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Synthesis of Fused, Isolated and Spiro 1,2,4-triazinoindole Derivatives

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The synthesis of fused, isolated and spiro 1,2,4-triazinoindole derivatives have been achieved by the reaction of isatin-3-thiosemicarbazone-(I) and or 3-(cyano)-3-thiosemicarbazide(X) with chloroacetic acid and aromatic aldehydes in neutral or acidic medium. The structures of new the compounds have been confirmed from spectral and analytical data.

INTRODUCTION

In continuation of our earlier work on 1,2,4-triazinoindole derivatives[1,2], the present study deals with the synthesis of some fused, isolated and or spiro 1,2,4-triazinoindole derivatives starting from isatin-3-thiosemicarbazone[3](I).

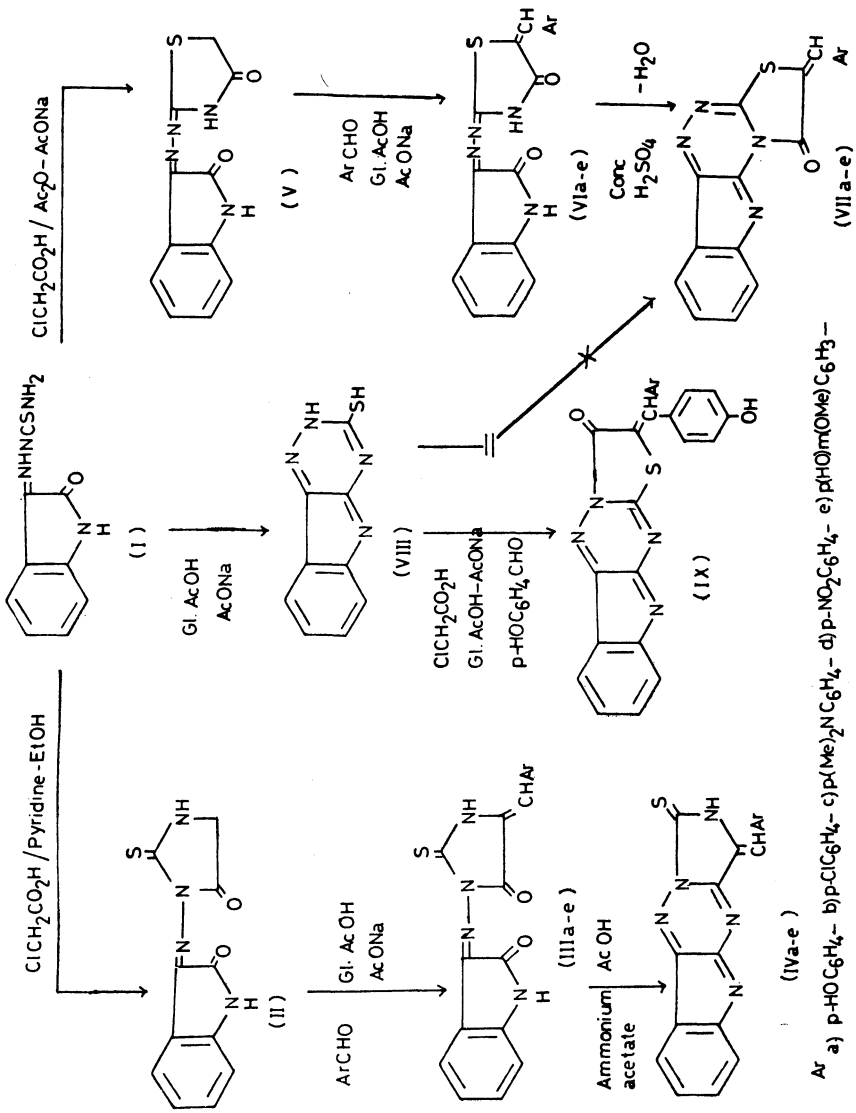
RESULTS AND DISCUSSION

Reaction of isatin-3-thiosemicarbazone(I) with chloroacetic acid in the presence of pyridine-ethanol[4] give 3-(3-iminoisatin)-2-thiohydantoin(II) which condensed with aromatic aldehydes in glacial acetic acid-fused sodium acetate gave the corresponding arylidene III, which fused with ammonium acetate containing a few drops of glacial acetic acid 5-arylidene-2-thiohydantoino [3,4-b] [1,2,4] triazino [5,6-b] indoles(IV] was isolated.

