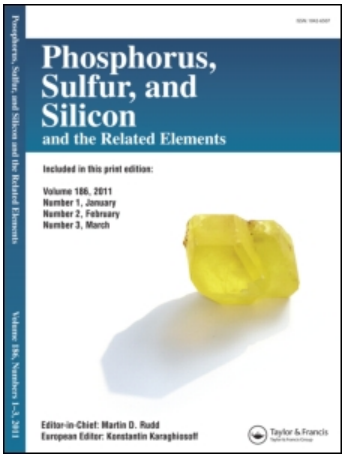

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FACILE SYNTHESIS OF SOME NEW FLUORINE CONTAINING SPIRO [3H-INDOLE-3,2'TETRAHYDRO-1,3-THIAZINE].2,4'(1H)-DIONES

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FACILE SYNTHESIS OF SOME NEW FLUORINE CONTAINING SPIRO [3H-INDOLE-3,2′TETRAHYDRO-1,3-THIAZINE].2,4′(1H)-DIONES

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Attempts have been made to synthesize exclusively 5′,6′-dihydro-spiro [3H-indol-3,2′-[2H-1,3] thiazine]-2,4′ (1H,3′H)-diones (V) under varying reaction conditions such as temperature, reaction period and molar ratio of the two reactants, by the reaction of fluorinated indole-2,3-diones (I) with fluorinated anilines (II) and 3-mercaptopropanoic acid (IV). The reaction of 3-indolylimines (III) with a slight excess of IV at room temperature, resulted in the formation of an acidic compound (VI), instead of expected spiro product (V), which has been further subjected to acetylation and chloroacetylation. The compounds have been characterized on the basis of elemental and spectral studies.

Keywords: Fluorinated indole-2,3-diones; fluorinated spiro[indole-thiazine]; 3-mercaptopropanoic acid; spectral studies

INTRODUCTION

Thiazine derivatives are well recognised as useful drugs in the field of medicinal chemistry.[1–3]A large number of thiazines have shown insecticidal, herbicidal, antibacterial and antiviral activities.[4–7] These are also used as antidandruff agents, antibiotics and antiepileptics[8–10]. Similarly indole nucleus possesses diverse biological activities.[11–13] It is a main constituent unit in most ofthe alkaloids such as psilobin, harmine, strychnine, ibogo, aspidosperma etc. 5-Hydroxytryptamine, an indole derivative, is an brain amine and is reported as a modulator of neurohormonal activity.[14] More recently, a number of spiro indolines have been investigated by

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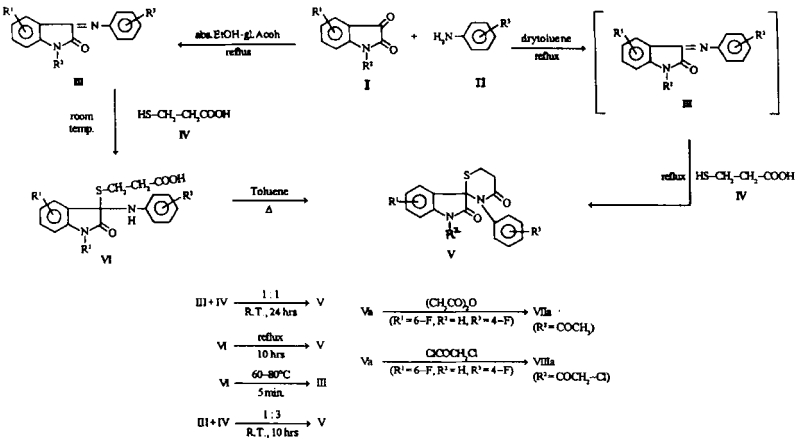
chemists due to their interesting stereochemistry and their successful therapeutic utilization in the field of medicinal chemistry.[15–17] It has been observed that fluorine incorporation in heterocydes is reported to alter the bioactivity.[18–20] Fluorine containing spiro[3H-indol-3,2′-thiazolidine]-2,4′-(1H)-diones are associated with various type of pharmacological activities.[21–23] However, there is scanty information in the literature for the spiro[3H-indol-3,2′[2H]-1,3-thiazine]-2 (1H)ones which incorporates the bioactive indole and thiazine nuclei. An analogous type of compound spiro [3H-indole-3,2′[2H]-1,3-thiazine]-2 (1H)-ones, synthesized from isatin, 3-mercaptopropylamine hydrochloride and potassium cyanate, is a patent and found to possess antiinflammatory, analgesic and anticonvulsant activities.[24] Popp et al[25] reported the synthesis ofthese spiro compounds in two-steps, in 28–46% yield. Prompted by these observations, and our earlier interest on the synthesis of fluorine containing bioactive spiro indoles[26–29], we now report the syntheses of some new spiro heterocycles V, VI, VII and VIII, which may lead to the discovery of a new class of drugs.

