STUDIES IN SPIROHETEROCYCLES: PART IX : A NEW ELEGANT SYNTHESIS AND REACTIONS OF SOME NOVEL FLUORINE-CONTAINING SPIRO[3H-INDOLE-3,2'-TETRAHYDRO-1,3-THIAZINE]-2,4'(1H)-DIONES

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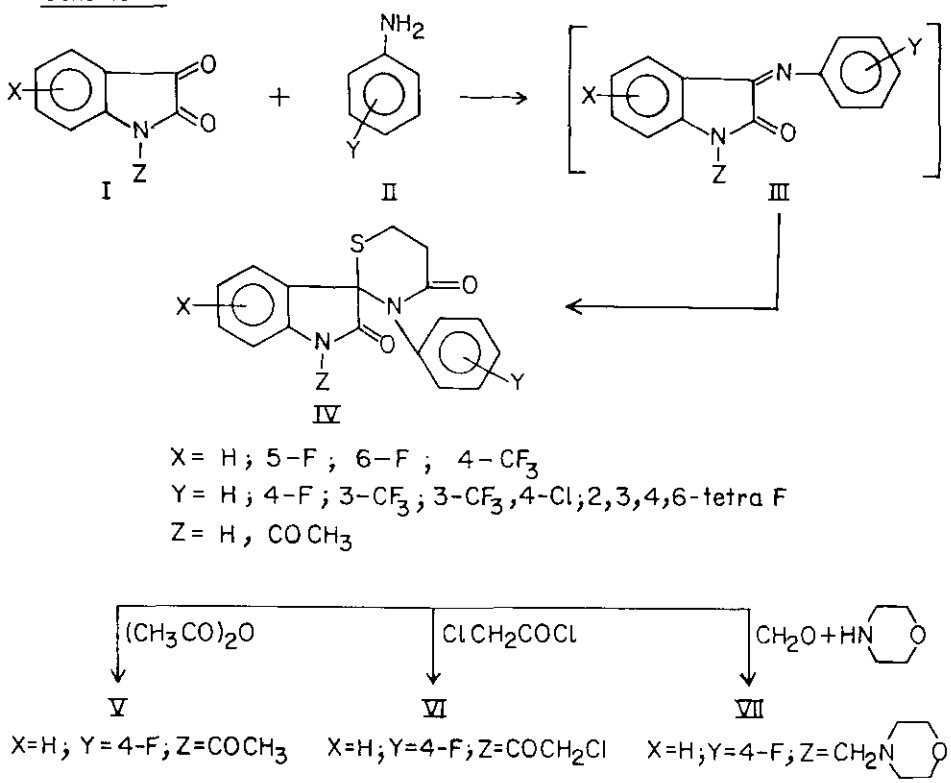
Abstract - A number of novel fluorine-containing spiro[3H-indole-3,2'-tetrahydro-1,3-thiazine]-2,4'(1H)-diones have been synthesized by an elegant one-step procedure involving the condensation of fluorine-containing indole-2,3-diones, fluorinated aromatic amines and 3-mercaptopropanoic acid without isolating the intermediate isatin-3-anils. The spiro compounds have been further subjected to acetylation, chloroacetylation and Mannich reactions. N-Acetylated spiro compound was simultaneously synthesized from 1-acetylindole-2,3-dione and aniline. The structures of all the compounds have been confirmed on the basis of elemental analyses, ir, ^{1}H nmr, ^{13}C nmr, ^{19}F nmr and mass spectral studies.

In continuation to our previous work on biologically active indoles[1-5] and spiro-indolines[6-14], we now report a new synthesis of fluorine-containing spiro[3H-indole-3,2'-tetrahydro-1,3-thiazine]-2,4'(1H)-diones and some of their derivatives. Recently, we reported[6,7] the synthesis of spiro[3H-indole-3,2'-thiazolidine]-2,4'(1H)-diones by the condensation of indole-2,3-diones, aromatic amines and mercaptoacetic acid. In order to explore the possibility of formation of another novel spiro ring system containing thiazine ring we used 3-mercaptopropanoic acid instead of mercaptoacetic acid and this resulted in the formation of the novel spiroheterocycle(IV) bearing an indoline and thiazine moiety. This heterocyclic system appears to be of great interest due to (i) the broad spectrum of biological activity associated with sulphur-containing heterocyclic systems[15-19], (ii) presence of different reactions sites (>C=O, >NH, $\underset{O}{\overset{\|}{C}}-\underline{CH_2}$ or $-\underset{OH}{\overset{|}{C}}=CH$ and $-S-\underline{CH_2}-$) and (iii) non-availability of

