Journal of Fluorine Chemistry, *44* (1989) 59–72

Received: September 17, 1988; accepted: March 19, 1989

STUDIES IN SPIROHETEROCYCLES. PART XVI. SYNTHESIS OF NEW FLUORINE-CONTAINING SPIRO-3-INDOLINE DERIVATIVES

KRISHNA C. JOSHI, ANSHU DANDIA and SANGEETA SANAN

Department of Chemistry, University of Rajasthan, Jaipur-302004 (India)

SUMMARY

The reaction of fluorinated phenylthioureas, with some new fluorine-containing 3-(2-oxocycloalkylidene)indol-2-ones (2) in ethanolic KOH medium, yielded a series of new fluorine containing 5',6'-cyclopenta-2'-thioxo-3'-phenyl spiro [3H-indole-3,4'(3'H)-pyrimidin]-2(1H)-ones and 2',4'a,5',6',7',8'-hexahydro-2'-thioxo-3'-phenyl spiro [3H-indole-3,4'(3'H)-quinazolin]-2(1H)-ones in 55-68% yields. New fluorine-containing 3-(2-oxocycloalkylidene)indol-2-ones (2) were synthesized by the Knoevenagel reaction of indole-2,3-diones with cyclic ketones (cyclopentanone/cyclohexanone) in presence of diethylamine as a basic catalyst followed by dehydration in concentrated hydrochloric acid and glacial acetic acid medium. All the compounds have been characterized by their analytical and spectral (IR, ^{1}H NMR, ^{19}F NMR and Mass) data.

INTRODUCTION

In continuation of our earlier work on the synthesis of novel fluorine-containing spiro-3-indolines [1-4], we have now synthesized a number of new fluorinated 5',6'-cyclopenta-2'-

0022-1139/89/$3.50 © Elsevier Sequoia/Printed in The Netherlands

thioxo-3'-phenyl[spiro 3H-indole-3,4'(3'H)-pyrimidin]-2(1H)-ones and 2',4'a,5',6',7',8'-hexahydro-2'-thioxo-3'-phenyl-spiro [3H-indole-3,4'(3'H)-quinazolin]-2(1H)-ones.

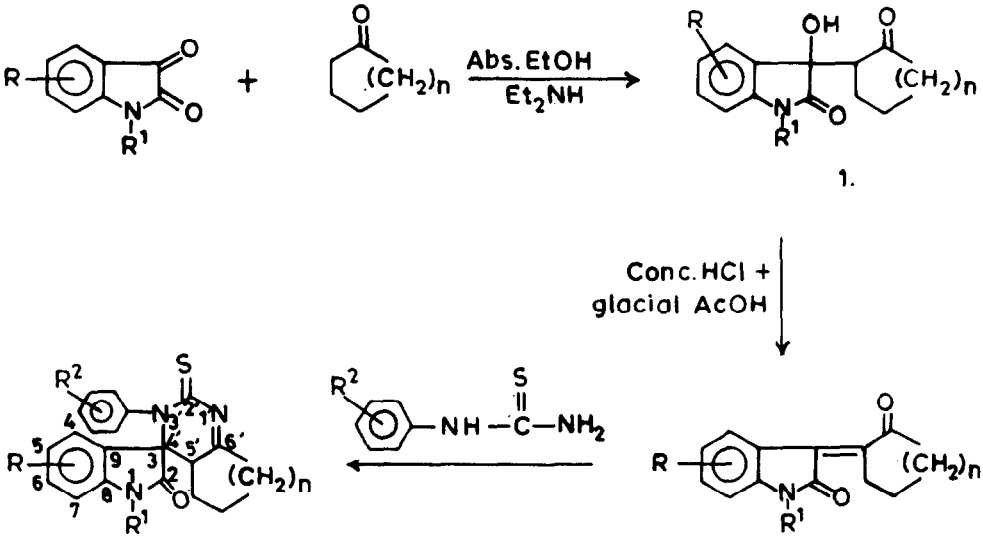
Compounds possessing the indole nucleus, including those carrying F or CF_3, groups are associated with important biological activities[5-10], as are indoles, with C-3 in the form of spiro carbon[11]. The chemical and biological behaviour of fluorine containing quinazolinethiones and pyrimidinethiones have received little attention. Pyrimidines, with halogen at active sites, undergo a great variety of reactions. Development of the antimalarial "Daraprim"[12,13] led to the preparation of a number of pyrimidines with fluorophenyl groups[14]. Fluorinated quinazolinones also exhibit CNS activity, hyposedative[15] properties and low toxicity[15]. However, no attention has been paid to the synthesis of fluorinated spiro-indole-pyrimidine/quinazoline-thiones. Prompted by these observations, we have synthesized spiro-indolines, with fluorine substituents and incorporating both the indole and pyrimidine/quinazoline moieties.

