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Synthesis and Biological Studies of Some 2,3-Diphenylthiazolidin-4-ones and Condensed Pyrazolines

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ABSTRACT

2,3-Diphenylthiazolidin-4-one and its different benzylidenes have been used as the starting material in the present work. 4-Thiazolidinones are known to exhibit antitubercular, antibacterial, anticonvulsant, antifungal, antithyroid activities. These benzylidene derivatives possess unsaturated carbonyl group which are further allowed to react with hydrazine hydrate and its phenyl derivatives to form different pyrazoline rings after cyclisation. Pyrazolines are found to be antipyretic, and show good antimicrobial and antifungal properties.

Key words: diphenylthiazolidinones, bezylidenes , pyrazolines, biological activities, antifungal, antimicrobial.

INTRODUCTION

Benzothiazole derivatives were prepared and known to exhibit various biological activities as anti-tuberculotic[1], anti-allergic[2]. Pyrazole ring system is of some practical importance, because many drugs and medicines contain a pyrazole ring system. As early as 1884 Knorr discovered the antipyretic (temperature reducing) action of a pyrazole derivative in human beings and due to its antipyretic property, he named the compound “Antipyrine”. Schiff Base gives good antimicrobial activity and pharmacological applications[3] and it can be prepared by the acid catalyzed reaction of amines & ketones or aldehydes. It gives a good fungicidal activity[4]. 4-Thiazolidinones gives good pharmacological properties[5]. 4-Thiazolidinones are known to exhibit antitubercular[6], antibacterial[7], anticonvulsant[8], antifungal[9], antithyroid activities.

The starting compound aniline N-benzylidene has been synthesized from aniline and benzaldehyde[10] to yield Schiff Base [3]. The Schiff base obtained was reacted with thioglycolic acid to yield 2,3-diphenylthiazolidin-4-one. Tetra hydro derivative of thiazole is known as thiazolidine and oxo derivative of thiazolidine is known as thiazolidinone. A large number of thiazolidinones are reported for their biological activities such as anaesthetic, analgesic, antibiotic, antifungal diuretic activity, anti-inflammatory agents and anticancer [11-17]. Pyrazolines are the parent substance of a large number of heterocyclic compounds. Pyrazolines can be regarded as a cyclic amidine and the chemical behavior of its derivatives is dominated by this fact. A number of compounds of this group have found their importance as important drugs. Among sulpha drugs sulphadiazine, sulphamerazine and sulphamethazine are actually pyrazoline derivatives. These agents are inhibitors of folic acid biosynthesis in microorganisms. The barbiturates are pyrazoline derivatives, which possess potent depressant action in the central nervous system [18-23].

EXPERIMENTAL

All the melting points are uncorrected. The ultraviolet spectra were recorded on "Beckman DU-2 spectrophotometer and infrared spectra on "Perkin Elmer-577" spectrophotometer. The ^{1}H NMR spectra were recorded from CDRI Lucknow.

Synthesis of compounds

Aniline N- benzylidene(I):

The compound was prepared according to method reported in the literature [24].

2,3-Diphenylthiazolidin-4-one (II)

In a 100ml round bottom flask, a mixture of 2g (0.01mole) benzalaniline, 15 mL dry benzene and 1g (0.01mole) thioglycolic acid were taken and refluxed on water bath for nearly eight hours. The hot contents were cooled and then poured into distilled water at normal temperature and left for an hour. A layer of desired organic compound was obtained.

2,3-Diphenyl 5-benzylidenethiazolidin-4-one(III)

In a 100 mL round bottom flask 2.5g (0.01 mol) 2,3-diphenylthiazolidin-4-one, 1.10g (0.01mol) benzaldehyde and 25 ml dry benzene were mixed with little quantity of sodium ethoxide. The contents were well shaken and then refluxed on water bath for 12 hours. The refluxed contents were then cooled and poured into ice cold water followed by the addition of little amount of glacial acetic acid to acidify it. The solution was then separated from the benzene layer . It was dried by passing through anhydrous calcium chloride and then evaporated till the solid product was obtained.

Yield 50%, M.P. 145^{O} C.

^{1}H NMR δ 1.4-1.8 (S, 1H, CH Benzyl)

δ 7-7.8 (m-11H, NH, 2C_6H_5).