Scheme - 1



data*, particularly of fluorinated analogues. Further, there is only one reference[20] in the literature for an analogues type of compound, spiro [3H-indole-3,2'[2H]-1,3-thiazine]-2(1H)-ones, which is a patent. The compounds have been prepared from isatin, 3-mercaptopropylamine hydrochloride and potassium cyanate and are reported to possess antiinflammatory, analgesic and anticonvulsant activities. These observations prompted us further to prepare these novel spiroheterocycles which may lead to the discovery of a new class of drugs. We, therefore, now report a new one-step convenient synthesis of spiro compounds(IV), without isolating the intermediates isatin-3-anils(III), and also some of their derivatives. The condensation of fluorine containing indole-2,3-diones and 1-acetylindole-2,3-dione with fluorinated aromatic amines in dry toluene, afforded isatin-3-anils, which, in situ, were cyclized with 3-mercaptopropanoic acid to give title compounds (IV a-g) in 70-85% yield. It

* While communicating this paper, we have come across a report of synthesis of spiro [3H-indole-3,2'-tetrahydro-1,3-thiazine]-2,4'(1H)-diones by Popp et al.[21] However none of these compounds is a fluorinated derivative and have not been subjected to acetylation and chloroacetylation reactions.

is interesting to point out that in this case, both indole-2,3-dione and N-acetylindole-2,3-dione yielded a spiro compound in contrast to some of our previous reports in which the products varied[10,11].

The spiro compounds were characterized by ir absorption bands at 1680-1730 cm^{-1} (both $>C=O$), 3150-3350 ($>NH$) and ^1H nmr signals at δ9.01(NH), 2.8($-\overset{O}{\overset{\|}{C}}-\underline{CH_2}-CH_2-$), 3.8($-CH_2-\underline{CH_2}-S-$) and 6.85-7.49 ppm (aromatic protons). The structure was further confirmed by ^{13}C nmr spectra, which showed signals at δ172.11(s, $>\underline{C}=O$), 163.93(s, $>\underline{C}=O$), 117-139(12 aromatic ring carbons), 110.84(spiro carbon), 31.33(t, $CH_2-\underline{CH_2}-S$) and 31.9(t, $-\overset{O}{\overset{\|}{C}}-\underline{CH_2}-CH_2$) ppm. The mass spectra further supported the formation of the compound as the parent peak (M^+ at 328 m/z) corresponded to their molecular weight (IVa). Presence and the position of fluorine was confirmed by ^{19}F nmr using hexafluorobenzene as external standard. Fluorine, attached to indole ring, was observed at -113 to -117 ppm, CF_3 of indole ring and aryl ring at -62.968 and -63.249 ppm (IVg). Four fluorines of tetrafluoroaryl ring of thiazine moiety (IVe) were observed at -135.123(s, F^6), -151.225 to -151.457 (d, F^4), -151.804 to -152.268(t, F^3) and -147.808(b, F^2); in the last case, expected doublet of F^2 appears to coalesce to give broad ill defined doublet probably due to quadrupole moment of ortho nitrogen. Further, acetylation, chloroacetylation and Mannich reactions of spiro compound (IVa) were undertaken. Acetylation and chloroacetylation were carried out by refluxing(IVa) with acetic anhydride and chloroacetyl chloride respectively. For Mannich reaction, spiro compound (IVa) was refluxed with formaldehyde solution (40%) and morpholine in molar ratio using absolute ethanol as the condensation medium for 10 h. Although there are different reaction sites, viz, NH, $-\underset{H}{\underset{|}{C}}=\underset{OH}{\underset{|}{C}}-$, reactive methylene group of thiazine ring, the substitution occurs at indole nitrogen. Acetylation at indole nitrogen is also confirmed by simultaneous synthesis of N-acetylated spiro compound (V) from N-acetylated isatin and the corresponding amine.

