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A Novel Synthetic Route to 3,5-Diaryl-N-Formyl-2-Pyrazoline

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Some new 3,5-diaryl-N-formyl-2-pyrazoline derivatives (**IIIa–c**) have been prepared. Treatment of (**IIIa–c**) with hydrazine hydrate yielded N-formyl hydrazone derivatives (**IVa–c**), N-formyl aryl hydrazone derivatives (**Va–d**) were prepared by condensing compound (**IIIa–c**) with aromatic amine, treatment of (**IIIa–c**) with isonicotinic hydrazide in ethyl alcohol afforded N-formyl-1-isonicotinic hydrazone derivatives (**VIa–c**), N-substituted-thiazolidin-4-one-derivatives (**VIIa–f**) was prepared. Compounds (**IIIa–c**) condensed with hydroxylamine to give the corresponding oxime derivatives (**VIIIa–c**).

Key words: 3,5-Diaryl-N-formyl-2-pyrazoline, synthesis, characterization

INTRODUCTION

Pyrazolines are important nitrogen heterocycles possessing diverse biological activities and also considerable interests as a chemotherapeutic agent[1–4]. These facts encourage us to prepare new N-formyl-2 pyrazoline derivatives which might result in potential biologically active agents.

EXPERIMENTAL

All melting points are uncorrected and were determined in capillary tube. IR spectra were recorded in potassium bromide on Perkin-Elmer 380 and 783 spectrometers. The ^{1}H-NMR spectra were recorded on Varian EX 100 or FTNMR-Junmex-400 spectrometers using TMS as an internal reference in $CDCl_3$. Elemental analysis was performed on a Heraeus CHN analyser.

3,5-Diaryl-2-pyrazoline derivatives (IIa–c):

They were synthesized according to the literature procedures[5].

3,5 Diaryl-N-formyl-2-pyrazoline derivatives (IIIa–c):

Method A: A mixture of (**Ia–c**) (0.01 mol) in 15 mL formic acid was refluxed with hydrazine hydrate (0.02 mol) for 4 h. The reaction mixture was then cooled, poured into ice-cold water and the product was separated and recrystallized from the proper solvent (Table-1).

TABLE-1
ANALYTICAL DATA OF COMPOUNDS (III–VIII)

