

Synthesis of New Heterocyclic Thiazolidinone and Azetidinone Compounds and Their Antibacterial Activity

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Thiazolidinones and azetidinones have been prepared by the reaction of various Schiff bases with thioglycolic acid and chloroacetyl chloride respectively. The intermediate Schiff bases were synthesised by the condensation of diamino diphenyl methane with various pyrazolines. The structures of the compounds have been confirmed by elemental analysis and spectral analysis. The antibacterial activity of the compounds has also been screened.

Key Words: Synthesis, Thiazolidinone, Azetidinone, Antibacterial activity.

INTRODUCTION

Diaminodiphenyl methane derivatives were prepared and known to exhibit various biological activities. Pyrazolo 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". Thiazolidinones are known to exhibit antitubercular¹, antibacterial^{2,3}, anticonvulsant^{4,5}, antifungal⁶, antithyroid activities. Azetidinones (β -lactams) were tested as antibiotics, antidepressants and sedatives; so an attempt was made to synthesise some thiazolidinones and azetidinones using diaminodiphenyl methane as the starting material and test them as antibacterial drugs. Diaminodiphenyl methane was condensed with different aromatic pyrazolines to yield di-imines (I) (Schiff Base).

The di-imines (Schiff base, I) were further reacted with thioglycolic acid and chloroacetyl chloride to yield thiazolidinone (II) and azetidinone (III) respectively⁸.

EXPERIMENTAL

All the melting points were taken in open capillary tube and are incorrect. The IR spectra were recorded with KBr pellets on Perkin-Elmer 783 spectrophotometer. Purity of the compounds in addition to elemental analysis was checked by TLC.

Preparation of 4,4'-bis-{1''-(substituted phenyl)-3''-methyl/carboxyl-5''-pyrazole}-1,1'-dibenzmethane [Schiff bases]⁹ [I]

Diamino diphenyl methane (0.01 mol, 2.48 g) was taken in a Deanstark apparatus and to it 1-phenyl-3-methyl-5-pyrazole (0.02 mol, 3.49 g) was added over a period of 15 min. Then the mixture was refluxed for 5 h. During the course of the reaction the water was removed continuously. The benzene was then distilled off to get the product. The Schiff base was recrystallised in benzene. Other substituted Schiff bases were prepared in a similar manner. Data for various substituted Schiff bases are given in Table-1.

TABLE-1
ANALYTICAL DATA OF THE SCHIFF'S BASE (I)

No.	R	R ₁	R ₂	R ₃	R ₄	m.f. (m.w.)	Yield (%)	m.p. (°C)	% Analysis Found (Calcd.)		
									C	H	N
K ₁	CH ₃	H	H	H	H	C ₃₃ H ₂₆ N ₆ (506)	82	142	78.26 (78.30)	5.14 (5.18)	16.60 (16.64)
K ₂	COOH	H	H	H	H	C ₃₃ H ₂₄ N ₆ O ₁₂ S ₂ (712)	80	152	55.62 (55.64)	3.37 (3.40)	11.80 (11.83)
K ₃	CH ₃	H	H	H	H	C ₃₅ H ₃₂ N ₆ (536)	85	129	78.36 (78.40)	5.98 (5.99)	15.67 (15.71)
K ₄	CH ₃	Cl	H	SO ₃ H	SO ₃ H	C ₃₃ H ₂₆ N ₆ O ₆ S ₄ Cl ₂ (801)	87	142	49.44 (49.47)	3.25 (3.28)	10.49 (10.52)
K ₅	CH ₃	Cl	H	H	H	C ₃₃ H ₂₆ N ₆ Cl ₂ (577)	84	161	68.36 (68.39)	4.51 (4.55)	14.56 (14.60)
K ₆	CH ₃	H	Cl	H	H	C ₃₃ H ₂₆ N ₆ Cl ₂ (577)	87	165	68.36 (68.40)	4.51 (4.53)	14.56 (14.59)
K ₇	CH ₃	H	H	SO ₃ H	H	C ₃₃ H ₂₈ N ₆ O ₆ S ₂ (668)	76	153	59.28 (59.31)	4.19 (4.22)	12.57 (12.60)
K ₈	CH ₃	Cl	H	SO ₃ H	Cl	C ₃₃ H ₂₆ N ₆ O ₆ S ₂ Cl ₄ (808)	78	147	49.00 (49.03)	3.22 (3.25)	10.40 (10.43)
K ₉	CH ₃	Cl	H	SO ₃ H	H	C ₃₃ H ₂₆ N ₆ O ₆ S ₂ Cl ₂ (737)	75	153	53.73 (53.76)	3.53 (3.57)	11.40 (11.43)
K ₁₀	CH ₃	H	SO ₃ H	H	H	C ₃₃ H ₂₈ N ₆ O ₆ S ₂ (668)	80	136	59.28 (59.31)	4.19 (4.22)	12.57 (12.60)

