Asian Journal of Chemistry Vol. 9, No. 4 (1997), 804–811

Synthesis and Antifungal Activity of a Series of Trifluoromethyl Substituted Indole and Spiro Indole Derivatives

ANSHU DANDIA*, MITALI SAHA, ASHA SHIVPURI† and VARINDER SEHGAL
Department of Chemistry
University of Rajasthan, Jaipur-302 004, India

Various fluorinated 3-indolylimines on cyclocondensation at refluxing temperature with mercaptoacetic acid/mercaptopropionic acid afforded 3′-phenyl spiro[indole-3,2′-thiazolidine]-2,4′ (1H)-diones (V) while on stirring at room temperature gave [[2,3-dihydro-3-phenyl amino-2-oxo-1H-indol-3-yl]thio] ethanoic acid (IV). The reaction of (V) with acidic H_2O_2 resulted in corresponding 3′-phenyl spiro[3H-indol-3,2′-thiazolidine]-2,4′ (1H)-dione-1′,1′-dioxide (VI), while reaction with P_2S_5 in anhydrous pyridine yielded 3′-phenyl spiro [3H-indole-3,2′-thiazolidine]-2,4′(1H)-dithione (VII). The compounds have been characterized on the basis of elemental and spectral studies. The synthesized 34 compounds have been screened *in vitro* for antifungal activity against *Rhizoctonia solani*, *Fusarium oxysporum* and *Colletotrichum capsici*. IIIb (X = 5-Cl; R^2 = 2-CF_3), IIIe (X = 7-NO_2; R^2 = 2-CF_3), Vc (X = 5-Cl; R = CH_3; R^2 = 2-CF_3), VIC (X = 5-Cl; R = CH_3; R^2 = 3-CF_3; R^2 = 2-CF_3) VIIb (X = H; R = CH_3) and VIIC (X = H; R = CH_3; R^2 = 3-CF_3) have shown remarkable activity against these pathogens.

INTRODUCTION

The great importance of fluorine containing indole[1–6] and spiro indole derivatives[7–11] having diverse biological activities is well known. In the past recent years, the chemistry of fluorinated spiro indole derivatives has been of considerable interest due to the variation in the physico-chemical properties of these derivatives as compared to their non-fluorinated analogues.[12–14] The fluorine or CF_3 incorporation in heterocycles is known to affect the course of reaction besides influencing the biological activity.[15–18] It has been observed that introduction of CF_3 group tends to increase drug persistence by increasing its solubility in lipoid material and fat deposits in the body, with greater thermal stability.

Thiazolidinones have been found to be associated with a wide variety of biological activities.[19–21] The presence of N—C—S linkage is believed to account for the fungicidal, antibacterial and antiviral activities.[22–27] They are also known to possess amoebicidal and anticonvulsant activities.

The recent literature survey reveals a wide range of pharmacological properties associated with spiro [indole-thiazolidine] diones[28–32], which have been synthe-

†Department of Pathology, Durgapura, Jaipur.

sized earlier by a two step procedure in 40–60% yield.[33,34] The sulfoxide derivatives have been found to possess enhanced bioactivity.[35,36] Hence, we now report, in this communication, the reactions of fluorinated 3-aryl-imino-2H-indol-2-ones to give a series of new fluorine containing spiro [indole-thiazolidine] derivatives.

