

SYNTHESIS OF NOVEL 3-SPIRO INDOLINES CONTAINING BENZ(g) INDAZOLE, BENZ(h)PYRAZOLO(3,4-b)QUINOLINE AND NAPHTHISOXAZOL MOIETIES

Anshu Dandia*, Rahul Joshi, Varinder Sehgal, C.S. Sharma and Mitali Saha
Department of Chemistry, University of Rajasthan, Jaipur - 302 004, India.

Abstract : 1,3-Dihydro-3-(3,4-dihydro-1-oxonaphthalenyl-2-idene)-2H-indol-2-ones were condensed with phenyl hydrazine, 3-Amino-1-phenyl-2-pyrazolin-5-one and hydroxylamine hydrochloride to obtain novel 3,3a,4,5-tetrahydrospiro [2H-benz(g)indazole-3,3'(3H)-indol]-2'-(1H)-one, 3'a,4'a,5',6'-tetrahydro-2'-phenyl spiro [3H-indole-3,4'-benz(h)-[4H]pyrazolo[3,4-b]quinoline]-2(1H), 3'-dione and 4,5-dihydro-spiro[3H-indole-3,3'[3aH]-2,1-naphthisoxazol-2(1H)-ones respectively. Structural assignments have been made on the basis of analytical and spectral data.

Introduction

Indole-2,3-dione (Isatin) has been an interesting reaction intermediate for synthetic organic chemists due to its reactivity. Considerable work has been reported from our laboratory on the reactions of isatin with methyl ketone (1) and cyclic ketones (2,3). Our more recent work involves the reactions of isatins with heterocyclic ketones (4,5). In an attempt to extend the work to ketones of the naphthalene series, 1,3-dihydro-3-(3,4-dihydro-1-oxonaphthalenyl-2-idene)-2H-indol-2-ones **1** have been prepared. It is apparent that these compounds possess an α,β -unsaturated carbonyl moiety which involves both the carbonyl group of the indole ring and the carbonyl group of naphthalene ring. Thus, incorporation of these systems in the final product cannot be ruled out.

Taking advantage of the presence of a chalcone moiety in these intermediates **1**, the reactions of these compounds with some nitrogen containing nucleophiles were expected to be interesting leading to the formation of novel heterocycles.

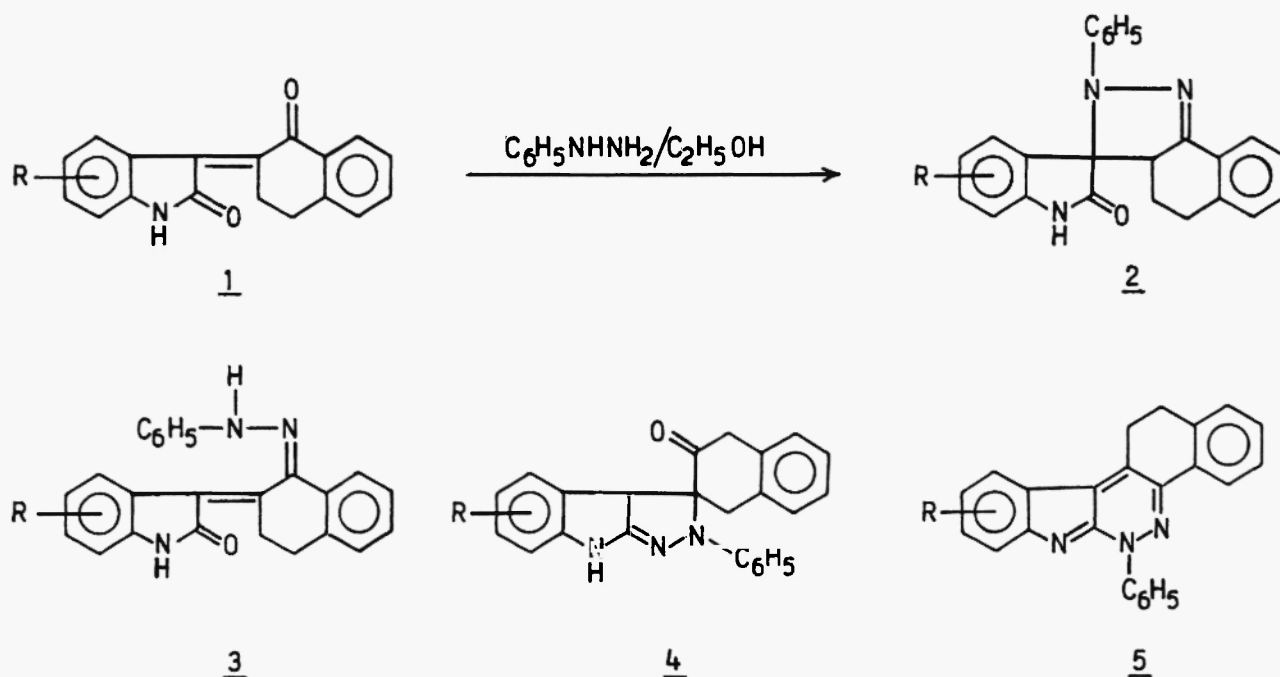
In this communication, we are reporting the synthesis of some novel spiro derivatives (2,6,10) obtained exclusively by the reaction of chalcone **1**, with phenyl hydrazine, hydroxylamine hydrochloride and 3-amino-1-phenyl-2-pyrazolin-5-one respectively. It may be noted that the present investigations resulted in the exclusive formation of spiro derivatives and are at variance with our earlier studies (1-3)(6-10) with other chalcones and their reactions with various compounds containing amino group.