3-[2-(4-Thiazolideneone) diazo] indol-2-one(V) was prepared by the reaction of I with chloroacetic acid in the presence of glacial acetic acid-fused sodium acetate[6], which condensed with aromatic aldehydes produce 3-[2-(5-arylidene-4-thiazolidene one) diazo] indol-2-ones (VI) which underwent cyclo-dehydration[7] with conc H_2SO_4 to furnish 2-arylidene-3-oxo-thiazolo [2,3-c] [1,2,4] triazino [5, 6-b] indoles(VII).

Isatin-3-thiosemicarbazone(I) underwent ring closure on heating with glacial acetic acid-fused sodium acetate to give 5H-[1,2,4] triazino [5,6-b] indole-3-thione (VIII), which reacts with chloroacetic acid and aromatic aldehydes in presence of Ac_2O fused-sodium acetate[8] afforded 2-arylidene-3-oxo-thiazolo [3,2-b][1,2,4] triazino [5,6-b] indoles (IX) and not VII (m.pt. and mixed m.pt. of IX and VII gave depression) [Scheme 1].

When compound I was allowed to react with KCN[9] in the presence of piperidine-ethanol, 3-(cyano)-3-thiosemicarbazido-indol-2(1H)one(X) was obtained, which underwent ring closure when heated with glacial acetic acid-fused sodium acetate to give 1,6-dihydro-3-mercapto-1,2-cyano [1,2,4]



Scheme 1

triazino [5,6-b] indole (XI), which react with chloroacetic acid in glacial acetic acid-fused sodium acetate led to the formation of 3-(cyano)-3-amino-[2-(thiazolideneone)diazo] indol-2-ones [XII] On the other hand when the same reaction was carried out in ethanol-pyridine gave 3-(cyano)-3-(5′-dihydro-3′-mercapto-1′,2′,4′-triazin-6′-one-1′-yl) indol-2(II) one (XIII) (Scheme 2).

When compound (X) underwent the reaction with 1,2-dibromethane in ethanolic KOH[10], 3-(cyano)-3-(3′-thioxo-5′,6′-tetrahydro-1′,2′,4-triazin-1′-yl)-indol-2(H) one (XIV) was obtained.

Acidic hydrolysis of compound (X) using[9] conc HCl, gave the spiro [3H-indole-3,6′-1,2,4-triazine]2,5′(1H)diones-3′-mercapto (XV), while 3-carboxylic-3-thiosemicarbazido-indol-2(1H)one(XVI) was produced by treating (X) with dil. HCl. Decarboxylation of (XVI) using aq. K_2CO_3 led to the formation of thiosemicarbazide (XVII) which on refluxing with glacial acetic acid-fused sodium acetate give 3-mercapto dihydro [1,2,4] triazino [5,6-b] indole (XVIII) [Scheme 2].

EXPERIMENTAL

All melting points are uncorrected. IR spectra (KBr) in λ_{max} cm^{-1} on a Beckman IR-4 spectrophotometer, UV spectra in ethanol on a Perkin Elmer (Type 550 S) UV Vis spectrophotometer (ν_{max} in nm) and PMR spectra in DMSO-d_6 on an EM 390 90 MHz NMR spectrometer using TMS as internal standard (chemical shifts in δ, ppm) (Table 1). Isatin-3-thiosemicarbazone (I) was synthesized according to the method of Daunis *et al*[3].

3-(3-Iminoisation)-2-thiohydantoin (II)

