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

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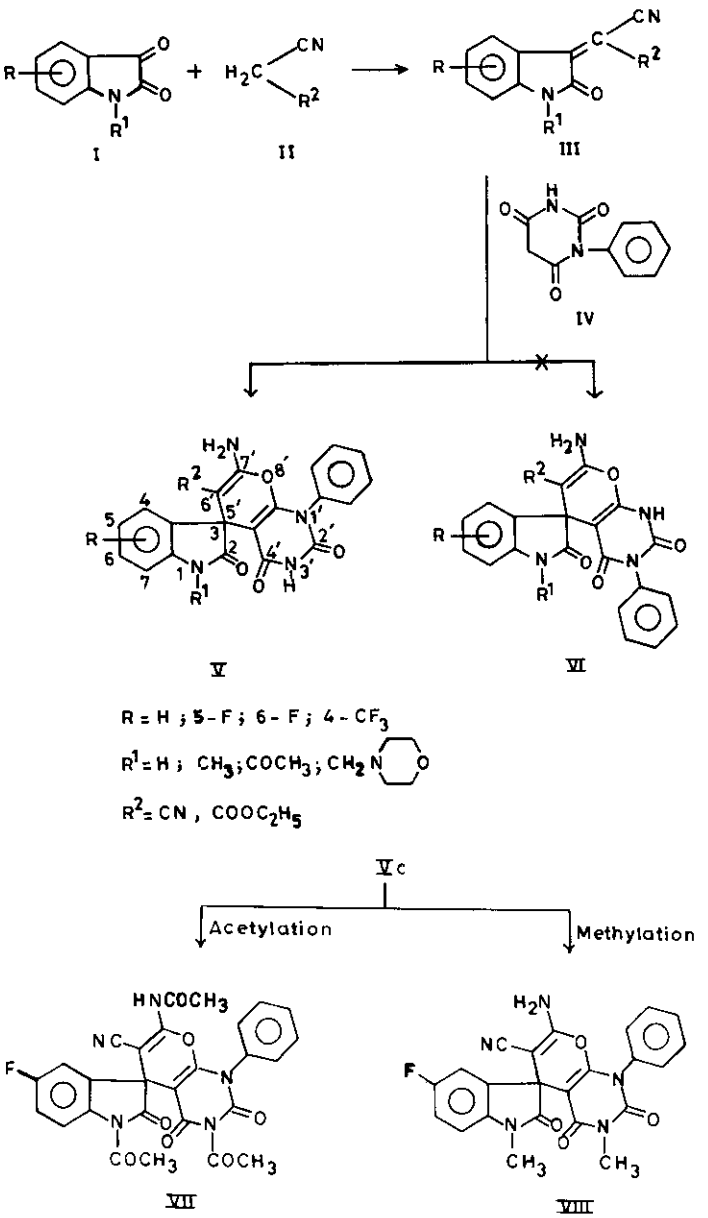
Abstract - A number of novel fluorine containing spiro[3H-indole-3,5'-[5H]pyrano[2,3-d]pyrimidine]-6'-carbonitriles and ethyl carboxylates have been synthesized by the Michael reaction of 3-dicyano- and carboethoxycyanomethylene-2-oxindole with phenylbarbituric acid. As the reaction offers two possibilities,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

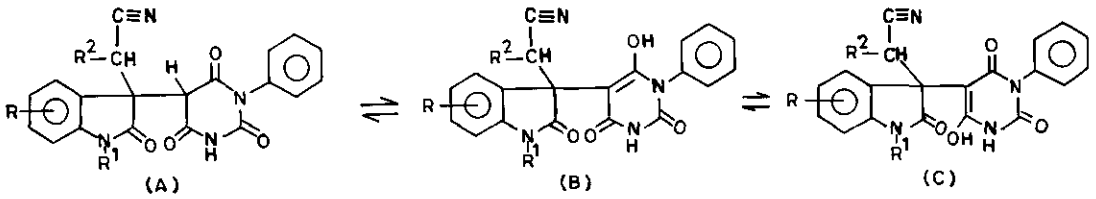
In continuation to our earlier work on biologically active fluorinated indoles[1-5] and spiroindolines,[6-10] we now report the synthesis of fluorine containing 7'-amino-1,1', 2,2', 3', 4'-hexahydro-2,2',4'-trioxo-1'-phenylspiro[3H-indole-3,5'-[5H]pyrano[2,3-d]pyrimidine]-6'-carbonitriles and ethyl carboxylates. 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 $\geq C=O$ 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 $\geq NH$ is found to appear quite downfield (δ12.20 - 12.00) indicating that it has carbonyl group on both the sides which is not possible in structure VI.