RESULTS AND DISCUSSION

New fluorine-containing 3-(2-oxocycloalkylidene)indole-2-ones (2)were synthesized by the Knoevenagel reaction of indole-2,3-diones with cyclic ketones(cyclopentanone/cyclohexanone)(Scheme 1 and Table 1). Reaction of indole-2,3-diones with cyclopentanone/

cyclohexanone in absolute ethanol using diethylamine as a basic catalyst, gave 3-hydroxy-3-(2-oxocycloalkyl)indol-2-ones(1). The latter, on dehydration in the presence of concentrated hydrochloric acid and glacial acetic acid, gave 3-(2-oxocycloalkylidene)indol-2-ones(2). During the formation of 4-trifluoromethyl and 1-methyl derivatives of 3-(2-oxocycloalkylidene)indol-2-one (2b-2d), the intermediate (1) were found to be sticky and intractable; therefore the dehydration stages were performed directly on the crude products. The structures of products (2a-2e) were established on the basis of elemental analyses and spectral studies (Tables 1 and 2). IR spectra of (2a-2e) showed the disappearance of -OH stretching at 3440 cm^{-1}, shifting of carbonyl group of the cyclic ring from 1700 to 1685 cm^{-1} due to conjugation and the -NHCO absorption at 1720 cm^{-1} [16]. Other characteristic absorptions were observed at 3200-3280(NH), 2980-2800(CH_2 of cycloalkyl) and 1620 cm^{-1}(C=C). Disappearance of -OH signal at δ 4.8 ppm in the ^1H NMR also confirmed the formation of 2 [16].

When a 3-(2-oxocyclohexylidene)indol-2-one(2) was refluxed for 10-12 hr with fluorine-containing phenylthiourea in ethanolic KOH, there was obtained the corresponding 2,4'a,5',6',7',8'-hexahydro-2'-thioxo-3'-phenyl spiro [3H-indole-3,4'(3'H)-quinazolin]-2(1H)-one(3). Similar reaction with a 3-(2-oxocyclopentylidene)indol-2-one(2) gave a 5',6'-cyclopenta-2'-thioxo-3'-phenyl spiro [3H-indole-3,4'(3'H)-pyrimidin]-2(1H)-one(3).



1.

2.

3.

	R	R^1	R^2	n
3a ,	6-F	H	4-F	2
3b ,	H	H	3-CF_3	2
3c ,	H	H	2-CF_3	2
3d ,	5-F	H	3-CF_3	2
3e ,	4-CF_3	H	3-CF_3	2
3f ,	H	CH_3	3-CF_3	2
3g ,	5-F	H	4-F	1
3h ,	H	H	3-CF_3	1
3i ,	4-CF_3	H	2-CF_3	1
3j ,	6-F	H	2-CF_3	1

	R	R^1	n
2a ,	H	H	1
2b ,	H	CH_3	2
2c ,	4-CF_3	H	2
2d ,	4-CF_3	H	1
2e ,	6-F	H	1
2f ,	5-F	H	1
2g ,	H	H	2
2h ,	5-F	H	2
2i ,	6-F	H	2

SCHEME 1

Structural assignments for the spiro products (3a-3i) were made by elemental analysis and spectra (Tables 3, 4 and 5). Retention of NHCO absorptions at 1700-1710 cm^{-1} and complete disappearance of conjugated C=O absorption at 1685 cm^{-1} and exocyclic C=C at 1620 cm^{-1} in the Ir spectra of compound(3) indicated the participation of the α, β-unsaturated carbonyl system, thereby

TABLE 1

Analytical data of new 3-(2-oxocycloalkylidene)indol-2-ones.

