2-diazole nucleus and N-substituted derivatives are known to possess various biological activity1.

Among these types of molecules have been shown to have various important biological activity such as antibacterial,antifungal,antiviral,diuretic,antitiuberculostatic,antiHIV,antihistaminic,anticancer,anticonvulsant,anti-inflammatory and analgesic properties 3-7. Sulfa/substituted 1,2-diazoles may serve as the alternative sources for the development of new anti-inflammatory agents due to their biological activity. Sulfa/substituted 1,2-diazoles used for the treatment of anti-inflammatory in different systems of medicine have shown diuretic activity when tested on animal models. On the basis of the use of diuretics, but no previous pharmacological study was carried out to test anti-inflammatory the activity of sulfa/substituted 1,2-diazoles. The main aim of the present investigation was to evaluate the claimed anti-inflammatory activity of sulfa/substituted 1,2-diazoles.

II. MATERIAL AND METHOD

The 1,3-diketones,sulfanilamide,3-Nicotinoyl hydrazine and all reference compound were purchased from Aldrich Chemicals, Ethanol, sodium acetate, glacial acetic acid and all other reagents were purchased from S.D. Chem. TLC was performed on pre-coated plastic sheets of silica gel G/UV-254 of 0.2 mm thickness(Macherey-Nagel,Germany).

Melting points of the N^1-(3Nicotinoyl)3,5-dimethyl-4-(N-4-sulfamoylphenylazo)-1,2-diazole were determined using an open-ended capillary tube method and are uncorrected. The purity of the synthesized compound was checked by TLC. A FT-IR spectrum was recorded on a Perkin-Elmer1605 series FT-IR in a KBr disc,1H NMR spectra was recorded at 300MHz on a Burker FT-NMR spectro-photometer using TMS as internal standard.

Step1; Synthesis of N^1-4-sulfamoylphenyl hydrazono-3,5-dimethyl propane-1,3-dione-

An ice cooled solution of 3,5-dimethyl propane-1,3-dione(0.03 mole) in ethanol containing sodium acetate(6gms) is a diazotized solution of sulfonamide(0.05 mole) were gradually added with stirring and cooling. The reaction mixture was further stirring for 20 minutes, the colouredhydrazono compounds precipitated by addition of ice cold water. It was filtered off, washed with water, dried and recrystallized from ethanol/acetic acid[Fig.1]. On analysis, it was found to be N1-4-sulfamoylphenyl hydrazono-3,5-dimethyl propane-1,3-dione.

Synthesis of novel N^1-(3-Nicotinoyl),5-dimethyl-4(N-4-sulfamoylphenylazo)-1,2-diazole.

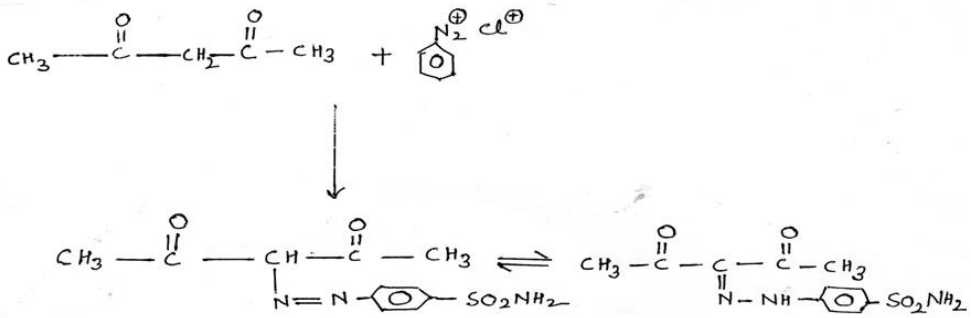

Fig.1- Synthesis of N^1-4-sulfamoylphenyl hydrazono-3,5-dimethyl propane-1,3-dione.

N^1-4-sulfamoylphenyl hydrazono 3,5-dimethyl propane-1,3-dione:A yellow crystalline powder,Mp 198-200^{o}C, Yield 82.34%, molecular formula $C_{16}H_{15}O_4N_3S$(348.76);C,55.10;H,4.34;0,18.35;N, 12.04;S,10.17. Found:54.92;4.56;O,18.17;N,12.48; S,9.87,IR(KBr) in cm-1 1440(C-C),1560(C=C of aromatic ring), 1260(C-N), 1680(C=O), 3087(NH), 3275(SO_2NH_2). 1HNMR ($CdCl_3$) in ppm, 2.81(s, 3H CH_3), 6.75-7.68(m, 9H, Ar-H), 6.929(s,2H NH_2),10.43(s, 1H NH).

