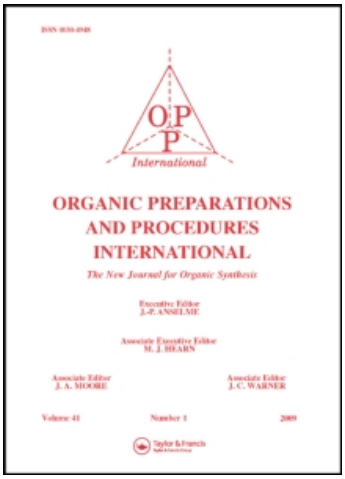

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REACTIONS OF INDOLE-2,3-DIONES WITH 3-AMINOPROPANOL

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REACTIONS OF INDOLE-2,3-DIONES WITH 3-AMINOPROPANOL

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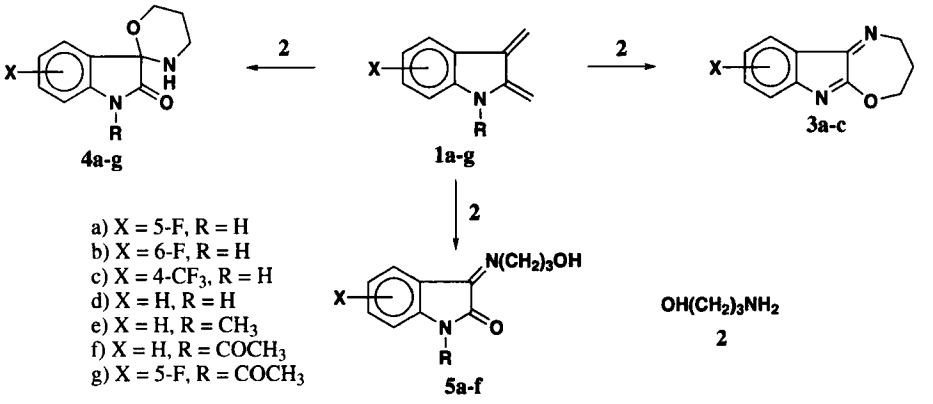
The importance of isatin as a versatile molecule for the synthesis of novel spiro heterocycles was reviewed in 1999.[1] Isatin derivatives exhibit significant biological, medicinal and pharmacological activities,[2] such as antituberculous, anticonvulsant, antihyperglycemic, antifertility[3] action. Some are also active against salmonella typhi and vibrio cholerae bacteria. Besides, they are used in the treatment and prevention of pest virus.[4] In continuation to our earlier work on reactions of fluorine containing indole-2,3-diones,[5-10] we noted that the reactions of such compounds with amino alcohols have not been studied. A literature survey[11,12] revealed that the reaction of 1,2-aminoalcohols with aldehydes or ketones can lead either to imino compound or oxazolidine. However, there are exceptions[13] depending upon the nature of carbonyl compounds. In view of the various possibilities offered by these reactions along with a number of biological activities associated with imino compounds[14-16] and oxazinoindoles,[17,18] we investigated this reaction and determined the reaction conditions for the sole preparation of a new tricyclic ring system, 7,8-dihydro-6*H*-9-oxa-5,10-diaza-benzo[*a*]azulene derivatives (**3**), spiroindolines (**4**), and iminoindoles (**5**). It may be pointed out that there are only two references to the synthesis of spiro[3*H*-indole-3,6'-[6*H*-1,3]oxazin]-2 (1*H*)-ones[19-20] and one reference for the synthesis of 1*H*-1,2 oxazepino [6,5-*b*] indoles[21] by different routes.



The reactions of indole-2,3-diones (**1a-g**) and 3-aminopropanol (**2**) were studied under different conditions of time and temperature. The progress of the formation of the products was checked by tlc on silica gel. The yields and nature of the products depended on the reaction conditions (*Table 1*).