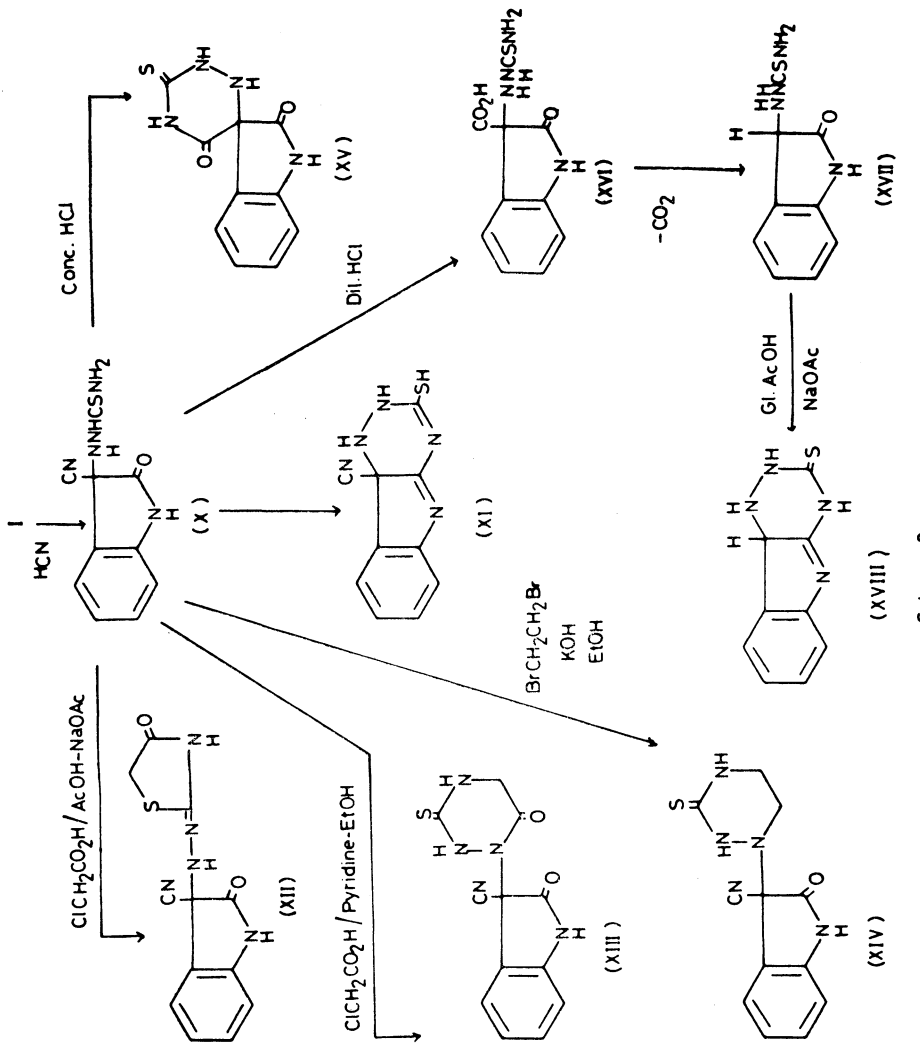
A mixture of thiosemicarbazone(I) (0.01 mol) and monochloroacetic acid (0.01 mol) was treated with dry pyridine (20 ml) and warmed a little till an exothermic reaction took place. After cooling, the reaction mixture was treated with ethanol (20 ml) and refluxed for 2 hrs. The contents were poured into crushed ice when a yellow compound separated out, filtered, dried and recrystallised to give (II) (Table 1).

The Arylidene (III)

A mixture of thiohydantoin derivative (II) (0.01 mol), appropriate aromatic aldehydes (0.01 mol) and anhyd. NaOAc (0.02 mol) in glacial acetic acid (20 ml) was refluxed for 2 hrs, cooled and poured into crushed ice. The yellow mass obtained was filtered, washed several times with water and recrystallized to give (III) (Table 1).

5-Arylidene-2-thiohydantoin [3,4-b][1,2,4] triazino [5,6-b] indoles (IV)

A mixture of (III) (0.01 mol) and ammonium acetate (10 g) in a few drops of glacial acetic acid (1 ml) was refluxed for 8 hrs, cooled and the


I
HCN
(X)
Conc. HCl
Dil. HCl
(XV)
(XVI)
-CO2
(XVII)
Gl. AcOH
NaOAc
(XVIII)
(XI)
BrCH2CH2Br
KOH
EtOH
ClCH2CO2H/AcOH-NaOAc
(XII)
ClCH2CO2H/Pyridine-EtOH
(XIII)
(XIV)

Scheme 2

TABLE 1

PHYSICAL DATA OF THE COMPOUNDS (II-XVIII)

