Studies in Spiroheterocycles.

Part XIII. Synthesis of a Novel Spiro System:

Spiro[9*H*-Acridine-9,3'-[3H]indol]-2'(1'*H*)-one and Related Compounds from New Fluorinated Spiro[3*H*-indole-3,9'-[9*H*]xanthen]-2(1*H*)-ones

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A new spiroheterocyclic system spiro[9*H*-acridine-9,3'-[3*H*]indol]-2'(1'*H*)-one and related compounds have been prepared by the reaction of spiro[3*H*-indole-3,9'-[9*H*]xanthen]-2(1*H*)-ones with aromatic amine or ammonium acetate. The latter were prepared by heating fluorinated indole-2,3-diones with m-/p-cresols or α -naphthol in the presence of sulphuric acid at 230-240°. The synthesized compounds have been characterized on the basis of their elemental analyses, ir, nmr (1_H, 13_C, 19_F) and mass spectral data.

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The importance of the indole nucleus is well established in the field of pharmaceutical chemistry [1]. Various acridine derivatives are also well known for their biological activities. Acridine has 7.6 times the smooth muscle-relaxing activity of papaverine [2]. Its various

derivatives show platelet aggregation inhibiting [2], diuretic [2], antitumor and immunenhancing activity [3]. 10-Carboxymethyl-9-acridinone is used in chemotherapy of keratitis in rabbits [4]. Dihydroacridinediones having a trifluoromethyl group have pronounced antimalarial ac-

Scheme 1 230-40 O 230-240° 230-240° R 2a-j 2k-r 3f,g

 $X = 5-F, 6-F, 4-CF_3; Y = 2,7-diCII_3; 3-6-diCII_3; 2,7-di-F; Z = H, 4-F; R = II, CII_3, COCII_3, COC_6II_5, CII_2NR_2; NR_2 = N_2 + N_3 + N_3 + N_4 + N_3 + N_3$

tivity [5].

Prompted by these observations, we undertook the synthesis of spiroacridines and now wish to report the synthesis of a novel spiroheterocyclic system, viz: spiro[9H-acridine-9,3'-[3H]indol]-2'(1'H)-ones 3 besides some new fluorine containing spiroxanthenes 2. The synthetic steps are summarized in Scheme 1.

Compounds 2 were prepared either by heating fluorine containing indole-2,3-diones or 1,3-dihydro-3,3-bis(2-hydroxy-4/5-methylphenyl/naphthyl)indol-2-ones 1 with m-/p-cresols or α -naphthol at 230-40° in the presence of sulphuric acid. Compounds 1 were obtained by the reaction of indole-2,3-dione with m-/p-cresol or α -naphthol at 140-150°. Reaction of 2 with substituted aniline/ammonium acetate in glacial acetic acid gave a new spiroheterocyclic system 3.

Compounds 2 are characterized by ir absorption band at 1260 cm⁻¹ (characteristic of xanthene type). In the pmr of compound 2a, characteristic signals at δ 2.2 (a sharp singlet of methyl protons integrating for six protons), 6.4-7.0 (a multiplet of aromatic protons integrating for

Scheme 2

CH₃
CH₃
CH₃
2, m/z 316 (100%)

nine protons) and 7.5-7.6 ppm (slightly broad singlet for -NH protons) were observed. The position of the NH was confirmed on deuteration. In the mass spectrum, com-

Table I

Analytical Data of Spiro[3H-indole-3,9'-[9H]xanthen]-2(1H)-ones 2a-2i and Spiro[9H-dibenzo[c,h]xanthene-9,3'-[3H]indol]-2'(1'H)-ones 2k-2r