Compd. No.	R	R^1	n	M.P. ^oC	Molecular formula	Yield %	Elemental Analysis Calc/Found C	H	N
2a	H	H	1	269	$C_{13}H_{11}NO_2$	75	73.2/73.2	5.2/5.1	6.6/6.5
2b	H	CH_3	2	164-5	$C_{15}H_{15}NO_2$	55	74.7/74.6	6.2/6.2	5.8/5.8
2c	4-CF_3	H	2	172	$C_{15}H_{12}F_3NO_2$	55	61.0/61.1	4.1/4.2	4.7/4.7
2d	4-CF_3	H	1	214	$C_{14}H_{10}F_3NO_2$	60	59.8/59.7	3.5/3.5	5.0/4.9
2e	6-F	H	1	245-6	$C_{13}H_{10}FNO_2$	60	67.5/67.5	4.3/4.3	6.1/6.1
*2f	5-F	H	1	157	$C_{13}H_{10}FNO_2$	60			
*2g	H	H	2	169	$C_{14}H_{13}NO_2$	78			
*2h	5-F	H	2	260	$C_{14}H_{12}FNO_2$	65			
*2i	6-F	H	2	160	$C_{14}H_{12}FNO_2$	60			

marked * compounds have been reported earlier [23]. Analytical data are in agreement with our observations.

TABLE 2

Spectral data of new 3-(2-oxocycloalkylidene)indol-2-ones.

Compd. No.	IR(cm^{-1})	^1H NMR (δ ppm) =C-CH_2	N-CH_3	-CH_2-CH_2-	C-CH_2	Ar-H	NH
2a	3260-3190, 2920-2860, 1720, 1685, 1620, 1490, 1460, 1370, 1250, 1120, 1080, 1020 960, 760, 550, 500, 440	1.57(t)	-	2.20-2.53 (m)	4.10(t)	6.20-7.12 (m)	9.01 (br,s)
2b	2920-2840, 1720, 1685, 1620, 1480, 1460, 1410, 1370,1340, 1250, 1160, 1120, 1080,1010, 930, 650, 560	1.68(t)	2.01(s)	2.26-2.92 (m)	4.14(t)	6.20-7.01 (m)	-
2c	3260-3200, 2960-2820, 1725, 1690, 1620, 1465, 1320, 1260, 1185, 1150, 1050, 1030, 925, 890, 820, 780, 725, 670, 640, 590	1.68(t)	-	2.22-2.82 (m)	4.16(t)	6.40-7.32 (m)	9.12 (br,s)
2d	3280-3200, 2920-2840, 1720 1680, 1620, 1465, 1320, 1260, 1185, 1150, 1050, 1030, 925, 890, 820, 780, 725, 670, 590	1.57(t)	-	2.22-2.62 (m)	4.10(t)	6.53-7.12 (m)	9.01 (br,s)
2e	3260-3200, 2910-2840, 1720, 1685, 1620, 1460, 1420, 1330, 1290, 1220, 1180, 1110, 1040, 950, 910, 860, 710, 650	1.54(t)	-	2.22-2.58 (m)	4.10(t)	6.26-6.92 (m)	8.98 (br,s)

