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SYNTHESIS, ^{19}F NMR SPECTRAL STUDIES AND ANTIBACTERIAL EVALUATION OF SOME NEW FLUORINE CONTAINING INDOLE DERIVATIVES*

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SUMMARY

The condensation behaviour of various fluorine containing 3-indolylimino derivatives with mercaptoacetic acid and with chloroacetyl chloride has been studied. The cyclocondensation of 3-arylimino-2H-indol-2-ones(III; Ar = 4-FC_6H_4, 3-$CF_3C_6H_4$, 2-Cl-3-$CF_3C_6H_3$, 2,3,4,5-tetra-FC_6H and 2,3,4,6-tetra-FC_6H) with mercaptoacetic acid yielded 3'-phenylspiro[3H-indole-3,2'-thiazolidine]-2,4'(1H)-diones (IV) in 75-90% yields. Reaction of anil (III; Ar = 2,3,4,5-tetra-FC_6H) with chloroacetyl chloride gave spiro[azetidine-2,3'- 3H indole]-2',4(1'H)-dione (VI) in 75% yield. However, similar reactions in the case of 3-(pentafluorophenylimino)-2H-indol-2-one did not give the expected spiro compounds: 3-indolylmercaptoacetic acid (V) was obtained with mercaptoacetic acid, while the product from chloroacetyl chloride could not be characterized. Further, the reactions of various fluorine containing isatin-3-hydrazones (VII; Ar = 4-FC_6H_4, C_6F_5, 1,2,4-triazino[5,6-b]indole,

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benzimidazole) with mercaptoacetic acid also did not give corresponding spiro compounds and unchanged compounds (VII) were recovered.

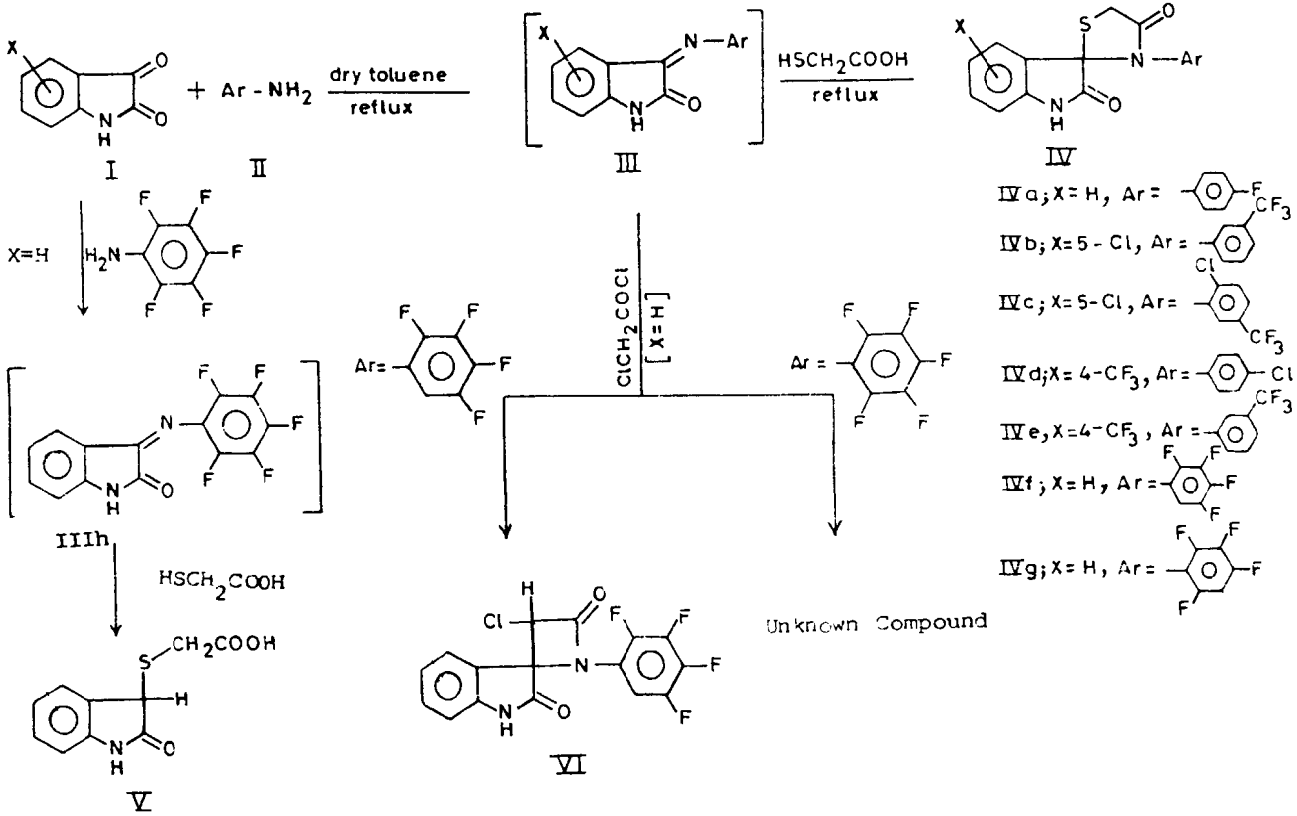
The compounds synthesized have been characterized by their analytical and spectral (IR, ^{1}H NMR & ^{19}F NMR) data, and were screened for antibacterial activity.

