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SYNTHESIS AND MASS FRAGMENTATION PATTERN OF FLUORINATED SPIRO [3H-INDOLE-3,9'-[9H] XANTHENE]-1',2,8'(1H,2'H,5'H)-TRIONES

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SUMMARY

Some new fluorine containing spiro-xanthenes and spiro-acridines have been synthesized. Spiro-xanthenes were obtained by the reaction of fluorinated indole-2,3-diones with 1,3-cyclohexanedione by three different routes. Further, spiro-xanthenes were treated with ammonium acetate or fluorinated anilines in acidic medium resulting in corresponding spiro-acridines. All synthesized compounds have been characterized on the basis of elemental analyses,IR, ^{1}H and ^{19}F NMR and Mass spectral studies.

INTRODUCTION

The chemistry of fluorinated spiro-indole derivatives has been of considerable interest due to the variation in physicochemical properties of these derivatives as compared to their non-fluorinated analogues [1-3]. Spiro-xanthenes, based on a three ring system, having an oxygen atom, find useful applications in medicinal chemistry in view of the wide range of biological activities associated with their

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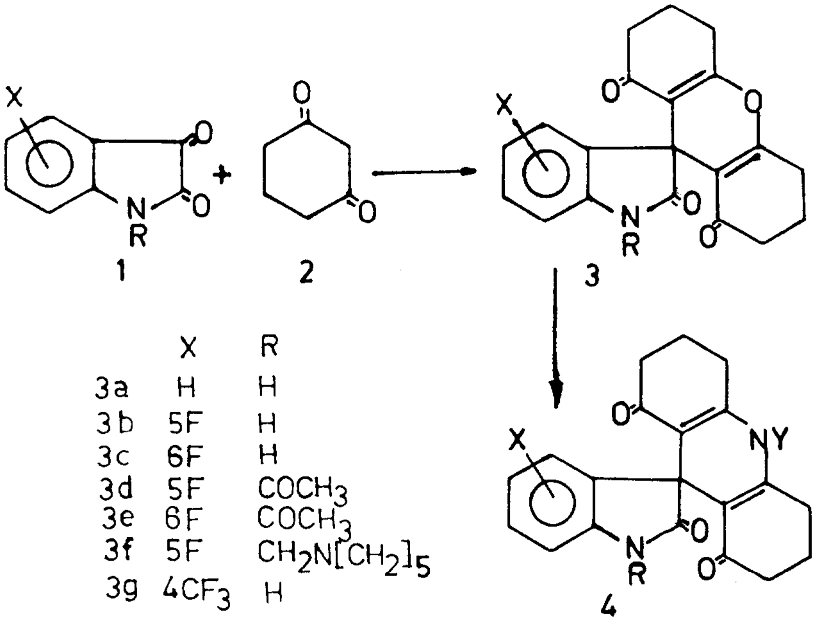
derivatives, viz., dioxolanes[4], chromans[5], coumarins[6] and naphthofurans[7].

Scanty information is available in the literature concerning the chemistry of such heterocyclic systems containing fluorine and no attention seems to have been given to their mass fragmentation studies. We now wish to report the synthesis and mass spectral studies of new fluorinated spiro [3H-indole-3,9'-[9H]xanthene]-1',2,8'(1H,2'H,5'H)-triones and synthesis of spiro [9H-acridine-9,3'-[3H] indole]-1,2',8 (1'H,2H,5H)-triones (Scheme 1) .



	X	R
3a	H	H
3b	5F	H
3c	6F	H
3d	5F	$COCH_3$
3e	6F	$COCH_3$
3f	5F	$CH_2N[CH_2]_5$
3g	$4CF_3$	H