5-(4-Methoxy) benzylidene2,3-diphenylthiazolidin-4-one. (IV)

In a round bottom flask 4g(0.01 mol) 2:3-diphenyl thiazolidin-4-one , 6mL anisaldehyde and 6g fused sodium acetate in 45mL glacial acetic acid was refluxed for six hours on water bath. After twenty minutes of refluxing all the contents in the flask dissolved and a clear solution resulted. After few minutes, deep yellow crystals started appearing. The crystals were filtered after cooling, washed with alcohol and crystallized from glacial acetic acid.

Yield 85%, M.P. 170^{O} C.

2,3-Diphenylthiazolidin-^{2}–5-phenyl(3,4-d)pyrazoline (V)

In a 100mL round bottom flask 3.5g (0.01mol) benzylidene(III), 10 mL glacial acetic acid, 1g sodium acetate and 1 mL hydrazine hydrate were taken. These contents were refluxed for seven hours over a wire gauze. The contents were hot filtered to remove undissolved substances and cooled. Some amount of water was added and the mixture was boiled once again for fifteen minutes and cooled. The orange crystals were obtained. M.P. – 163^{0}C, Yield – 80%

^{1}H NMR δ 1.2-1.5 (d, 1H, testCH)

δ 4.9-5.5(s, 2H, CH benzylic, NH)

2,3-Diphenylthiazolidin-Δ^2–1,5-diphenyl(3,4-d)pyrazoline (VI)

In a 100mL round bottom flask 3.5g (0.01mol) benzylidene(III), 25 mL glacial acetic acid, 1g sodium acetate and 2 mL phenylhydrazine were taken. These contents were refluxed for six hours over wire gauze. The contents were hot filtered to remove undissolved substances and cooled. Some amount of water was added and the mixture was boiled once again for fifteen minutes and cooled. The yellow crystals were obtained.

M.P. – 178^{0}C Yield – 75%

2,3-Diphenylthiazolidin-Δ^2–1-(2,4-dinitrophenyl)-5-phenyl(3,4-d)pyrazoline (VII)

2gm ofthe benzylidene compound (III), 2gm of 2,4 –dinitro phenyl hydrazine were taken with 20 ml of glacial acetic acid in a 100 ml round bottom flask .All contents were refluxed for about six hours. The colour of the solution became red. The mixture was left over night. Next day crystals were obtained. They were washed with ethanol and crystallized from glacial acetic acid.

M.P. –309^0 , Yield – 78%

PMR Spectrum

The significant signals that were observed could be interpreted as

δ 1.1-1.3 (d 1H, ter.CH), 4.7-5.3 (s, 2H, CH benzylic, NH)7.2-7.7 (t, 15H, NH, $3C_6H_5$)

2,3-Diphenylthiazolidin-Δ^2–5-(4-methoxphenyl)(3,4-d)pyrazoline (VIII)

In a 100mL round bottom flask 3.8g (0.01mol) benzylidene(VII), 10 mL glacial acetic acid, 1g sodium acetate and 1 mL hydrazine hydrate were taken. These contents were refluxed for seven hours over a wire gauze. The contents were hot filtered to remove undissolved substances and cooled. Some amount of water was added and the mixture was boiled once again for fifteen minutes and cooled. The orange crystals were obtained.

M.P. – 172^0C , Yield – 80%

2,3-Diphenylthiazolidin-Δ^2–5-(4-methoxphenyl)-1-phenyl(3,4-d)pyrazoline (IX)

In a 100mL round bottom flask 3.8g (0.01mol) benzylidene(VII), 25 mL glacial acetic acid, 1g sodium acetate and 2mL phenylhydrazine were taken. These contents were refluxed for seven hours over wire gauze. The contents were hot filtered to remove undissolved substances and cooled. Some amount of water was added and the mixture was boiled once again for fifteen minutes and cooled. The

light yellow crystals were obtained.

M.P. – 285^0C ,Yield – 76%

2,3-Diphenylthiazolidin-Δ^2–5-(4-methoxphenyl)-1-(2:4-dinitrophenyl)(3,4-d)pyrazoline (X)

In a 100mL round bottom flask 3.8g (0.01mol) benzylidene(VII), 25 mL glacial acetic acid, 1g sodium acetate and 2g 2:4-dinitrophenylhydrazine were taken. These contents were refluxed for seven hours over wire gauze. The contents were hot filtered to remove undissolved substances and cooled. Some amount of water was added and the mixture was boiled once again for fifteen minutes and cooled. The light yellow crystals were obtained.

