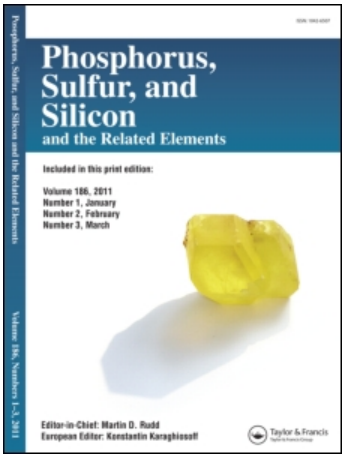
This article was downloaded by:
On: *28 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis of 7-ethoxy- and 7-fluoro-phenothiazines

Thandi Lal Kachhee; Vandana Gupta; D. C. Gautam; R. R. Gupta

Online publication date: 18 June 2010

To cite this Article Kachhee, Thandi Lal , Gupta, Vandana , Gautam, D. C. and Gupta, R. R.(2003) 'Synthesis of 7-ethoxy- and 7-fluoro-phenothiazines', Phosphorus, Sulfur, and Silicon and the Related Elements, 178: 12, 2671 — 2678
To link to this Article: DOI: 10.1080/714040982
URL: http://dx.doi.org/10.1080/714040982

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

Phosphorus, Sulfur, and Silicon, 178:2671–2678, 2003
Copyright © Taylor & Francis Inc.
ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500390252308

Taylor & Francis
Taylor & Francis Group

SYNTHESIS OF 7-ETHOXY- AND 7-FLUORO-PHENOTHIAZINES

Thandi Lal Kachhee, Vandana Gupta, D. C. Gautam, and R. R. Gupta
University of Rajasthan, Jaipur, India

(Received February 6, 2003; accepted June 24, 2003)

Synthesis of 7-ethoxy- and 7-fluoro-phenothiazines is reported by Smiles rearrangement of 5-ethoxy- and 5-fluoro-2-formamido-2′-nitrodiphenylsulfides. The later were obtained by the formylation of 2-amino-5-ethoxy/5-fluoro-2′-nitrodiphenylsulfides which were prepared by the condensation of 2-amino-5-ethoxy/5-fluoro-benzenethiols with o-halonitrobenzenes.

Downloaded At: 10:39 28 January 2011

Phenothiazines, have been used as tranquilizer, antihistaminics,[1] neuroleptics,[2] antiemetics,[3–5] diuretics,[6,7] sedatives,[8] tuberculostatics,[9] analgesics,[10] and soon. Phenothiazines have also shown anticancer activities.[11–14] Therefore, it is considered worthwhile to synthesize hitherto unknown phenothiazines in order to make them available for biomedical investigations.[15] Synthesized phenothiazines have been characterized by IR, ^{1}H NMR, and mass spectral analysis.

RESULTS AND DISCUSSION

In the present investigation, 7-ethoxy/7-flouro-phenothiazines [**Va–d**] have been synthesized by Smiles rearrangement[16,17] of 5-ethoxy- and 5-fluoro-2-formamido-2′-nitrodiphenyl sulfides [**IVa–d**] in alcoholic potassium hydroxide solution. The formyl derivatives were prepared by the formylation of resultant diphenylsulfides [**IIIa–d**] obtained by the condensation of 2-aminobenzenethiols[18–21] [**I**] with

Authors express sincere thanks to CDRI, Lucknow to provide NMR and mass spectra.
Address correspondence to R. R. Gupta, Department of Chemistry, University of Rajasthan, Jaipur 302004, India.

