

STUDIES IN SPIROHETEROCYCLES : PART XXII : SYNTHESIS OF NOVEL
 FLUORINE CONTAINING SPIRO[3H-INDOLE-3,5'-[5H]PYRANO[2,3-d]PYRIMIDINE]-
 6'-CARBONITRILES AND ETHYL CARBOXYLATES

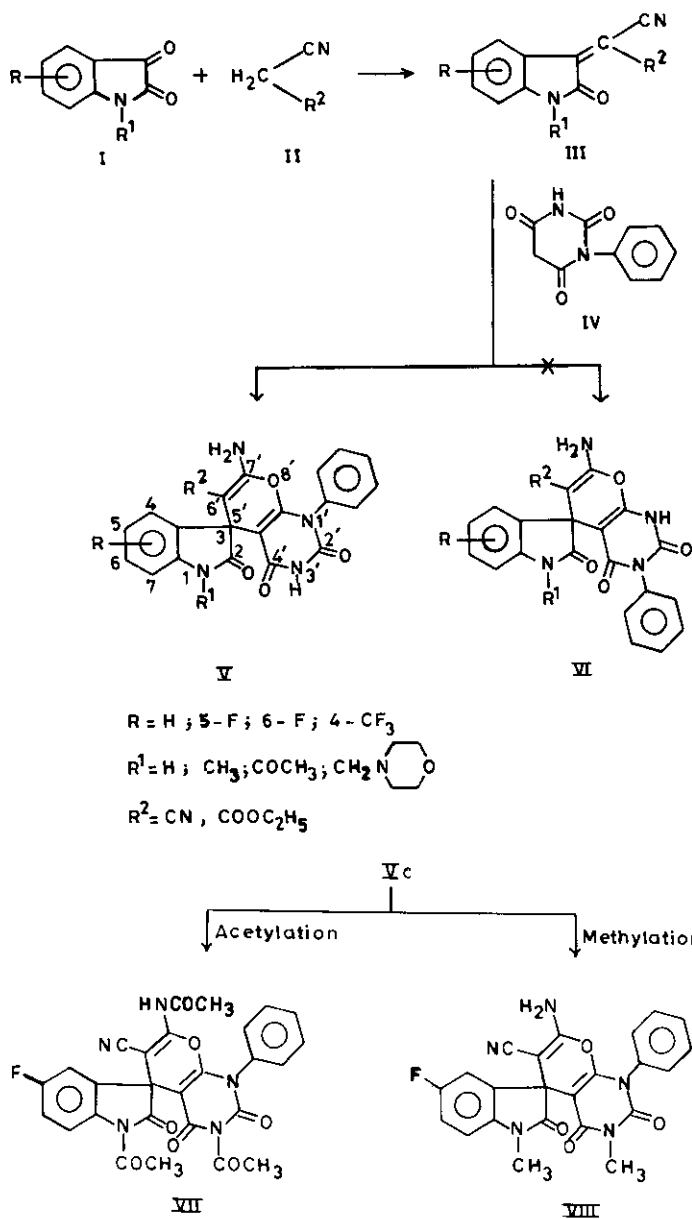
Krishna C. Joshi*, Renuka Jain, and Saroj Nishith
 Department of Chemistry, University of Rajasthan,
 Jaipur-302004, India

Abstract - A number of novel fluorine containing spiro[3H-indole-3,5'-[5H]pyrano[2,3-d]pyrimidine]-6'-carbonitriles and ethyl carboxylates have been synthesized by the Michael reaction of 3-dicyano- and carboethoxycyanomethylene-2-oxindole with phenylbarbituric acid. As the reaction offers two possibilities, the formation of the preferred product has been discussed. Further, the spiro compounds have been subjected to acetylation and methylation.

In continuation to our earlier work on biologically active fluorinated indoles¹⁻⁵ and spiroindolines,⁶⁻¹⁰ we now report the synthesis of fluorine containing 7'-amino-1,1', 2,2', 3', 4'-hexahydro-2,2',4'-trioxo-1'-phenylspiro[3H-indole-3,5'-[5H]pyrano[2,3-d]pyrimidine]-6'-carbonitriles and ethyl carboxylates. This spiro system appears to be of interest because (i) it incorporates indole and pyranopyrimidine moieties which are interesting with respect to biological responses; (ii) it possesses different reaction sites (three $>C=O$, two $>NH$ and $-NH_2$) and lastly (iii) there is non-availability of data for this derivative and its fluorinated analogues. There are only two references in the literature for analogous pyrano[2,3-d]pyrimidine system obtained by the treatment of 3-dicyano- and carboethoxycyanomethylene-2-oxindole (III) with barbituric acid;^{11,12} the former being obtained by the reaction of indole-2,3-diones(I) with malononitrile and ethyl cyanoacetate (II) respectively. For our studies, we opted for phenylbarbituric acid (IV) instead of barbituric acid and its reaction with 2-oxindole (III) including some fluorinated ones was examined (Scheme I).