INTRODUCTION

We have a continuing interest in the cyclization reactions of 3-indolylimines [1-3]. The spiro[indole-thiazolidine]diones find useful pharmaceutical applications [4-9] and compounds containing the azetidine nucleus are also biologically important [10,11] but scanty information is available regarding their fluorinated analogs. The reaction of 3-indolylimines with mercaptoacetic acid is reported to give spiro[indole-thiazolidine]diones in 40-65% yield [1] and with chloroacetyl chloride, spiro[azetidine-2,3'-indole]diones are reported in 40-70% yield [3]. Rather surprisingly, no report describes the effect of fluorine incorporation on the course of synthesis as well as bioactivity.

These findings prompted us to study the reactions of various fluorine containing 3-arylimino-2H-indol-2-ones (III; Scheme 1) with mercaptoacetic acid and with chloroacetyl chloride.

Isatin-3-hydrazones have also been reported as potential anticonvulsants [12]. We have also synthesized various new fluorinated isatin-3-hydrazones and extended our studies to observe their condensation behaviour towards mercaptoacetic acid (Scheme 2).


dry toluene
reflux
HSCH2COOH
reflux
I
II
III
IV
IVa; X = H, Ar =
IVb; X = 5-Cl, Ar =
IVc; X = 5-Cl, Ar =
IVd; X = 4-CF3, Ar =
IVe, X = 4-CF3, Ar =
IVf; X = H, Ar =
IVg; X = H, Ar =
X=H
IIIh
HSCH2COOH
ClCH2COCl
[X=H]
Ar=
Ar =
V
VI
Unknown Compound

Scheme 1.

The role of fluoroaryl groups in cyclocondensation reactions has also been studied and it was found that the course of the reaction differs when different fluorinated anilines and hydrazones, are subjected to cyclocondensation.

RESULTS AND DISCUSSION

New fluorine containing 3'-phenylspiro[3H-indole-3,2'-thiazolidine]-2,4'(1H) diones (IV) have been synthesized in improved yields by an elegant one-step procedure[1]involving condensation of indole-2,3-diones (I) with fluorinated anilines (II) in dry toluene under reflux yielding 3-arylimino-2H-indol-2-ones (III) which, in situ, were cyclized with mercaptoacetic acid.