RESULTS AND DISCUSSION

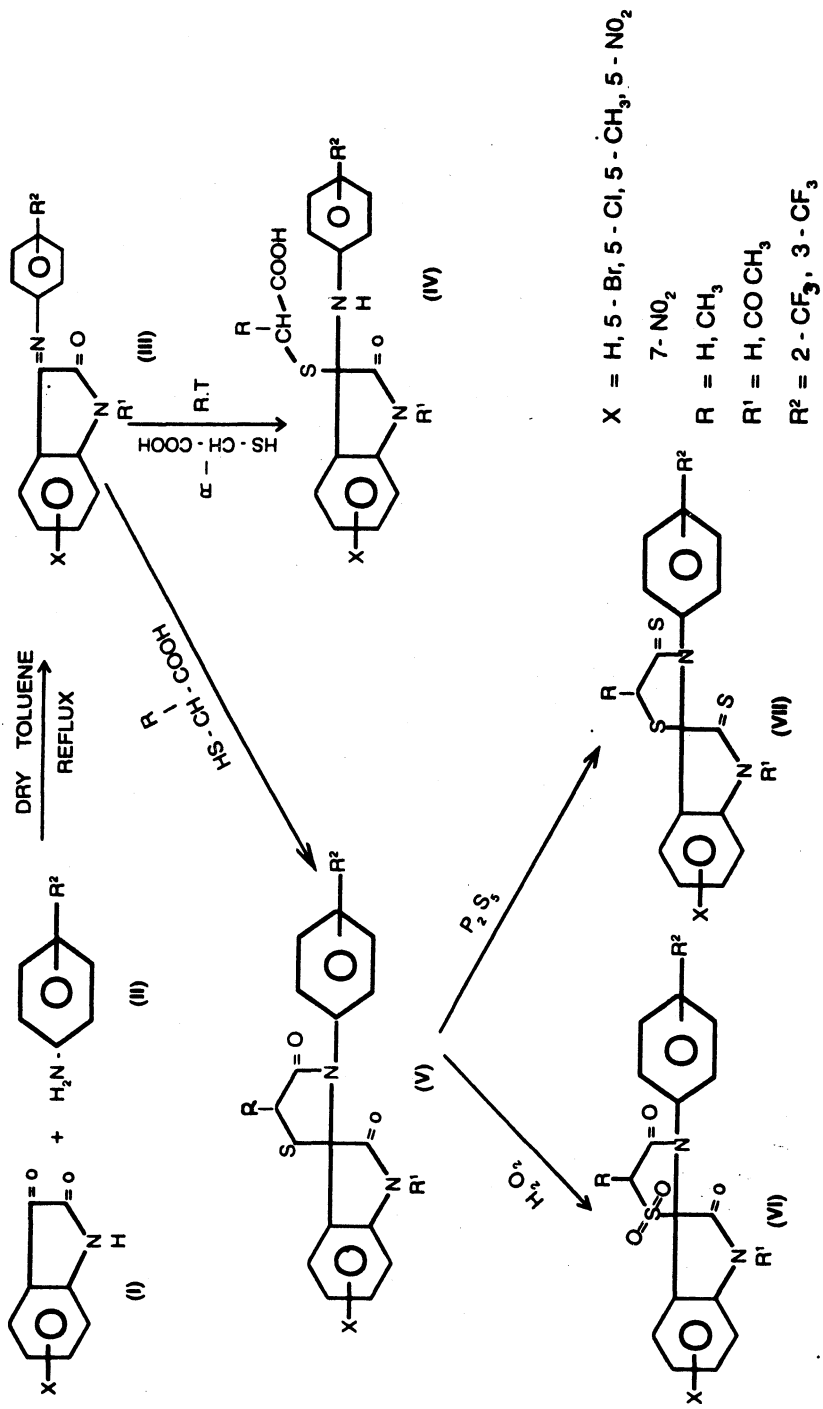
The condensation reaction of indole-2,3-diones (I) with fluorinated anilines (II) in dry toluene under reflux gave 3-aryl-imino-2H-indol-2-ones (III). The IR spectra (in KBr, ν_{max} in cm^{-1}) of the intermediate (IIIa–d) showed characteristic absorption bands at 3300–3240, 1680 and 1620 cm^{-1} indicating the presence of NH, C=O and C=N groups respectively. In the PMR spectra (chemical shifts in δ scale) of III-d the indole NH signal was observed in the region 9.65–9.80, along with aromatic protons at 6.80–7.40 ppm. To study the temperature effect on the reaction process, III were stirred with slight excess of mercaptoacetic/mercapto- propionic acid at room temperature which resulted in the formation of [[2,3-dihydro-2-oxo-1H-indol-3-yl]thio] ethanolic acid (IV). The IR spectrum of the compound (IVb) showed strong absorption at 3450–3400 (OH), 3340–3290 (NH) and 1740–1690 cm^{-1}due to both C=O groups. In PMR spectrum, a broad singlet of O<u>H</u> proton was observed in the region 9.55. A doublet signal of —CH—C<u>H</u>$_3$ was observed at 2.30–2.40, while C<u>H</u> showed quartet absorption band at δ 4.60–4.80 ppm. The indole NH signal was observed at 9.1, along with —NH— proton in the region 8.85.