TABLE 3

Analytical data of new spiro-3-indoline derivatives

S. No.	Starting materials: 3-(2-oxocycloalkylidene)-indol-2-one	Starting materials: Phenyl thiourea R^2	Compd. No.	R	R^1	R^2	n	M.P. ^oC	Molecular forumula	Yield %	Elemental Analysis Calc./Found: C	H	N	S
1.	2i	4-F	3a	6-F	H	4-F	2	360	$C_{21}H_{17}F_2N_3OS$	55	63.4/63.4	4.3/4.3	10.5/10.6	8.1/8.1
2.	2g	3-CF_3	3b	H	H	3-CF_3	2	360	$C_{22}H_{18}F_3N_3OS$	60	61.5/61.5	4.2/4.1	9.8/9.7	7.4/7.4
3.	2g	2-CF_3	3c	H	H	2-CF_3	2	360	$C_{22}H_{18}F_3N_3OS$	60	61.5/61.5	4.1/4.1	9.8/9.7	7.4/7.4
4.	2h	3-CF_3	3d	5-F	H	3-CF_3	2	360	$C_{22}H_{17}F_4N_3OS$	55	59.1/59.1	3.8/3.8	9.3/9.3	7.1/7.1
5.	2c	3-CF_3	3e	4-CF_3	H	3-CF_3	2	360	$C_{23}H_{17}F_6N_3OS$	55	55.5/55.5	3.4/3.4	8.4/8.4	6.4/6.4
6.	2b	3-CF_3	3f	H	CH_3	3-CF_3	2	360	$C_{23}H_{20}F_3N_3OS$	65	62.3/62.3	4.5/4.5	9.5/9.4	7.2/7.1
7.	2f	4-F	3g	5-F	H	4-F	1	360	$C_{20}H_{15}F_2N_3OS$	65	62.7/62.6	3.9/3.9	10.9/10.9	8.3/8.4
8.	2a	3-CF_3	3h	H	H	3-CF_3	1	360	$C_{21}H_{16}F_3N_3OS$	55	60.7/60.7	3.8/3.8	10.1/10.1	7.7/7.8
9.	2d	2-CF_3	3i	4-CF_3	H	2-CF_3	1	360	$C_{22}H_{15}F_6N_3OS$	68	54.6/54.6	3.1/3.1	8.7/8.6	6.6/6.6
10.	2e	2-CF_3	3j	6-F	H	2-CF_3	1	360	$C_{21}H_{15}F_4N_3OS$	58	58.2/58.1	3.5/3.4	9.7/9.6	7.4/7.4

TABLE 4

IR spectral data and major mass fragments of new spiro-3-indoline derivatives

Compd. No.	IR(cm^{-1})	Mass spectra m/z (%)
3a	3300-3230; 2920-2860; 1700; 1600; 1590; 1460; 1390; 1330; 1230; 1140; 1050, 1020, 1000; 950; 750; 660; 610; 550; 440.	397(100)(M^+); 369(50.2)(M^+-CO); 325(40) (369-C=S); 283(23)(325-C_3H_6); 225(82)(283-$C_2H_6N_4$); 211(20) (225-CH_2); 159(50) (225-C_3H_3F).
3b	3310-3230; 2920-2840; 1700; 1600; 1590; 1460; 1400; 1320; 1220; 1130; 1020; 830; 740; 670; 620; 510; 450.	429(30.2)(M^+); 401(40)(M^+-28); 357(30.2)(401-C=S); 265(15)(343-C_5H_4N); 207(100)(357-$C_7H_7F_3$); 193(32.2) (207-CH_2); 164(18)(193-CHO).
3c	3300-3210; 2900-2800; 1710; 1600; 1580; 1450; 1400; 1330; 1230; 1130; 1010; 910; 830; 690; 610; 530; 410.	-
3d	3300-3230; 2900-2810; 1700; 1600; 1590; 1460; 1400; 1340; 1210; 1140; 1010; 890; 810; 720; 640; 500; 410.	447(29.01)(M^+); 419(100)(M^+-CO); 375(20.1) (419-C=S); 283(25)(375-C_6H_6N); 225(92)(M^+-$C_{10}H_7FN_2OS$); 211(10)(225-CH_2); 182(16)(225-HCN).
3e	3310-3210; 2920-2800; 1700; 1610; 1590; 1460; 1400; 1320; 1230; 1130; 1020; 950; 840; 710; 650; 550; 420.	-
3f	2920-2800; 1700; 1610; 1590; 1455; 1380; 1310; 1220; 1150; 1020; 880; 710; 660; 580; 410.	-
3g	3310-3210; 2900-2810; 1700; 1600; 1590; 1460; 1390; 1320; 1230; 1140; 1030; 910; 820; 680; 610; 520; 430.	-
3h	3300-3230; 2900-2820; 1700; 1610; 1590; 1460; 1390; 1310; 1220; 1140; 1040; 950; 840; 710; 620; 410.	-
3i	3310-3210; 2910-2820; 1710; 1610; 1590; 1450; 1400; 1320; 1210; 1150; 1040; 980; 810; 730; 680; 510; 420.	483(25.2)(M^+); 455(35.2)(M^+-CO); 411(100)(455-C=S); 320(25)(411-$C_5H_3N_2$); 276(85)(M^+-$C_8H_8F_3NS$); 262(19) (276-CH_2), 174(32)(262-C_6H_2N).
3j	3300-3210; 2900-2820; 1700; 1600; 1590; 1460; 1400; 1310; 1230; 1120; 1020; 950; 820; 760; 640; 530; 430.	433(100)(M^+); 405(38.8)(M^+-CO); 361(46.6)(405-C=S); 269(20)(361-C_6HF); 225(89.3)(269-C_2H_6N); 211(31.2) (225-CH_2); 123(10.1)(211-C_7H_4).