DISCUSSION

The synthesis of fluorinated 5′6′-dihydro spiro[3H-indol-3,2′-[2H-1,3] thiazine]-2,4′ (1H, 3′H)-diones appeared interesting due to the (i) broad spectrum of biological activity associated with sulfur containing heterocylic systems[30–32] (ii) presence of different reaction sites (C=O, NH, $COCH_2$ or $\underset{\underset{OH}{|}}{C=CH}$ and -S-CH_2) and (iii) the extraordinary versatility of fluorinated compounds on account of small size of fluorine, high electronegativity, increased oxidative and thermal stability of carbon-fluorine bond. The general synthetic approach involved the condensation of fluorinated indole-2,3-diones (I) with fluorinated anilines (II) in dry toluene under reflux yielding 3-arylimino-2H-indol-2-ones (III) (Scheme 1) which, *in situ,* were cyclized with 3-mercaptopropanoic acid (IV) to give the spiro compounds (V) in 58–81% yield. These compounds were characterized by IR absorption bands at 3400–3150 (NH) and 1720–1670 (two C=O) cm^{-1}. The ^1H NMR spectra showed signals at δ 2.61 $\left(t, 2H, -C-\underset{\underset{O}{\|}}{C}H_2\right)$, 3.75 (t,

2H-S-C$\underline{H}_2$), 6.83–7.50 (m, 7H, Ar-$\underline{H}$) and 9.04 (S, 1H, N$\underline{H}$) ppm. Presence and position of NH proton was confirmed on deuteration. The structure was also confirmed by ^{13}CNMR spectrum, which showed signals at 170.72 $\underline{C}$=O), 160.84 ($\underline{C}$=O), 145.89–115,14 (12, aromatic ring carbons), 110.11 (Spiro carbon), 30.45 ($\underline{C}H_2$-S) and 30.1 ($\underline{C}$-CH_2) ppm. The mass spectrum of (VIC) further supported the formation of the compounds, as the molecular ion peak M* at m/z 328 (32.2%) correspond to its molecular weight. The reaction was studied extensively under differing conditions of(a) temperature (b) reaction period and (c) molar ratio of the two reactants. Progress of the reaction was monitored by TLC. In few cases, intermediate isatin-3-anil (III) has also been isolated as crystalline compounds to study the comparative yield.



SCHEME 1

Reaction of IIIa (R^1=6F; R^2=H, R^3=m4-F) with slight excess of IV in dry toluene at room temperature for 6 hours resulted in the formation of a white amorphous acidic compound (VIa) in quantitative yield (82%). Its IR spectrum showed strong absorptions at 3420–3380 (-OH), 3340–3280 (>NH) and 1710–1680 (>C=O) cm-1. In the PMR spectrum, the methylene protons were observed at δ 2.68 (t, 2H, COC$\underline{H}_2$) and 3.61 (t, 2H, S-C$\underline{H}_2$) ppm. Besides, signals at δ 6.70–7.83 (m, 7H, Ar-$\underline{H}$), 8.77 (S, 1H, N$\underline{H}$), 9.04 (b_r, 1H, N$\underline{H}$) and a broad signal at 10.02 (br, I H, COO$\underline{H}$) ppm were also observed. Further, in the mass spectrum of VI a, the molecular ion peak was observed at m/z 396 (37.6%).