The reactions of III(Ar = 4-FC_6H_4, 3-$CF_3C_6H_4$, 2-Cl-5-$CF_3C_6H_3$, 2,3,4,5-tetra-FC_6H, 2,3,4,6-tetra-FC_6H) with mercaptoacetic acid gave the expected spiro compounds IV in 75-90% yields (Scheme 1). Introduction of fluorine into the indole or aryl ring along with fifty percent excess of mercaptoacetic acid, gave the spiro compounds in enhanced yields. These spiro compounds(IV) were characterised (see Table 3) by IR absorption bands at 3350-3200(>NH) and 1720-1680(both >C=O) cm^{-1} and ^1H NMR signals at δ 3.8-4.15(dd, 2H, -CH_2-), 6.7-7.6(m, aromatic protons) and 8.9-9.2(s, 1H, NH) ppm. The structure was further confirmed by ^{13}C NMR spectra of IVb. Two characteristic signals were observed in the carbonyl region at δ 176.27 and at 171.78 ppm. The former can be assigned to the carbonyl group of thiazolidene ring while the latter is attributed to the indole carbonyl group. The intensity of the indole carbonyl group (imidic >C=O) is slightly more due to its

more effective relaxation. The other signals are observed at δ 147.27 to 115.38 (signal due to aromatic ring carbon), 110.72 (spiro carbon) and at 69.01 (-S-$\underline{C}H_2$-CO) ppm. Presence and position of fluorine was confirmed by ^{19}F NMR spectra (Table 4). A single fluorine attached to aryl ring (IVa) was observed at δ -111.26 ppm. Trifluoromethyl groups of the indole ring and the aryl ring were observed in IVe at δ -63.075 and -65.142 ppm respectively. In spiro compounds IVf and IVg four fluorines of the tetrafluoroaryl groups were observed.

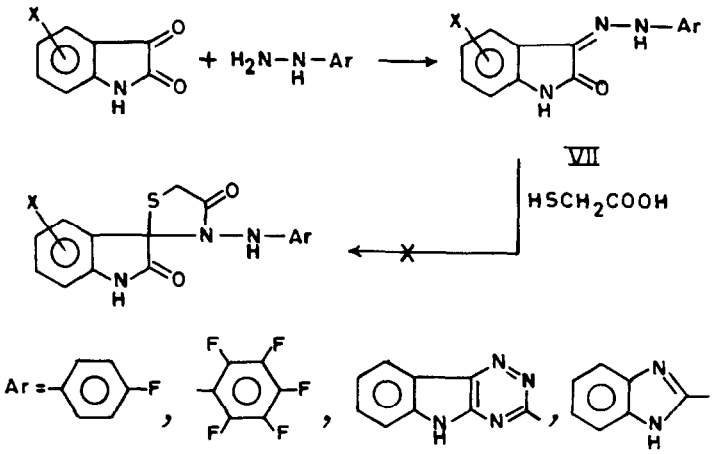
While increased fluorine incorporation in the series (IVa-g) resulted in the cyclocondensation reaction being more facile and requiring less reaction time with enhanced yields, the analogous reaction of 3-(pentafluorophenylimino)-2H-indol-2-one (IIIh) resulted in the formation of a product (V) which surprisingly displayed no fluorine signal in ^{19}F NMR. The IR spectrum of this compound displayed absorption bands at 3450-3400 (-OH), 3380-3330 (>NH), 1710(>C=O) cm^{-1} and ^{1}H NMR signals at δ 4.0-4.5(dd, 2H, -$\underline{C}H_2$-), 5.1(s, 1H, -$\underline{C}H$), 6.68-7.80(m, aromatic protons), 8.55(s,1H, NH) and 9.13(s, br, $\underline{O}H$) ppm. Further, in the mass spectrum, the molecular ion peak was observed at m/z 223 (18.5%) and other peaks at 221(M^+-2H), 179(M^+-CO_2), 151(179-CO), 132(M^+-S-CH_2CO_2H). Hence, compound V was 3-indolylmercaptoacetic acid, and the pentafluorophenyl group was eliminated in the process [C_f 13]

Some fluorine containing 3-arylimino-2H-indol-2-ones(IIIf,g,h) have been isolated as crystalline compounds and the details of their ^{19}F NMR chemical shifts are given in Table 4.