Formation of N-acetylated (V) and N-chloroacetylated spiro compound (VI) from the corresponding spiro compound has been confirmed on the basis of complete disappearance of NH absorptions in ir and ^1H nmr spectra. The resonance signals of $-S-\underline{CH_2}$ and $-\overset{O}{\overset{\|}{C}}-\underline{CH_2}$ protons remained as such. Formation of compounds V and VI has been confirmed by appearance of a new C=O absorption band in the region of 1680-1720 cm^{-1} due to $-COCH_3$ and $-COCH_2Cl$ group in ir spectra. An

additional signal was observed at δ2.4(s, 3H, $CO\underline{CH}_3$) and at 4.9(s, 2H, $CO\underline{CH}_2Cl$) in ^{1}H nmr spectra of compounds V and VI respectively. Formation of 1-acetyl and 1-chloroacetyl spiro compounds V and VI from the corresponding spiro compound (IVa) is also confirmed by appearance of a new carbonyl (>C=O, s) resonance signal in ^{13}C nmr at the δ 164.72 and 163.58 ppm respectively. In ^{13}C nmr spectra of V the absorption signal at δ35.528 ($-CO\underline{CH}_3$, q) ppm is associated due to methyl group while signal at 54.05 ppm in ^{13}C nmr of VI is due to methylene (>CH_2, t) group of the chloroacetyl group. Formation of Mannich base (VII) from corresponding spiro compound (IVa) has been confirmed by appearance of new resonance signals centered at δ2.7-2.98, 3.4-3.9 and 4.1-4.7 ppm in ^{1}H nmr due to morpholino group.

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were recorded on Perkin-Elmer (model-577) in KBr pellets and ^{1}H nmr were recorded on Jeol (model-FX 90 Q) at 89.55 MHz using TMS as external reference and ^{13}C nmr spectra were taken in DMSO-d_6 at 22.49 MHz (chemical shifts in δ, ppm). ^{19}F nmr spectra were taken in TFA at 84.25 MHz using hexafluorobenzene as external standard. Purity of all compounds was checked by tlc done on silica gel plates. 5-Fluoroindole-2,3-dione, 6-fluoroindole-2,3-dione and 4-trifluoromethylindole-2,3-dione were prepared by literature methods[22-24].

3'-(4-Fluorophenyl)-spiro [3H-indole-3,2'-tetrahydro-1,3-thiazine] -2,4'(1H)-dione (IVa) - A mixture of indole-2,3-dione (0.01 mole) and 4-fluoroaniline(0.01 mole) was refluxed in dry toluene (30 ml) for 2.5 h and theoretical amount of water was collected azeotropically. On cooling the mixture, 3-mercaptopropanoic acid (0.011 mole) was added and refluxed again for 4-5 h under similar conditions till the formation of water from the reaction ceased. On cooling, a solid was obtained which was purified by recrystallization from ethanol, mp 210°C, yield 2.62g (80%). (Found: N, 8.42, S, 9.71, $C_{17}H_{13}FN_2O_2S$ requires N, 8.53, S, 9.75%). $\nu_{max}^{cm^{-1}}$ 3300(NH), 1730, 1680 (both >C=O), 1500($-CH_2-$) and 1000-1100(C-F), ^{1}H nmr (DMSO-d_6):δ3.8(t, 2H, $-C-\underline{CH}_2-S$), 2.8(t, 2H, $-\underset{\underset{O}{\|}}{C}-\underline{CH}_2$), 6.85-7.49 ppm (m, 8H, aromatic protons), 9.1(b, 1H, $N\underline{H}$);MS : m/z 328 (M^+); 300(M^+-CO); 241($M^+-C_6H_5$). ^{13}C nmr: δ172.119 & 163.938(both C=O), 139.614-117.132 (aromatic ring carbon), 110.847(spiro carbon), 31.33($CH_2-\underline{CH}_2-S-$) and 31.9($-\underset{\underset{O}{\|}}{C}-\underline{CH}_2-CH_2$) ppm. All other compounds (IVb-g Table I) were prepared in a similar manner.