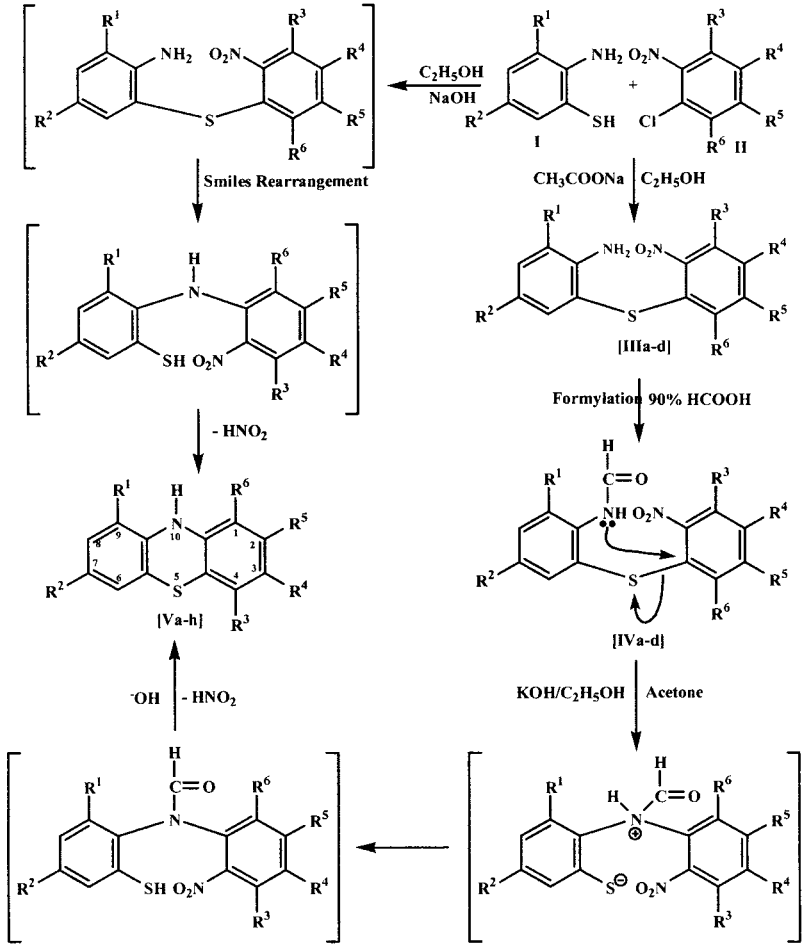
o-halonitrobenzenes [**II**] in ethanolic sodium acetate solution. 2-Aminobenzenethiols, required in the synthesis of phenothiazines, have been prepared by the hydrolytic cleavage of 2-aminobenzothiazoles which were prepared by the action of ammonium thiocyanate[22] and bromine on p-phenitidine and 4-fluoro-2-methyl aniline.

A single-step synthesis of nitrophenothiazines have been achieved by the condensation of 2-aminobenzenethiol [**I**] with halonitrobenzene [**II**] containing nitro groups at both ortho positions to halogen atom in the presence of NaOH involving Smiles rearrangement and ring closure occurs in situ due to combined resonance and inductive effect of two nitro groups (Scheme 1).

The IR spectra of all the synthesized diphenylsulfides [**IIIa–d**] exhibit two peaks in the region 3400–3340 cm^{-1} and 3320–3260 cm^{-1} due to asymmetric and symmetric vibrations of the primary amino group. Two peaks observed in the region 1580–1510 cm^{-1} and 1370–1330 cm^{-1} are attributed to the asymmetric and symmetric vibrations of nitro group respectively. The two bands in the regions 1260–1240 cm^{-1} and 1060–1020 cm^{-1} appear in all diphenylsulfides having OC_2H_5 group due to C—O—C asymmetric and symmetric vibrations respectively. In compound [**IIId**] two sharp peaks observed at 1360–1350 cm^{-1} and 1170–1120 cm^{-1} can be assigned to C—F stretching vibrations. All the synthesized diphenylsulfides exhibits a single sharp peak at 810–760 cm^{-1} due to C—Cl stretching vibrations. The peak in the region 1490–1420 cm^{-1} and 1370–1290 cm^{-1} are due to asymmetric and symmetric C—H deformation vibrations of CH_3 group in compound [**IIId**]. The IR spectra of all 2-formamido-diphenylsulfides resemble the spectra of their parent diphenylsulfides. However a single peak is observed in the region 3310–3260 cm^{-1} due to N—H stretching vibrations and an additional peak in the region 1640–1610 cm^{-1} is obtained due to C=O stretching vibrations. Two bands obtained in the region 1580–1530 cm^{-1} and 1350–1320 cm^{-1} can be assigned to asymmetric and symmetric vibration of nitro group respectively. Compound [**IVd**] shows two peaks at 1370–1320 cm^{-1} and 1160–1150 cm^{-1} due to C—F stretching vibrations. The two sharp peaks at 1250–1230 cm^{-1} and 1070–1040 cm^{-1} obtained in all compounds [**IVa–d**] can be attributed to C—O—C asymmetric and symmetric vibrations due to OC_2H_5 group respectively. All compounds [**IVa–d**] exhibits a single sharp peak at 800–760 cm^{-1} due to C—Cl stretching vibrations.