The cyclization reaction of 3-indolylimines (III) with thioacids at refluxing temperature gave 3′-phenyl spiro [3H-indole-3,2′-thiazolidine]-2,4′(1H)-diones (V). The formation of the compounds (Vg–k) was confirmed by the presence of both CO absorptions at 1720–1690 cm^{-1} and absence of OH absorption at 3450–3400 cm^{-1}. The oxidation of V to the corresponding thiazolidine-1′,1′-dioxide derivatives (VI) was accomplished successfully by the reaction of V with acidic H_2O_2. The compounds (VIa–b) were characterized by two absorption bands in IR spectra at 1350–1330 (sym.) and 1180–1150 cm^{-1} (asym.) stretching of —SO_2— group, while in the PMR spectra the CH—C<u>H</u>$_3$ signal is shifted remarkably downfield in the region 2.40–2.60 and C<u>H</u>—CH$_3$ in the region δ 4.75–4.85 ppm due to adjacent —SO_2— group.

Further extending our studies to the reaction of these spiro compounds with P_2S_5 in anhydrous pyridine resulted in the formation of 3′-phenyl spiro [3H--indole-3,2′-thiazolidine]-2,4′-(1H)-dithione (VII). The IR spectrum of (VIIa) showed complete disappearance of both C=O absorption bands, which confirms the thionation at both C=O groups. The presence and position of fluorine in the compounds were confirmed by ^{19}F NMR spectra. Trifluoromethyl group of the aryl ring was observed at δ –63.249 ppm.

All the synthesized compounds were tested against three pathogenic fungi namely, *Rhizoctonia solani* Kuhn (Collar rot of okra), *Fusarium oxysporum* (Wilt of mustard) and *Colletotrichum capsici* (Fruit rot of chilli). Out of 34 compounds tested 18 were found significantly superior over check (9.0 cm) in controlling the

SCHEME-1


DRY TOLUENE
REFLUX
R.T
α – HS - CH - COOH
R – CH - COOH
HS-CH-COOH
R
P2S5
H2O2
(I)
(II)
(III)
(IV)
(V)
(VI)
(VII)
(VIII)
X = H, 5 - Br, 5 - Cl, 5 - CH3, 5 - NO2
7- NO2
R = H, CH3
R' = H, CO CH3
R2 = 2 - CF3, 3 - CF3

radial growth (1.00–5.83 cm) of all the three pathogens. Rest were at par with check.

It was found that compound IIIe (X = 7-NO_2; R^2 = 2-CF_3) was most effective against *F. oxysporum* and *C. capsici* (1.00–2.08 cm). This may be due to the presence of —NO_2 group in this compound. Similarly VIa (X = 5-CH_3; R^2 = 2-CF_3) VIc (X = 5-Cl; R^2 = 3-CF_3); VIIb (X = H; R^2 = 2-CF_3) and VIIc (X = H; R^2 = 3-CF_3) have shown remarkable activity against the three pathogens (1.00–3.25 cm)

The compounds Vc (X = 5-Cl; R = CH_3; R^2 = 2-CF_3), Vf (X = 7-NO_2; R = H; R^2 = 2-CF_3), Vg (X = H; R = CH_3; R^2 = 3-CF_3), Vi (X = 5-Cl; R = CH_3; R^2 = 3-CF_3) and VId (X = H; R = CH_3; R^1 = $COCH_3$; R^2 = 3-CF_3) have shown moderate activity (1.08–3.42 cm) against these pathogens. Further, all the above mentioned compounds will be tested in pot trials against these pathogens.

EXPERIMENTAL

Melting points, determined on a Toshniwal melting point apparatus (capillary method) are uncorrected. The purity of the synthesized compounds was tested by thin layer chromatography on silica gel in various non-aqueous solvents. IR spectra were recorded in KBr on a Perkin Elmer 577 grating spectrometer (ν_{max} in cm^{-1}) and PMR spectra in $CDCl_3$ on a Jeol FX900 (89.55 MHz) using TMS as an internal reference (^{19}F NMR on the same instrument).