Further, we have also studied the reaction of anils(IIIf and h) with chloroacetyl chloride. It was confirmed that the reaction of IIIf yielded the corresponding spiro [azetidine-2,3'- 3H indole]-2',4(1'H)-dione (VI) in 75% yield, as reported earlier [3]. This compound was characterized by IR absorption band at 1705(monocyclic β-lactam ring) and 750-780(C-Cl group) and ^{1}H NMR signal at δ 4.35 (s, 1H, CH) along with aromatic protons in the region 6.9-7.8 and NHproton at 8.65 ppm[3]. In the ^{19}F NMR spectrum signals were observed at δ -138.338(t, F^4), -157.576(t, F^3), -171.246(br, F^2) and -183.565(d, F^5) ppm.

However, a similar raction with 3-pentafluorophenylimino-2H-indol-2-one (IIIh) did not give the expected spiro compound as found from its spectral studies. Although in the ^{19}F NMR spectrum of the product, a broad hump was observed in the region δ -156.28 to -179.56 ppm, no clear splitting pattern was observed for a C_6F_5 group and its presence could not be confirmed : studies are continuing.

The reaction of isatin-3-phenylhydrazone with mercaptoacetic acid is reported [14] to give the corresponding spiro compound. When 4-fluorophenyl (VIIa) and pentafluorophenyl (VIIb) hydrazones of 6-fluoroisatin were subjected to analogous reactions, no spiro compound was obtained and the unchanged hydrazone was recovered. Even prolongation of reaction time and presence of a dehydrating reagent e.g. $ZnCl_2$, could not facilitate the reaction. 5-Fluoro-isatin-3-hydrazones of 3-hydrazino triazino-indole (VIIc) and 2-hydrazino benzimidazole (VIId) also behaved similarly and no spiro compound was obtained (Scheme-2).



X = 5-F, 6-F (See Table 5)

Scheme 2.

Formation of fluoroisatin-3-hydrazones was confirmed in the IR by the disappearance of one carbonyl absorption at 1690 cm^{-1} and the appearance of a C=N absorption at 1625 cm^{-1}. The ^{1}H NMR spectral displayed indole NH at δ 9.7 and imino NH at 8.8 ppm along with aromatic protons. In the ^{19}F NMR spectrum of VIIb (X = 6-F, Ar = C_6F_5), the fluorine attached to the indole ring was observed at δ -112.246(S) and the five fluorines of the C_6F_5 group were observed as three clusters in which the signal for F^4 shifted remarkably and appeared at -105.644 (t,F^4): other signals were observed at -151.857(dd, F^2F^6) and -161.297(m, F^3F^5) ppm.

Thus, our observations indicated that fluoroaryl groups play a significant role in various cyclocondensation reactions.

Evaluation of Antibacterial activity

Some of the synthesized compounds were screened against gram positive bacteria - Staphylococcus albus and gram negative bacteria Escherichia coli. The Kirby Bauer method [15] was used in screening the ethanolic solution of compounds for antibacterial activity. The Oxford strain of Staphylococcus albus (NCTC 6571) was always kept as control for both the tests. The area of inhibition of growth of bacteria, produced by diffusion of compounds from disc to the surrounding medium was measured in milimeter (mm). The results obtained are given in Table-1.

The results indicate that the incorporation of fluorine in a compound increases the antibacterial activity against both gram-positive and gram-negative bacteria. The isatin-3-anils(III) and isatin-3-hydrazones (VII) are good antibacterial agents.

EXPERIMENTAL

Melting points were determined in open glass capillary and were uncorrected. IR spectra were recorded on a Perkin-Elmer(model-577) in KBr pellets. ^{1}H and ^{19}F NMR were recorded on Jeol (model-FX 90Q) using $CDCl_3$ as solvent at 89.55 and 84.25 MHz respectively. TMS was used as internal reference for ^{1}H NMR and hexafluorobenzene as external reference for ^{19}F NMR. Mass spectra were recorded on Kratos 30 and 50 mass spectrometers. All compounds were homogeneous on TLC in various solvent systems. 5-Fluoroindole-2,3-dione, 6-fluoro-indol-2,3-dione, 4-trifluoromethylindole-2,3-dione and 5-chloroindole-2,3-dione were prepared by literature methods [16-19].