Compd. No.	Solvent (m.p., °C)	Yield (%)	Ar_1/Ar_2	Ar_3	m.f. (m.w.)	% Analysis, calcd. (found)		
						C	H	N
IIIa	Benzene (240)	86	4-$CH_3C_6H_4$ 9-$C_{14}H_9$	—	$C_{25}H_{20}N_2O$ (364)	82.41 (82.26)	5.49 (5.40)	7.69 (7.38)
IIIb	Benzene-petroleum ether (130)	85	4-BrC_6H_4 9-$C_{14}H_9$	—	$C_{24}H_{17}BrN_2O$ (428.9)	67.14 (67.11)	3.96 (3.78)	6.52 (6.31)
IIIc	Benzene (208)	88	4-$C_{12}H_9$ 9-$C_{14}H_9$	—	$C_{30}H_{22}N_2O$ (426)	84.50 (84.50)	5.16 (5.15)	6.57 (6.52)
IVa	AcOH (220)	66.5	4-$CH_3C_6H_4$ 9-$C_{14}H_9$	—	$C_{25}H_{22}N_4$ (378)	79.36 (79.20)	5.82 (5.72)	14.81 (14.80)
IVb	Benzene (206)	65	4-BrC_6H_4 9-$C_{14}H_9$	—	$C_{24}H_{19}BrN_4$ (442.9)	65.02 (65.00)	4.28 (4.20)	12.64 (12.59)
IVc	Benzene (224)	58	4-$C_{12}H_9$ 9-$C_{14}H_9$	—	$C_{30}H_{24}N_4$ (440)	81.81 (81.75)	5.45 (5.30)	12.72 (12.65)
Va	Benzene (230)	55	4-$CH_3C_6H_4$ 9-$C_{14}H_9$	4ClC_6H_4	$C_{31}H_{24}ClN_3$ (473.5)	78.56 (78.41)	5.06 (5.00)	8.87 (8.80)
Vb	Benzene (120)	50	4-BrC_6H_4 9-$C_{14}H_9$	4ClC_6H_4	$C_{30}H_{21}ClBrN_3$ (538.4)	66.86 (66.70)	3.90 (3.90)	7.80 (7.65)
Vc	Benzene (230)	60	4-$CH_3C_6H_4$ 9-$C_{14}H_9$	4BrC_6H_4	$C_{31}H_{24}BrN_3$ (517.9)	71.82 (71.82)	4.63 (4.60)	8.10 (8.00)
Vd	Benzene (212)	64.3	4-BrC_6H_4 9-$C_{14}H_9$	4BrC_6H_4	$C_{30}H_{21}Br_2N_3$ (582.8)	61.77 (61.49)	3.60 (3.60)	7.20 (7.10)
VIa	Benzene (206)	58	4-$CH_3C_6H_4$ 9-$C_{14}H_9$	—	$C_{31}H_{25}N_5O$ (483)	77.01 (77.00)	5.17 (5.17)	14.49 (14.40)
VIb	Benzene (200)	62	4-BrC_6H_4 9-$C_{14}H_9$	—	$C_{30}H_{22}BrN_5O$ (547.9)	65.70 (65.60)	4.01 (4.01)	12.77 (12.70)
VIc	Dioxane (270)	74.4	4-$C_{12}H_9$ 9-$C_{14}H_9$	—	$C_{36}H_{27}N_5O$ (547.9)	79.26 (79.21)	4.95 (4.90)	12.84 (12.80)
VIIa	Ethyl acetate (194)	89.5	4-$CH_3C_6H_4$ 9-$C_{14}H_9$	—	$C_{27}H_{24}N_4OS$ (452)	71.68 (71.56)	5.30 (5.30)	12.38 (12.30)
VIIb	Ethyl acetate (246)	73.69	4-BrC_6H_4 9-$C_{14}H_9$	—	$C_{26}H_{21}BrN_4OS$ (516.9)	60.35 (60.16)	4.06 (4.05)	10.83 (10.57)
VIIc	AcOH (230)	70	4-$CH_3C_6H_4$ 9-$C_{14}H_9$	4ClC_6H_4	$C_{33}H_{26}ClN_3OS$ (547.5)	72.32 (72.54)	4.74 (4.68)	7.67 (7.86)
VIId	EtOH (140)	70.3	4-BrC_6H_4 9-$C_{14}H_9$	4ClC_6H_4	$C_{32}H_{23}ClBrN_3OS$ (612.4)	62.70 (62.71)	3.75 (3.74)	6.85 (6.85)
VIIe	Dioxane (228)	70	4-$CH_3C_6H_4$ 9-$C_{14}H_9$	4BrC_6H_4	$C_{33}H_{26}BrN_3OS$ (591.9)	66.90 (66.90)	4.39 (4.31)	7.09 (7.00)
VIIf	EtOH (164)	83.4	4-BrC_6H_4 9-$C_{14}H_9$	4BrC_6H_4	$C_{32}H_{23}Br_2N_3OS$ (656.8)	58.46 (58.40)	3.50 (3.66)	6.39 (6.32)
VIIIa	Ethyl acetate (230)	81	4-$CH_3C_6H_4$ 9-$C_{14}H_9$	—	$C_{25}H_{21}N_3O$ (379)	79.15 (79.15)	5.54 (5.50)	11.08 (11.00)
VIIIb	EtOH (132)	86	4-BrC_6H_4 9-$C_{14}H_9$	—	$C_{24}H_{18}BrN_3O$ (443.9)	64.87 (64.77)	4.05 (4.05)	9.46 (9.40)
VIIIc	Benzene (180)	84	4-$CH_{12}H_9$ 9-$C_{14}H_9$	—	$C_{30}H_{23}N_3O$ (441)	81.63 (81.60)	5.21 (5.21)	9.52 (9.45)

Method B: A mixture of appropriate 2-pyrazoline derivative **(II)** (0.01 mol) in formic acid (20 mL) was refluxed for 3 h, the reaction mixture cooled and poured into ice-cold water, filtered, washed with ethanol, dried and recrystallized from the proper solvent (Table-1).