3-Arylimino-2H-indol-2-ones (IIIa–f)

A mixture of substituted indole-2,3-dione (0.01 mole) and 2/3-trifluoromethyl aniline (0.01 mole) was refluxed in dry toluene (20 mL) for 3–4 h. On cooling, crystals separated out were filtered and recrystallized from ethanol to give (IIIa–f).

TABLE-1
ANALYTICAL AND PHYSICAL DATA OF (IIIa–f) AND (IVa–f)

Compd. No.	X	R^1	R^2	R	m.p. (°C)	Yield (%)	Molecular Formula*
IIIa	5-CH_3	H	2-CF_3	—	165	67.53	$C_{16}H_{11}F_3N_2O$
IIIb	5-Cl	H	2-CF_3	—	167	66.58	$C_{15}H_8ClF_3N_2O$
IIIc	5-NO_2	H	3-CF_3	—	165	85.50	$C_{15}H_8F_3N_3O_3$
IIId	5-Br	H	3-CF_3	—	175	74.10	$C_{15}H_8BrF_3N_2O$
IIIe	7-NO_2	H	2-CF_3	—	165	66.00	$C_{15}H_8F_3N_3O_3$
IIIf	5-CH_3	H	H	—	204	62.40	$C_{15}H_{12}N_2O$
IVa	5-CH_3	H	2-CF_3	H	124	80.90	$C_{18}H_{15}F_3N_2O_3S$
IVb	5-CH_3	H	2-CF_3	CH_3	176	81.30	$C_{19}H_{17}F_3N_2O_3S$
IVc	H	$COCH_3$	3-CF_3	CH_3	172	74.09	$C_{20}H_{17}F_3N_2O_4S$
IVd	H	H	2-CF_3	CH_3	145	90.09	$C_{18}H_{15}F_3N_2O_3S$
IVe	5-Br	H	3-CF_3	H	198	72.34	$C_{16}H_{12}BrF_3N_2O_3S$
IVf	5-CH_3	H	H	CH_3	195	65.08	$C_{18}H_{18}N_2O_3S$

*C, H and N have been analysed.

[2,3-dihydro-3-phenylamino-2-oxo-1H-indol-3-yl]thio] ethanoic acid (IVa–f)

A mixture of III (0.01 mole) and mercaptoacetic/mercaptopropionic acid (0.015 mole) in dry toluene was stirred for 8–10 h at 35–40°C. The solid thus separated out was filtered and dried to give compounds (IVa–f). The crude compound was found to be pure on TLC.

3′-phenyl spiro[3H-indol-3,2′-thiazolidine]-2,4′(1H)-diones (Va–*l*)

A mixture of III (0.01 mole) and mercaptoacetic/mercaptopropionic acids (0.015 mole) was refluxed in dry toluene (25 mL) for 6–8 h, with the azeotropical removal of water formed. The whole mixture was then allowed to cool to room temperature and the supernatent liquid was removed under reduced pressure. The solid compound so obtained was recrystallized from ethanol to give (Va–*l*).

TABLE-2
ANALYTICAL AND PHYSICAL DATA OF (Va–*l*)

Compd. No.	X	R^1	R^2	R	m.p. (°C)	Yield (%)	Molecular Formula
Va	5-CH_3	H	2-CF_3	CH_3	190	57.81	$C_{19}H_{15}F_3N_2O_2S$
Vb	5-CH_3	H	2-CF_3	H	181	61.32	$C_{18}H_{13}F_3N_2O_2S$
Vc	5-Cl	H	2-CF_3	CH_3	270 (d)	59.90	$C_{18}H_{12}ClF_3N_2O_2S$
Vd	5-NO_2	H	3-CF_3	H	191	70.90	$C_{17}H_{10}F_3N_3O_4S$
Ve	5-Br	H	3-CF_3	H	204	72.40	$C_{17}H_{10}BrF_3N_2O_2S$
Vf	7-NO_2	H	2-CF_3	H	225	60.00	$C_{17}H_{10}F_3N_3O_4S$
Vg	H	H	3-CF_3	CH_3	218 (lit. m.p. 216)	82.00	$C_{18}H_{13}F_3N_2O_2S$
Vh	H	H	2-CF_3	CH_3	180 (lit. m.p. 182)	88.80	$C_{18}H_{13}F_3N_2O_2S$
Vi	5-Cl	H	3-CF_3	CH_3	195 (lit. m.p. 196)	79.00	$C_{18}H_{12}ClF_3N_2O_2S$
Vj	5-Cl	H	2-CF_3	H	330 (lit. m.p. 331)	82.00	$C_{17}H_{10}ClF_3N_2O_2S$
Vk	H	$COCH_3$	3-CF_3	CH_3	192 (lit. m.p. 194)	73.00	$C_{20}H_{14}F_3N_2O_3S$
V*l*	5-CH_3	H	H	CH_3	250 (d)	62.00	$C_{18}H_{16}N_2O_2S$