TABLE 1

Antibacterial Activity

Compound No.	Gram Negative Bacteria	Gram Positive Bacteria	Standard strain for comparison (NCTC 6571)
IIIf	12 mm (P.S.)	8 mm (P.S.)	8 mm (P.S.)
IIIg	14 mm (S)	10 mm (P.S.)	10 mm (P.S.)
IVa	R	R	8 mm (P.S.)
IVb	8 mm (P.S.)	R	8 mm (P.S.)
IVc	R	8 mm (P.S.)	8 mm (P.S.)
IVd	10 mm (P.S.)	8 mm (P.S.)	-
IVf	12 mm (P.S.)	14 mm (S)	8 mm (P.S.)
V	8 mm (P.S.)	12 mm (P.S.)	R
VI	12 mm (P.S.)	10 mm (P.S.)	14 mm (S)
VIIa	10 mm (P.S.)	8 mm (P.S.)	12 mm (P.S.)
VIIb	16 mm (S)	14 mm (S)	14 mm (S)

R = Resistant Range $<$ 8 mm zone per disc.

P.S. = Partial sensitive range 8 mm to 12 mm per disc.

S = Sensitive range $>$ 12 mm per disc.

Synthesis of 3-(2,3,4,6-tetrafluorophenyl)imino-2H-indol-2-one (IIIg)

A mixture of indole-2,3-dione (0.01 mol) and 2,3,4,6-tetrafluoroaniline (0.01 mol) was refluxed in absolute ethanol (20 ml) in presence of 2-3 drops of glacial acetic acid for thirty minutes [20]. On cooling, crystals separated out and were filtered and recrystallized from ethanol as yellow needles. M.P. 199°C, yield 79% . Elemental analysis : Found : C, 57.2; H, 2.1; N, 9.6. $C_{14}H_6F_4N_2O$ Requires : C, 57.1; H, 2.0; N, 9.5.

IIIh (Ar = C_6F_5); M.P. 264°C, yield 76% . Elemental Analysis : Found : C, 53.7; H, 1.7; N, 8.8. $C_{14}H_5F_6N_2O$ Requires: C, 53.8; H, 1.6; N, 8.9.

Synthesis of 3'-(2,3,4,5-tetrafluorophenyl)spiro[3H-indole-3,2'-thiazolidine]-2,4'(1H)-dione (IVf)

A mixture of indole-2,3-dione (0.01 mol) and 2,3,4,5-tetrafluoroaniline (0.01 mol) was refluxed in dry toluene for one hour with azeotropical removal of water formed. After cooling the mixture, mercaptoacetic acid (0.011 mol) was added and refluxing was continued for two hours under similar conditions. The whole mixture was then allowed to cool to room temperature and the supernatant liquid was removed under reduced pressure. The solid compound (IVf) so obtained was recrystallized from benzene. M.P. 176°C, yield 82% . All other compounds (IVa-IVg) were synthesized by the same method. The analytical and spectral data are recorded in Tables-2,3 & 4.

TABLE 2

Analytical data of 3'-phenylspiro[3H-indole-3,2'-thiazolidine]-2,4'(1H)-diones (IV)

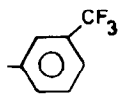
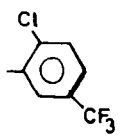
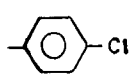
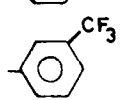
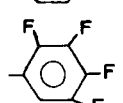
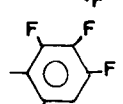
Compd No.	X	Ar	M.P. °C	Yield %	Molecular formula	Elemental Analysis Calcd/Found			
						C	H	N	S
IVa	H		244[a]	78	$C_{16}H_{11}FN_2O_2S$	-	-	-	-
IVb	5-Cl		216	75	$C_{17}H_{10}ClF_3N_2O_2S$	51.1 / 51.2	2.5 / 2.4	7.0 / 7.1	8.0 / 8.1
IVc	5-Cl		146	74	$C_{17}H_9Cl_2F_3N_2O_2S$	47.1 / 47.0	2.0 / 2.1	6.4 / 6.5	7.3 / 7.2
IVd	4-CF_3		224	76	$C_{17}H_{10}ClF_3N_2O_2S$	51.1 / 51.0	2.5 / 2.6	7.0 / 7.1	8.0 / 7.9
IVe	4-CF_3		273	77	$C_{18}H_{10}F_6N_2O_2S$	50.0 / 50.1	2.3 / 2.2	6.4 / 6.4	7.4 / 7.5
IVf	H		176	82	$C_{16}H_8F_4N_2O_2S$	52.1 / 52.2	2.1 / 2.0	7.6 / 7.5	8.6 / 8.7
IVg	H		209	80	$C_{16}H_8F_4N_2O_2S$	52.1 / 52.0	2.1 / 2.2	7.6 / 7.7	8.6 / 8.6