3-5-Diaryl-2-pyrazoline-N-formyl hydrazone derivatives (IVa–c)

A sotution of the appropriate N-formyl-2-pyrazoline derivative **(III)** (0.01 mol) in ethanol (20 mL) was refluxed with hydrazine hydrate (0.015 mol) for 5 h. After concentration, the product was separated, dried and recrystallized (Table-1).

3-5-Diaryl-2-pyrazoline-N-formyl aryl hydrazone derivatives (Va–d)

A solution of appropriate N-formyl derivatives **(IIIa–c)** (0.01 mol) in ethanol (20 mL) was refluxed with arylamine (0.012 mol) for 5 h, cooled and diluted with water. The precipitated crude product was filtered off and recrystallized from the appropriate solvent (Table-1).

3-5-Diaryl-2-pyrazoline-N-formyl isonicotinic hydrazone derivatives (VIa–c)

A mixture of **(III)** (0.01 mol) and isonicotinic hydrazide (0.012 mol) in ethanol (20 mL) was refluxed for 3 h, cooled and diluted with water. The crude product was filtered off and recrystallized from the proper solvent (Table-1).

3-5-Diaryl-2-pyrazoline-1-yl-N-substituted-thiazolidin-4-one derivatives (VIa–f)

A mixture of **(IV)** or **(V)** (0.01 mL) and thioglycolic acid (0.011 mol) in dry benzene (20 mL) was refluxed for 4 h, benzene was removed under reduced pressure, the solid mass dissolved with water and with ammonia (2 mL). The crude product was purified by recrystallization (Table-1).

3-5-Diaryl-2-pyrazoline-N-formyl oxime derivatives (VIIIa–c)

A solution of the appropriate 2-pyrazoline **(II)** (0.01 mol) in ethanol (20 mL) was refluxed with a mixture of hydroxylamine (0.15 mol) and sodium hydroxide (1 g) in water (5 mL) for 2 h. The reaction mixture was then poured into water; the product was separated by filtration and recrystallization from appropriate solvent (Table-1).

RESULTS AND DISCUSSION

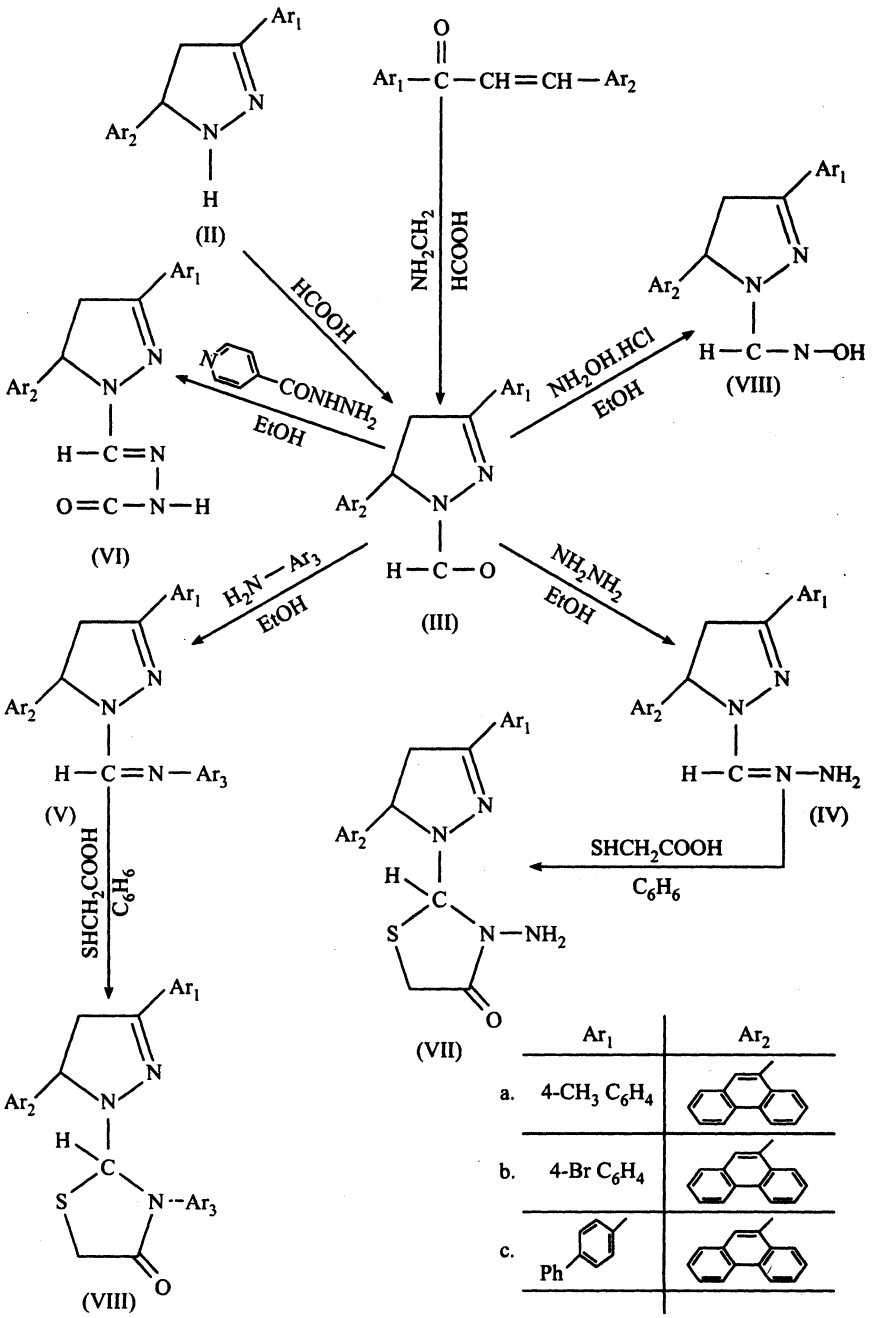
Interaction of **(Ia–c)** with formic acid and hydrazine hydrate afforded the corresponding N-formyl derivatives **(IIIa–c)**. These could be obtained also by the reaction of **(IIa–c)** with formic acid (Scheme-1).