d = decomposes

3′-phenyl spiro [3H-indole-3,2′-thiazolidine]-2, 4′-(1H)-dione-1′, 1′-dioxide (VIa–f)

A mixture of (V) (0.01 mole) and H_2O_2 (30%, 15 mL) in presence of acetic acid (6 drops) was stirred for 6 h, at 35–40°C and then diluted with distilled water. The product obtained was filtered and recrystallized from aqueous ethanol to give compounds (VIa–f).

TABLE-3
ANALYTICAL AND PHYSICAL DATA OF VIa–f AND VIIa–d

Compd. No.	X	R^1	R^2	R	m.p. (°C)	Yield (%)	Molecular formula
VIa	5-CH_3	H	2-CF_3	CH_3	206	48.50	$C_{19}H_{15}F_3N_2O_4S$
VIb	H	H	3-CF_3	CH_3	203	40.00	$C_{18}H_{13}F_3N_2O_4S$
VIc	5-Cl	H	3-CF_3	CH_3	205	45.20	$C_{18}H_{12}ClF_3N_2O_4S$
VId	H	$COCH_3$	3-CF_3	CH_3	170	32.00	$C_{20}H_{15}F_3N_2O_5S$
VIe	H	H	2-CF_3	CH_3	198	47.10	$C_{18}H_{13}F_3N_2O_4S$
VIf	5-CH_3	H	H	CH_3	215	45.38	$C_{18}H_{16}N_2O_4S$
VIIa	5-CH_3	H	2-CF_3	CH_3	>360	87.00	$C_{19}H_{15}F_3N_2S_3$
VIIb	H	H	2-CF_3	CH_3	>360	80.00	$C_{18}H_{13}F_3N_2S_3$
VIIc	H	H	3-CF_3	CH_3	>360	89.00	$C_{18}H_{13}F_3N_2S_3$
VIId	5-CH_3	H	H	CH_3	>360	78.00	$C_{18}H_{16}N_2S_3$

3′-phenyl spiro [3H-indole-3,2′-thiazolidine]-2,4′-(1H)-dithione(VIIa–d)

A mixture of V (0.01 mole) and P_2S_5 (0.03 mole) in anhydrous pyridine (40 mL) was refluxed for 17–20 h. The solvent was removed under vacuum. The sticky mass thus obtained was dissolved in 10% aqueous NaOH. The precipitated compound was filtered and recrystallized from benzene to give (VIIa–d).

Antifungal activity

The stock solutions of 1000 ppm and 500 ppm of all compouds were prepared in acetone and then incorporated in required quantities to Potato Dextrose Agar medium (PDA) before dispersing into petri-plates. 100 mL of PDA was uniformly distributed into three petri-plates, served as replicates. Three plates containing unamended PDA were maintained as control.

The petri-plates were inoculated with 4 mm disc cut from 7 days old fungus culture. The inoculated plates were incubated at 25 ± 1°C for 5 days. The radial growth of the fungal colonies was measured on 6th day and data were statistically analysed.