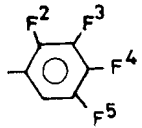
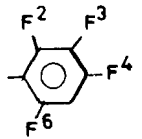
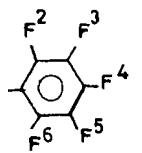
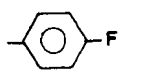
TABLE 3

IR and ^{1}H NMR spectral data of new 3'-phenylspiro[3H-indole-3,2'-thiazolidine]-2,4'(1H)-diones(IV)

Compd No.	IR (cm^{-1})	^{1}H NMR (δ ppm)		
		$-CH_2-$	Ar-H	NH
IVb	3340-3260, 1710, 1680, 1600, 1470, 1400, 1320, 1260, 1150, 1030, 960, 850, 760, 690, 540.	3.9-4.1 (dd)	6.9-7.8 (m)	8.9 (br,s)
IVc	3290-3210, 1705, 1680, 1590, 1450, 1360, 1260, 1170, 1060, 940, 860, 750, 640, 520.	3.95-4.1 (dd)	7.0-7.85 (m)	9.05 (br,s)
IVd	3280-3200, 1720, 1690, 1600, 1510, 1430, 1350, 1240, 1190, 1080, 930, 820, 740, 650, 560.	4.0-4.15 (dd)	6.95-7.9 (m)	9.1 (br,s)
IVe	3330-3250, 1710, 1690, 1600, 1480, 1350, 1270, 1140, 1070, 940, 830, 740, 650, 560.	3.85-4.15 (dd)	6.9-7.75 (m)	9.0 (br,s)
IVf	3310-3240, 1700, 1680, 1580, 1470, 1350, 1270, 1180, 1050, 960, 840, 720, 610, 530.	3.9-4.15 (dd)	7.05-7.80 (m)	8.95 (br,s)
IVg	3320-3270, 1710, 1690, 1600, 1480, 1320, 1260, 1150, 1030, 920, 810, 720, 610, 540.	4.05-4.15 (dd)	7.1-7.9 (m)	9.15 (br,s)

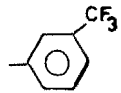
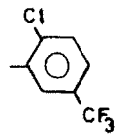
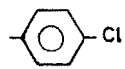
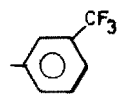
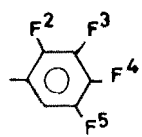
TABLE 4

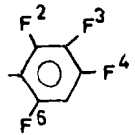
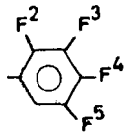
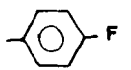
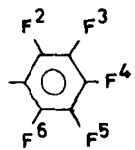
^{19}F NMR spectral data of compounds III, IV, VI & VII.(δ ppm)

Compd No.	X	Ar			
IIIf	-		-138.868(F^4), (t)	-146.650(F^3), (t)	-154.678(F^2), (br) 172.284(F^5) (d)
IIIg	-		-132.548(F^6), (s)	-142.642(F^2), (br)	-153.336(F^4) (d) -159.172(F^3) (t)
IIIh	-		-161.877(F^2F^6), (sextet)	-165.583(F^3F^5), (heptate)	-175.48 (F^4) (t)
IVa	-		-111.262(4-F) (s)		

(continued)

TABLE 4 (cont.)