	X	R	Y
4a	H	H	H
4b	H	H	$C_6H_4F(1,4)$
4c	5F	H	$C_6H_4F(1,4)$

Scheme 1

RESULTS AND DISCUSSION

The reactions of suitable indole-2,3-diones (1) with 1,3-cyclohexanedione (2) under three different conditions [8], viz. (i) direct fusion (ii) in neutral medium and (iii) in acidic medium [9] gave the title compounds (3) . All the fluoro spiro-[3H-indole-3,9'-[9H] xanthene]-1',2,8' (1H,2'H,5'H)-triones (3b-g) were obtained best by the direct fusion method as it gave maximum percentage yields. The IR spectrum of compound (3a) showed the characteristic absorption peak at 3470 cm^{-1} for $>$N-H stretching, at 1720 and 1660 cm^{-1} for carbonyl groups and at 2920 cm^{-1} for $\geq$ C-H stretching. Along with these, the presence of a band at 1190 cm^{-1} due to the ether linkage confirms the nature of the compound to be of the xanthene type [10] . In the ^1H NMR spectrum the $>CH_2$ protons of tetrahydroxanthene are obtained in the form of three clusters viz. a quartet from δ 1.07-1.47 ppm and two multiplets from δ 1.47-1.74 ppm and δ 1.8-2.2 ppm, each integrating for four protons. The protons near carbonyl groups being more deshielded, the $>CH_2$ protons at C-2' and C-7' positions appear in the region δ 1.8-2.2 ppm. Protons at C-4' and C-5' positions are only slightly deshielded (close to the unsaturated carbon and xanthene oxygen) and appear at δ 1.47-1.74 ppm. The least deshielded ones i.e., C-3' and C-6' position protons appear at δ 1.07-1.47 ppm. Apart from these, a multiplet for aromatic protons at δ 6.03-6.61 ppm and a singlet at δ 10.02 ppm for $>$NH proton were also observed.

The presence and position of fluorine were confirmed by ^{19}F NMR using hexafluorobenzene as external standard. Fluorine attached to the indole ring compound (3b-f) was observed at -113 to -117 and the CF_3 of compound (3g) was at -63.248 ppm. Additional support was obtained by mass spectra as molecular ion peak M^+ at 335(3a), 353(3b) and 395(3e) corresponded to their molecular weights (Table 1).

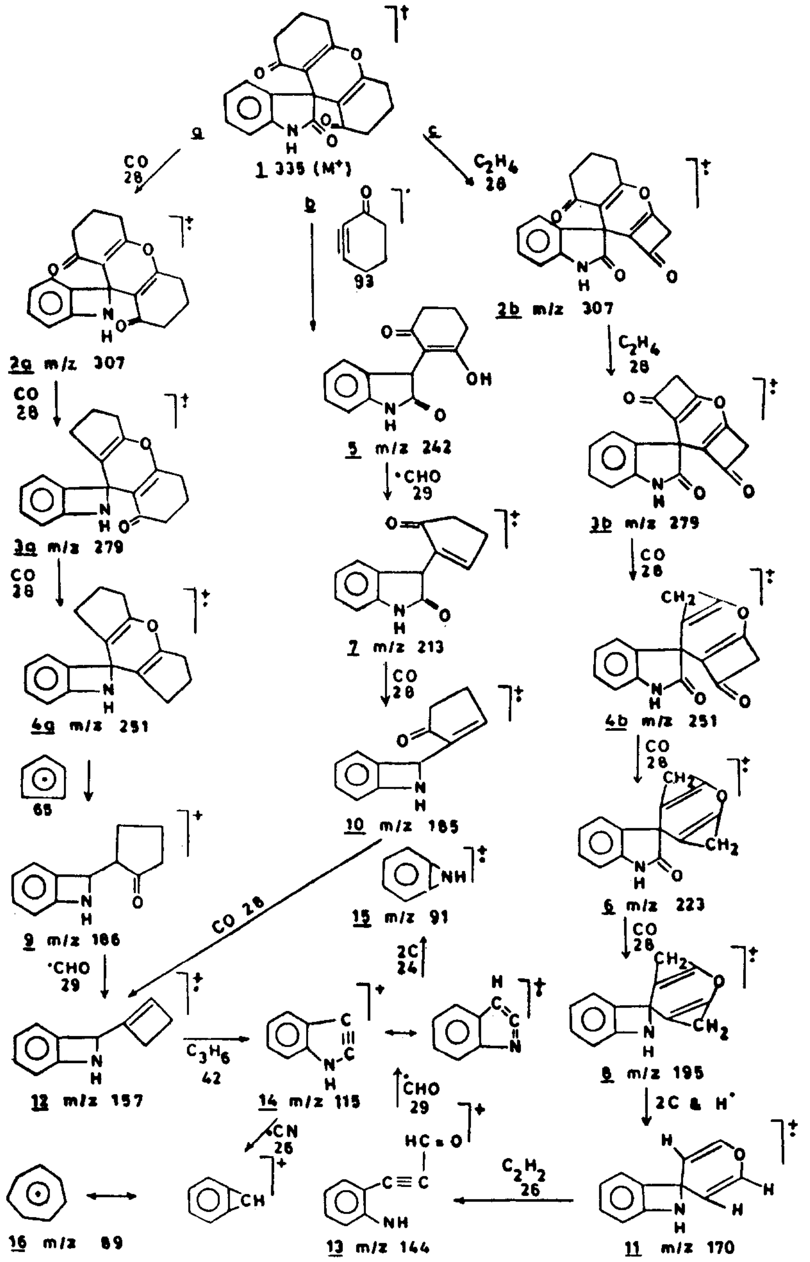
In the mass spectrum of compound (3a), (Scheme2) the parent peak appeared at 335 (M^+), which constitutes the base peak and confirms its molecular formula as $C_{20}H_{17}NO_4$. The molecular ion 1 (m/z 335, 100%, base peak) under electron impact may decompose following paths a, b and c. In path a, the molecular ion 1, eliminates three neutral CO molecules successively resulting in the formation of cation radical 2a (m/z 307, 14.7%), 3a (m/z 279, 57.7%) and 4a (m/z 251, 27.2%). This is followed by the loss of C_5H_5 radical giving rise to the cation 9 (m/z 186, 17.5%) which fragments a CHO radical to give 12 (m/z 157, 26.0%) as cation radical.

