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A novel synthesis of spiro[5*H*-1,4-diazepine-5,3′-[3*H*]indol]-2′(1′H)-ones and spiro[2*H*-1,5-benzodiazepine-2,3′-[3*H*]indol]-2′(1′*H*)-ones

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Reactions of 3-aroylmethyleneindol-2(*H*)-ones **4** with ethylenediamine and *o*-phenylenediamine have been investigated for the first time leading to novel system of spiro compounds **5** and **8** respectively. Schiff's bases **6** and **9** have also been isolated and properly characterized.

Diazepines and benzodiazepines are important seven membered heterocyclic ring systems widely acclaimed for their physiological activities. Librium, valium and anthramycin are but a few examples of this diverse group of diazepines[1]. A comprehensive literature survey revealed that indolyl carbinols on treatment with ethylenediamine and *o*-phenylenediamine afford exclusively spiro[5*H*-1, 4-diazepine-5,3′-[3*H*] indol]-2′(1′*H*)-one and spiro [2*H*-1,5-benzo-diazepine-2,3′-[3*H*] indol]2′(1′*H*)-one respectively[2,3]. Similar reactions with 3-aroylmethylene-indol-2(*H*)-ones **4** have not been studied so far. It was therefore thought worthwhile to investigate these reactions. Since **4** are quite reactive compounds with an alkene system flanked on either side by two carbonyl groups, their reaction with each of these diamines theoretically offers three possibilities, viz. formation of a spiro derivative **5/8**, a Schiff's base **6/9** and a condensed system **7/10** (cf. Scheme I). Isolation of products indicated the formation of spiro derivatives **5** and **8** along with Schiff's bases **6** and **9** with ethylene-diamine and *o*-phenylenediamine, respectively. The condensed systems (**7** and **10**) were not formed with either of the diamines-probably because of the involvement of eight membered rings.

Fluorinated isatin **1**, prepared by literature method[4,5] from the corresponding aniline, on treatment with acetophenones **2** in the presence of diethylamine as catalyst, afforded 3-aroylmethylene-3-hydroxyindol-2-ones **3** which on dehydration in hydrochloric acid-glacial acetic acid yielded the corresponding compound[6,7] **4.** Reaction of **4** with ethylenediamine in absolute ethanol under reflux for 10-12 hr gave a mixture which showed two spots on TLC plate visualized in iodine. Column chromatography of the mixture on a silica gel column afforded compounds **5** and **6** (added yields of the spiro products and Schiff's bases (**5** and **6**) were >90%. Physical data of all the synthesized compounds are given in Table I.

The reaction mixture obtained by reacting 1,2-phenylenediamine with **4** under exactly similar conditions although showed one spot on the TLC plate when visualized in iodine vapours, it revealed the presence of a second compound under UV lamp which fluoresced in ultra violet light. Separation of the two compounds **8** and **9** was effected by preparative TLC, over silica gel G run in benzene; ethyl acetate (80:20) system, under UV lamp. Physical data of isolated compounds **8** and **9** are listed in Table II.

To check that the Schiff's bases **6** and **9** are not intermediates but stable products and do not get cyclised to the corresponding spiro products **5** and **8**, the uncyclised products **6** and **9** were further refluxed in absolute ethanol for 28-30 hr. It was observed that respective percentage yields of the two products (spiro : Schiff's bases) remained unchanged for both the diamines.

Appearance of a peak in the region 1660-1700 cm^{-1} for >C=O absorption in IR spectra of the products formed eliminated the possibility of the