The IR spectra of all phenothiazines exhibits a sharp peak in the region 3430–3280 cm^{-1} due to N—H stretching vibrations. Phenothiazines [**Va–d**] containing no nitro group at 1-position exhibit this band in the region 3340–3240 cm^{-1} while in 1-nitrophenothiazines [**Ve–h**]

Downloaded At: 10:39 28 January 2011



Compounds			R¹	R²	R³	R⁴	R⁵	R⁶
IIIa	IVa	Va	H	OC_2H_5	H	H	H	Cl
IIIb	IVb	Vb	H	OC_2H_5	H	Cl	H	H
IIIc	IVc	Vc	H	OC_2H_5	H	Cl	Cl	H
IIId	IVd	Vd	CH_3	F	H	H	H	Cl
		Ve	H	OC_2H_5	H	CF_3	H	NO_2
		Vf	H	OC_2H_5	Cl	Cl	H	NO_2
		Vg	CH_3	F	H	CF_3	H	NO_2
		Vh	CH_3	F	Cl	Cl	H	NO_2

SCHEME 1 Synthesis of phenothiazines via Smiles rearrangement.

Downloaded At: 10:39 28 January 2011

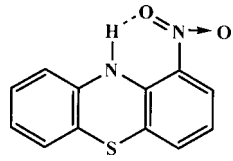


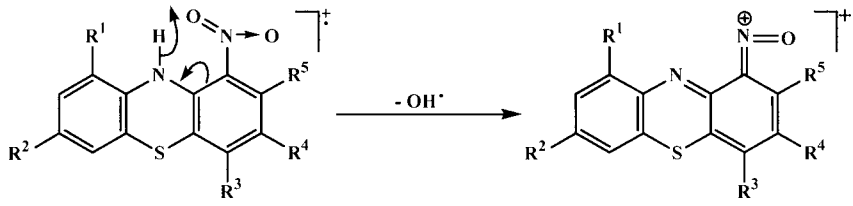
FIGURE 1

it appears at 3380–3290 cm^{-1}. The shift to a lower frequency region in 1-nitrophenothiazines suggests a six membered chelation of high stability through a strong (—NH—O=N) hydrogen bonding (Figure 1). 1-Nitropheno-thiazines exhibits two peaks of medium intensity in the region 1500–1570 cm^{-1} and 1390–1320 cm^{-1} due to asymmetric and symmetric vibrations of aromatic nitro groups. The peaks in the region 1280–1250 cm^{-1} and 1070–1020 cm^{-1} are due to asymmetric and symmetric —C—O—C deformation vibrations of $—OC_2H_5$ group. The two peaks in the region 1470–1430 cm^{-1} and 1350–1290 cm^{-1} are due to asymmetric and symmetric C—H deformation vibrations of CH_3 group. A single sharp peak in the region 790–720 cm^{-1} in compounds [**Va–d, Vf** and **Vh**] is due to C—Cl stretching vibrations. In compounds [**Ve** and **Vg**] two sharp peaks are observed in the region 1350–1340 cm^{-1} and 1170–1120 cm^{-1} are due to C—F stretching vibrations of CF_3 group.

In NMR spectra phenothiazines without a nitro group at 1-position exhibit a single peak in the region δ 9.214–8.81 due to N—H proton which is shifted to δ 9.68–9.35 in 1-nitrophenothiazines. The shifting of this peak towards down field in 1-nitrophenothiazines is ascribed to intramolecular hydrogen bonding (as —NH—O=N) which has been also suggested by infrared spectra. All the synthesized phenothiazines exhibit multiplets in the region δ 8.48–6.64 due to aromatic protons. A singlet is observed in region δ 2.038–2.20 due to CH_3 protons at C_9. A quartet in the region δ 2.96–2.21 and triplet centred in the region δ 1.62–0.82 are observed due to methylene and methyl protons of ethoxy group respectively.