The IR spectra of **(IIIa)** exhibited two bands at 1680 cm^{-1} and 1620 cm^{-1} due to (C=O) and (C=N) groups respectively.

^{1}H-NMR spectrum of compounds **(IIIa)** in $CDCl_3$ showed peaks at δ 2.4 (s, 3H, CH_3), δ 3.1 (d, d, H, H-a); δ 3.9 (dd, 1H, H-b); δ 6.3 (dd, 1H, H-c); δ 7.1–8.8 (m, 13H, ArH'S), δ 9.7 (s, 1H, C=O).

Condensation of (IIIa–c) with hydrazine hydrate gave the hydrazone deriva-

SCHEME-1


Ar1
Ar2
N
H
(II)
O
Ar1—C—CH=CH—Ar2
NH2CH2
HCOOH
HCOOH
Ar1
Ar2
N
H—C=N
O=C—N—H
(VI)
N
CONHNH2
EtOH
Ar1
Ar2
N
H—C—O
(III)
NH2OH.HCl
EtOH
Ar1
Ar2
N
H—C—N—OH
(VIII)
H2N—Ar3
EtOH
Ar1
Ar2
N
H—C=N—Ar3
(V)
NH2NH2
EtOH
Ar1
Ar2
N
H—C=N—NH2
(IV)
SHCH2COOH
C6H6
Ar1
Ar2
N
H
C
S
N—NH2
O
(VII)
SHCH2COOH
C6H6
Ar1
Ar2
N
H
C
S
N--Ar3
O
(VIII)
Ar1
Ar2
a. 4-CH3 C6H4
b. 4-Br C6H4
c. Ph

tives **(IVa)**; structures of the compounds were proved by their elemental analysis and IR and ^{1}H-NMR spectra.

IR spectrum of compound **(IVa)** showed broad band at 3400 cm^{-1} due to NH_2 stretching.

^{1}H-NMR spectra of compound **(IVa)** in $CDCl_3$ showed peaks at δ 1.6 (s, 1H, NH_2), δ 2.4 (s, 1 H, 3H); δ 3.2 (dd, 1H, H-a), δ 3.7 (dd, 1H, H-b), δ 6.3 (dd, 1H, H-c); δ 7.2–8.8 (m, 13 H, ArH's), δ 9.2, (s, 1H, H—C=N) (Table-2).

Interaction of **(IIIa–c)** with different aromatic aldehydes afforded the corresponding Schiff bases **(Va)**.

