Studies in Spiroheterocycles. Part XVII.

Synthesis of Novel Fluorine Containing Spiro[indole-pyranobenzopyran] and Spiro[indenopyran-indole] Derivatives

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An elegant one-step synthesis of two novel spiro ring systems *viz*: spiro[3*H*-indole-3,4'-(2'-amino-3'-carbonitrile-[4'*H*]-pyrano[3,2-*c*]benzopyran)]-2,5'(1*H*)-diones and spiro[(2-amino-3-carbonitrile-indeno[1,2-*b*]pyran)-4(5*H*),3'-[3*H*]indole]-2',5(1'*H*)-diones in 80-85% yields is described. The spiro heterocycles were prepared by the reactions of fluorine containing 3-dicyanomethylene-2*H*-indol-2-ones with 4-hydroxy-2*H*-1-benzopyran-2-one and 1*H*-indene-1,3(2*H*)-dione respectively. The synthesized compounds have been characterized on the basis of elemental analyses, ir, pmr, ^{19}F nmr and mass spectral data.

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As a part of our continuing interest on the synthesis of new fluorine containing heterocycles incorporating spiro indolines [1] for possible pharmacological evaluation, we now wish to report the synthesis of a novel ring system, *viz*: spiro[3*H*-indole-3,4'-(2'-amino-3'-carbonitrile-[4'*H*]-pyrano[3,2-c]benzopyran)]-2,5'(1*H*)-dione (**2**) by the reaction of fluorine containing 3-dicyanomethylene-2*H*-indol-2-ones **1** with 4-hydroxy-2*H*-1-benzopyran-2-one. Further, we report another new facile approach to the synthesis of a seccond spiro system, *viz*: spiro[(2-amino-3-carbonitrile-indeno[1,2-*b*]pyran)-4(5*H*),3'-[3*H*]indole]-2',5(1'H)-dione (**3**) by the reaction of **1** with 1*H*-indene-1,3(2*H*)-dione.

The medicinal application of spiro[indolo-pyrans] as muscle relaxants and antiinflammatory agents is well known [2,3]. Further, the bioactivity of coumarins [4,5] and the indene derivatives [6] is well established. Recently Michael adduct of arylidene indenedione with coumarins were reported as active anticoagulant [7]. Nevertheless, no report has been cited on spiro indolines incorporating pyranobenzopyrans and with indenopyrans, which may lead to the production of compounds with altered/enhanced bioactivity. Besides, practically no work has been done on fluorine containing spiro[indolo-pyrans]. The coumarin and indene derivatives have, however, been reported to undergo Michael addition reaction [8,9].

In view of these observations, we have now investigated the reaction of **1** with 4-hydroxy-2*H*-1-benzopyran-2-one to explore the possibility of the formation of a novel spiro system incorporating indole and pyranobenzopyran moieties. In yet another attempt to obtain a different spiro system, we explored the reaction of **1** with 1*H*-indene-