1-Acetyl-3'-(4-fluorophenyl)-spiro[3H-indole-3,2'-tetrahydro-1,3-thiazine]-2,4'-(1H)-dione (V) - The title compound was prepared by two methods: (a) A mixture of 1-acetylisatin (0.01 mole), 4-fluoroaniline (0.01 mole) was refluxed in dry toluene (50 ml) for 2 h in a Deen-Stark apparatus, water being removed azeotropically, after cooling, 3-mercaptopropanoic acid (0.011 mole) was added and the mixture refluxed for 4-5 h till the formation of all water from the reaction stopped. On cooling, a solid was obtained which was recrystallized from ethanol, mp 250°C, yield 2.4g (80%). (Found: N, 7.41; S, 8.42 $C_{19}H_{15}FN_2O_3S$ requires N, 7.56; S, 8.64%). $\nu_{max}^{cm^{-1}}$ 1680, 1700, 1720 (three >C=O) 1500(-CH_2-) and 1000-1100(C-F). ^{1}H nmr (DMSO-d_6): δ2.4(s, $CO\underline{CH_3}$, 3H), 2.8(t, -$\overset{O}{\overset{\|}{C}}$-$\underline{CH_2}$, 2H) 3.8(t, -S-$\underline{CH_2}$-$CH_2$, 2H) and 6.85-7.49 ppm (m, aromatic protons, 8H); MS: m/z 370 (M^+). (b) Compound IVa (0.01 mole) was refluxed with acetic anhydride(25 ml) for 6 h and on cooling the mixture, the desired compound was obtained which was purified by recrystallization from ethanol, yield 1.8g (60%). The mp and analytical data were identical for both compounds confirming that they are same.

1- Chloroacetyl-3'-(4-fluorophenyl)-spiro[3H-indole-3,2'-tetrahydro-1,3-thiazine]-2,4'(1H)-dione (VI) - A mixture of IVa(0.01 mole) and chloroacetyl chloride (25 ml) was refluxed for 6 h. On cooling, crystals separated out which was purified from ethanol, mp 205°C, yield 3.45g (75%) (Found: N, 9.05; S, 6.91. $C_{22}H_{21}ClFN_3O_3S$ requires N, 9.11; S, 6.94%). $\nu_{max}^{cm^{-1}}$ 1690, 1700 and 1730 (three >C=O). ^{1}H nmr (DMSO-d_6): δ4.9(s, $CO\underline{CH_2}Cl$, 2H), 2.85(t, -$CO\underline{CH_2}$, 2H), 3.75(t, -S-$\underline{CH_2}$, 2H) and 6.85-7.49 ppm (m, aromatic protons, 8H); MS: m/z 461(M^+).

1-Morpholinomethyl-3'-(4-fluorophenyl)-spiro[3H-indole-3,2'-tetrahydro-1,3-thiazine]-2,4'(1H)-dione (VII) - A mixture of compound IVa (0.01 mole), formaldehyde solution (0.012 mole, 40%) and morpholine (0.01 mole) was refluxed in absolute ethanol for 10 h. On cooling, desired compound was obtained. It was filtered and recrystallized from ethanol, mp 240°C, yield 2.98 g (70%). (Found: N, 9.75; S, 7.55, $C_{22}H_{22}FN_3O_3S$ requires N, 9.83; S, 7.49%). $\nu_{max}^{cm^{-1}}$ 2850-2900(CH_2), 1720, 1680, (two >C=O). ^{1}H nmr (DMSO-d_6): δ2.7-2.98(m, O<$\underline{CH_2}$ and $\underline{CH_2}$> and -$\overset{O}{\overset{\|}{C}}$-$\underline{CH_2}$-, 6H), 3.4-3.9(m, -S-$CH_2$- and -N<$\underline{CH_2}$, 6H), 4.7(s, N-$\underline{CH_2}$N, 2H), 6.85-7.49 ppm(m, aromatic protons, 8H). MS: m/z 427 (M^+).

Table - I

Physical and analytical properties of spiro [3H-indole-3,2'-tetrahydro-1,3-thiazine]-2,4'(1H)-diones IV.

S.No.	X	Y	Z	M.P. (°C)	Yield %	Molecular formula	N %		S %	
							Calc	Found	Calc	Found
a.	H	4-F	H	210	80	$C_{17}H_{13}FN_2O_2S$	8.53	8.42	9.75	9.71
b.	5-F	H	H	190	85	$C_{17}H_{13}FN_2O_2S$	8.53	8.49	9.75	9.68
c.	5-F	4-F	H	220	80	$C_{17}H_{12}F_2N_2O_2S$	8.09	8.18	9.24	9.21
d.	5-F	3-CF_3	H	105	70	$C_{18}H_{12}F_4N_2O_2S$	7.07	7.02	8.08	8.11
e.	5-F	2,3,4,6-F	H	180	75	$C_{17}H_9F_5N_2O_2S$	7.00	7.13	8.00	8.05
f.	6-F	3-CF_3, 4-Cl	H	200	75	$C_{18}H_{11}ClF_4N_2O_2S$	6.51	6.45	7.44	7.23
g.	4-CF_3	3-CF_3	H	230	70	$C_{19}H_{12}F_6N_2O_2S$	6.27	6.23	7.17	7.13

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