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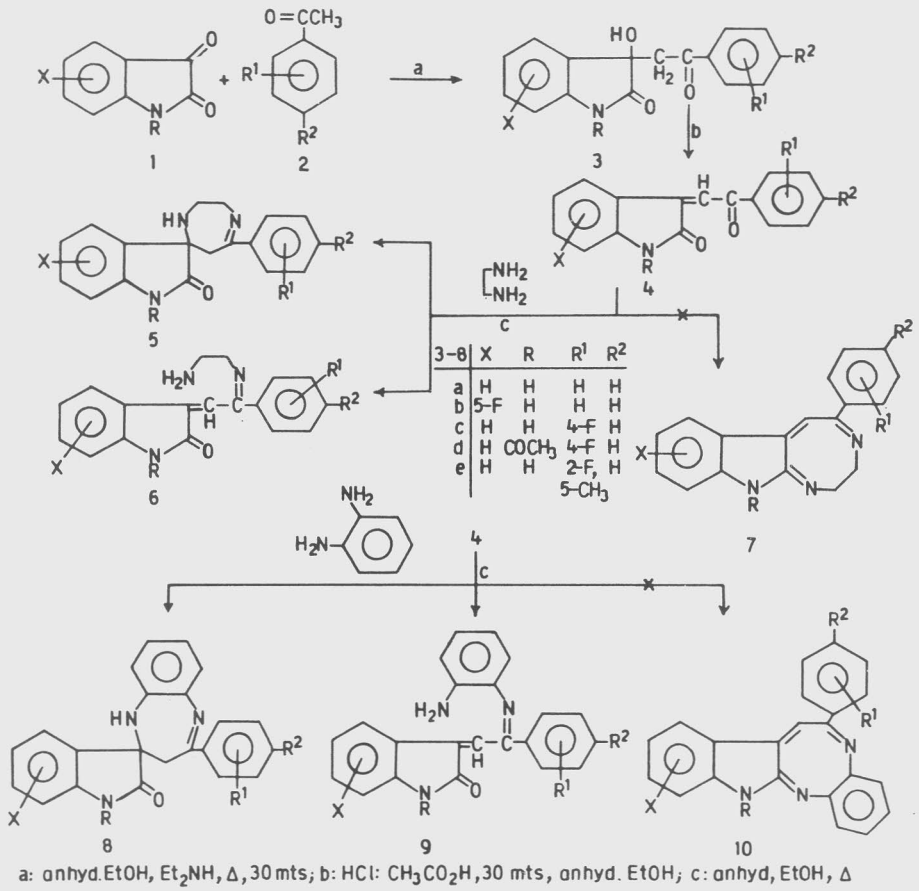


Scheme I

Table I—Analytical data of 7-aryl-2,3-6-tetrahydrospiro[5*H*-1,4-diazepine-5,3′-[3*H*]indol]-2′(1′*H*)-ones **5** and 1,3-dihydro-3-{1-[(2-iminoethyl)amine]-2-arylethylidene}indol-2′(*H*)-ones **6**

Compd	Yield (%)	m.p. °C	Mol.formula	Found % (Calcd)		
				C	H	N
5a	48	216-18	$C_{18}H_{17}N_3O$	74.14 (74.20	5.90 5.88	14.50 14.42)
5b	51	222	$C_{18}H_{16}FN_3O$	69.86 (69.88	5.20 5.21	13.61 13.58)
5c	53	201	$C_{18}H_{16}FN_3O$	69.77 (69.88	5.27 5.21	13.51 13.58)
5d	52	225	$C_{20}H_{18}FN_3O_2$	68.38 (68.36	5.09 5.16	12.01 11.96)
5e	50	236	$C_{19}H_{18}FN_2O$	70.74 (70.57	5.56 5.61	13.03 12.99)
6a	50	239-42	$C_{18}H_{17}N_3O$	74.37 (74.20	5.83 5.88	14.39 14.42)
6b	46	240	$C_{18}H_{16}FN_3O$	69.73 (69.88	5.27 5.21	13.53 13.58)
6c	45	209-10	$C_{18}H_{16}FN_3O$	69.72 (69.88	5.28 5.21	13.60 13.58)
6d	40	235	$C_{20}H_{18}FN_3O_2$	68.27 (68.36	5.18 5.16	11.87 11.96)
6e	45	257	$C_{19}H_{18}FN_3O$	70.45 (70.57	5.55 5.61	13.00 12.99)

Table II—Analytical data of 4-aryl-2,3-dihydrospiro[2*H*-1,5-benzodiazepine-2,3′-[3*H*]indol]-2′(1′*H*)-ones **8** and 1,3-dihydro-3-{1-[(2-iminophenyl) amine]-2-arylethylidene}indol-2(*H*)-ones **9**