The structures of these aryl hydrazones (Schiff bases) **(Va–d)** were established by elemental analysis and IR and ^{1}H-NMR spectra.

IR spectrum of compound **(Va)** showed the absorption bands at 1650 due to C=N stretching and at 3010 CH aromatic.

^{1}H-NMR spectrum of compound **(Va)** in $CDCl_3$ show peaks at δ 2.4 (s, 3H, CH_3), δ 3.2 (dd, 1H, H-a); δ 3.9 (dd, 1H, H-b); δ 6.3 (dd, 1H, H-c); δ 7.2–8.8 (m, 17H, ArH'S), δ 9.2 (s, $1H_1$, H—C=N) (Table-2).

On the other hand, the N-formyl derivatives **(IIIa–c)** allowed to react with isonictonic acid hydrazide to give isonicotinic hydrazone derivatives[7] **(VIa–c).**

IR spectrum of compound **(VIa)** showed absorption bands at 3380 cm^{-1} due to NH function and at 1680 cm^{-1} of C=O group.

^{1}H-NMR spectrum of compound **(VIa)** in $CDCl_3$ showed peaks, δ 2.4 (s, 3H, CH_3), δ 3.1 (dd, 1H, H-a), δ 3.8 (dd, 1H, H-b), δ 4.0 (br, s, 1H, NH), δ 6.3 (dd, 1H, H-c), δ 7.2–8.9 (m, 17H, ArH and pyridyl protons), δ 9.2 (s, 1H, H, H—C=N) (Table-2).

It is well known that 4-thiazolidinones are generally obtained by the reaction of thioglycolic acid and Schiff bases[8–10]. 4-Thiazolidinone ring system **(VII)** was obtained by cyclo-condensation of thioglycolic acid with **(VI)** and **(V)**. Structures of the thiazolidinone derivatives **(VIIa–f)** were proved by their elemented analysis as well as compatible spectral data.

IR spectrum of compound **(VIIa)** shows broad band around 3400 cm^{-1} due to NH_2 group and at 1680 cm^{-1} for the (C=O) group.

^{1}H-NMR spectrum of compound **(VIIa)** showed signals at δ 1.6 (br, s, 2H, NH_2), δ 2.4 (s, 3H, CH_3), δ 3.1 (dd, 1H, H-a), δ 3.7 (m, 3H, H-b and CH_2 of thiazolo ring); δ 5.0 (s, 1H, CH of thiazolo ring); δ 6.3 (dd, 1H, H-c); δ 7.2–8.8 (m, 13H, ArH's).

Similarly, condensation of **(III)** with hydroxylamine afforded the corresponding N-formyl oxime derivatives **(VIIIa–c)**. The structures of these new compounds were confirmed by combination of elemental and spectral data.

The IR spectrum of compound **(VIIIa)** showed characteristic absorption band for OH group at 3440 cm^{-1}.

^{1}H-NMR spectrum for compound **(VIIIa)** showed peaks at δ 2.4 (s, 3H, CH_3), δ 3.1 (dd, 1H, H-a), δ 3.9 (dd, 1H H-b); δ 6.3 (dd, 1H, H-c), δ 7.2–8.8 (m, 13H, ArH'S), δ 9.2 (s, 1H, H—C=N), δ 9.8 (S, 1H, OH) (Table-2).

TABLE-2
SPECTRAL DATA OF COMPOUNDS (III–VIII)