However, when the reaction was prolonged under identical conditions, the acid VI disappeared. After stirring for 24 hr, a white compound again started separating, which was identified as the spiro compound Va. Further, VIa when heated on a steam bath it turned red and on cooling gave the starting isatin-3-anil IIIa. Efforts to purify the intermediate VIa by recrystallization from a wide range of solvents or by extracting with aqueous sodium bicarbonate were not successful. The spiro product Va was directly obtained on refluxing VIa in toluene for 10 hours, with azeotropic removal of the water formed. Furthermore, when IIIa and IV were taken in 1:3 molar ratio, again instead of the acid VI, the spiro compound Va was obtained directly after stirring for 10 hr at room temperature. IIIb (R_1=6F, R_2=H, R_3=3-CF_3) behaved similarly when treated with IV under the above conditions.

Thus, it can be concluded that the spiro compounds V can be synthesized in quantitative yields at room temperature by prolonging the reaction period or taking excess of 3-mercaptopropanoic acid. The reaction at room temperature is a better method for the synthesis of V as the solid amorphous compound separates itself after the reaction, while at higher temperature, the compound has to be isolated from the reaction mixture by reducing the volume of the solvent under vacuum, and is obtained as a sticky substance which is to be trituted.

The spiro compound Va was also subjected to acetylation and chloroacetylation. It was found that substitution reactions occur preferentially at indole nitrogen which was confirmed by spectral studies along with simultaneous synthesis of acetylated spiro compound from the N-acetylated isatin and amines in 62–76% yield. Formation of VIIa has been assured on the basis of complete disappearance of NH absorption in IR and ^{1}H NMR spectrum. A new absorption band appeared in the region 1730–1680 cm^{-1} due to (-$COCH_3$) group in IR spectrum. In ^{1}HNMR, the resonance signals of (-S-C$\underline{H}_2$) and (-COC$\underline{H}_2$) protons remained as such at δ 2.61 and 3.75 ppm, along with additional protons signal at δ 2.41 ppm due to (-COC$\underline{H}_3$) group. The structure of VIIIa was confirmed by appearance of another (C=O) absorption in the region 1720–1690 cm^{-1} in IR and additional ^{1}HNMR signal at δ 4.89 (S, 2H, -COC$\underline{H}_2$Cl) ppm.

The presence and position of fluorine in the synthesized compounds V was confirmed by 19FNMR spectra. Single fluorine attached to indole ring and aryl rings were observed at δ-116.25 and −111.29 ppm while the trif-

luoromethyl group of the indole and aryl rings were observed at 6–62.84 and –63.25 ppm.

EXPERIMENTAL

Melting points were 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}). ^{1}H and ^{19}F NMR were recorded on Jeol FX 90 Q using $CDCl_3$ as solvent at 89.55 and 84.25 MHz respectively, and mass spectra were recorded on Kratz 30 and 50 mass spectrometer at 70 ev. 6-Fluoro and 4-trifluoromethyl-indole-2,3-diones were prepared by methods reported in the literature.[33,34]

(i) 1,3-Dihydro-6-fluoro-3-[(4-fluorophenyl)imino]-2H-indol-2-one (IIIa)

A mixture of 6-fluoroindole-2,3-dione (0.01 mole) and 4-fluoroaniline (0.01 mole) was refluxed in absolute ethanol (20 ml) in presence of 2–3 drops of glacial acetic acid for half an hour. On cooling crystals separated out, which was filtered and recrystallized from ethanol as yellow needles, m.p. 185°C; yield, 74%.

IIIb has been synthesized by following a similar procedure, m.p. 212–215°C; yield 64%.