TABLE 5

NMR Spectral data of new spiro-3-indoline derivatives

Compd. No.	^{1}H NMR (δ ppm) HC-$\underline{CH_2}$	N-$\underline{CH_3}$	$\underline{CH_2}$-$\underline{CH_2}$/$\underline{CH_2}$	N=C-$\underline{CH_2}$	C-$\underline{H}$	Ar-H	NH	^{19}F NMR (δ ppm) R	R^1
3a	1.66(m)	-	2.34-2.92 (m)	3.38 (t)	4.34 (dd)	6.80-7.30 (m)	8.96 (br,s)	6-F, -113 (s)	4-F, -105.29 (s)
3b	1.66(m)	-	2.28-2.84 (m)	3.38 (t)	4.34 (dd)	6.68-7.62 (m)	8.96 (br,s)	-	3-CF_3,-135.20 (s)
3c	1.66(m)	-	2.34-2.92 (m)	3.38 (t)	4.34 (dd)	6.89-7.30 (m)	8.90 (br,s)	-	2-CF_3,-132.30 (s)
3d	1.66(m)	-	2.34-2.86 (m)	3.38 (t)	4.34 (dd)	6.80-7.30 (m)	8.96 (br,s)	5-F, -115 (s)	3-CF_3,-134.75 (s)
3e	1.66(m)	-	2.34-2.92 (m)	3.38 (t)	4.34 (dd)	6.68-7.42 (m)	8.82 (br,s)	4-CF_3,-60.70 (s)	3-CF_3,-135.32 (s)
3f	1.66(m)	2.02 (s)	2.38-3.01 (m)	3.38 (t)	4.34 (dd)	6.68-7.62 (m)	-	-	3-CF_3,-134.92 (s)
3g	1.42(m)	-	2.02-2.32 (m)	3.30 (t)	4.20 (dd)	6.68-7.62 (m)	8.96 (br,s)	5-F,-115 (s)	4-F,-105.2 (s)
3h	1.42(m)	-	2.10-2.43 (m)	3.30 (t)	4.20 (dd)	6.68-7.62 (m)	8.80 (br,s)	-	3-CF_3,-135.3 (s)
3i	1.42(m)	-	2.10-2.43 (m)	3.30 (t)	4.20 (dd)	6.80-7.32 (m)	8.96 (br,s)	4-CF_3,-61.01 (s)	2-CF_3,-132.2 (s)
3j	1.42(m)	-	2.02-2.42 (m)	3.30 (t)	4.20 (dd)	6.80-7.42 (m)	8.90 (brs)	6-F,-113 (s)	2-CF_3,-132.01 (s)

leading to the formation of spiroheterocyclic compounds at position-3 of the 2-oxoindoles. Other characteristic absorptions were observed at 3230-3300(NH), 1590(C=N), 1460-1450(C=N-C=S) and 1230-1210(C=S) [16,17]. The structure was further confirmed by the ^{1}H NMR spectra. Methine protons displayed a double doublet at δ 4.34 ppm because this proton coupled with nearby methylene protons with different dihedral angles. The methylene protons of the cycloalkyl ring appeared in the form of three clusters viz. a multiplet at δ1.66-1.42(CH-$\underline{CH}_2$-CH_2), multiplet from δ2.34-2.92(integrating for 4$\underline{H}$ in cyclohexyl and $\underline{2H}$ in cyclopentyl) and a triplet at δ3.38 ppm(2H,-N=C-$\underline{CH}_2$). Apart from these, multiplets for aromatic protons at δ6.83-7.42 and a singlet at δ 8.96 ppm for NH were also observed.