Preparation of 4,4'-bis-[spiro-{1''-(substituted phenyl)-3''-methyl/carboxyl-pyrazole}-4-oxothiazolidine]-1,1'-dibenzmethane¹⁰ [II]

The Schiff base (0.0075 mol, 4.17 g) in benzene was taken in Deanstark apparatus and to it thioglycolic acid (0.015 mol, 1.36 g) in benzene was added

slowly. Then it was refluxed for 15–16 h. During the course of the reaction the water was removed continuously. The benzene was distilled off to get the product. Other substituted thiazolidinones were prepared in similar manner. The analytical data for different substituted thiazolidinones are given in Table-2.

TABLE-2
ANALYTICAL DATA OF THE THIAZOLIDINONES [II]

No.	R	R ₁	R ₂	R ₃	R ₄	m.f. (m.w.)	Yield (%)	m.p. (°C)	% Analysis Found (Calcd.)		
									C	H	N
K ₁₁	CH ₃	H	H	H	H	C ₃₇ H ₃₀ N ₆ O ₂ S ₂ (654)	142	70	67.88 (67.90)	4.59 (4.62)	12.84 (12.87)
K ₁₂	COOH	H	H	H	H	C ₂₇ H ₂₆ N ₆ O ₁₂ S ₄ (874)	149	75	50.80 (50.85)	2.97 (2.99)	9.61 (9.65)
K ₁₃	CH ₃	H	H	H	H	C ₃₉ H ₃₄ N ₆ O ₂ S ₂ (682)	138	72	68.62 (68.65)	4.98 (5.01)	12.32 (12.35)
K ₁₄	CH ₃	Cl	H	SO ₃ H	SO ₃ H	C ₃₇ H ₂₈ N ₆ O ₈ S ₄ Cl ₂ 134 (883)		90	50.28 (50.32)	3.17 (3.20)	9.51 (9.56)
K ₁₅	CH ₃	Cl	H	H	H	C ₃₇ H ₂₈ N ₆ O ₂ S ₂ Cl ₂ 115 (723)		71	61.41 (61.44)	3.87 (3.90)	11.62 (11.64)
K ₁₆	CH ₃	H	Cl	H	H	C ₃₇ H ₂₈ N ₆ O ₂ S ₂ Cl ₂ 125 (723)		68	61.41 (61.45)	3.87 (3.90)	11.62 (11.66)
K ₁₇	CH ₃	H	H	SO ₃ H	H	C ₃₇ H ₃₀ N ₆ O ₈ S ₄ (814)	118	72	54.54 (54.57)	3.69 (3.71)	10.32 (10.36)
K ₁₈	CH ₃	Cl	H	SO ₃ H	Cl	C ₃₇ H ₂₆ N ₆ O ₈ S ₄ Cl ₄ 105 (952)		63	46.64 (46.66)	2.73 (2.75)	8.82 (8.85)
K ₁₉	CH ₃	Cl	H	SO ₃ H	H	C ₃₇ H ₂₈ N ₆ O ₈ S ₂ Cl ₂ 98 (819)		66	54.21 (54.23)	3.42 (3.45)	10.26 (10.23)
K ₂₀	CH ₃	H	SO ₃ H	H	H	C ₃₇ H ₃₀ N ₆ O ₈ S ₄ (814)	121	68	54.54 (54.58)	3.69 (3.72)	10.32 (10.36)

Preparation of 4,4'-bis-[spiro-{1''-(substituted phenyl)-3''-methyl/carboxyl-pyrazole}-3-chloro-2-oxo azetidine]-1,1'-dibenzmethane [III]

The Schiff base (0.075 mol, 4.17 g) in benzene was taken in a 50 mL flat bottom flask. To it chloroacetyl chloride (0.0015 mol, 1.67 g) triethylamine (0.0015 mol, 1.50 g) in benzene were added slowly. It was then refluxed for