Molecular ion peaks are in accordance with their molecular weights. 1-Nitrophenothiazines have exhibited the characteristics of an aromatic nitro group[10] in the fragmentation besides the other fragmentations caused by different substituents. Moieties M^+-30, M^+-46 and M^+-47 are observed with variable intensity in 1-nitrophenothiazines and are ascribed to the loss of NO, NO_2 and HNO_2 respectively. 1-Nitrophenothiazines exhibit a peak at M^+-17 which is assigned to the loss of $OH^·$ radical by Mc-Lafferty rearrangement[23–25] as shown in (Scheme 2).

Downloaded At: 10:39 28 January 2011



SCHEME 2

EXPERIMENTAL

All the melting points are uncorrected. The purity was checked by thin layer chromatography and characterized by spectral studies. The infrared spectra were recorded on FT-IR spectrometer. MAGNA-IR 550, NICOLET using potassium bromide discs. ^{1}H NMR spectra were recorded on Brucker WM-400 (400 MHz FT-NMR) spectrometers (chemical shift are in δ ppm using TMS as internal standard), the mass spectra were recorded on Jeol D-300 spectrometer using electron ionization technique. Physical data of synthesized compounds are summarized in Table I.

Downloaded At: 10:39 28 January 2011

Preparation of 2-Amino-5-ethoxy/5-fluoro-2′-nitrodiphenylsulfides (IIIa–d)

2-Amino-5-ethoxy/ 5-fluorobenzenethiol [**I**, 0.01 mmol] was dissolved in ethanol (20 ml) containing anhydrous sodium acetate (0.01 mmol) and halonitrobenzene[26](**II**; 0.01 mmol) in ethanol (10 ml) was added. The reaction mixture was refluxed for 4 h, concentrated, and cooled in an ice bath overnight. The solid separated out was filtered and washed with 30% ethanol. Crystallization from methanol afforded the desired product. Physical data are recorded in Table I.

Preparation of 5-Ethoxy/5-fluoro-2-formamido-2′-nitrodiphenylsulfides (IVa–d)

A mixture of diphenylsulfide (**IIIa–c**, 0.01 mmol) and 90% formic acid (20 ml) was refluxed for 4 h. The contents were poured into a beaker containing crushed ice. The solid separated out was filtered and washed with water until the filtrate was neutral and crystallized from benzene/methanol.

Downloaded At: 10:39 28 January 2011

TABLE I Physical Data (Compounds III–V)