Step-II; Synthesis of N^1-(3-Nicotinoyl, 3,5-dimethyl-4(N-4-sulfamoyl phenylazo)-1,2-diazole:
A solution of N^1-4-sulfamoylphenyl-hydrazono 3,5-dimethyl propane-1,3-dione (0.02 mole) in glacial acetic acid was added to 3-Nicotinoyl hydrazine (0.05 mole) refluxed on water bath for 4 hours and left overnight. On cooling, shining recrystallized crystals, separated out which was collected by filtration, washed well with water, dried and recrystallized from glacial acetic acid to give N^1-(3-Nicotinoyl)3,5 dimethyl-4(N-4-sulfamoylphenylazo)-1,2-diazole.
[Fig. 2]

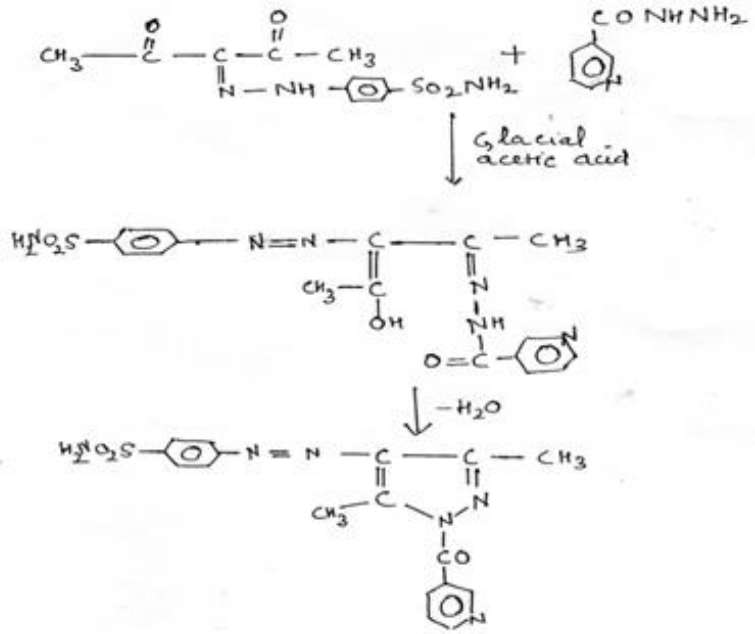

Fig.2: Synthesis of N^1-(3-Nicotinoyl) N^1-3,5-dimethyl-4(N-4-sulfamoylphenylazo)-1,2-diazole

N^1(3-Nicotinoyl)-3,5-dimethyl-4-(N-sulfamoylphenylazo)-1,2-diazole: A yellow crystalline powder, mp 226-228^{o}C, Yield 72.13%. Molecular formula C23H20O3N5anal.Calcd for C23H20O3N6S (463.90); C,59.55; H,4.34; O,10.35; N,18.12; S,7.64. Found: C,58.97; H,4.64; O,10.29; N,18.37; S,7.73. IR(KBr) in cm-1 740(C-C), 1240(C-N), 1535(C=C of aromatic ring), 1585(C=N), 1460(N=N), 3055(aromatic C-H), 3135(NH), 1707(C=O), 3082(NH_2). ^{1}HNMR(CdCl3) in ppm, 2.79(s, 3H CH_3), 6.65-7.58(m, 13, Ar-H), 7.10(m, 4H NH_2).
Animals: Adult's male Wistaralbino rats, each in the weight range of 180-200 gm were used for this experiment. They were procured from National Vertinary Research centre, Bareilly, India. The animals were randomly allocated to six treatment groups of six animals each and kept in polypropylene cages and housed under standard conditions of temperature, humidity, dark light cycle (12h-12h) and diet.
Anti-inflammatory activity[8]:

The activity of the newly synthesized compounds compared to indomethacin as a reference compound was measured before and 4h after carrageenan injection. Percent of the oedema inhibition was calculated as regards saline control group and potency was calculated as regards percentage of the change of indomethacin and tested compounds, as depicted in Table1. All the tested compounds showed a reasonable inhibition of oedema size ranging between a 12.5% for compound 25.4% for compound (b) 28% for compound, 32.7% for compound sulfanomide 1,2-diazole (c), 44.4% for compound sulfapyrimidine 1,2-diazole (d) and 29.9% for indomethacin. In activity relationship point of view, the anti-inflammatory activity of the pyrimidine was found to be the promising one. But sulfonamide also showed good anti-inflammatory activity(32.7%)

Table 1: Anti-inflammatory effect of sulpha/substituted-1,2-diazoles

Compound	Dose (mg/kg)	Oedema		Oedema (%) (X±SE)	Oedema inhibition (%)	Potency
		Zero min (basal)	4 h oedema (cm) (% increase)			
Control	1 ml saline	0.23±0.006	0.46±0.01	109.1±6.3	–	–
a $C_{14}H_{10}NCl$	70	0.20±0.002	0.37±0.01	81.3±4.8	-25.48	0.9
b $C_{14}H_{10}NF$	70	0.22±0.002	0.38±0.03	78.3±4.1	-28	0.9
c $C_{14}H_{10}N_2O_2$	70	0.21±0.003	0.41±0.2	94.8±5.3	-13.1	0.4
d $C_{20}H_{16}N_2O_2S$	70	0.22±0.002	0.37±0.02	73.4±4.4	-32.7	1.1
e $C_{24}H_{18}N_4O_2S$	70	0.20±0.00	0.32±0.001	60.7±4.9	-44.4	1.5
f $C_{24}H_{18}N_4O_2S$	70	0.20±0.00	0.32±0.004	60.7±4.9	-44.4	1.5
Indomethacin	35	0.26±0.003	0.39±0.03	76.5±3.6	-29.9	1

III. CONCLUSION

The present study reveals that synthesized compound N^1 (3-Nicotinoyl)-3,5-dimethyl4(N-4-sulfamoylphenylazo)-1,2-diazole possess significant at 100 and 200 mg/kgbut the effect declined at higher dose.

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