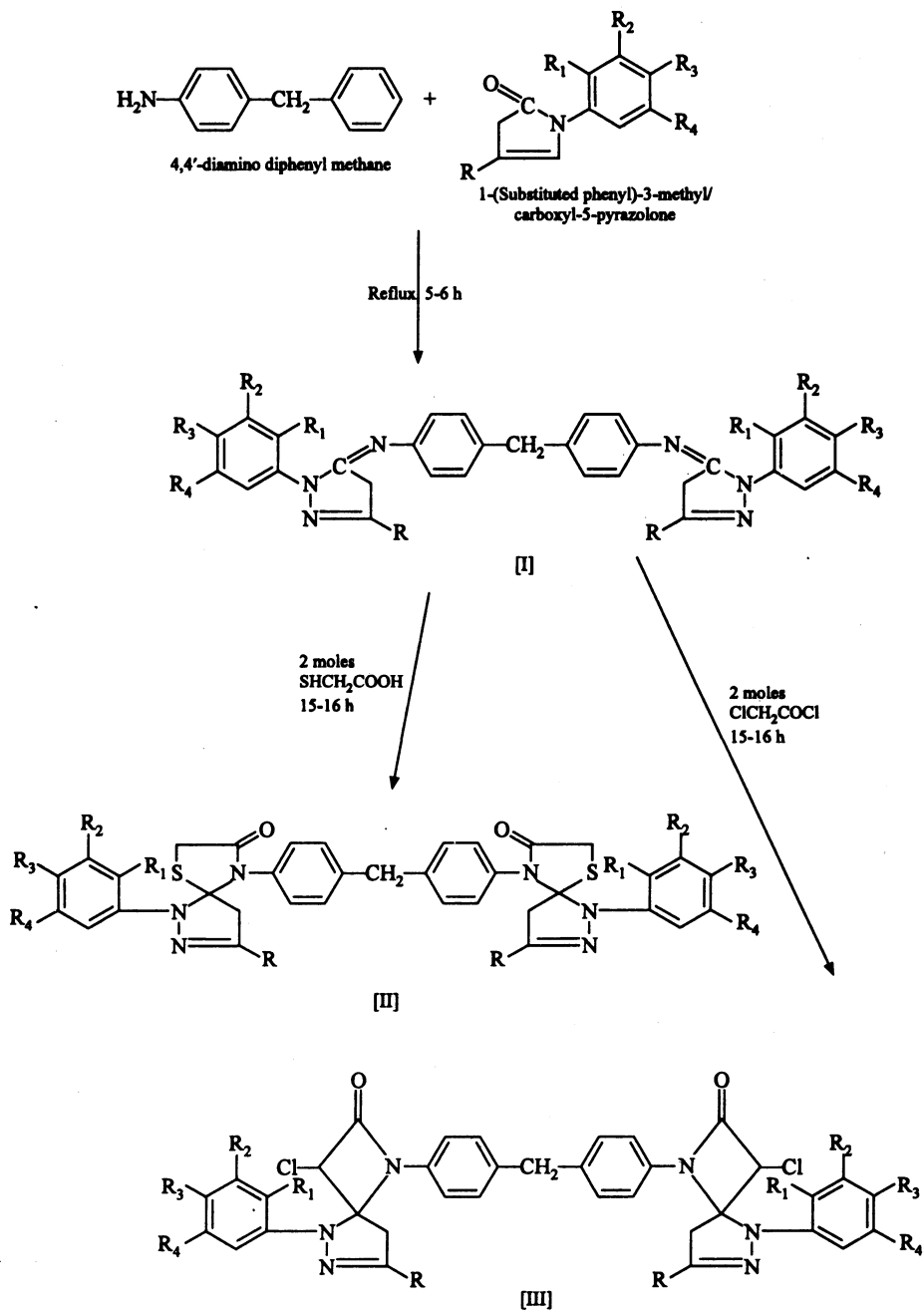
15–16 h. The triethylamine hydrochloride was removed and the benzene was distilled off to get the product. Other substituted azetidiones were prepared in a similar manner. The analytical data for different substituted azetidiones are given in Table-3.

TABLE-3
ANALYTICAL DATA OF THE AZETIDINONES [III]

No.	R	R ₁	R ₂	R ₃	R ₄	m.f. (m.w.)	Yield (%)	m.p. (°C)	% Analysis Found (Calcd.)		
									C	H	N
K ₂₁	CH ₃	H	H	H	H	C ₃₇ H ₂₈ N ₆ O ₂ Cl ₂ (659)	60	>250	67.37 (67.40)	4.25 (4.28)	12.75 (12.80)
K ₂₂	COOH	H	H	H	H	C ₃₇ H ₂₄ N ₆ O ₁₂ S ₂ Cl ₂ (879)	65	>250	50.51 (50.54)	2.73 (2.75)	9.56 (9.59)
K ₂₃	CH ₃	H	H	H	H	C ₃₉ H ₃₂ N ₆ O ₂ Cl ₂ (687)	62	>250	68.12 (68.15)	4.66 (4.69)	12.23 (12.25)
K ₂₄	CH ₃	Cl	H	SO ₃ H	SO ₃ H	C ₃₇ H ₂₆ N ₆ O ₈ S ₄ Cl ₂ (881)	58	>250	50.40 (50.43)	2.95 (2.98)	9.53 (9.55)
K ₂₅	CH ₃	Cl	H	H	H	C ₃₇ H ₂₆ N ₆ O ₂ Cl ₄ (728)	61	>250	60.99 (61.02)	3.57 (3.60)	11.54 (11.56)
K ₂₆	CH ₃	H	Cl	H	H	C ₃₇ H ₂₆ N ₆ O ₂ Cl ₄ (728)	55	>250	60.99 (61.01)	3.57 (3.61)	11.54 (11.57)
K ₂₇	CH ₃	H	H	SO ₃ H	H	C ₃₇ H ₂₈ N ₆ O ₈ S ₂ Cl ₂ (819)	71	>250	54.21 (54.25)	3.42 (3.45)	10.26 (10.30)
K ₂₈	CH ₃	Cl	H	SO ₃ H	Cl	C ₃₇ H ₂₄ N ₆ O ₈ S ₂ Cl ₆ (957)	64	>250	46.39 (46.42)	2.51 (2.55)	8.77 (8.81)
K ₂₉	CH ₃	Cl	H	SO ₃ H	H	C ₃₇ H ₂₆ N ₆ O ₈ S ₂ Cl ₄ (888)	56	>250	50.00 (50.04)	2.93 (2.95)	9.46 (9.48)
K ₃₀	CH ₃	H	SO ₃ H	H	H	C ₃₇ H ₂₈ N ₆ O ₈ S ₂ Cl ₂ (819)	58	>250	54.21 (54.25)	3.42 (3.45)	10.26 (10.29)