2a-2j

$$X \leftarrow \bigcup_{N \text{ of } N}$$

2k-2r

								Analysis %				
Compound No.	X	Y	R	Yield %	Mp °C	Formula	С	H Calcd.	N	С	H Found	N
2 a 2 b 2 c 2 d 2 e	5-F 5-F 5-F 6-F 6-F	3,6-diCH ₃ 2,7-diCH ₃ 2,7-di F 3,6-diCH ₃ 2,7-diCH ₃	H H H H	80 85 50 80 85	268 165 >300 278 273	C ₂₂ H ₁₆ FNO ₂ C ₂₂ H ₁₆ FNO ₂ C ₂₀ H ₁₀ F ₃ NO ₂ C ₂₂ H ₁₆ FNO ₂ C ₂₂ H ₁₆ FNO ₂	76.52 76.52 67.98 76.52 76.52	4.63 4.63 2.83 4.63 4.63	4.05 4.05 3.96 4.05 4.05	76.62 76.45 67.89 76.59 76.60	4.61 4.66 2.80 4.59 4.67	4.21 4.18 4.12 3.98 3.81
2 f 2 g	6-F 6-F	2,7-di F 3,6-diCH ₃	H COCH ₃	50 65	>300 247	C ₂₀ H ₁₀ F ₃ NO ₂ C ₂₂ H ₁₈ FNO ₃	67.98 66.11	2.83 4.95	3.96 3.85	68.09 66.20	2.81 4.93	4.00 3.92
2 h	5-F	3,6-diCH ₃	CH ₂ N_O	80	170	$\mathrm{C}_{27}\mathrm{H}_{25}\mathrm{FN}_2\mathrm{O}_3$	72.97	5.63	6.30	72.86	5.61	6.40
2 i	5-F	3,6-diCH ₃	CH ₂ N	80	278	$\mathrm{C_{28}H_{27}FN_2O_2}$	76.01	6.10	6.33	75.92	6.18	6.30
2 ј	5-F	3,6-diCH ₃	$CH_2N \subset C_2H_5$	80	282	$\mathrm{C}_{27}\mathrm{H}_{27}\mathrm{FN}_2\mathrm{O}_2$	75.34	6.27	6.51	75.22	6.32	6.60
2 k 2 l 2 m 2 n 2 o 2 p	5-F 6-F 4-CF ₃ 5-F 5-F	- - - -	H H COC ₆ H ₅ COCH ₃ CH ₃	80 78 70 78 60 80	345 335 300 220 240 245	C ₂₈ H ₁₆ FNO ₂ C ₂₈ H ₁₆ FNO ₂ C ₂₉ H ₁₆ F ₃ NO ₂ C ₃₅ H ₂₀ FNO ₃ C ₃₀ H ₁₈ FNO ₃ C ₂₉ H ₁₈ FNO ₂	80.57 80.57 74.51 80.61 78.43 80.74	3.83 3.83 3.42 3.83 3.92 4.17	3.06 3.06 2.76 2.68 3.05 3.24	80.65 80.69 74.45 80.52 78.55 80.82	3.77 3.90 3.50 3.89 3.90 4.22	3.15 3.20 2.91 2.66 3.08 3.29
2 q 2r	5-F 5-F	-	$CH_2N \longrightarrow C_2H_5$ $CH_2N \subset C_2H_5$ C_2H_5	O.J	330 350	$C_{33}H_{25}FN_2O_3$ $C_{33}H_{27}FN_2O_2$	76.74 78.88	4.84 5.37	5.42 5.57	76.86 78.98	4.89 5.40	5.40 5.61
			C ₂ 115									

pounds 2 showed a molecular ion peak (M⁺) at their appropriate molecular masses. This also indicated ketoenol tautomerism as is evident by the loss of -CHO of mass 29 to generate a cation 2 at m/z 316 which forms the base peak (Scheme 2).

Spiro[9H-acridine-9.3'-[3H]indol]-2'(1'H)-ones 3a are characterized by the disappearance of ir absorption signal at 1260 cm⁻¹. In the pmr of **3b** (400 MHz, deuteriochloroform) characteristic signals are observed. Two methyl groups appear as a sharp singlet at δ 2.3, indicating the chemical equivalence of the two phenyl rings of the acridine nucleus. The H₂ and H₆ protons of the N-phenyl ring of the acridine nucleus appear as both singlets at δ 6.5-6.6; H₃ and H₅ couples with fluorine to give a doubletdoublet at δ 6.75-6.8 ppm; protons H₄; H₅ and H₄, appear as a singlet due to m-coupling at δ 7.05, ortho coupled protons H_{6'7}; H_{1,2} and H_{7,8}; appear each as a double doublet in the region δ 6.7-7.0 and NH at δ 8.98 ppm. These pmr data gave strong evidence for the formation of the compounds. The presence and position of fluorine in all compounds was confirmed by 19F nmr spectra. A single fluorine attached to the indole ring system was observed as a singlet at -115 to -117 ppm and the trifluoromethyl group of the indole ring gave a singlet at δ 62.968 ppm. The ¹³C nmr spectra of the spiro compounds 2k,1,m showed signals at δ 193.68 (>C=0), 113.98-163.61 (aromatic ring carbons) and at 110.72 (spiro carbon). Presence of 16 singuls for aromatic ring carbons instead of 26 signals in the spectra suggested the chemical equivalence of the two naphthalene rings. Additional support was obtained from the mass spectral data where the molecular ion peak corresponded to their molecular mass.