	Compound						m.p.	Yield	Molecular	% found (Cald.)		
	R_1	R_2	R_3	R_4	R_5	R_6	°(C)	(%)	formula	C	H	N
IIIa	H	OC_2H_5	H	H	H	Cl	98	54	$C_{14}H_{13}N_2O_3SCl$	51.82 (51.77)	4.05 (4.03)	8.50 (8.63)
IIIb	H	OC_2H_5	H	Cl	H	H	86	85	$C_{14}H_{13}N_2O_3SCl$	51.82 (51.77)	4.02 (4.03)	8.57 (8.63)
IIIc	H	OC_2H_5	H	Cl	Cl	H	153	29	$C_{14}H_{12}N_2O_3SCl_2$	46.55 (46.81)	3.39 (3.37)	7.78 (7.80)
IIId	CH_3	F	H	H	H	Cl	111	75	$C_{13}H_{10}N_2O_2SClF$	49.88 (49.92)	3.20 (3.22)	9.05 (8.96)
IVa	H	OC_2H_5	H	H	H	Cl	127	92	$C_{15}H_{13}N_2O_4SCl$	51.10 (51.07)	3.68 (3.71)	7.92 (7.94)
IVb	H	OC_2H_5	H	Cl	H	H	128	80	$C_{15}H_{13}N_2O_4SCl$	51.16 (51.07)	3.72 (3.71)	7.90 (7.94)
IVc	H	OC_2H_5	H	Cl	Cl	H	131	73	$C_{15}H_{12}N_2O_4SCl_2$	46.44 (46.52)	3.09 (3.12)	7.26 (7.23)
IVd	CH_3	F	H	H	H	Cl	27	49	$C_{14}H_{10}N_2O_3SClF$	49.60 (49.35)	2.92 (2.96)	8.28 (8.22)
Va	H	OC_2H_5	H	H	H	Cl	83	80	$C_{14}H_{12}NOSCl$	60.54 (60.54)	4.38 (4.35)	5.02 (5.04)
Vb	H	OC_2H_5	H	Cl	H	H	142	83	$C_{14}H_{12}NOSCl$	60.41 (60.54)	4.38 (4.35)	5.01 (5.04)
Vc	H	OC_2H_5	H	Cl	Cl	H	115	65	$C_{14}H_{11}NOSCl_2$	53.74 (53.86)	3.57 (3.55)	4.49 (4.49)
Vd	CH_3	F	H	H	H	Cl	126	78	$C_{13}H_9NSClF$	58.58 (58.76)	3.38 (3.41)	5.25 (5.27)
Ve	H	OC_2H_5	H	CF_3	H	NO_2	146	89	$C_{15}H_{11}N_2O_3SF_3$	50.61 (50.56)	3.12 (3.11)	7.80 (7.86)
Vf	H	OC_2H_5	Cl	Cl	H	NO_2	172	31	$C_{14}H_{10}N_2O_3SCl_2$	47.14 (47.07)	2.80 (2.82)	7.84 (7.84)
Vg	CH_3	F	H	CF_3	H	NO_2	114	79	$C_{14}H_8N_2O_2SF_4$	48.59 (48.84)	2.30 (2.34)	8.12 (8.14)
Vh	CH_3	F	Cl	Cl	H	NO_2	178	44	$C_{13}H_7N_2O_2SCl_2F$	45.36 (45.23)	2.03 (2.04)	8.10 (8.12)

Preparation of 7-Ethoxy and 7-Fluorophenothiazines (Va–d)

To the refluxing solution of formyl derivatives (**IVa–d**; 0.01 mmol) in acetone (15 ml) was added an alcoholic solution of potassium hydroxide (0.2 g in 5 ml ethanol). The contents were heated for .5 h. A second portion of potassium hydroxide (0.2 mmol in 5 ml ethanol) was added to the reaction mixture and refluxed for 2 h. The contents were poured into a beaker containing crushed ice. The solid separate out was filtered, washed with cold water, and finally washed with 30% ethanol. Crystallization from methanol/benzene afforded phenothiazines. The physical data of synthesized phenothiazines are tabulated in Table I.

Preparation of 1-Nitrophenothiazines (Ve–h)

To a stirred suspension of halonitrobenzene (2, 0.01 mmol), 2-amino-5-ethoxybenzenethiol (**I**, 0.01 mmol), sodium hydroxide (0.01 mmol) and absolute ethanol (20 ml) was refluxed for 2 h. The reaction mixture was concentrated on water bath, cooled down, and filtered. The solid separated out was washed with hot water and 30% ethanol. The crystallization from methanol/acetone afforded 1/9-nitrophenothiazines. Physical data are included in Table I.