Scheme 1

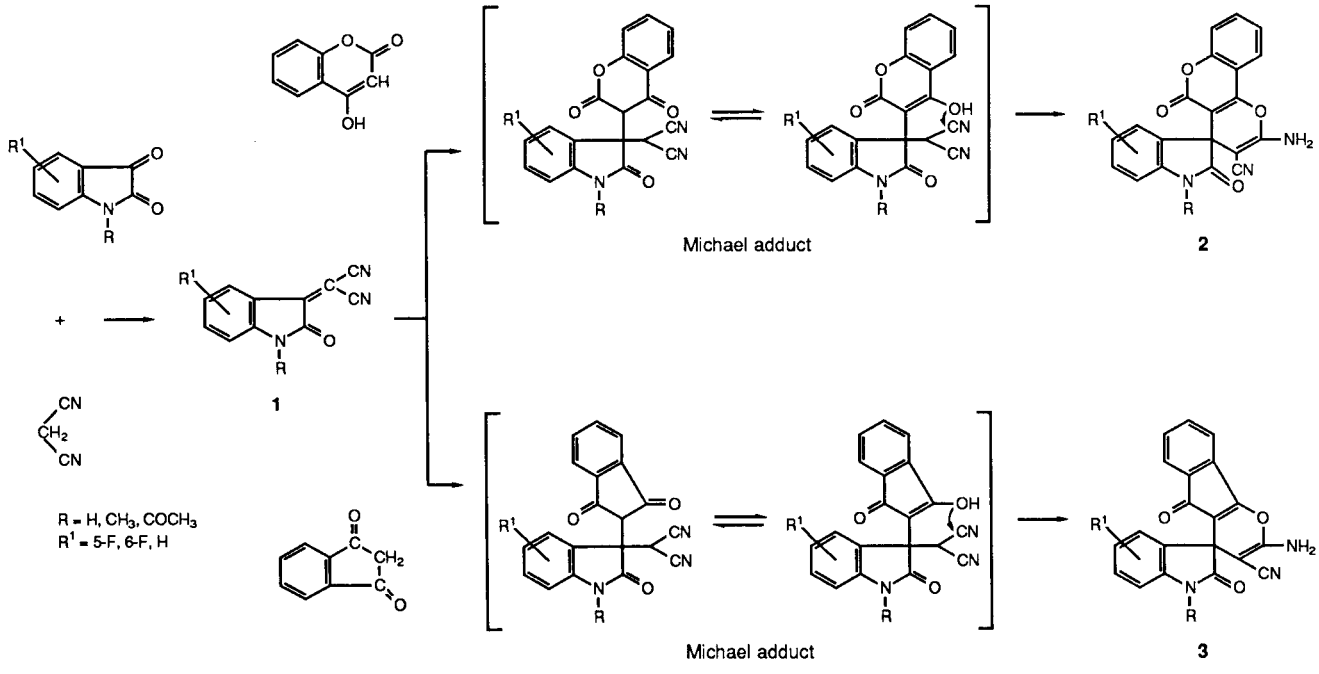

Table I

Characteristic Physical and Analytical Data of Spiro[indole-pyranobenzopyran] and spiro[indenopyran-indole] Derivatives

Compound No.	R	R'	MP °C	Yield %	Formula	Analysis % C	H Calcd.	N	C	H Found	N
2a	H	H	291	86	$C_{20}H_{11}N_3O_4$	67.22	3.08	11.76	67.28	3.12	11.72
2b	$COCH_3$	H	276	88	$C_{22}H_{13}N_3O_5$	66.16	3.25	10.52	66.12	3.28	10.56
2c	H	5-F	321	84	$C_{20}H_{10}FN_3O_4$	64.00	2.66	11.20	64.08	2.62	11.24
2d	H	6-F	279	85	$C_{20}H_{10}FN_3O_4$	64.00	2.66	11.20	64.05	2.60	11.18
3a	H	H	242	87	$C_{20}H_{11}N_3O_3$	70.38	3.22	12.31	70.35	3.25	12.34
3b	CH_3	H	236	64	$C_{21}H_{13}N_3O_3$	71.38	3.68	11.89	71.40	3.65	11.84
3c	H	5-F	249	86	$C_{20}H_{10}FN_3O_3$	66.85	2.78	11.69	66.82	2.76	11.66
3d	H	6-F	210	90	$C_{20}H_{10}FN_3O_3$	66.85	2.78	11.69	66.88	2.80	11.71

1,3(2*H*)-dione to afford spiro[indenopyran-indole]. There is only one report in the literature mentioning the synthesis of spiro[indenopyran-indole], but this is through a complicated route involving the cycloaddition of 2-(2-oxindolin-3-ylidene)-1,3-indenedione with ethyl vinyl ether and gives comparatively low yields [10].

The reaction of an appropriate indole-2,3-dione with malononitrile in absolute ethanol, in presence of piperidine, results in the formation of 1,3-dihydro-3-dicyanomethylene-2*H*-indol-2-ones **1**. The Michael reaction of **1**, having an electron attracting group on the exomethylene carbon is interesting, as it can afford either a Michael adduct which can exist as such or this adduct can be enolized and converted into the spiro-pyran system of C-3 of oxindole (Scheme 1).