Additional support for the formation of spiro products was obtained by mass spectra as molecular ion peaks M^+ at 397(3a), 429(3b), 447(3d), 483(3i) and 433(3j) corresponding to their molecular masses. Characteristic peaks were observed at M^+-28 in mass spectra of all the compounds either by the loss of neutral CO or C_2H_4 molecule. This is followed by the loss of C=S radical to give peaks at (M-72). Other characteristic peaks are shown in Table 4.

The presence and position of fluorine were confirmed by the ^{19}F NMR spectra, details being given in Table 5. The single fluorine attached to indole ring at position 5 in compound (3d,3g) appeared as a singlet at δ -115 and the fluorine at position 6 in compounds(3a,3j) was observed at δ -113 ppm. A characteristic signal in the range of δ-60.70 to δ-57.80 ppm

was assigned to the trifluoromethyl group at the 4-position of the indole ring in compounds (3e,3i). The CF_3 group attached at 3-position of phenyl ring in compounds(3b,3d,3e, 3f,3h) was observed at δ -135.2-134.75 ppm and CF_3 at position-2 in compounds (3c,3i,3j) at δ -132.3 ppm. The single fluorine attached to the phenyl ring of compounds (3a,3g) appeared at δ -105.29 ppm.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on Perkin-Elmer machine (model-557) in KBr discs. ^1H and ^{19}F NMR were recorded on a Jeol machine(model-FX 90 Q) using trifluoroacetic acid and deuterated dimethyl sulfoxide respectively as solvents, tetramethylsilane as internal standard for ^1H NMR at 89.55 MHz and hexafluorobenzene as external standard for ^{19}F NMR at 84.25 MHz. Mass spectra were recorded on Kratos 30 and 50 mass spectrometers. All compounds were homogeneous on TLC in various solvent systems. 5-Fluoro-indole-2,3-dione 6-fluoro-indol-2,3-dione and 4-trifluoromethyl-indole-2,3-dione were prepared by literature methods [18-20]. Fluorinated phenylthioureas were prepared by Douglass and Danis' method [21,22].

1,3-Dihydro-6-fluoro-3-hydroxy-3-(2-oxocyclopentyl)indol-2-one (1)

A mixture of 6-fluoro-indole-2,3-dione (0.01 mole) cyclo-pentanone (0.013 mole) and diethylamine (0.3 ml) in 30-40 ml

absolute ethanol was refluxed for 1 hr on a steam bath. After standing for 48 hrs at room temperature, a solid separated and was filtered, dried and recrystallized from ethanol. M.P. 160°C, yield 65%. Elemental analysis : Found : C, 62.7; H, 4.8; N, 5.7. Required: C, 62.6; H, 4.8; N, 5.6.

Reactions of 4-trifluoromethyl [20] and 1-methyl-indole-2,3-dione and cyclic ketones under similar conditions gave a sticky mass which was directly dehydrated to give products (2).

1,3-Dihydro-6-fluoro-3-(2-oxocyclopentylidene)indole-2-one (2)

A mixture of 6-fluoro-3-hydroxy-3-(2-oxocyclopentyl)indol-2-one (0.01 mole), 0.5 ml conc. HCl and 15 ml glacial acetic acid was heated for 15 minutes and poured into ice-cold water to yield the desired compound. The solid, thus obtained, was filtered, dried in air and recrystallized from ethanol. M.P. 245-6°C, yield 60% . Data for the new compounds (2a-2e) are recorded in Table 1 and Table 2.

Synthesis of 2',4'a,5',6',7',8'-hexahydro-2'-thioxo-4-trifluoromethyl-3'-(3-trifluoromethylphenyl)-spiro-[3H-indole-3,4'(3'H)-quinazolin]-2(1H)-one (3e)

A mixture of 1,3-dihydro-4-trifluoromethyl-3-(2-oxocyclohexylidene)indol-2-one (2c) (0.01 mole) and 3-trifluoromethyl phenylthiourea [21] (0.01 mole), in 30 ml ethanolic KOH was refluxed for 12 hrs. The mixture was kept overnight. The

solid, thus obtained, was filtered off dried and recrystallized from ethanol. M.P. >360, yield 55%.