Alternatively, the molecular ion may decompose by path b, where it eliminates two radicals C_6H_5O and CHO giving the cation 5 (m/z 242, 83.8%) and cation radical 7 (m/z 213, 32.8%) respectively. This is followed by loss of two neutral CO moieties giving odd electron species 10 (m/z 185, 15.0%) and 12. The molecular ion 1 may follow still another pathway c, where it successively eliminates two neutral C_2H_4 followed by the elimination of three CO moieties giving rise to the cation radicals 2b, 3b, 4b, 6 (m/z 223, 15.8%) and 8 (m/z 195, 12.5%). The fragment 8 may further decompose into cation 11 (m/z 170,25.0%) by loss of a hydrogen radical and two neutral carbons. This cation fragments a neutral C_2H_2 molecule giving rise to the cation 13 (m/z 144, 20.0%), which eliminates CHO radical and gives the cation radical 14 (m/z 115, 27.1 %). This cation radical is also formed from 12 obtained by paths a and b by the loss of neutral C_3H_6 moiety. This cation radical 14 may decompose to give cation 16 (m/z 89 , 10.5 %) and cation radical

TABLE 1

Major mass fragments of representative compounds

Fragment No.	Compound No.3a		Compound No. 3b		Compound No.3e		Compound No.4a	
	m/z	Relative intensity %	m/z	Relative intensity %	m/z	Relative intensity %	m/z	Relative intensity %
1	M$^+$ 335	100	M$^+$ 353	12.5	M$^+$ 395	12.3	M$^+$ 334	17.5
2	307	14.7	325	22.5	367	14.6	306	27.5
3	279	57.7	297	5. 0	339	20.9	278	37.2
4	251	27.2	269	15.5	311	81.4	250	12.5
5	242	83.8	260	40.0	302	18.6	241	25.0
6	223	15.8	241	45.0	283	100	222	17.5
7	213	32.8	231	12.5	273	16.5	212	27.5
8	195	12.5	213	17.5	255	27.3	192	67.5
9	186	17.5	204	25.0	246	53.6	183	32.5
10	185	15.0	188	27.5	217	57.6	167	20.0
11	170	25.0	175	97.5	204	23.2	154	87.5
12	157	26.0	162	100	151	13.9	125	40.0
13	144	20.0	133	47.9	149	16.2	111	100
14	115	27.1	119	97.0	133	23.0	92	15.0
15	91	10.0	-	-	-	-	-	-
16	89	10.5	-	-	-	-	-	-



Scheme 2. Mass fragmentation pattern 3',4',6',7'-tetrahydro-spiro [3H-Indole-3-9'-[9H] xanthene] - 1',2,8'(1H,2'H,5'H)-trione.

15 (m/z 91, 10.0%) by elimination of CN radical and two neutral carbons respectively.