Table 1. Reaction of **1a-g** with 3-Aminopropanol (**2**).Yields, mps and Elemental Analyses

Cmpd	Yield (%)	Time (hrs)	mp (°C)	Elemental Analyses (Found) C	H	N
3a	40	3[a]	>360	64.70 (64.82)	4.41(4.59)	13.72 (13.54)
3b	39	3[a]	>360	64.70 (64.79)	4.41 (4.39)	13.72 (13.62)
3c	38	3[a]	>360	56.69 (56.50)	3.54 (3.55)	11.02 (10.97)
4a	70	6[b]	220-222	59.45 (59.65)	4.95 (4.97)	12.61 (12.73)
4b	69	6[b]	101-103	59.45 (59.30)	4.95 (5.10)	12.61 (12.59)
4c	46	6[b]	170-172	52.94 (53.13)	4.04 (4.10)	10.29 (10.30)
4d	42	8[b]	270-273	64.70 (64.86)	5.88 (5.87)	13.72 (13.75)
4e	39	8[b]	84-86	66.05 (65.97)	6.42 (6.41)	12.84 (12.87)
4f	75	4[b]	103-105	63.41 (63.52)	5.69 (5.77)	11.38 (11.41)
4g	62	6[b]	198-199	59.09 (59.15)	4.92 (4.96)	10.60 (10.69)
5a	70	25[b]	135-136	59.45 (59.37)	4.95 (4.94)	12.61 (12.71)
5b	68	25[b]	200 (dec)	59.45 (59.49)	4.95 (4.97)	12.61 (12.56)
5c	58	24[b]	230-231	52.94 (53.03)	4.04 (4.16)	10.29 (10.32)
5d	55	30[b]	98-100	64.70 (64.87)	5.88 (5.91)	13.72 (13.75)
5e	50	28[b]	181-182	66.05 (66.23)	6.42 (6.36)	12.84 (12.87)

(a) In EtOH –HOAc at 40-45°C, (b) Reflux in EtOH-HOAc.

In the reaction of isatins (**1a-c**) with 3-aminopropanol (**2**), the condensed product **3** appears first and upon extension of the reaction time, the spiro compound **4** and imino compound **5** were then obtained. However, with isatin (**1d**), 1-methylisatin (**1e**) and 1-acetylisatins (**1f, 1g**), no condensed system was formed; only the spiro and imino compounds were obtained depending on the reaction conditions. 4-Aminobutanol was less reactive under these conditions; with 5-fluoroisatin (**1a**), only the imino compound **5f** was obtained in low yield and no reaction occurred even after 48 h reflux with 1-acetylisatins (**1f, g**). The structure of the compounds was established on the basis of ^{1}H NMR, IR, mass spectral and correct elemental analyses (*Tables 1-3*). The IR spectra of the condensed system **3,** showed the complete disappearance of both C=O and NH absorption while strong absorptions were observed at 1580-1595 (C=N) and 1175-1190 cm^{-1} (C-O-C). The ^{13}C NMR spectrum of representative compound **3a** showed signals at δ 31.6 ($CH_2\underline{C}H_2CH_2$), 42.8 (NCH_2), 66.9 (OCH_2), 162.8-165.2 (both C=N), 117.6, 119.4, 123.6, 135.3, 146.0, 159.8 (6 aromatic ring carbons). The IR spectra of the spiro compounds **4** showed the presence of NHCO at 1700 and absence of C=O at 1720 cm^{-1} confirming the involvement of only the C-3 carbonyl group during the condensation, a C-O-C bond was observed at 1175-1190 cm^{-1}. The ^{13}C NMR spectrum of the representative compound **4f** showed characteristic signals at δ 13.8 ($CO\underline{C}H_3$), 36.2 ($CH_2\underline{C}H_2CH_2$), 40.7 (N CH_2), 62.9 (OCH_2), 102.3 (spiro-C), 166.3-167.4 (both CO), 120.2, 123.6, 127.5, 127.8, 129.2, 139.7 (6 aromatic ring carbons). The imino compounds **5** were characterized by a strong absorption at 1610 cm^{-1} due to C=N, in addition to a

C=O absorption at 1685-1690 cm^{-1} and a broad absorption of N-H at 3560-3420 cm^{-1}, respectively. The ^{13}C NMR spectrum of the representative compound **5f** showed characteristic signals at δ 14.2 ($CO\underline{C}H_3$), 26.4-29.9 (CH_2 ($\underline{C}H_2$)$_2$ CH_2), 45.7 (NCH_2), 61.6 (OCH_2), 155 ($NH\underline{C}O$), 162.8 (C=N) 165.2 ($\underline{C}OCH_3$), 121.3, 123.8, 125.5, 128.8, 129.2, 140.7 (6 aromatic ring carbons).