Compound No.	Solvent	M. Pt. (°C)	Yield (%)	Molecular formula*	Found/Calcd Cl	
II	EtOH	255–256	85	$C_{11}H_8N_4SO_2$		
IIIa	AcOH	153–155	80	$C_{18}H_{12}N_4SO_3$		
IIIb	AcOH	194–195	86	$C_{18}H_{11}N_4SClO_2$	8.57	9.13
IIIc	MeOH	200–202	80	$C_{20}H_{17}N_5SO_2$		
IIId	DMF	194–195	75	$C_{18}H_{11}N_5SO_4$		
IIIe	AcOH	199–200	90	$C_{18}H_{14}N_4SO_4$		
IVa	MeOH	231–232	60	$C_{18}H_{11}N_5SO$		
IVb	EtOH	235–237	65	$C_{18}H_{10}N_5SCl$	9.35	9.85
IVc	MeOH	210–212	60	$C_{20}H_{16}N_6S$		
IVd	DMF	140–142	55	$C_{18}H_{10}N_6SO_2$		
IVe	AcOH	180–181	60	$C_{18}H_{13}N_5SO_2$		
V	AcOH	248–250	86	$C_{11}H_8N_4SO_2$		
VIa	AcOH	260–262	89	$C_{18}H_{12}N_4SO_3$		
VIb	AcOH	258–260	90	$C_{18}H_{11}N_4SClO_2$	8.75	9.13
VIc	AcOH	207–208	75	$C_{20}H_{17}N_5SO_2$		
VId	MeOH	270–272	67	$C_{18}H_{11}N_5SO_4$		
VIe	AcOH	220–221	85	$C_{18}H_{14}N_4SO_4$		
VIIa	MeOH	289–290	65	$C_{18}H_{10}N_4SO_2$		
VIIb	AcOH	280–281	67	$C_{18}H_9N_4SClO$	9.23	9.67
VIIc	AcOH	265–266	64	$C_{20}HI_5N_5SO$		
VIId	AcOH	280–282	60	$C_{18}H_9N_5SO_3$		
VIIe	AcOH	270–271	84	$C_{18}H_{12}N_4SO_3$		
VIII	AcOH	243–245	90	$C_9H_6N_4S$		
IX	DMF	210–212	80	$C_{18}H_{10}N_4SO_2$		
X	EtOH	250–251	65	$C_{10}H_9N_5SO$		
XI	AcOH	239–240	75	$C_{10}H_7N_5S$		
XII	EtOH	240–241	70	$C_{12}H_9N_5SO_2$		
XIII	EtOH	245–247	65	$C_{12}H_9N_5SO_2$		
XIV	Dil. EtOH	225–227	60	$C_{12}H_{11}N_5SO$		
XV	EtOH	232–234	55	$C_{10}H_8N_4SO_2$		
XVI	Dil. EtOH	225–226	67	$C_{10}H_{10}N_4SO_3$		
XVII	EtOH	240–242	60	$C_9H_{10}N_4SO$		
XVIII	AcOH	ab. 300	85	$C_9H_9N_4S$		

*Satisfactory C, H, N and S analysis have been obtained for all the compounds.

mass triurated with little methanol and the solid obtained recrystallized resultant to give (IV) (Table 1).

Reaction of (I) with Chloroacetic Acid : Formation of thiazolidenone (V)

A mixture of I (0.01 mol) chloroacetic acid (0.01 mole) and anhyd. NaOAc (5 g) in glacial acetic acid (20 ml) was refluxed for 2 hrs, cooled and poured into crushed ice. The yellow solid obtained was filtered, washed with cold water and crystallized to give (V) (Table 1).

Condensation of (V) with Aromatic Aldehydes: Formation of Arylidenes (VI)

Compound VI was obtained following the above procedure used for the formation of III.

Cyclodehydration of (VI): Formation of Triheterocyclic Systems (VIIa-e)

Compounds VIa-e (0.01 mol) were treated dropwise with conc. H_2SO_4 (5 ml). The mixture was stirred under cooling for 1 hr and then water added. On basification with aq. ammonia, the precipitate products were filtered, washed with cold water and crystallized to give (VII) (Table 1).

5H-1,2,4-Triazino [5,6-b] indole-3-thione (VIII)

A mixture of I(0.01 mol) and anhyd. NaOAc (10 g) in glacial acetic acid (20 ml), was heated under refluxed for 6 hrs cooled and poured into crushed ice. The solid obtained was filtered and crystallized to give (VIII) (Table 1).

Reaction of (VIII) with Chloroacetic Acid and Aromatic Aldehydes: Formation of (IX)

A mixture of (VIII) (0.01 mol), chloroacetic acid (0.01 mol) and anhyd. NaOAc (0.03 mol) was refluxed in glacial acetic acid and Ac_2O (20 ml : 20 ml) for 40 min. An appropriate aromatic aldehydes (0.01 mol) was added and the mixture was further refluxed for 6 hrs. The reaction mixture was cooled and the solid obtained was filtered and crystallized to give (IX) (Table 1).