The Michael reaction of violet coloured **1** with 4-hydroxy-2*H*-1-benzopyran-2-one and 1*H*-indene-1,3(2*H*)-dione afforded light yellow coloured compounds. The ir spectra of these compounds displayed characteristic absorption bands at 3380 cm^{-1} corresponding to free NH_2 group and at 3120 cm^{-1} due to NH stretching. Strong absorption bands corresponding to conjugated C=N and two carbonyl groups were observed at 2200-2190, 1700 and 1680 cm^{-1} respectively. The pyran ether linkage was observed at 1180 cm^{-1}. Formation of light coloured compounds and disappearance of exocyclic C=C absorption at 1620 cm^{-1} indicated the relief in the conjugation of oxindolidene system of **1**. The pmr spectra displayed aromatic protons in the region δ 6.8-7.4 and a characteristic broad signal at 7.7-7.9 ppm corresponding to NH_2 protons which disappeared on deuteration. An inspection of ir and pmr provides no evidence for the Michael adduct as characteristic C-H stretching and hydroxyl absorption in ir and two singlet, corresponding to methine proton and O*H* group in pmr spectra should have been observed. On the basis of these observations, along with the spectral data, the products formed with 4-hydroxy-2H-1-benzopyran have been identified as spiro[indole-pyranobenzopyran] derivatives **2a-d** and with 1*H*-indene-1,3(2*H*)-dione as spiro[indenopyran-indole] derivatives **3a-d**.

Formation of spiro compounds **2a-d** and **3a-d** has further been confirmed on the basis of mass spectra. In the mass spectrum of compound **2c**, the molecular ion peak was observed at m/z 375 (100%) and in **3c** at m/z 359 (100%) corresponding to their molecular weights.

The presence and position of fluorine was also confirmed by ^{19}F nmr. Fluorine attached at the 5- and 6-position of indole ring was observed at δ -115 and -112 ppm respectively.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded using Perkin-Elmer 557 spectrophotometer. Pmr spectra were recorded on Jeol (model FX 90Q) at 89.55 MHz using TMS as external reference and DMSO-d_6 or TFA as solvents. ^{19}F nmr spectra were recorded on Jeol (model FX 90Q) at 84.25 MHz and taken in DMSO-d_6 using hexafluorobenzene (at δ -162.9 ppm) as external reference. The mass spectra were recorded on MS-30 and MS-50 Kratos mass spectrometer operating at an ionisation potential of 70 eV.

1,3-Dihydro-3-dicyanomethylene-2*H*-indol-2-ones **1**.

These compounds were prepared following the method of Yokayama [11] using appropriate indole-2,3-dione and malononitrile. However, the 1-methyl derivative was obtained at room temperature on mixing the 1-methylindole-2,3-dione and malononitrile in absolute ethanol even in the absence of a catalyst.

1-Methyl-1,3-dihydro-3-dicyanomethylene-2*H*-indol-2-one.

This compound was obtained in 74% yield, mp 214°.

Spiro[3*H*-indole-3,4'-(2'-amino-3'-carbonitrile-[4'*H*]-pyrano[3,2-*c*]-benzopyran]-2,5'(1*H*)-diones **2a-d**.

A mixture of appropriate 3-dicyanomethylene-2*H*-indol-2-one *(1) (0.01 mole) and 4-hydroxy-2H-1-benzopyran-2-one (0.01 mole)*

in absolute ethanol (40 ml) was treated with two drops of piperidine as a catalyst and the mixture was stirred at room temperature. After two hours, a light yellow coloured compound separated which was filtered and recrystallized from ethanol.

The 1-acetyl derivative **2b** was obtained after stirring for 30 minutes.

Spiro[(2-amino-3-carbonitrile-indeno[1,2-*b*]pyran)-4(5*H*),3'-[3*H*]-indole]-2',5(1'*H*)-diones **3a-d**.

These compounds were prepared following the same procedure as above, using appropriate **1** and 1*H*-indene-1,3(2*H*)-dione.

The physical and analytical data of synthesized spiro compounds **2a-d** and **3a-d** are recorded in Table I.

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