Reaction of (III) with (IV) in the presence of piperidine proceeds smoothly to give the spiro compound (V) in good yield without formation of VI. The active methylene group present in phenylbarbituric acid initially undergoes Michael reaction to give the Michael adduct (A) which may exist in tautomeric forms B and C. The enolate form of the Michael adduct (B) would attack the electrophilic centre to give the final spiro product V. Structure V is further stabilized by intramolecular H-bonding which is evident from the ir spectrum ($>NH$ near 3000

Scheme I



cm⁻¹ and >C=O absorption near 1630 cm⁻¹). This stabilization is lacking in structure VI. Additional proof for the formation of V is obtained from the nmr spectra where one of the >NH is found to appear quite downfield (δ 12.20 - 12.00) indicating that it has carbonyl group on both the sides which is not possible in structure VI.

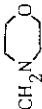
recorded on Perkin-Elmer (Model-577) in KBr pellets (ν max in cm^{-1}). ^1H Nmr and ^{19}F nmr were recorded on Jeol (Model FX-90Q) at 89.55 and 84.25 MHz respectively (chemical shift in δ , ppm) using TMS as internal reference for ^1H nmr and hexafluorobenzene as external standard for ^{19}F nmr. Mass spectra were recorded on Kratos MS-30 and MS-50 spectrometer at 70 eV. Purity of all the compounds was checked by tlc done on silica gel plates. 5- and 6-Fluoroindole-2,3-diones,^{13,14} 4-trifluoromethylindole-2,3-dione,¹⁵ 1-acetylindole-2,3-dione,¹⁶ 1-methylindole-2,3-dione,¹⁷ phenylbarbituric acid¹⁸ and 3-carboethoxycyano- and dicyanomethylene-2-oxindoles¹⁹ were prepared by literature methods.

7'-Amino-1,1',2,2',3',4'-hexahydro-2,2',4'-trioxo-1'-phenylspiro[3H-indole-3,5'-[5H]pyrano-[2,3-d]pyrimidine]-6'-carbonitrile Va - A mixture of 3-dicyanomethylene-2-oxindole (1.95 g, 0.01 mol) and phenylbarbituric acid (2.04 g, 0.01 mol) in absolute ethanol (40 ml) was treated with piperidine (0.20 ml) and stirred at room temperature for 3 h.¹¹ The supernatant ethanol was removed and the light coloured solid obtained was filtered, rinsed thoroughly with dichloromethane and recrystallized from ethanol to give violet coloured prisms, mp 204°C, yield 3.51 g, 88% (Found : C, 63.26; H, 3.30; N, 17.43 $\text{C}_{21}\text{H}_{13}\text{N}_5\text{O}_4$ requires C, 63.15; H, 3.28; N, 17.54%). $\nu_{\text{max}}^{\text{cm}^{-1}}$ 3210, 3180 ($-\text{NH}_2$), 3050 ($>\text{NH}$), 3000 ($3' >\text{NH}$, H-bonded), 2100 ($-\text{C}\equiv\text{N}$), 1710, 1670, 1630 (three $>\text{C}=\text{O}$) and 1180 (C-O-C); ^1H nmr ($\text{DMSO}-d_6$) : δ 6.03-7.01 (m, 9H, aromatic protons), 7.30 (s, 2H, $7'-\text{NH}_2$), 9.98 (s, 1H, 1 $>\text{NH}$), 12.10 (s, 1H, 3' $>\text{NH}$); MS : m/z 399(M^+); 356(M^+-HCNO), 328, 300, 119 (base peak). All other compounds (Vb-j) given in table-I were prepared in a similar manner.