Addition of HCN on (I): Formation of (X)

A mixture of I(0.01 mol) and KCN(0.01 mol, in few drops of water) in presence of ethanol (100 ml, in few drops of piperidine) was refluxed for 8 hrs, cooled and poured into ice. The solid obtained was filtered and crystallized to give (X) (Table 1).

Cyclocondensation of (X): Formation of (XI)

A mixture of (X) (0.01 mol) and anhyd. NaOAc (0.02 mol) in glacial acetic acid (20 ml) was heated under reflux for 6 hrs, cooled and diluted with cold water. The solid obtained was crystallized to give (XI) (Table 1).

Reaction of Chloroacetic acid with (X)

(a) *Formation of (XII)* as following the above procedure for the formation of (V) (Table 1).

(b) *Formation of (XIII)* as following the above procedure for the formation of (II) (Table 1).

TABLE 2

CHARACTERISTIC INFRARED GROUP FREQUENCIES OF SOME NEW COMPOUNDS (λ_{max} : cm^{-1})

II: 3400 (OH), 3300–3240 (NH), 3120 (NH), 3010 (CH aromatic): 2850 (CH aliphatic), 1690, 1660 (>C=O), 1610, 1580 (C=N), 1480–1450 (def. CH), 1340 (NCS), 1190–1660 (C=S) and 1040 (phenyl).

IIIc: 3400 (OH, 3220, 3120 (NH), 3010 (CH aromatic), 2720 (CH aliphatic), 1690, 1660 (>C=0), 1610, 1580 (C=C, C=N), 1455 (def. CH), 1340 (NCS), 1160 (C=S), 1040, 880–850 (phenyl).

IVc: 3300–3200 (NH), 2880 (CH aliphatic), 1610 (C=C), 1575 (C=N), 1440 (def. CH), 1340 (NCS), 1160 (C=S), and 1000–900 (aryl and phenyl groups).

V: 3400 (OH), 3300–3050 (NH), 3010 (CH aromatic) 2790 (CH aliphatic), 1750–1650 (>C=O), 1610–1570) (C=N), 1440 (def, CH), 1320 (NCS), 1170 (C=S) and 1040, 895 (phenyl).

VIc: 3400–3170 (OH, NH), 3010 (CH aromatic), 2800 (CH aliphatic), 1730–1650 (>C=O), 1610 1580 (exo and endo C=N), 1430 (def. CH), 1310 (NCS), 1170 (C=S), 1030, 920–875 (aryl and phenyl).

VIIc: 3010 (aromatic CH), 1710 1690 (C=O), 1620 (C=C), 1580 (C=N), 1450 (def. CH) 1320 (NCS, 1150–1125 (C=S), and 1040, 890, 850 (aryl and phenyl groups).

IX: 3400–3300 (OH), 3020 (CH aromatic), 2750 (CH aliphatic), 1750, 1680 (C=O), 1610 (C=C), 1590 (C=N), 1450 (def. CH), 1330 (NCS), 1170 (C=S), 1040, 880 (aryl and phenyl).

XII: 3420–3080 (OH, NH), 3020 (CH aromatic), 2829 (CH aliphatic), 2280 C≡N), 1730–1680 (2C=O), 1620 (C=N), 1590 (C=N), 1450 (def. CH), 1330) (NCS), 1170 (C=S), 1030, 890 (phenyl).

XIII: 3400–3040 (OH, NH), 3010 (CH aromatic), 2940 (CH aliphatic), 2250 (C≡N), 1750–1700, 1670–1645 (C=O), 1440 (def. CH), 1320 (NCS), 1170 (C=S) and 1030, 980 (phenyl group).

XIV: 3410 (OH), 3300, 3220, 3120 (NH), 3010 (CH aromatic), 2900 (CH aliphatic), 2280 (C≡N), 1700–1670 (C=O), 1620, 1580 (C=N), 1460 (def. CH), 1340 (NCS), 1145 (C=S), 1020 (phenyl).

XV: 3400 (OH), 3300–3190 (NH), 3120 (NH), 3010 (CH aromatic), 1690, 1670 (>C=O), 1610–1590 (C=N), 1330 (NCS), 1185 (C–S), and 1045, 890, 850 (phenyl group).