Compd No.	X	Ar		
IVb	-		- 63.249 (3-CF_3) (s)	
IVc	-		- 64.046 (5-CF_3) (s)	
IVd	4-CF_3, -62.968 (s)		-	
IVe	4-CF_3, -63.075 (s)		- 65.142 (3-CF_3 (s)	
IVf	-		-140.852 (F^4), (t)	-158.459 (F^3), (t)
				-174.677 (F^2) (b)
				-193.211 (F^5) (d)

IVg	-		-135.242(F^6), (s)	-148.366(F^2), (b)	-151.378(F^4) (d) -152.432(F^3) (t)
VI	-		-138.338(F^4), (t)	-157.576(F^3), (t)	-171.246(F^2) (b) -183.565(F^5) (d)
VIIa	6-F,-113.042		-109.346(4-F) (s)		
VIIb	6-F,-112.246		-105.644(F^4), (t)	-151.857(F^2F^6), (dd)	-161.297(F^3F^5) (m)

Synthesis of 3-indolylmercaptoacetic acid (V)

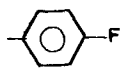
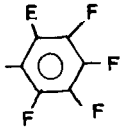
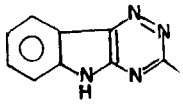
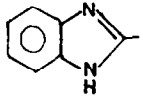
A mixture of indole-2,3-dione (0.01 mol), pentafluoroaniline (0.01 mol) and mercaptoacetic acid (0.011 mol) was treated as in case IVf above. The solid compound, so obtained, was recrystallized from ethanol. M.P. 186°C, yield 78% . Elemental Analysis: Found : C, 53.9; H, 4.0; N, 6.3; S, 14.4. $C_{10}H_9NO_3S$ Requires : C, 53.8; H, 4.0; N, 6.2; S, 14.3. Spectral data : IR: 3450-3420 (-OH), 3400-3350(>NH), 1710(>C=O), 1520, 1460, 1410, 1340, 1250, 1170, 1120, 1010, 930, 840, 750 cm^{-1}. ^1H NMR : δ4.0-4.5(dd, 2H, -CH_2), 5.1(s, 1H, -CH), 6.68-7.80(m, aromatic protons), 8.55(s, 1H, NH), 9.13(s, br, OH), MS : m/z 223(M^+)(18.5), 221(55) (M^+-2H), 179(28)(M^+-CO_2), 151(34.5) (179-CO), 132(27) ($M^+-SCH_2CO_2H$).

Synthesis of 3-chloro-1-(2,3,4,5-tetrafluorophenyl)spiro-[azetidine-2,3'-[3H]indole]-2',4(1'H)-dione (VI)

To a well stirred solution of 3-(2,3,4,5-tetrafluorophenyl)-imino-2H-indol-2-one (IIIf) (0.01 mol) and triethylamine(0.01 mol) in dry benzene, was added chloroacetyl chloride (0.01 mol) dropwise at room temperature[22]. After addition of chloroacetyl chloride was complete, the mixture was stirred for extra 5 hours and left at room temperature for 3 days. The precipitated triethylamine hydrochloride was filtered off and washed thoroughly with dry benzene. The solvent from the filtrate was evaporated in vacuo and the residue (VI) was then recrystallized from benzene-petroleum ether. M.P. 218°C, yield 75% . Elemental analysis : Found :C,51.7; H, 1.9; N, 7.6. $C_{16}H_7ClF_4NO_2S$. Requires : C, 51.8; H, 1.8; N, 7.5. Spectral data : IR : 3350-3280(>NH), 1705(monocyclic β-lactam ring)

TABLE 5

Analytical data of isatin-3-hydrazones (VII)

Compd No.	X	Ar	M.P. °C	Yield %	Molecular formula	Elemental Analysis Calcd/Found		
						C	H	N
VIIa	6-F		244	74	$C_{14}H_9F_2N_3O$	61.5 61.6	3.2 3.3	15.3 15.4
VIIb	6-F		252	79	$C_{14}H_5F_6N_3O$	48.6 48.7	1.4 1.3	12.1 12.0
VIIc	5-F		300	71	$C_{17}H_{10}FN_7O$	58.7 58.6	2.8 2.9	28.2 28.1
VIId	5-F		120	73	$C_{15}H_{10}FN_5O$	61.0 61.1	3.3 3.2	23.7 23.8

1690(>C=O), 1550, 1430, 1360, 1230, 1180, 1050, 960, 850, 780-750(C-Cl group), 690 cm^{-1}. ^1H NMR : 4.35(s, 1H, CH), 6.9-7.8(m, aromatic protons), 8.65(s, 1H, NH) ppm.