All other compounds(3a-3f)were synthesized by similar method. The analytical data are listed in Table 3, and spectral data in Tables 4 and 5.

Synthesis of 5',6'-cyclopenta-2'-thioxo-5-fluoro-3'-(4-fluoro-phenyl)-spiro[3H-indole-3,4'(3'H)-pyrimidin]-2(1H)-ones (3g)

Reaction of 1,3-dihydro-5-fluoro-3-(2-oxocyclopentylidene)-indol-2-one (2f) (0.01 mole) with 4-fluorophenylthiourea (0.01 mole) was carried out by refluxing for 12 hr in ethanolic KOH media. The reaction mixture was kept for 24 hrs at room temperature. The solid, thus obtained, was filtered off, dried and recrystallized from ethanol. M.P. >360, yield 65%.

All other compounds 3g-3i were synthesized by the same method. The analytical and spectral data of all the compounds are recorded in Tables 3,4 and 5.

ACKNOWLEDGEMENT

The authors are thankful to the Ministry of Defence,New Delhi, India for financial support.

REFERENCES

1 K.C. Joshi, V.N. Pathak and R. Gupta, J. Fluorine Chem., 38, (1988) 153.

2 K.C. Joshi, R. Jain, A. Dandia and V. Sharma, J. Heterocyclic Chem., 23 (1986) 97.

3 K.C. Joshi, A. Dandia and N. Ahmed, Heterocycles. 24(9), (1986) 2479.

4 K.C. Joshi, P. Chand and R. Patni, Heterocycles, 16 (1981) 1555.

5 V.M. Sim, J. Forensic Sci., 6 (1961) 39.

6 M. Mueller, Med. Exp., 7 (1962) 155.

7 B.B. Molloy, U.S. Pat., 3 882 236 (1975); Chem. Abstr., 83 (1975) 79075y.

8 B.A. Whittle and E.H.P. Young, J. Med. Chem., 6 (1963) 378.

9 A. Kalir and S. Szara, J. Med. Chem., 6 (1963) 716.

10 J. Szmuszkoviz, U.S. Pat., 3 551 451 (1970); Chem. Abstr., 74 (1971) 141523n.

11 K.C. Joshi, R. Jain and P. Chand, Heterocycles, 23(4) (1985) 957.

12 Hitchinoes. Rollo, Goodwin and Watney, Trans. Roy. Soc. Trop. Med. Hyg., 46 (1952) 467.

13 Falco, Goodwin, Hitchings, Rollo and Russell, J. Pharmacol., 6 (1951) 185.

14 Russell and Hitchings, J. Am. Chem. Soc., 73 (1951) 3763.

15 T.A. Voronina, G.N. Gorduchuk, S.A. Andronati, T.L. Goribova, Z.I. Zhetina, Khim. Farm Zh., 15(7) (1981) 55; Chem. Abstr., 95 (1981) 203865v.

16 K.M. Hassan and Z.H. Khalil, J. Prakt. Chem., 321 (1979) 870.

17 R.M. Silverstein, G.C. Bassler and T.C. Morrill, 'Spectrometric Identification of Organic Compounds', VI edn. (1981) 105.

18 Y.Q. Yen, N.P. Buu-Hoi and N.D. Xuong, J. Org. Chem., 23 (1958) 1858.

19 P.W. Salder, J. Org. Chem., 21 (1956) 169.

20 P.W. Maginnity and C.A. Gautin, J. Am. Chem. Soc., 73 (1951) 3579.

21 H.A. Lubs and A.L. Fox, U.S.Pat., 2 061 243; Chem. Abstr., 31 (1937) 885.

22 F. Kurzer and J. Canelle, Tetrahedron, 19 (1963) 1603.

23 S. Garg, Ph.D. Thesis, University of Rajasthan, Jaipur, India, 1984.