Compd	Yield (%)	m.p. °C	Mol.formula	Found % (Calcd) C	H	N
8a	70	68-69	$C_{22}H_{17}N_3O$	77.77 (77.85	5.12 5.05	12.40 12.38)
8b	68	98	$C_{22}H_{16}FN_3O$	74.85 (73.93	4.52 4.51	11.81 11.76)
8c	70	110	$C_{22}H_{16}FN_3O$	73.98 (73.93	4.47 4.51	11.69 11.76)
8d	61	115	$C_{24}H_{18}FN_3O_2$	76.88 (75.97	4.80 4.78	11.11 11.08)
8e	65	121	$C_{23}H_{18}FN_3O$	74.44 (74.37	4.91 4.88	11.37 11.31)
9a	28	130	$C_{22}H_{17}N_3O$	77.98 (77.85	5.03 5.05	12.32 12.38)
9b	25	93	$C_{22}H_{16}FN_3O$	73.87 (73.93	4.46 4.51	11.69 11.76)
9c	20	105	$C_{22}H_{16}FN_3O$	73.81 (73.93	4.54 4.51	11.74 11.76)
9d	22	135	$C_{24}H_{18}FN_3O_2$	75.89 (75.97	4.76 4.78	11.12 11.08)
9e	25	114	$C_{23}H_{18}FN_3O$	74.48 (74.37	4.84 4.88	11.34 11.31)

formation of a condensed system **(7/10)**. Formation of spiro compound **5a** from **4** was evidenced by IR spectrum having absorption bands at 3280, 3160-3060 cm^{-1} for the two >NH groups, at 1680 for carbonyl group and at 1610 cm^{-1} for >C=N stretching. ^1H NMR spectrum showed a singlet at δ 2.40 for $-CH_2-$ and two triplets centered at δ 2.88 and δ 3.42 for the two $-CH_2-$ groups attached to the sp^3 and sp^2 hybridized nitrogen respectively. A multiplet in the region δ 6.63-7.71 integrating for 9 aromatic protons and singlets at δ 9.45 and δ 10.85 (NH) were also observed. Mass spectrum of **5a** depicted M^+ at m/z 291, corresponding to the molecular formula $C_{18}H_{17}N_3O$. Molecular ion peak was also the base peak. IR spectrum of Schiff's base **6a** revealed, a doublet at 3030 and 3060 cm^{-1} representing the 'free' asymmetrical and symmetrical stretching due to $-NH_2$ group and singlets at 3100 (–NH stretching),1680 (>C=O stretching) and 1610 cm^{-1} (>C=N stretching). In the ^1H NMR spectrum of **6a**, two triplets at δ 3.14 and δ 3.65 (two $-CH_2-$ groups) and a singlet at δ 5.60 (=CH–) were observed. A multiplet in the region δ 6.09-7.59 integrating for 9 aromatic protons and singlets at δ 9.23 (NH) and d 10.48 ($-NH_2$) were also present. The presence of molecular ion peak at m/z 291 corresponding to the molecular formula $C_{18}H_{17}N_3O$ and of a base peak, obtained by the loss of a neutral H_2 molecule at 289 further confirmed the structure assigned.

The conversion of compound **4** to **8a** on its reaction with 1,2-phenylenediamine was evidenced by the presence of absorption bands at 3260 and 3140-3050 (two >NH groups), 1675 (C=O) and 1610 cm^{-1} (C=N stretching) in the IR spectrum. ^1H NMR spectra of **8a** revealed a singlet at δ 1.67 ($-CH_2-$), a multiplet integrating for 13 aromatic protons at δ 7.17-8.37 and singlets at δ 9.38 and δ 9.62 for >NH protons. In the mass spectrum of **8a** M^+ was observed at m/z 339 which correspond to the molecular formula $C_{22}H_{17}N_3O$. The molecular ion peak was also the base peak. IR spectrum of the Schiff's base **9a** showed an absorption band at 3360-3240 (>NH stretching) and a doublet at 3040 and 3080 cm^{-1} representing respectively the 'free' asymmetrical and symmetrical stretching of amino group. Absorption bands at 1680 (C=O) and 1610 cm^{-1} (>C=N) were also observed. Its ^1H NMR spectrum exhibited a resonance signal at δ 3.51 characteristic of the methine proton. Aromatic protons at δ 6.70-7.37 and imido and amino proton resonance signals at δ 8.61 and 10.20 respectively were also observed. The presence of molecular ion

peak at m/z 339 corroborating with $C_{22}H_{17}N_3O$ and of a base peak obtained by the loss of a H_2 moiety at 337, further supported the proposed sturcture. Subsequent fragmentation follows two major pathways viz. loss of a C_6H_5CN (103) moiety from the base peak or alternatively, loss of a C_6H_5 (77) free radical followed by a neutral CO(28) fragment from the molecular ion peak, giving a radical cation, in both the cases, of m/z 234 which may thus have two structures **a** and **b** (Fig. 1).