1,3'-Diacetyl-7'-acetylamino-5-fluoro-1,1',2,2',3',4'-hexahydro-2,2',4'-trioxo-1'-phenylspiro-[3H-indole-3',5'-[5H]pyrano[2,3-d]pyrimidine]-6'-carbonitrile VII - Compound Vc (4.17 g, 0.01 mol) was refluxed with excess of acetic anhydride (20 ml) for 4 h. On cooling, the desired compound was obtained which was purified by recrystallization from ethanol, mp 268°C, yield 4.07 g, 75% (Found : C, 59.75; H, 3.03; N, 12.97 $\text{C}_{27}\text{H}_{18}\text{FN}_5\text{O}_7$ requires C, 59.67; H, 3.33; N, 12.98%). $\nu_{\text{max}}^{\text{cm}^{-1}}$ 3100 cm^{-1} ($>\text{NH}$), 1710, 1700, 1695, 1685, 1670, 1650 (six $>\text{C}=\text{O}$), 1182 (C-O-C) and 1000-1100 (C-F); ^1H nmr ($\text{DMSO}-d_6$) : δ 10.40 (s, $>\text{NH}$, 1H), 6.85-7.40 (m, aromatic protons, 8H), 2.80, 2.50, 2.30 (each s, $-\text{CH}_3$, 9H); ^{19}F nmr : δ -115.11.

7'-Amino-5-fluoro-1,1',2,2',3',4'-hexahydro-1,3'-dimethyl-2,2',4'-trioxo-1'-phenylspiro[3H-indole-3',5'-[5H]pyrano[2,3-d]pyrimidine]-6'-carbonitrile VIII - Compound Vc (1.11 g, 0.0026 mol) in absolute ethanol (20 ml) was treated dropwise with ethanolic KOH (5 ml, 10%) while stirring. Dimethyl sulphate (freshly distilled, 0.65 g, 0.0052 mol) was subsequently added at

Table - I
Physical and Analytical Properties of Spiro[3H-indole-3,5'-[5H]pyranol[2,3-d]pyrimidine]-6'-carbonitriles and ethyl carboxylates

Compd.	R	R ¹	R ²	mp (°C)	Yield	Molecular formula	Calc.		Analysis %		Found	
							C	H	N	C	H	N
a.	H	H	CN	204	88	C ₂₁ H ₁₃ N ₅ O ₄	63.15	3.28	17.54	63.26	3.30	17.43
b.	H	H	COOC ₂ H ₅	210	87	C ₂₃ H ₁₈ N ₅ O ₆	61.88	4.06	12.55	62.02	4.03	12.60
c.	5-F	H	CN	197	89	C ₂₁ H ₁₂ FN ₅ O ₄	60.43	2.90	16.78	60.32	2.91	16.69
d.	5-F	H	COOC ₂ H ₅	214-15	88	C ₂₃ H ₁₇ FN ₅ O ₆	59.48	3.69	12.07	59.55	3.71	11.98
e.	6-F	H	CN	240	85	C ₂₁ H ₁₂ FN ₅ O ₄	60.43	2.90	16.78	60.51	2.89	16.85
f.	4-CF ₃	H	CN	264-65	80	C ₂₂ H ₁₂ F ₃ N ₅ O ₄	56.53	2.59	14.99	56.42	2.61	15.05
g.	4-CF ₃	H	COOC ₂ H ₅	270	80	C ₂₄ H ₁₇ F ₃ N ₅ O ₆	56.03	3.33	10.89	55.89	3.28	10.93
h.	H	CH ₃	CN	245	87	C ₂₂ H ₁₅ N ₅ O ₄	63.92	3.66	16.94	64.08	3.70	17.05
i.	H	COCH ₃	CN	253-55	89	C ₂₃ H ₁₄ N ₅ O ₅	62.73	3.20	15.90	62.82	3.18	15.84
j.	H		COOC ₂ H ₅	235	85	C ₂₈ H ₂₇ N ₅ O ₇	61.64	4.99	12.83	61.75	5.02	12.74

60°C with vigorous shaking to the above suspension and stirred for 1.5 h. The residue obtained thereafter was filtered and recrystallized from ethanol, mp 257°C, yield 0.83 g, 70% (Found : C, 62.97; H, 3.59; N, 15.85 $C_{23}H_{16}FN_5O_4$ requires C, 62.02; H, 3.62; N, 15.73%).
 $\nu_{\text{max}}^{\text{cm}^{-1}}$ 3210, 3180 (-NH₂), 1690, 1680, 1675 (three >C=O) 1175 (C-O-C) and 1000-1100 (C-F);
 1H nmr (DMSO-d₆) : δ 7.60 (s, -NH₂, 2H), 6.01-7.04 (m, aromatic protons, 8H), 1.81 and 1.95 (s, -CH₃, 6H); ¹⁹F nmr : δ -115.20.

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