RESULTS AND DISCUSSION

Structures of compounds synthesised have been elucidated by elemental analysis, IR measurements. The Schiff base of above starting compound shows IR absorption park at 1600–1548 cm⁻¹ (C=N stretching). The thiazolidinone compounds were characterized by their IR absorption bands at 700–650 cm⁻¹ (C—S—C stretching), 1750–1680 cm⁻¹ (C=O stretching) and 1590–1560



cm^{-1} (C—N stretching). The azetidinone compounds were characterized by their IR absorption bands at $1730\text{--}1680\text{ cm}^{-1}$ (C=O stretching), 1715 cm^{-1} and 730 cm^{-1} (C—Cl stretching and bonding).

Antibacterial Activity: This part deals with the *in-vitro* screening of newly synthesised compounds for their antimicrobial activity for filter paper disc method at a concentration of $50\text{ }\mu\text{g}$; the species, *Staphylococcus aureus* and *Escherichia coli* have been taken for the antibacterial activity.

The maximum activity was found in compounds $\text{K}_2, \text{K}_4, \text{K}_9$ (zone of inhibition-11.0 mm) and K_{20} (zone of inhibition-12.0 mm) and K_{24} (zone of inhibition-12.0 mm) and minimum activity were found in compounds K_8 (zone of inhibition-7.0 mm) and $\text{K}_{11}, \text{K}_{15}, \text{K}_{19}$ (zone of inhibition 8.0 mm) and K_{25} (zone of inhibition-7.0 mm) against *Staphylococcus aureus*. The maximum activity were found in compounds K_2, K_5 (zone of inhibition-12.0 mm) and K_{15} (zone of inhibition 11.0 mm) K_{24} (zone of inhibition 12.0 mm) and minimum activities were found in compounds K_7 (zone of inhibition 7.0 mm) and K_{11} (zone of inhibition 6.0 mm) and $\text{K}_{22}, \text{K}_{30}$ (zone of inhibition 7.0 mm) against *Escherichia coli*. The compounds possess moderate to good activity against all stains in comparison with ampicillin, penicillin and tetracycline against *Escherichia coli* (Table-4).

TABLE-4
ANTIBACTERIAL ACTIVITY OF NEWLY SYNTHESIZED COMPOUNDS,
ZONE OF INHIBITION (mm)

No.	<i>S. aureus</i>	<i>E. coli</i>	No.	<i>S. aureus</i>	<i>E. coli</i>	No.	<i>S. aureus</i>	<i>E. coli</i>
K_1	10.0	9.0	K_{11}	8.0	6.0	K_{21}	9.0	8.0
K_2	11.0	12.0	K_{12}	9.0	10.0	K_{22}	11.0	7.0
K_3	10.0	10.0	K_{13}	10.0	8.0	K_{23}	8.0	9.0
K_4	11.0	11.0	K_{14}	9.0	9.0	K_{24}	12.0	10.0
K_5	8.0	12.0	K_{15}	8.0	11.0	K_{25}	7.0	9.0
K_6	9.0	11.0	K_{16}	11.0	8.0	K_{26}	8.0	10.0
K_7	10.0	8.0	K_{17}	9.0	8.0	K_{27}	8.0	9.0
K_8	7.0	10.0	K_{18}	10.0	7.0	K_{28}	9.0	11.0
K_9	11.0	9.0	K_{19}	8.0	10.0	K_{29}	10.0	8.0
K_{10}	10.0	11.0	K_{20}	12.0	9.0	K_{30}	8.0	7.0

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