Synthesis of 6-fluoro-3-[(pentafluorophenyl)hydrazone]-1H-indole-2,3-dione (VIIb)

A mixture of 6-fluoroindole-2,3-dione (0.01 mol) and pentafluorophenyl hydrazine (0.01 mol) was refluxed for 4 hours in absolute ethanol with one drop of glacial acetic acid. On cooling the mixture, a yellow crystalline compound separated which was filtered and recrystallized from benzene. M.P. 252°C, yield 79% .

The other hydrazones (VIIa-VIId) were synthesized following the same procedure. The analytical data are given in Table-5.

4-Fluorophenyl hydrazine[23,24], pentafluorophenyl hydrazine [25], 3-hydrazino-1,2,4-triazino[5,6-b]indole[26]and 2-hydrazino benzimidazole[27]were synthesized following the literature procedure.

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REFERENCES

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

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

3 K.C. Joshi, R. Jain and V. Sharma, J. Indian Chem. Soc., LXIII (1986) 430.

4 M. Wolf and A.A. Mascitti, U.S.Pat., 3 458 525 (1969); Chem. Abstr., 72 (1970) 21715p.

5 G.C. Rovnyak, V.L. Narayanan and R.D. Hauwrtz, U.S.Pat., 4 053 613 (1977); Chem. Abstr., 88 (1978) 22889r.

6 B.M. Kirichenko, A.V. Vladzimirskaya and P.M. Steblyak, Farm. Zh. (Kiev), (1981) 61; Chem.Abstr., 95 (1981) 169060s.

7 B.J. Sweetman, M. Bellas and L. Field, J. Med. Chem., 12 (1969) 888.

8 F.D. Popp and M. Rajopadhye, J. Heterocycl. Chem., 21 (1984) 289.

9 A.M. El-Khawaga and A.M. Abd-Alla, M.T. Ismail, Bull. Fac. Sci., 11(1) (1982) 9.

10 L. Fowden, J. Biochem., 64 (1956) 323.

11 D.T. Propop, Acta Biochem. Biophys., 175 (1969) 156.

12 F.D. Popp, J. Heterocycl. Chem., 21(6) (1984) 1641.

13 P. Tarrant, Fluorine Chem. Rev., Vol. 8 (1977) 19.

14 K.M. Hassan and Z.H. Khalil, Z. Naturforsch., 34b (1969) 621.

15 K. Bauer, Sherris and Turck, Am. J. Clin. Pathol., 45 (1966) 492.

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

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

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

19 Heller, Ber., 43 (1910) 2895.

20 R.M. Piccrelli and F.D. Popp, J. Heterocycl. Chem., 10 (1973) 671.

21 E. Piscopo, M.V. Diurno, M. Antonucci, F. Imperadrice, V. Caliendo and M.T. Cataldi, Boll-Soc. Ital. Biol. Sper., 61(9) (1985) 1327; Chem. Abstr., 104 (1984) 65714w.

22 K.M. Hassan, A.K. El-Shavei and H.S. El-Kashev, Z. Naturforsch Teil B, 33 (1978) 1515.

23 F.D. Chattaway and W.G. Humprey, J. Chem. Soc., (1927) 1323.

24 H. Suschitzky, J. Chem. Soc., (1953) 3326.

25 J.M. Birchall, R.N. Haszeldine and A.R. Parkinson, J. Chem. Soc., (1966) 4966.

26 K.C. Joshi and P. Chand, J. Heterocycl. Chem., 17 (1980) 1783.

27 N.P. Bednyagina and I.Y. Postovakii, Zh. Obsch. Khim., 30 (1960) 1431.