Benzoylation, methylation, acetylation and Mannich reaction of spiroxanthenes 2 were also carried out and the products formed were characterized by disappearance of the the NH signals and appearance of additional signals at δ 2.3 (N-CH₃) in compounds 2p; at 2.6 ppm (COCH₃) in compounds 2g,2o; at 4.2-4.3 (CH₂), 2.4-2.7 (CH₂-O-CH₂), 3.5-3.8 (CH₂-N-CH₂) for 2h,2q and at 1.3-1.7 (CH₂-CH₂-CH₂), 2.3-2.8 ppm (CH₂N-CH₂) for 2i compounds.

EXPERIMENTAL

All the melting points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer Model 337 spectrophotometer in potassium bromide pellets. The pmr spectra were recorded on Perkin-Elmer Model R-32 (90 MHz) and Bruker 400 WM (at 400 MHz) in deuteriochloroform using TMS as the internal standard. The ¹⁹F nmr were taken in TFA at 84.25 MHz using hexafluorobenzene as the external standard. The ¹³C nmr were taken in DMSO-d₆ at 22.49 MHz. All chemical shifts are in δ ppm. Mass spectra were recorded on Kratos-30 and on Varian MAT 711, mass spectrometer at 70 eV. Purity was routinely checked by tlc.

1,3-Dihydro-3,3-bis(2-hydroxy-4/5-methylphenyl/naphthyl) indol-2-ones 1.

A mixture of fluorinated indole-2,3-dione (1.0 g), m-/p-cresol or α -naphthol (3.0 g) and concentrated sulphuric acid (0.05 g) was heated at 140-150° for 5 minutes [6]. The solid, which separated out on cooling, was recrystallized with acetic acid to give needles of compounds 1.

Spiro[3H-indole-3,9'-[9H]xanthen]-2(1H)-ones 2.

A mixture of fluorinated indole-2,3-dione (1.0 g), m-/p-cresol or α -naphthol (3.0 g) and concentrated sulphuric acid (0.05 g) was heated at 230-240° for 10 minutes. This was then cooled to room temperature and ethanol (25 ml) was added to give the corres-

Analysis %

Table II

Analytical Data of Spiro[9H-acridine-9,3'-[3H]indole]-2'(1'H)-ones 3a-3b and Spiro[9H-dibenzo[c,h]acridine-9,3'-[3H]indol]-2'(1'H)-ones 3c-3g

3a-3b

3c-3g

							Timary Sis 70						
Compound No.	X	Y	Z	Yield %	$^{Mp}_{\circ C}$	Formula	С	H Calcd.	N	С	H Found	N	
3a 3b 3c 3d 3e 3f 3g	5-F 5-F 5-F H 5-F 5-F 6-F	2,7-diCH ₃ 3,6-diCH ₃ - - -	C_6H_5 4-F C_6H_4 4-F C_6H_4 4-F C_6H_5 H	60 45 75 70 75 60 60	245 290 190 200 125 350 340	C ₂₈ H ₂₁ FN ₂ O C ₂₈ H ₂₀ F ₂ N ₂ O C ₃₄ H ₂₀ F ₂ N ₂ O C ₃₄ H ₂₁ FN ₂ O C ₃₄ H ₂₁ FN ₂ O C ₂₀ H ₁₇ FN ₂ O C ₂₀ H ₁₇ FN ₂ O	80.00 76.71 80.00 82.92 82.92 75.00 75.00	5.00 4.56 3.92 4.26 4.26 5.31 5.31	6.66 6.39 5.49 5.69 5.69 8.75 8.75	80.10 76.85 80.12 82.80 82.81 75.11 74.89	4.95 4.50 3.88 4.21 4.30 5.25 5.35	6.68 6.25 5.21 5.21 5.40 6.21 6.01	
Jg	0-1	-	11	00	540	020111711120	75.00	5.51	0.75	, ,,,,,,	5.55	0.01	

ponding spiro compounds 2. The compounds thus obtained were filtered and recrystallized from acetic acid.