M.P. – 298^0C ,Yield – 73%

PMR Spectrum

The significant signals that were observed could be interpreted as

δ 1.1-1.2 (T 1H, ter.CH),1.9-2.0 (s, 1H, benzylic CH) 3.7- 3.8 (s, 4H, NH, OCH_3), 6.8 – 7.8 (m, 15H, $3C_6H_5$)

Anti-microbial activity

The cup-plate method 9, 10 using Mueller – Hinton agar medium was employed to study the preliminary anti-bacterial activity of II-X against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli* and *Pseudomonas aeruginosa*. Preparation of base layer medium, agar medium and peptone water was done as per the standard procedure. Each test compound (10 mg/ml) was prepared by dissolving 50mg in 5ml of dimethyl formamide and used for testing. Same cup-plate method using PDA medium was employed to study

Table 1: Elemental Analysis of the Compounds

Sl. No.	Compound	% Analysis, Found/Calculated		
		C	H	N
I.	$C_{13}H_{11}N$	86.19(86.22)	6.08(6.10)	7.73(7.80)
II.	$C_{15}H_{13}NOS$	86.19(86.15)	6.08(6.10)	5.49(5.50)
III.	$C_{22}H_{17}NOS$	76.96(76.83)	4.95(4.82)	4.08(4.10)
IV.	$C_{23}H_{19}NO_2S$	74.00(74.00)	5.09(5.13)	3.75(3.76)
V.	$C_{22}H_{19}N_3S$	73.94(73.84)	5.32(5.37)	11.76(11.82)
VI.	$C_{28}H_{23}N_3S$	77.60(77.63)	5.31(5.33)	9.70(10.02)
VII.	$C_{28}H_{21}N_5O_4S$	64.24(64.35)	4.01(4.07)	13.38(13.21)
VIII.	$C_{23}H_{21}N_3OS$	71.31(71.35)	5.42(5.37)	10.85(11.02)
IX.	$C_{29}H_{25}N_3OS$	75.16(75.13)	5.40(4.38)	09.07(09.13)
X.	$C_{29}H_{23}N_5O_5S$	62.92(63.01)	4.15(4.17)	12.65(12.63)

the preliminary antifungal activity of II-X against Candida albicans and A. niger. Preparation of nutrient broth, sub culture, base layer medium and PDA medium was done as per the standard procedure. Each test compound 50μ g/cup was used for testing.

The cups of 9 mm diameter were made by scooping out medium with a sterilized cork borer in a petri dish which was streaked with organisms. The solutions of each compound were added separately in the cups and petri dishes were subsequently inoculated. Ampicillin and Griesofulvin (6 μg/cup and 25μ g/cup respectively) were used as standard reference drugs and dimethylformamide (DMF) used as control which did not show any inhibition. Zone of inhibition produced by each compound was measured in mm and the results are presented in Table II**.**

Table 2: Zone of Inhibition of Compounds [4a-i]

Compound Code	*S.aureus*	*B.subtilis*	*E.coli*	*P.aerugina*	*C. albicans*	*A.niger*
II	6	8	7	10	9	7
III	5	9	8	10	12	13
IV	6	8	5	7	9	17
V	12	10	9	10	7	8
VI	7	8	9	6	8	6
VII	8	10	6	9	12	7
VIII	8	9	7	6	7	9
IX	14	8	10	5	11	12
X	7	8	9	6	10	13
Ampicillin	14	12	13	17	-	-
Griseofulvin	-	-	-	-	14	15
DMF	-	-	-	-	-	-

RESULTS AND DISCUSSION

All the tested compounds have shown antibacterial activity to some extent. Among the tested compounds III, V, VII and IX showed very good activity against the tested organisms. Compounds II, V and VIII are moderate antibacterial activity. The compounds II, III and X showed good antifungal activity and IV and VII showed moderate antibacterial activity. All the compounds synthesized possess electron releasing groups, on both the aromatic rings. Therefore from the results it is evident that compounds having electron releasing groups like methyl, hydroxy and methoxy may be responsible for antibacterial and antifungal activities.

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