TABLE 3

H^1- NMR OF SOME NEW COMPOUNDS

Compound	Chemical Shift	Multiplicity	Preliminary assignment
IVc	1.8	singlet	First CH_3
	2.2	singlet	Sc. CH_3
	3.45	singlet	$=CH-$
	6.0–6.3	multiplet	$-C_6H_4N(Me)_2$
	6.5–7.4	multiplet	indole protons
	8.9	singlet	NH of 1,2,4-triazine
VIIc	1.7	singlet	First CH_3
	2.3	singlet	Sc. CH_3
	3.25	singlet	$=CH-$
	5.7–6.2	multiplet	$-C_6H_4N(Me)_2$
	6.25–6.5	multiplet	indole protons
XII	2.6	singlet	CH_2
	3.2	singlet	$-CH=C-OH$
	5.6–6.0	multiplet	aromatic protons
	6.5	singlet	NH ⎫
	6.7	singlet	NH ⎬ of thiazole and indole protons
	8.65	singlet	NH ⎭
XIII	2.65	singlet	CH_2
	3.3	singlet	$-CH=C-OH$
	5.8–6.25	multiplet	aromatic protons
	6.9	singlet	OH
	7.3	singlet	NH ⎫
	8.65	singlet	NH ⎬ of 1,2, 4-triazine and indole protons
	9.0	singlet	NH ⎭
XIV	2.2	singlet	CH_2
	2.6	singlet	CH_2
	5.6–6.0	multiplet	aromatic protons
	6.25	singlet	OH ⎫
	7.0	singlet	NH ⎬ of 1,2,4-triazine protons
	7.25	singlet	NH ⎬
	9.0	singlet	NH ⎭

Reaction of (X) with 1,2-Dibromoethane : Formation of (XIV)

A mixture of (X) (0.01 mol) and 1,2-dibromoethane (0.01 mol) in ethanolic KOH (50 ml, 10% was refluxed for 4 hrs, cooled, diluted with water and the solid obtained was crystallized to give (XIV) (Table 1).

Acidic Hydrolysis of (X) : Formation of (XV)

A solution of compound (X) in conc. HCl (50%) was boiled under reflux for 4 hrs; the reaction mixture was then cooled in ice and filtered. The resultant solid was crystallized to give (XV) (Table 1).

Acidic Hydrolysis of (X) : Formation of (XVI)

A solution of compound (X) in dil. HCl (5%) was boiled under reflux for 1 hr, cooled, and basified with aq. ammonia, the solid product was filtered washed with cold water and crystallized to give XVII (Table 1).

Cyclocondensation of (XVII) : Formation of (XVIII)

A hot solution of (XVI) (0.01 mol) in glacial acetic acid (50 ml) was treated with anhyd. NaOAc (5 g). The reaction mixture was refluxed for 4 hr. The solid which was obtained after cooling was filtered and crystallized to give (XVIII) (Table 1).

TABLE 4

UV ABSORPTION BANDS OF SOME NEW COMPOUNDS

Compound	$n - \pi^*$	$n - \sigma^*$	$\pi - \pi^*$	$\sigma - \sigma^*$
IVc	360 345	295	245	195
VIIc	480 340	235	—	190
XII	370 345	240	—	190
XIII	360	260	225	190
XIV	355	258	228	190

REFERENCES

1. R. M. Abdel-Rahman, Z. El-Gendy and M. B. Mahmoud, *Indian J. Chem.*, **29B**, 352 (1990).
2. R. M. Abdel-Rahman, Z. El-Gendy and E. A. Mohamed, *J. Chem. Soc. Pakistan* (in press) (1990).
3. J. Daunis, R. Jacquier, M. Rigall and P. Viallefont, *Bull. Soc. Chim. Fr.*, 2289 (1970).

4. S. S. Meher, S. Naik, R. K. Behera and A. Nayak, *J. Indian Chem. Soc.*, **58**, 274 (1981).
5. P. V. Laakso, R. Robison and H. P. Vandrewala, *Tetrahedron*, **1**, 103 (1957).
6. Krishna C. Joshi, Vijai N. Pathak and Surendra K. Jain, *J. Indian Chem. Soc.*, **57**, 1176 (1980).
7. H. Singh, L. D. S. Yadav and A. K. Singh, *J. Indian Chem. Soc.*, **62**, 147 (1985).
8. I. A. Mohamed, Abdou A. El Sayed and Hamid A. Hammouda, *J. Prakt. Chem.* **317**, 163 (1974).
9. Leurs C. March, Khizar Wasti and Madeleme M. *J. Chem. Soc., Perkin Trans.*, 1, 83 (1976).
10. R. M. Abdel-Rahman, *Pak. J. Sci. Ind. Res.*, **30**, 490 (1987).

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