Spiro compounds 2 were also obtained by heating fluorinated 1,3-dihydro-3,3-bis(2-hydroxy-4/5-methylphenyl/naphthyl)indol-2-ones 1 (1.0 g), m-/p-cresol or δ-naphthol (3.0 g) and concentrated sulphuric acid (0.05 g) at 230-240° [6]. Melting points and elemental analyses are in agreement with the compounds directly obtained from the indole-2.3-diones.

N-Acetyl-6-fluoro-3',6'-dimethylspiro[3H-indole-3,9'-[9H]-xanthen]-2(1H)-one 2g.

Compound 2d (1.0 g) was refluxed in acetic anhydride (70 ml) for 6 hours. On cooling, crystals separated out, which were filtered, washed well with a little acetic acid and recrystallized from acetic acid.

N-Acetyl-5'-fluorospiro[9H-dibenzo[c,h]xanthen-9,3'-[3H]indol]-2'(1'H)-one 2o.

This compound was similarly prepared from 2k (1.0 g) and acetic anhydride (70 ml).

N-Benzoyl-5'-fluorospiro[9H-dibenzo[c,h]xanthen-9,3'-[3H]indol]-2'(1'H)-one **2n**.

To a cooled stirred solution of 2k (1.66 g) in pyridine (19 ml), benzoyl chloride (62 ml) was added dropwise. The solution was stirred further for 2 hours, kept at 0° and 0.7N sulphuric acid was added. The desired compound separated as white crystals and was filtered and recrystallized from ethanol.

5'-Fluoro-N-methylspiro[9H-dibenzo[c,h]xanthen-9,3'-d[3H]indol]-2'(1'H)-one **2p**.

To a stirred solution of **2k** (5.67 g) in ethanol (30 ml), was added a solution of ethanolic potassium hydroxide (10%, 10 ml), portionwise, during 20 minutes. Freshly distilled dimethyl sulphate (15 ml) was added to the deep purple solution and the mixture was further stirred for 30 minutes. The reaction mixture was filtered and the ethanol from the filtrate was distilled off, the residue left behind was recrystallized from acetic acid.

N,N-Dialkylaminomethyl-5-fluoro-3',6'-dimethylspiro[3H-indole-3,9'-[9H]xanthen]-2'(1'H)-ones **2h**.

Compound 2d (0.01 mole), N,N-dialkylamine (0.012 mole), formaldehyde (40%, 0.015 mole, 0.5 g) and ethanol (25 ml) were refluxed on a steam bath for 45 minutes. On cooling, crystals separated out, which were filtered, dried and recrystallized from ethanol.

Other N,N-dialkylaminomethyl substituted compounds 2i, 2j, 2q and 2r were prepared in a similar manner.

Physical and analytical data of the synthesized compounds are listed in Table I.

Spiro[9H-acridine-9,3'-[3H]indol]-2'(1'H)-one 3.

Spiro[3*H*-indol-3,9'-[9*H*xanthen]-2'(1'*H*)-ones **2** (1.0 g) substituted aniline (1.0 g)/ammonium acetate (3.0 g) and glacial acetic acid (25 ml) were heated to reflux on a hot plate for 4-6 hours. The reaction mixture was then cooled to room temperature. The solid, thus obtained was filtered, washed and recrystallized from ethanol to give a tlc pure compound.

All synthesized compounds are listed in Table II with their physical and analytical data.

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REFERENCES AND NOTES

- [1] K. C. Joshi and P. Chand, Pharmazie, 37, 1 (1982).
- [2] Y. H. Wu and W. G. Lobeck Jr., Swiss Patent CH 629,801; Chem. Abstr., 97, 110025x (1982).
- [3] K. C. Murdock, M. R. Damiani and F. E. Durr, U. S. Patent, 4,314,061; Chem. Abstr., 96, 181164a (1982).
- [4] W. J. O'Brien, J. L. Taylor, D. W. Clough and R. O. Schuttz, Herpetische Angenerkr, 255 (1980, published in 1981).
- [5] Yoelii, P. Berghei, W. Raether and E. Fink, Ann. Trop. Med. Parasitol., 76, 507 (1982); Chem. Abstr., 98, 65116u (1985).
 - [6] H. Wexler and V. Barboiu, Rev. Roum. Chim., 21, 127 (1976).