(ii) 6-Fluoro-[(3-[(4-fluorophenyl)amino]-2,3-dihydro-2-oxo-1H-indol-3-yl)thlo] propanoic acid (VIa)

A mixture of IIIa (0.01 mole) and IV (0.015 mole) in dry toluene (30 ml) was stirred for 6 hours at room temperature (22°C). The white product separated was filtered and washed thrice with anhydrous toluene and twice with anhydrous ether and found to be pure on TLC, m.p. 168°C; yield 82%.

VIb was synthesized in a similar manner, starting from IIIb.

(iii) 5′,6′-Dihydro-6-fluoro-3′-(4-fluorophenyl)-spiro[3H-indole-3,2′-[2H-1,3] thiazine]-2,4′ (1H, 3′H)-dione (Va)

This compound was synthesized by the following methods in variable yields.

a. A mixture of 6-fluoro indole-2,3-dione Ia (0.01 mole) and 4-fluoro-aniline II (0.01 mole) was refluxed in dry toluene (30 ml), for 3 hr. with azeotropical removal of the water formed. On cooling the mixture, 3-mercaptopropanoic acid IV (0.011 mole) was added and refluxed again for 10 hr under similar condition. The mixture was then allowed to cool to room temperature and supernatant liquid was removed under reduced pressure. The sticky solid obtained was titruted with pet. ether and recrystallized from ethanol, m.p. 170–173°C; yield 71%.

b. A mixture of IIIa (0.01 mole) and IV (0.015 mole) in dry toluene (30 ml) was stirred at room temperature for 24 hr when a white crystalline compound separated out. It was filtered and recrystallized from ethanol, yield 76%.

c. A mixture of IIIa (0.01 mole) and IV (0.03 mole) in dry toluene (30 ml) was stirred at room temperature for 10 hr when Va separated out as a white compound. It was recrystallized from ethanol, yield 78%.

d. When VIa (0.01 mole) in dry toluene was refluxed for 10 hours, the desired compound Va was isolated which was recrystallized from ethanol, yield 74%.

e. A mixture of Ia (0.01 mole), II (0.01 mole) and IV (0.015 mole) in 50 ml of dry toluene was refluxed for 20 hr and the water formed was removed azeotropically. The reaction mixture was cooled, the product filtered, dried and recrystallized from toluene, yield 40%.

The remaining spiro compounds (Vb-h; Table I) were prepared by method a, without isolating the anils.

(iv) 1-Acetyl-5′,6′-dihydro-6-fluoro-3-(4-fluorophenyl)-spiro [3H-indole-3,2′-[2H-1,3]-thiazine]-2,4′ (1H, 3′H) dione VIIa)

This compound has been synthesized by two methods.

TABLE I Analytical & Physical data of compounds Va-h

Compound no.	R^1	R^2	R^3	*M.P. °C*	*Yield %.*	*Molecular formula*	*Analysis (%)*		*Found (Calcd)*	
							N		*S*	
Va	6F	H	4-F	170	76	$C_{17}H_{12}F_2N_2O_2S$	8.21	(8.09)	9.41	(9.24)
Vb	6F	H	3-CF_3	220(d)	58	$C_{18}H_{12}F_4N_2O_2S$	7.30	(7.07)	8.29	(8.08)
Vc	H	H	2-F	190	81	$C_{17}H_{13}FN_2O_2S$	8.38	(8.53)	9.87	(9.75)
Vd	H	H	3-F,4-Cl	112(d)	48	$C_{17}H_{12}ClFN_2O_2S$	7.50	(7.73)	9.08	(8.83)
Ve	6F	$COCH_3$	2-F	181(d)	71	$C_{19}H_{14}F_2N_2O_3S$	7.68	(7.21)	8.57	(8.24)
Vf	H	$COCH_3$	2-CF_3	165(d)	58	$C_{20}H_{14}F_3N_2O_3S$	6.84	(6.66)	7.40	(7.61)
Vg	H	H	H	75	72	$C_{17}H_{14}N_2O_2S$	9.31	(9.03)	10.50	(10.32)
Vh	4-CF_3	H	3CF_3	242	64	$C_{19}H_{12}F_6N_2O_2S$	6.41	(6.27)	7.34	(7.17)

d = decomposes.