Compd. No.	IR (cm^{-1})	1H-NMR δ (ppm)
IIIa	1690 ν(C=O) 1620 ν(C=N)	2.4 (s, 3H, CH_3); 3.1 (dd, 1H, H-a); 3.9 (dd, 1H, H-b); 6.3 (dd, 1H, H-c); 7.1–8.8 (m, 13H, ArH'S); 9.7 (s, 1H, HC=O)
IIIb	1680 ν(C=O) 1620 ν(C=N)	3.3 (dd, 1H, H-a); 3.9 (dd, 1H, H-b); 6.4 (dd, 1H, H-c); 7.2–8.8 (m, 13H, ArH'S); 9.8 (s, 1H, HC=O)
IIIc	1680 ν(C=O) 1620 ν(C=N)	3.4 (dd, 1H, H-a); 3.9 (dd, 1H, H-b); 6.4 (dd, 1H, H-c); 7.2–8.8 (m, 18H, ArH'S); 9.8 (s, 1H, HC=O)
IVa	3400 ν(br·NH_2) 1640 ν(C=N)	1.6 (br, s, 1H, NH); 2.4 (s, 3H, CH_3); 3.2 (dd, 1H, H-a); 3.9 (dd, 1H, H-6); 6.3 (dd, 1H, H-c); 7.2–9.2 (m, 13H, ArHS); 9.1 (s, 1H, HC=N)
IVb	3400 ν(br·NH_2) 1640 ν(C=N)	1.5 (br, s, 1H, NH); 3.2 (dd, 1H, H-a); 3.9 (dd, 1H, H-c); 7.1–8.8 (m, 13H, ArH'S); 9.1 (s, 1H, HC—N)
IVc	3490 ν(br·NH) 1640 ν(C=N)	1.5 (s, 1H, NH); 3.3 (dd, 1H, H-a); 3.9 (dd, 1H, H-b); 6.3 (dd, 1H, H-c); 7.2–8.9 (m, 18H, ArH'S); 9.1 (s, 1H, HC=N)
Va	1650 ν(C=N)	2.4 (s, 3H, CH_3); 3.2 (dd, 1H, H-a); 3.9 (dd, 1H, H-b); 6.3 (dd, 1H, H-c); 7.2–8.8 (m, 17HI, ArH'S); 92 (s, 1H, HC=N)
Vb	1654 ν(C=N)	—
Vc	1660 ν(C=N)	3.2 (dd, 1H, H-a); 3.9 (dd, 1H, H-b); 6.4 (dd, 1H, H-c); 7.1–8.8 (m, 17H, ArH'S); 9.2 (s, 1H, HC=N)
Vd	1640 ν(C=N)	3.2 (dd, 1H, H-a); 3.8 (dd, 1H, H-b); 6.4 (dd, 1H, H-c); 7.2–8.8 (m, 17H, ArH'S); 9.2 (s, 1H, HC=N)
VIa	3380 ν(br·NH) 1680 ν(C=O)	2.4 (s, 3H, CH_3); 3.1 (dd, 1H, H-a); 3.8 (dd, 1H, H-b); 4.0 (br, s, 1H, NH); 6.3 (dd, 1H, H-c); 7.2–8.8 (m, 17H, ArH'S and pyridyl protons); 9.2 (s, 1H, HC=N)
VIb	3400 ν(br·NH) 1680 ν(C=O)	3.1 (dd, 1H, H-a); 3.9 (dd, 1H, H-b); 4.1 (br, s, 1H, NH); 6.3 (dd, 1H, H-c); 7.1–8.8 (m, 17H, ArH'S and pyridyl protons); 9.2 (s, 1H, HC=N)
VIc	3370 ν(br·NH) 1680 ν(C=O)	3.1 (dd, 1H, H-a); 3.9 (dd, 1H, H-b); 4.1 (br, s, 1H, NH); 6.3 (dd, 1H, H-c); 7.2–8.2 (m, 17H, ArH'S and pyridyl protons); 9.1 (s, 1H, HC=N)
VIIa	3400 ν(br·NH) 1680 ν(C=O)	1.6 (s, 1H, NH); 2.4 (s, 3H, CH_3); 3.1 (dd, 1H, H-a); 3.7 (m, 3H, H-b and other thiazole ring); 6.3 (dd, 1H, H-c); 5.0 (s, 1H, CH of thiazole ring); 7.2–8.8 (m, 13H, ArH'S)
VIIb	3430 ν(br·NH) 1680 ν(C=O)	—
VIIc	1680 ν(C=O) 1590 ν(C=N)	2.4 (s, 3H, CH_3); 3.1 (dd, 1H, H-a); 3.7 (m, 3H, H-b and CH_2 of thiazole ring); 5.1 (s, 1H, CH of thiazole ring); 6.3 (dd, 1H, H-c); 7.2–8.8 (m, 17H, ArH'S)
VIIe	1670 ν(C=O) 1610 ν(C=N)	3.2 (dd, 1H, H-a); 3.8 (m, 3H, H-b and CH_2 of thiazole ring); 5.1 (s, 1H, CH of thiazole ring); 6.3 (dd, 1H, H-c); 7.2–8.8 (m, 17H, ArH'S)
VIIf	1670 ν(C=O) 1610 ν(C=N)	3.2 (dd, 1H, H-a); 3.9 (m, 3H, H-b and CH_2 of thiazole ring); 5.0 (s, 1H, CH of thiazole ring); 6.2 (dd, 1H, H-c); 7.2–8.8 (m, 17H, ArH'S)
VIIIa	3440 ν(br·OH) 1640 ν(C=N)	2.4 (s, 3H, CH_3); 3.1 (dd, 1H, H-a); 3.9 (dd, 1H, H-b); 6.3 (dd, 1H, H-c); 7.2–8.8 (m, 13H, ArH'S); 9.2 (s, 1H, HC=N); 9.8 (s, 1H, OH)
VIIIb	3440 ν(br·OH) 1640 ν(C=N)	3.2 (dd, 1H, H-a); 3.8 (dd, 1H, H-b); 6.3 (dd, 1H, H-c); 7.1–8.8 (m, 13H, ArH'S); 9.2 (s, 1H, HC=N); 9.8 (s, 1H, OH)
VIIIc	3440 ν(br·OH) 1640 ν(C=N)	3.2 (dd, 1H, H-a); 3.9 (dd, 1H, H-b); 6.3 (dd, 1H, H-c); 7.2–8.8 (m, 18H, ArH'S); 9.2 (s, 1H, HC=N); 9.9 (s, 1H, OH)