The spiro compounds were characterized by ir absorption bands in the region 3350-3000 cm^{-1}, one of the bands appearing as twin peaks represented the 'free' asymmetrical and symmetrical stretching due to $-NH_2$ group and two peaks for the >NH groups. The presence of the C=O groups was revealed by the appearance of three peaks in the region 1710-1630 cm^{-1}, and of the ethereal linkage C-O-C by an absorption band at 1170-1180 cm^{-1}. For compounds (Va, c,e,f,h,i, VII, VIII), a sharp peak at 2150-2100 cm^{-1} due to $-C\equiv N$ stretching and for compounds (Vb,d,g and j) an additional absorption for >C=O group at 1750-1740 cm^{-1} was observed. In ^1H nmr, signals were observed for compounds (Va - g) at δ 12.20-12.00 (3' >NH), 10.40-9.98 (1 >NH), 7.80-7.50 (7'-NH_2) and at 7.40-6.03 (aromatic protons). The mass spectra further supported the formation of the compounds as evidenced by the molecular ion peak (M^+ at m/z 399, Va). The base peak was obtained (at m/z 119) by the formation of a $PhNCO^{+\cdot}$ fragment. Further, acetylation and methylation of spiro compound (Vc) were undertaken. Acetylation was carried out by refluxing the spiro compound with acetic anhydride. For methylation the spiro compound in ethanol was treated with KOH (10%) and subsequently with dimethyl sulphate (freshly distilled) while stirring. Although there are three reaction sites, viz: $-NH_2$ and two >NH groups, we obtained a trisubstituted product on acetylation and a disubstituted product on methylation. The ir spectrum of the triacetylated product VII revealed only >NH absorption at 3100 cm^{-1}. A set of absorption bands centred at 1705, 1700, 1695, 1685, 1670 and 1650 cm^{-1} appeared for the six >C=O groups. ^1H Nmr revealed a single resonance peak at δ 12.30 for >NH and three additional peaks at δ 2.81, 2.50 and 2.32 for the three $-CH_3$ groups. The formation of the dimethylated product was confirmed by the complete disappearance of >NH absorption in the ir and ^1H nmr spectra. Two additional signals at δ 1.81 and 1.95 for the two $-CH_3$ groups appeared in the ^1H nmr. The resonance signal at δ 7.71 and the twin peaks at 3210, 3180 cm^{-1} for $-NH_2$ remained as such in the ^1H nmr and ir spectra respectively.

EXPERIMENTAL

Melting points were taken in open glass capillaries and are uncorrected. Ir spectra were

recorded on Perkin-Elmer (Model-577) in KBr pellets (ν max in cm^{-1}). ^{1}H 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 ^{1}H 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 acid[18] and 3-carboethoxycyano- and dicyanomethylene-2-oxindoles[19] were prepared by literature methods.

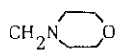
7'-Amino-1,1',2,2',3',4'-hexahydro-2,2',4'-trioxo-1'-phenylspiro[3H-indole-3,5'-[5H]pyrano-[2,3-d]pyrimidine]-6'-carbonitrile Va - A mixture of 3-dicyanomethylene-2-oxindole (1.95 g, 0.01 mol) and phenylbarbituric acid (2.04 g, 0.01 mol) in absolute ethanol (40 ml) was treated with piperidine (0.20 ml) and stirred at room temperature for 3 h.[11] The supernatent 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 $C_{21}H_{13}N_5O_4$ requires C, 63.15; H, 3.28; N, 17.54%). $\nu_{max}^{cm^{-1}}$ 3210, 3180 ($-NH_2$), 3050 (>NH), 3000 (3' >NH, H-bonded), 2100 (-C≡N), 1710, 1670, 1630 (three >C=O) and 1180 (C-O-C); ^{1}H nmr (DMSO-d_6) : δ 6.03-7.01 (m, 9H, aromatic protons), 7.30 (s, 2H, 7'-NH_2), 9.98 (s, 1H, 1 >NH), 12.10 (s, 1H, 3' >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 $C_{27}H_{18}FN_5O_7$ requires C, 59.67; H, 3.33; N, 12.98%). $\nu_{max}^{cm^{-1}}$ 3100 cm^{-1} (>NH), 1710, 1700, 1695, 1685, 1670, 1650 (six >C=O), 1182 (C-O-C) and 1000-1100 (C-F); ^{1}H nmr (DMSO-d_6) : δ 10.40 (s, >NH, 1H), 6.85-7.40 (m, aromatic protons, 8H), 2.80, 2.50, 2.30 (each s, $-CH_3$, 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]pyrano[2,3-d]pyrimidine]-6'-carbonitriles and ethyl carboxylates

Compd.	R	R^1	R^2	mp (°C)	Yield	Molecular formula	Analysis % Calc. C	Calc. H	Calc. N	Found C	Found H	Found N
a.	H	H	CN	204	88	$C_{21}H_{13}N_5O_4$	63.15	3.28	17.54	63.26	3.30	17.43
b.	H	H	$COOC_2H_5$	210	87	$C_{23}H_{18}N_4O_6$	61.88	4.06	12.55	62.02	4.03	12.60
c.	5-F	H	CN	197	89	$C_{21}H_{12}FN_5O_4$	60.43	2.90	16.78	60.32	2.91	16.69
d.	5-F	H	$COOC_2H_5$	214-15	88	$C_{23}H_{17}FN_4O_6$	59.48	3.69	12.07	59.55	3.71	11.98
e.	6-F	H	CN	240	85	$C_{21}H_{12}FN_5O_4$	60.43	2.90	16.78	60.51	2.89	16.85
f.	4-CF_3	H	CN	264-65	80	$C_{22}H_{12}F_3N_5O_4$	56.53	2.59	14.99	56.42	2.61	15.05
g.	4-CF_3	H	$COOC_2H_5$	270	80	$C_{24}H_{17}F_3N_4O_6$	56.03	3.33	10.89	55.89	3.28	10.93
h.	H	CH_3	CN	245	87	$C_{22}H_{15}N_5O_4$	63.92	3.66	16.94	64.08	3.70	17.05
i.	H	$COCH_3$	CN	253-55	89	$C_{23}H_{14}N_5O_5$	62.73	3.20	15.90	62.82	3.18	15.84
j.	H		$COOC_2H_5$	235	85	$C_{28}H_{27}N_5O_7$	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%). $\nu_{max}^{cm^{-1}}$ 3210, 3180 ($-NH_2$), 1690, 1680, 1675 (three >C=O) 1175 (C-O-C) and 1000-1100 (C-F); 1H nmr (DMSO-d_6) : δ 7.60 (s, $-NH_2$, 2H), 6.01-7.04 (m, aromatic protons, 8H), 1.81 and 1.95 (s, $-CH_3$, 6H); ^{19}F nmr : δ -115.20.

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