TABLE-4
EFFECT OF CONCENTRATIONS OF DIFFERENT CHEMICALS ON THE MEAN RADIAL GROWTH (cms) OF FUNGUS *IN VITRO*

Compd.	*Rhizoctonia solani*		*Fusarium oxysporum*		*Colletotrictum capsici*	
	1000 ppm	500 ppm	1000 ppm	500 ppm	1000 ppm	500 ppm
IIIa	9.00	9.00	2.92	5.83	5.50	5.50
IIIb	8.33	8.66	2.67	3.08	1.75	2.33
IIIc	6.83	8.83	5.08	7.42	2.00	3.33
IIId	4.42	9.00	4.08	5.17	5.25	5.25

Compd.	*Rhizoctonia solani*		*Fusarium oxysporum*		*Colletotrictum capsici*	
	1000 ppm	500 ppm	1000 ppm	500 ppm	1000 ppm	500 ppm
IIIe	5.92	6.50	2.08	4.00	1.00	2.17
IIIf	4.25	9.00	5.58	8.00	3.67	5.67
IVa	3.83	5.58	5.67	3.58	5.75	6.67
IVb	5.83	5.50	4.50	7.33	3.75	4.67
IVc	6.08	7.66	5.33	6.00	3.92	4.67
IVd	9.00	9.00	5.67	5.67	4.33	5.92
IVe	5.42	4.33	3.00	4.67	2.17	2.92
IVf	7.17	9.00	4.58	9.00	7.08	9.00
Va	4.50	4.50	4.50	6.67	2.08	6.33
Vb	5.75	6.33	4.08	6.92	5.25	7.25
Vc	9.00	9.00	2.92	3.83	2.67	3.42
Vd	7.33	9.00	6.83	9.00	5.33	7.00
Ve	9.00	9.00	3.50	4.75	2.92	5.08
Vf	6.00	9.00	3.50	5.00	1.42	3.17
Vg	3.58	9.00	3.17	2.75	1.08	3.83
Vh	4.08	5.58	4.50	7.83	4.08	5.58
Vi	9.00	9.00	3.33	4.75	1.92	2.50
Vj	9.00	9.00	7.08	7.75	7.75	7.83
Vk	3.83	5.33	4.67	9.00	3.83	5.33
Vl	5.25	7.00	5.33	6.58	3.75	6.92
VIa	3.33	1.33	6.67	6.50	3.50	6.33
VIb	9.00	9.00	5.08	6.33	5.08	5.08
VIc	5.08	5.08	2.50	2.67	1.83	2.67
VId	2.33	9.00	6.00	8.42	3.67	7.17
VIe	5.08	9.00	7.50	8.50	6.42	6.17
VIf	4.17	4.25	7.08	7.92	5.25	6.67
VIIa	9.00	9.00	4.42	6.33	2.75	4.08
VIIb	9.00	9.00	2.67	4.75	1.00	2.75
VIIc	1.92	9.00	3.25	4.58	1.67	3.00
VIId	8.75	9.00	6.58	9.00	4.92	6.50
Check	9.00	9.00	8.50	8.83	8.50	8.50
CD 1 %	1.43	1.46	1.92	1.67	1.50	1.69

□ Min. value.

——— At par with min. value.

ACKNOWLEDGEMENTS

Financial support from UGC and State DST is gratefully acknowledged.