a. A mixture of 6-fluoro-1-acetyl indole-2,3-dione I (0.01 mole), 4-fluoroaniline II (0.01 mole) and IV (0.015 mole) in dry toluene (30 ml) was refluxed for 20 hr, with azeotropical removal of water. The reaction mixture was cooled, product was filtered and recrystallized from ethyl acetate, m.p. 183 (d); yield 71%.

b. 5′,6′–Dihydro-6-fluoro-3′-(4-fluorophenyl)spiro[3 H-indole-3, 2′-[2H-I, 3]thiazine]-2,4′ (1H, 3′H)-dione Va (0.01 mole) was refluxed for 6 hr with acetic anhydride (25 ml) and on cooling the mixture, the desired compound was obtained which was purified by recrystallization from ethanol, m.p. 183–185°C (d); yield 58%.

(v) 1-N-chloroacetyl-5′,6′-dihydro-6-fluoro-3′-(4-fluoro phenyl) spiro[3H-indole-3,2′-[2H-1,3] thiazine]-2,4′ (1H,3′H)-dione (VIIIa)

A mixture of Va (0.01 mole) and chloroacetyl chloride (25 ml) was refluxed for 8 hours. On cooling, crystals separated out, which were recrystallized from ethanol, m.p. 239–242°C (d); yield 62%.

TABLE II IR and NMR data of the compound Va-h

Compd no.	*IR (cm^{-1})*	*1H NMR (δppm)*				
		S-C<u>H</u>$_2$	*-COC<u>H</u>$_2$*	*Ar-<u>H</u>*	*N<u>H</u>*	*-COC<u>H</u>$_3$*
Va	3280, 1720, 1680, 1560, 1510, 1480, 1370, 1330, 1150, 1080, 980, 860	2.61 (t,2H)	3.75 (t,2H)	6.83–7.50 (m,7H)	9.04 (s,1H)	-
Vb	3240, 1700, 1670, 1580, 1440, 1320, 1210, 1120, 1070, 860	2.81 (t,2H)	3.81 (t,2H)	6.70–8.37 (m,7H)	9.17 (s, 1H)	-
Vc	3260, 1710, 1690, 1570, 1510, 1490, 1360, 1320, 1160, 1090, 870	2.70 (t,2H)	3.80 (t,2H)	6.75–8.35 (m, 7H)	9.06 (s, 1H)	-
Vd	3300, 1690 1670, 1570, 1400, 1300, 1210, 1100, 1080, 980, 820	2.68 (t,2H)	4.02 (t,2H)	6.76–7.70 (m, 7H)	8.97 (s, 1H)	-
Ve	1720, 1680, 1660, 1580, 1480, 1310, 1200, 1130, 1060, 890	2.72 (t,2H)	3.89 (t,2H)	6.72–7.80 (m, 7H)	-	2.41 (s, 3H)

Compd no.	IR (cm^{-1})	1H NMR (δppm)				
		S-C<u>H</u>$_2$	-COC<u>H</u>$_2$	Ar-<u>H</u>	N<u>H</u>	-COC<u>H</u>$_3$
Vf	1730, 1690, 1670, 1570, 1490, 1320, 1210, 1120, 1070, 880	2.79 (t,2H)	3.77 (t,2H)	6.79–8.35 (m, 7H)	-	2.39 (s, 3H)
Vg	3250, 1710, 1650, 1590, 1450, 1310, 1200, 1130, 1080, 870	2.65 (t,2H)	3.76 (t,2H)	6.71–8.20 (m, 7H)	9.12 (s, 1H)	-
Vh	3270, 1700, 1670, 1560, 1500,1470, 1370, 1310, 1150, 1080, 840	2.74 (t,2H)	3.81 (t,2H)	6.79–8.36 (m, 7H)	9.06 (s, 1H)	-

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