Table 2. Mass Fragments of the Representative Compounds

Cmpd	M^+ (%)	m/z (%)
3a	204 (30)	174 (M^+ - OCH_2) (38); 160 (174 - CH_2) (100); 146 (160 - CH_2) (42); 120 (146 - CN) (60); 94 (120 - CN) (23); 68 (94 - C_2H_2) (31).
3b	204 (52)	174 (M^+ - OCH_2) (26); 160 (174 - CH_2) (42); 146 (160 - CH_2) (40); 120 (146 - HCN) (23); 106 (119 - CH) (100); 62 (106 - C_2HF) (13).
4a	(222)*	194 (M^+ - CO) (100); 178 (M^+ - OCH_2CH_2) (40); 164 (M^+ - C_3H_8N) (80); 149 (178 - CH_3N) (68); 120 (149 - CHO) (18); 94 (120 - CN) (38).
4d	204 (23)	176 (M^+ - CO) (82); 160 (M^+ - OCH_2CH_2) (28); 146 (176 - OCH_2) (100); 132 (146 - CH_2) (30); 118 (132 - CH_2) (39); 103 (118 - NH) (18).
5a	222 (21)	191 (M^+ - CH_2OH) (39); 163 (191 - C_2H_4) (48); 137 (163 - CN) (46); 109 (137 - CO) (100); 94 (109 - NH) (63).
5d	204 (07)	173 (M^+ - CH_2OH) (82); 159 (173 - CH_2) (28); 145 (159 - CH_2) (100); 119 (145 - CN) (23); 90 (119 - CHO) (63).

* Molecular ion peak was not obtained, base peak was obtained by the loss of fragment CO.

Table 3. ^1H NMR Data of the Products of Isatins (**1a-g**) with 3-Aminopropanol

Cmpd	$CH_2C\underline{H}_2CH_2$ (m)	$COCH_3$/ CH_3(s)	NCH_2 (t)	OCH_2 (t)	OH[a] (m)	Ar-H (m)	NH[a] (br)	NH[a]
3a*	143-1.85	----	3.55	4.41	----	6.52-7.39	----	----
3b*	1.39-1.87	----	3.52	4.45	----	6.45-7.45	----	----
3c*	1.44-1.84	----	3.49	4.52	----	6.98-7.49	----	----
4a	1.42-1.91	----	3.32	4.35	----	6.53-7.31	7.86	9.14
4b	1.40-1.89	----	3.20	4.30	----	6.40-7.02	7.92	9.01
4c	1.58-.2.08	----	3.43	4.25	----	6.38-7.20	8.05	9.18
4d	1.32-1.81	----	3.40	4.20	----	6.23-7.13	7.96	9.22
4e	1.38-1.92	2.12	3.28	4.27	----	6.47-7.25	7.88	----
4f	1.56-2.05	2.40	3.46	4.32	----	6.82-7.63	8.02	----
4g	1.48-1.92	2.46	3.32	4.42	----	6.80-7.58	7.95	----
5a	1.78-2.15	----	3.79	4.43	4.87	6.72-7.19	----	8.91
5b	1.69-1.98	----	3.68	4.38	4.76	6.32-7.01	----	8.98
5c	1.75-2.25	----	3.75	4.42	4.86	6.58-7.15	----	8.93
5d	1.62-2.00	----	3.80	4.40	4.96	6.26-7.12	----	8.96
5e	1.69-2.08	2.15	3.66	4.40	4.89	6.52-7.18	----	----

* Poor resolution due to low solubility, a) Exchangeable with deuterium.

EXPERIMENTAL SECTION

Mps were determined on a Toshniwal melting point apparatus and are uncorrected. FT-IR spectra were recorded using a Perkin-Elmer-577 spectrophotometer. The ^{1}H NMR & ^{13}CNMR spectra were obtained on a model Bruker-DRX-300 at 300.13 MHz and 75.47MHz, respectively, using TMS as an external reference and $CDCl_3$/TFA as the solvent. The mass spectra were recorded on Kratos-30 mass spectrometer operating at an ionization potential of 70 eV. The progress of the reactions and the purity of the products were checked by tlc using silica gel and spots were vizualized under iodine vapors/UV light.