REFERENCES

1. K.C. Joshi, A. Dandia and N. Ahmed, *Heterocycles.*, **24**, 2479 (1986).
2. K.C. Joshi, R. Jain, A. Dandia and V. Sharma, *J. Heterocycl. Chem.*, **23**, 97 (1986).
3. K.C. Joshi, A. Dandia, S. Baweja and A. Joshi, *J. Heterocycl. Chem.*, **26**, 1097 (1989).
4. K.C. Joshi, A. Dandia and S. Sanan, *J. Fluorine Chem.*, **49**, 59 (1989).
5. _____, *J. Heterocycl Chem.*, **26**, 1397 (1989).
6. K.C. Joshi, A. Dandia and S. Khanna (née Sanan), *Indian J. Chem.*, **29B**, 824 (1990).
7. K.C. Joshi, A. Dandia and N. Ahmed, *Indian J. Chem.*, **28B**, 639 (1989).
8. K.C. Joshi, A. Dandia and S. Sanan, *J. Fluorine Chem.*, **44**, 59 (1989).
9. K.C. Joshi, R. Jain, A. Dandia, S. Garg and N. Ahmed, *J. Heterocycl. Chem.*, **26**, 1799 (1989).
10. K.C. Joshi, A. Dandia and Sangeeta Khanna, *Indian J. Chem.*, **31B**, 169 (1992).
11. K.C. Joshi, A. Dandia and Sunita Bhagat, *J. Fluorine Chem.*, **48**, 169 (1990).
12. K.C. Joshi, R. Jain and S. Garg, *Pharmazie*, **40**, 21 (1985).
13. K.C. Joshi, R. Patni, P. Chand, V. Sharma, S.K. Bhattacharya and Y.V. Rao, *Pharmazie.*, **39**, 153 (194).
14. K.C. Joshi, V.N. Pathak and S.K. Jain, *J. Prakt. Chem. (B)*, **323**, 159 (1981).
15. R. Filler, *Chem. Tech.*, **4**, 752 (1974).
16. R.G. Plevey and J.C. Tatlow, *Sci. Org. Oxf.*, **58**, 481 (1970).
17. K.C. Joshi, A. Dandia and S. Baweja, *Indian J. Chem.*, **29B**, 766 (1990).
18. K.C. Joshi, A. Dandia and S. Khanna (née Sanan), *Indian J. Chem.*, **29B**, 1125 (1990).
19. J. Doran and H.A. Sonal, *J. Org. Chem.*, **3**, 193 (1938).
20. N.M. Turkevich, L.Y. Landaya, I.V. Pleshnev and O.L. Grom, *Khim, Issled. Farm.*, **64** (1970) through *Chem. Abstr.*, **76**, 34154 (1977).
21. H.D. Trautmann and L.M. Long, *J. Am. Chem. Soc.*, **70**, 3436 (1948).
22. Shishir K. Srivastava, R.B. Pathak and S.C. Bahel, *Indian J. Chem.*, **30B**, 620 (1991).
23. Al-Rashood, A. Khalid and Said M. Bayomi, *Sulfur. Lett.*, **13**, 151 (1991).
24. Al-Khamees, A. Hamad, Said M. Bayomi, Hesham A. Kandil, El-Tahir and E.H. Kamal, *Eur. J. Med. Chem.*, **25**, 103 (1990).
25. E. Piscopo, M.V. Diurno, R. Gagliardi, O. Mazzoni and G. Veneruso, *Boll-Soc. Ital. Biol. Sper.* **65**, 853 (1989).
26. J.S. Shukla and Roli Shukla, *J. Indian Chem. Soc.*, **66**, 209 (1989).
27. R.R. Mohan and M. Srivastava, *Indian Drugs*, **26**, 342 (1989).
28. Ali Raub, Bharati Mishra and Nizamuddin, *Indian J. Chem.*, **28B**, 526 (1989).
29. E. Piscopo, M.V. Diurno, O. Mazzoni and A.M. Ciaccio, *Boll.-Soc. Ital. Biol. Sper.*, **66**, 1181 (1990); *Chem. Abstr.*, **116**, 169944k (1992).
30. E. Piscopo, M.V. Diurno, O. Mazzoni, A.M. Ciaccio and G. Veneruso, *Boll-Soc. Ital. Biol. Sper.*, **66**, 1187 (1990); *Chem. Abstr.*, **116**, 169945m (1992).
31. Milind Rajopadhye and F.D. Popp, *J. Heterocycl. Chem.*, **24**, 1637 (1987).
32. F.D. Popp and M. Rajopadhye, *J. Heterocycl. Chem.*, **21**, 289 (1984).
33. H. Otomasu and S. Ohmiya, *Jap. Pat.*, **75**, 140, 441 (1975); *Chem. Abstr.*, **85**, 32991v (1976).
34. K.C. Joshi, R. Patni and P. Chand, *Heterocycles*, **16**, 1555 (1981).
35. M.S. Shingare, *Indian. J. Chem.*, **22B**, 714 (1983).
36. A.R. Survey and R. Cutler, *J. Am. Chem. Soc.*, **76**, 578 (1954).
37. A. Dandia, Mitali Saha and Asha Shivpuri, *Synthetic Comm.*, (Communicated).

(*Received:* 12 April 1997; *Accepted:* 2 June 1997) AJC-1297