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REFERENCES

1. H.A. Burch, *J. Med. Chem.*, **9**, 408 (1966).
2. H.Z. Katri and S.A. Vunil, *J. Indian Chem Soc.*, **58**, 168 (1981).
3. H.M. Mokhtar and H. M. Faidallah, *Pharmazie*, **42**, 481 (1987).
4. H. Katayama and T. Dshiyama, *Canad. J. Chem.*, **75**, 913 (1997).
5. E.M. Kassem, O.M. Fadhallah and A. Farouk, *Bull. NRC Egypt*, **22**, 97 (1997).
6. F. H. Havaldar and P.S. Fernandes, *J. Indian Chem. Soc.*, **65**, 691 (1988).
7. M.A.E. Sallam, M.A. Mostafa, N.A. Hussein and L.B. Townsend, *Alex. J. Pharm. Sci.*, **4**, 18 (1990).
8. S.A. Singh, S.S. Parmar, K. Raman and V.I. Stenberg., *Chem. Rev.*, **81**, 175 (1981).
9. H. M. Faidallah and H. M. Molehta, *Indian J. Chem.*, **27B**, 245 (1988).
10. M.S. Raash, *J. Heterocycl. Chem.*, **11**, 587 (1974).

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Errata

In *Asian J. Chem.*, Vol. 13, No. 4 (2001), p. 1615, Synthesis, Characterization, Cytotoxicity and Anticomplementary Activity of a Novel Dimethyltin(IV) Cyclobutyl Complexes of 8-Hydroxyquinoline, Fig. 2 is missing.

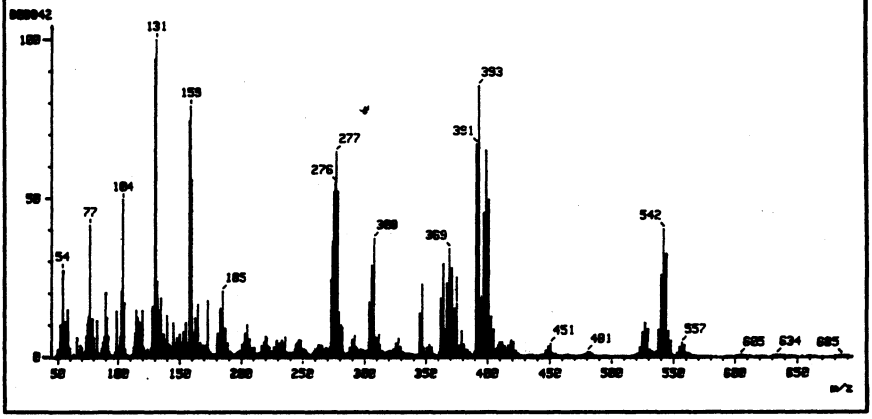

Fig. 2. Mass spectrum of the novel organotin(IV) complex