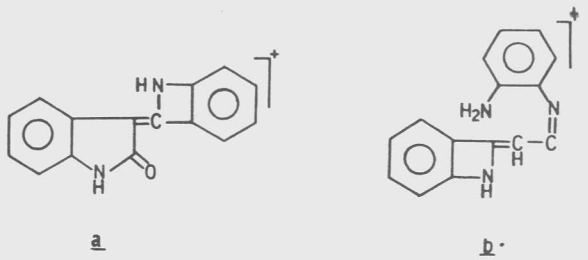
^{19}F NMR spectra of the fluorinated analogues of **5a**, **6a**, **7a** and **8a** revealed a fluorine attached to the indole ring at δ-112.474 to δ-116.061 and of aryl ring at δ-119.125 to δ-120.783, depending upon the substitution position.

Experimental Procedure

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer Ac-1 spectrophotometer (λ_{max} in cm^{-1}); ^1H NMR and ^{19}F NMR spectra were recorded on Perkin-Elmer R-32 spectrometer at 89.55 and 84.25 MHz respectively using TMS as internal reference for ^1H NMR and hexafluorobenzene as external standard for ^{19}F NMR spectra. Mass spectra were recorded on a Jeol JMS D-300 spectrometer. The elemental analyses were performed at RSIC, Lucknow. Purity of the compounds was checked on TLC plates.

3-Aroylmethyleneindol-2(*H*)-ones **4**, viz. 3-benzoylmethyleneindol-2-one, 5-fluoro-3-benzoylmethyleneindol-2-one, 3-(4′-fluorobenzoyl)-methyleneindol-2-one, 1-acetyl-3-(4′-fluorobenzoyl)-methyleneindol-2-one and 3-(2′-fluoro-5′-methylbenzoyl)-methyleneindol-2-one were prepared by literature methods[5,6].

7-Aryl-2,3,6-tetrahydrospiro [5*H*-1,4-diazepine-5,3′-[3*H*]indol]-2′(1′*H*)-ones 5a-e and 1,3-dihydro-3-{1-[(2-iminoethyl) amine]-2-arylethylidene} indol-2(*H*)-ones 6a-e. General procedure. A mixture of appropriate **4** (.01 mole) and ethylenediamine (0.01 mole, 0.60g) in absolute ethanol (60 mL) was refluxed for 10-12 hr. The residue obtained on concentrating and cooling showed two spots on TLC run in C_6H_6 : EtOAc (9:1) when visualized in I_2 vapours. Separation was effected by column chromatography on silica gel. The eluents were used in increasing order of polarity. Spiro compounds **5a-e** obtained from the benzene fraction were filtered and recrystallized from benzene. The Schiff's bases **6a-e** were obtained from the benzene ethyl acetate (80:20) fraction and recrystallized from ethanol. All the compounds along with their analytical data are given in Tables I and II.



a b

Figure 1

4-Aryl-2,3-dihydrospiro [2*H*-1,5-benzodiazepine-2,3′-[3*H*]indol]-2′ (1′*H*) ones 8a-e and 1,3-dihydro-3-{1-[(2-iminophenyl) amine]-2-arylethyledene}indol-2(*H*)-ones 9a-e. General procedure. Appropriate **4** (0.01 mole) and 1,2-phenylenediamine (0.01 mole, 1.08 g) were refluxed together in 50 mL of absolute ethanol for 5 hr. The solid mixture obtained showed two spots on TLC visualized under UV lamp and was therefore subjected to preparative TLC on silica gel G using benzene ethyl acetate (80:20) solvent system as irrigant. The fluorescent band was cut, taken in acetone, stirred and filtered. The filterate on concentration yielded a residue which was recrystallized from pet. ether to give needle shaped crystals of spiro compounds **8a-e**. The Schiff's bases **9a-e** appeared as brown spots and were also recrystallized from pet. ether.

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