The conversion of spiro-xanthenes to spiro-acridines (4) [11] was accomplished by the reaction of spiro-xanthene with ammonium acetate in glacial acetic acid medium. The absorption peak in the IR spectrum due to ethereal oxygen at 1190 cm^{-1} disappeared in the product 4(a-c) but the >N-H absorption from 3290-3090 cm^{-1} and carbonyl absorptions at 1720 and 1660 cm^{-1} remained as such. In the ^1H NMR spectra, >CH_2 protons appeared in the form of three groups of peaks each integrating for four protons. A quintet from δ 0.8-1.0 ppm corresponded to C-3 and C-4 positions, the multiplets from δ 1.0-1.3 corresponded to C-4 and C-5 methylene groups and multiplet from δ 1.64-1.87 ppm corresponded to C-2 and C-7 methylene groups, the most deshielded ones. Apart from these, four aromatic protons in the region δ 5.80-6.34 and two singlets, each integrating for one proton at δ 6.69 and 9.42 ppm for >NH protons were also observed.

Additional support for their formation was obtained by mass spectrum. 3,4,6,7-Tetrahydro-spiro [9H-acridine-9,3'-[3H] indole]-1,2',8 (1'H,2H,5H)-trione(4a) has molecular ion peak at 334 (M^+), which corresponded to molecular formula $C_{20}H_{18}N_2O_3$. Major mass fragments with their relative intensity are recorded in Table 1.

EXPERIMENTAL

Melting points were determined in open glass capillaries and were uncorrected. IR spectra were recorded on a Perkin-Elmer (Model-557) in KBr pellets. ^1H and ^{19}F NMR were recorded on Jeol (Model-FX 90Q) using DMSO d_6 as solvent at 89.55 and 84.25 MHz respectively. TMS was used as internal reference for ^1H NMR and hexafluorobenzene as external reference for ^{19}F NMR. Mass spectra were recorded on Kratos mass spectrometer (MS-30 and MS-50). TLC was done on prepared silica gel plates. 5-Fluoroindole-2,3-dione, 6-fluoroindole-2,3-dione and 4-trifluoromethylindole-2,3-dione were prepared by literature methods [12-14].

Spiro [3H-indole-3,9'- [9H]xanthene]-1',2,8'(1H,2'H,5'H)-triones (3)

Compound 3a was prepared by three different methods viz: (i) by direct fusion (ii) in neutral medium and (iii) in acidic medium. The percentage yields varied in each case [8] .

(i) A mixture of isatin (0.005 mole) and 1,3-cyclohexanedione (0.01 mole) was heated for 2 hours at 110-115°C in absence of any solvent. The mass obtained was triturated with cold ethanol (30 ml) and the residue was recrystallised from ethanol as white needles.
M.P. 336°C, Yield 88% .

(ii) A solution of isatin (0.005 mole) and 1,3-cyclohexanedione (0.01 mole) in absolute ethanol (30 ml) was refluxed for 6 hours. Ethanol (15 ml) was distilled off from reaction mixture, the solid obtained was filtered and recrystallised from ethanol as pale yellow crystals.
M.P. 336°C, Yield 78% .

(iii) A solution of isatin (0.005 mole) and 1,3-cyclohexanedione (0.01 mole) in glacial acetic acid (30 ml) was refluxed for 4 hours. The solid compound formed

TABLE 2

Analytical data of spiro [3H-indole-3,9'-[9H] xanthene]-1',2,8'-(1H,2'H,5'H)-triones

Compound No.	X	R	M.P. °C	Yield %	Molecular formula	Elemental analysis Calc./Found		
						C	H	N
3a	H	H	336	88	$C_{20}H_{17}NO_4$	71.64 71.61	5.07 5.00	4.18 4.15
3b	5-F	H	320	75	$C_{20}H_{16}FNO_4$	67.98 67.92	4.53 4.52	3.96 3.78
3c	6-F	H	295	78	$C_{20}H_{16}FNO_4$	67.98 67.81	4.53 4.48	3.96 3.82
3d	5-F	$COCH_3$	284	72	$C_{22}H_{18}FNO_5$	66.83 66.78	4.55 4.51	3.54 3.50
3e	6-F	$COCH_3$	260	70	$C_{22}H_{18}FNO_5$	66.83 66.79	4.55 4.50	3.54 3.52
3f	5-F	CH_2N 	160	65	$C_{26}H_{27}FN_2O_4$	69.33 69.20	6.00 5.91	6.22 6.18
3g	4-CF_3	H	258	63	$C_{21}H_{16}F_3NO_4$	62.53 62.50	3.97 3.92	3.47 3.41