A. Reaction of 5-Fluoroisatin (1a) with 3-Aminopropanol (2) ***Representative Procedures***

The reaction of **1a** and **2** was studied under the following conditions:

a) A mixture of **1a** (165 mg, 1 mmol) and **2** (150 mg, 2 mmol) in absolute ethanol (25 mL) and glacial acetic acid (2 drops) was stirred at room temperature (40-45°C) for 3 h. The progress of the reaction was monitored by tlc. The reaction mixture was cooled in refrigerator for 24 h. The white compound which separated out was collected, dried and recrystallized from acetic acid to give **3a** (40% yield).

b) A mixture of **1a** and **2** in 1:2 molar ratio in absolute EtOH (25 mL) and gl. AcOH (2 drops) was heated under reflux for 6 h. The reaction mixture was cooled and poured into ice cold water. The solid which separated was collected, dried and purified by column chromatography using benzene:ethyl acetate (1:9) as an eluent. A cream colored crystalline product was obtained in 70% yield and identified as **4a**.

c) A mixture of **1a** and **2** in 1:2 molar ratio was heated at reflux under the identical conditions for 25 h. The reaction mixture was cooled and excess of solvent was evaporated under vacuum. The yellow compound which separated out, was collected, dried and recrystallized from ethanol to give **5a** in 70% yield.

Similarly, the reactions of **1b** and **1c** with **2** gave products **3b,c** or **4b,c** or **5b,c** (*Table 1*).

B. Reaction of Isatin (1d) with 2.

a) A mixture of **1d** (147 mg, 1 mmol) and **2** (150 mg, 2 mmol) in absolute EtOH (25mL) and gl. AcOH (2 drops) was heated at reflux for 8 h. under identical conditions. The reaction mixture was poured into crushed ice and the solid thus obtained was collected, dried and subjected to column chromatography. The benzene:ethyl acetate (9:1) fraction gave 38% yield of a red crystalline compound identified as **5d,** while the ethyl acetate:benzene (1:9) fraction gave cream colored compound in 42% yield, which was identified as **4d**. No reaction occurred at room temperature.

b) A mixture of **1d** and **2** in 1:2 molar ratio was refluxed for 30 h under identical conditions. A red compound separated out on cooling, which was collected, dried and recrystallized from ethanol to give **5d** as red crystals in 55% yield.

C. Reaction of 1-Methylisatin (1e) with 2.

a) A mixture of **1e** (207 mg, 1 mmol) and **2** (150 mg, 2 mmol) in absolute EtOH (25 mL) and

gl. AcOH (2 drops) was heated under reflux for 8 h. The reaction mixture was poured into ice cold water and the solid thus obtained was collected, dried and subjected to column chromatography. The benzene:ethyl acetate (3:2) fraction gave 35% yield of a red compound identified as **5e** while, the ethyl acetate:benzene (5:2) fraction gave yellow crystalline compound **4e** in 39% yield.

b) A mixture of **1e** and **2** was heated under reflux under identical conditions for 28 h. The red solid which separated out on cooling, was collected and recrystallized from ethanol to give compound **5e** in 50% yield.

D. Reaction of 1-Acetylisatin (1f) with 2. A mixture of **1f** (189 mg, 1mmol) and **2** (150 mg, 2 mmol) was heated under reflux in absolute EtOH (25 mL) and gl. AcOH (2 drops) for 4 h. After 24 h at room temperature, light yellow crystalline compound **4f** separated out in 75% yield; it was found to be of sufficient purity (tlc). Analogous reaction of 1-acetyl-5-fluoroisatin (**1g**) with **2** under similar conditions gave yellow colored crystalline compound **4g** in 62% yield.

E. Reaction of 5-Fluoroisatin (1a) and 4-Aminobutanol. A mixture of **1a** (165 mg, 1 mmol) and 4-aminobutanol (178 mg, 2 mmol) in absolute EtOH (25 mL) and 2 drops of gl. AcOH was heated under reflux for 30 h. The reaction mixture was cooled and poured into ice cold water. The solid thus obtained was collected, dried and purified by column chromatography using benzene:ethyl acetate (1:4) as an eluent to give 0.39 mg (15% yield) of a red crystalline product **5f**, mp. 169-170°C

Anal. Calcd for $C_{12}H_{13}FN_2O_2$: C, 61.06; H, 5.50; N, 11.86. Found: C, 61.18; H, 5.52; N, 11.82

^{1}H NMR ($CDCl_3$) δ 1.74-3.17 (m, 4H, $CH_2CH_2CH_2$ CH_2), 3.78 (t, 2H, NCH_2), 4.45 (t, 2H, OCH_2), 4.74 (s, 1H, OH exchanged with D_2O), 8.94 (br, 1H, NH exchanged with D_2O), 6.30-7.08 (m, 3H, Ar-H); IR (KBr): 3560 (OH), 2980-2800 (CH_2), 1685 (C=O), 1625 cm^{-1} (C=N).

However, with 1-acetylisatins (**1f, g**) no reaction occurred even upon prolonged reflux up to 48 h.

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