Downloaded At: 10:39 28 January 2011

REFERENCES

[1] Y. Sugimoto, T. Tarumi, Q. E. Zhao, Y. Fujji, and C. Kamei, *Methods Find. Exp. Clin. Pharmacol.*, **20**(6), 457–462 (1998); *Chem. Abstr.*, **130,** 75926 (1999).
[2] E. N. Makareeva, E. L. Lozovskaya, and I. I. Saphezhinskii, *Biofizika*, **43**(2), 181–185 (1998); *Chem. Abstr.*, **131,** 84963 (1999).
[3] P. I. Williams, and M. Smith, *Eur. J. Anaestheiol*, **16**(9), 639–645 (1999); *Chem. Abstr.*, **131,** 332076 (1999).
[4] K. Mystakidou, S. Befon, C. Liossi, and L. Vlachos, *Cancer*, **83**(6), 1214–1223 (1998); *Chem. Abstr.*, **130,** 32919 (1999).
[5] S. Singh, P. K. Peshin, and D. Krishnamurthy, *Indian, Vet. J.*, **71**(10), 983–987 (1994); *Chem. Abstr.*, **122,** 96226 (1995).
[6] V. V. Vorontsov, I. M. Lerner, and E. I. Shchelkuno, *Farmocal. Toksikol.*, **43**(1), 81 (1980); *Chem. Abstr.*, **92,** 157547 (1980).
[7] Bristol-Myres Co. Belg., **838**, 243 (1976); *Chem. Abstr.*, **87,** 23310 (1977).
[8] H. V. Petts and B. J. Pleuvry, *Br. J. Anaesth.*, **55**, 437 (1983); *Chem. Abstr.*, **99,** 16444 (1983).
[9] R. L. Gupta, S. Jain, V. Talwar, H. C. Gupta, and P. S. Murthy, *Indian J. Clin. Biochem.*, **13**(2), 92–97 (1998); *Chem. Abstr.*, **130,** 346919 (1999).
[10] G. Acs, M. Palkovits, and P. M. Blumberg, *J. Pharmacol. Exp. Ther.*, **274**(3), 1090–1098 (1995); *Chem. Abstr.*, **123,** 235739 (1995).
[11] R. R. Gupta, ed., *Phenothiazines and 1,4-Benzothiazines-Chemical and Biomedical Aspects* (Elsevier, Amsterdam, 1988).

[12] M. Gordon, in *Medicinal Chemistry*, edited by M. Gordon, Academic Press, New York, (1967), vol. 2, p. 119.
[13] H. Keyzer, G. M. Eckert, I. S. Forrest, et al., eds., *Thiazines and Structurally Related Compounds*, Proceedings of Sixth International Conference on Phenothiazines and Structurally Related Psychotropic Compounds, Pasadena, California, September 11–14 1990, (Krieger Publishing, Malabar, FL, 1992).
[14] A. R. Safa, *Chimia*, **53**(6), 299 (1999); *Chem. Abstr.*, **131,** 193907 (1999).
[15] C. Bodea and I. Silberg, *Advances in Heterocyclic Chemistry*, edited by A. R. Katritzky and A. J. Boulton (Academic Press, New York and London, 1968), vol. 9.
[16] C. F. Weight and S. Smiles, *J. Chem. Soc.*, 340 (1935).
[17] A. A. Levy, H. C. Rains, and S. Smiles, *J. Chem. Soc.*, 3264 (1931).
[18] R. R. Gupta, S. K. Jain, N. K. Goswami, and G. S. Kalwania, *Heterocycles*, **14,** 831 (1980).
[19] E. Ongini, E. Bonizzoni, N. Ferri, S. Milani, and M. Trampus, *J. Phamacol. Exp. Ther.*, **266**(2), 726–731 (1993); *Chem. Abstr.*, **119,** 262286 (1993).
[20] B. L. Roth, S. Tandra, L. H. Burgess, D. R. Sibley, and H. Y. Mettzer, *Psychopharmacology*, **120**(3), 365–368 (1995); *Chem. Abstr.*, **123,** 24661 (1995).
[21] M. Sansone, M. Battaglia, and F. Pavona, *Pharmacol. Biochem. Behav.*, **62**(4), 613–618 (1999); *Chem. Abstr.*, **131,** 626 (1999).
[22] R. Adams, *Organic Reactions*, **3,** 259 (1957).
[23] F. W. Mc-Lafferty, *Anal. Chem.*, **31,** 82 (1959).
[24] F. W. Mc-Lafferty, *Interpretation of Mass Spectra* (New York, W. A. Benjamin, 1973), 2nd ed.
[25] F. W. Mc-Lafferty, *Mass Spectrometry of Organic Ions*, (New York, Academic Press, 1963).
[26] R. S. Rathore, M. Jain, A. Gupta, V. Saraswat, V. Gupta, and R. R. Gupta, *Pharmazie*, **47,** 1945 (1992).

Downloaded At: 10:39 28 January 2011