TABLE 3

Spectral data of spiro [3H-indole-3,9'-[9H]xanthene]-1',2,8'(1H,2'H,5'H)-triones

	IR (cm^{-1})			^1H NMR (δ ppm)								
Compd. No.	C=O (s)	NHC=O (s)	N-H (s)	CH_2 (3' and 6')	CH_2 (4' and 5')	CH_2 (2' and 7')	CH_3	NH	Ar-H	NCH_2-N	$\begin{matrix}-CH_2\\-CH_2\end{matrix}>CH_2$	$-N<\begin{matrix}CH_2-\\CH_2-\end{matrix}$
3a	1720	1660	3470	1.07- 1.47	1.47- 1.74	1.8- 2.2	-	10.2	6.03- 6.61	-	-	-
3b	1718	1665	3460	1.07- 1.46	1.48- 1.75	1.8- 2.1	-	9.88	6.20- 6.61	-	-	-
3c	1720	1660	3465	1.07- 1.47	1.47- 1.74	1.8- 2.1	-	9.99	6.15- 6.65	-	-	-
3d	1710	1670	-	1.08- 1.45	1.47- 1.78	1.8- 2.3	2.6	-	6.18- 6.72	-	-	-
3e	1722	1650	-	1.07- 1.47	1.47- 1.74	1.8- 2.2	2.6	-	6.25- 6.66	-	-	-
3f	1718	1660	-	1.07- 1.48	1.48- 1.81	1.9- 2.4	-	-	6.30- 6.78	4.0	1.5- 1.8	3.1- 3.3
3g	1720	1670	3470	1.07- 1.47	1.47- 1.74	1.8- 2.2	-	10.2	6.29- 6.82	-	-	-

TABLE 4

Analytical data of spiro [9H-acridine-9,3'-[3H] indole]-1,2',8(1'H,2H,5H)-triones

Compound No.	X	R	Y	M.P. °C	Yield %	Molecular formula	Elemental analysis Calc./Found		
							C	H	N
4a	H	H	H	315	80	$C_{20}H_{18}N_2O_3$	71.85 71.81	5.39 5.37	8.38 8.35
4b	H	H	4-C_6H_4F	305	70	$C_{26}H_{21}FN_2O_3$	72.89 72.48	4.90 4.78	6.54 6.52
4c	5-F	H	4-C_6H_4F	130	60	$C_{26}H_{20}F_2N_2O_3$	69.95 69.88	4.48 4.41	6.27 6.23

TABLE 5

Spectral data of spiro [9H-acridine-9,3'-[3H] indole]-1,2',8 (1'H,2H,5H)-triones

Compound	IR (cm^{-1})			1H NMR (δ ppm)					
No.	C=O (s)	NHC=O (s)	N-H (s)	CH_2 (3 and 6)	CH_2 (4 and 5)	CH_2 (2 and 7)	NH (10)	NH (1')	Ar-H
4a	1720	1660	3290-3090	0.8-1.0	1.0-1.3	1.64-1.87	6.69	9.42	5.80-6.34
4b	1718	1665	3290-3080	0.8-1.0	1.0-1.3	1.64-1.86	-	9.62	5.90-6.37
4c	1720	1668	3300-3080	0.7-1.1	1.15-1.32	1.66-1.87	-	9.47	5.85-6.32

on concentration was filtered and recrystallised from ethanol.
M.P. 336°C, Yield 38% .

All the other compounds listed in Table 2 were synthesized by the direct fusion method only as it gave the best yields. Spectral data of all compounds are given in Table 3 . All products 3a-3g showed one spot on TLC in Benzene-Ethyl acetate (3:2) solvent system.

Spiro [9H-acridine-9,3'-[3H] indole]-1,2',8 (1'H,2H,5H)-triones(4)

A solution of 3',4',6',7'-tetrahydro-spiro [3H-indole-3,9'-[9H] xanthene]-1',2,8'(1H,2'H,5'H)-trione (1 gm) and ammonium acetate (1 gm) in glacial acetic acid (10 ml) was refluxed for 5-10 minutes [11]. Ethanol (15 ml) was added to this when orange-red needles of compound (4a) were obtained and recrystallised from ethanol. M.P. 315°C, Yield 80% . Compounds 4b and 4c were obtained likewise using p-fluoroaniline instead of ammonium acetate. Analytical data and spectral data respectively are listed in Tables 4 and 5. All compounds showed one spot on TLC in Benzene-Ethyl acetate (3:2) solvent system.

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