Results and Discussion

New fluorine containing 1,3-dihydro-3-(3,4-dihydro-1-oxonaphthalenyl-2-idene)-2H-indol-2-ones **1** have been synthesized by the "Knoevenagel" reaction of fluorine containing indole-2,3-diones with α -tetralone in the presence of diethylamine as a catalyst (11).

Compound **1** was condensed with phenylhydrazine, hydroxylamine hydrochloride and 3-amino-1-phenyl-2-pyrazolin-5-one respectively to examine the possibility of formation of more than one product in each case.

Reaction of **1** with phenylhydrazine was carried out in absolute ethanol to explore the possibility of the formation of different products namely **2**, **3**, **4** and **5**. (Scheme I)

SCHEME - I

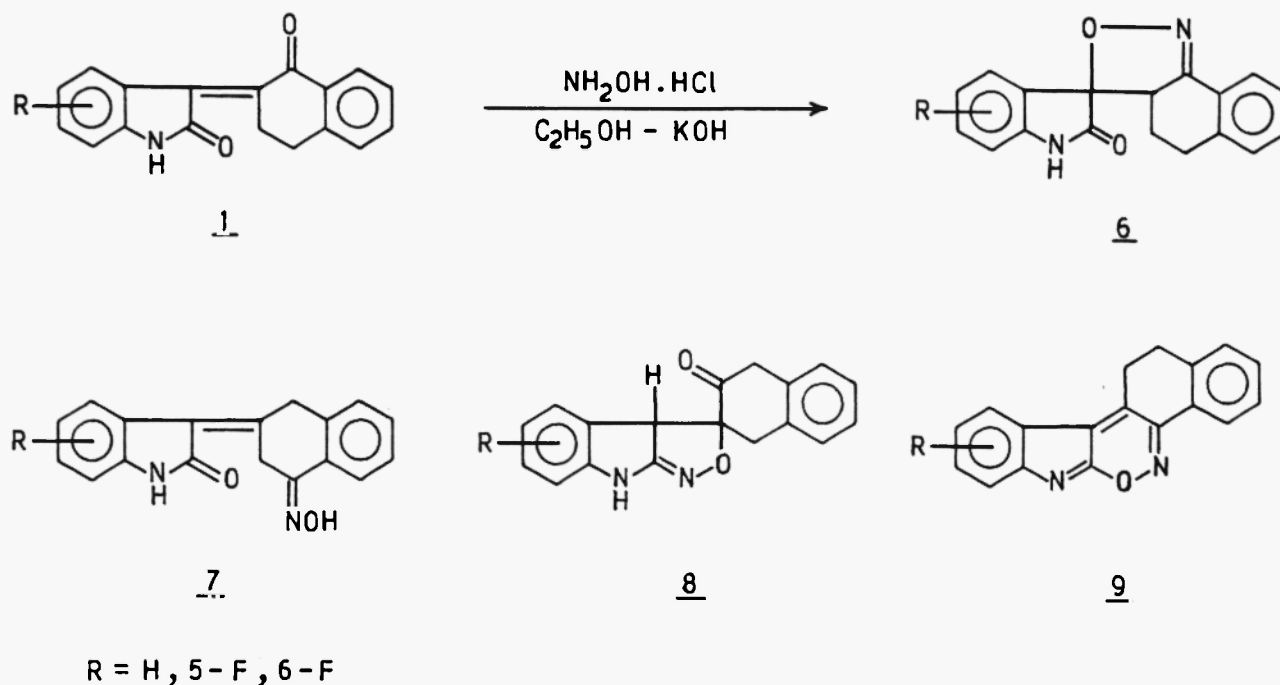
$\text{R} = \text{H}, 5\text{-F}, 6\text{-F}$

Reaction of **1** with phenylhydrazine yielded a bright yellow solid in each case. Its IR spectrum showed the disappearance of exocyclic $\text{C}=\text{C}$ at 1620 and $\text{C}=\text{O}$ absorption at 1660 cm^{-1} and appearance of the $\text{C}=\text{N}$ and $\text{C}=\text{O}$ absorption at 1610 and 1670 cm^{-1} respectively indicating the participation of α, β -unsaturated carbonyl system involving tetrahydro naphthalene ring. The ^1H NMR spectrum showed a double doublet for methine proton at δ 3.24 ppm due to coupling of this proton with nearby methylene protons with different dihedral angles. A multiplet was observed at δ 6.95-8.44 ppm due to aromatic protons along with a singlet at δ 10.91 ppm due to $-\text{NH}$ proton. The mass spectrum of the compound **2a** showed the molecular ion peak at m/z 365 (17.2%) corresponding to its molecular weight with additional peaks at m/z 321 ($365-\text{CONH}_2$) $^+$ (48%), $262(365-\text{C}_6\text{H}_4\text{CN})$ $^+$ (18.9%), $204(321-\text{C}_9\text{H}_9)$ $^+$ (21.8%) and $177(204-\text{HCN})$ $^+$ (100%) etc.

The presence of $\text{C}=\text{O}$ absorption at 1670 cm^{-1} in IR spectrum rules out the possibility of the formation of condensed derivative **5**. The presence of characteristic signal for $>\text{CH}$ (double doublet at δ 3.21) rules out the possibility of formation of either **3** or **4**. On the basis of these spectral studies, the products formed were identified as 3,3a,4,5-tetrahydro spiro [2H-benz(g) indazole- 3,3'(3H)-indol]-2'-(1H)one.

Reaction of **1** with NH_2OH , HCl has been carried out in ethanolic KOH to explore the possibility of the formation of different products **6,7,8** and **9** (Scheme II)

SCHEME - II



In the present case, reaction of **1** with $\text{NH}_2\text{OH} \cdot \text{HCl}$ resulted in the formation of a bright yellow coloured compound identified as a spiro derivative **6**.

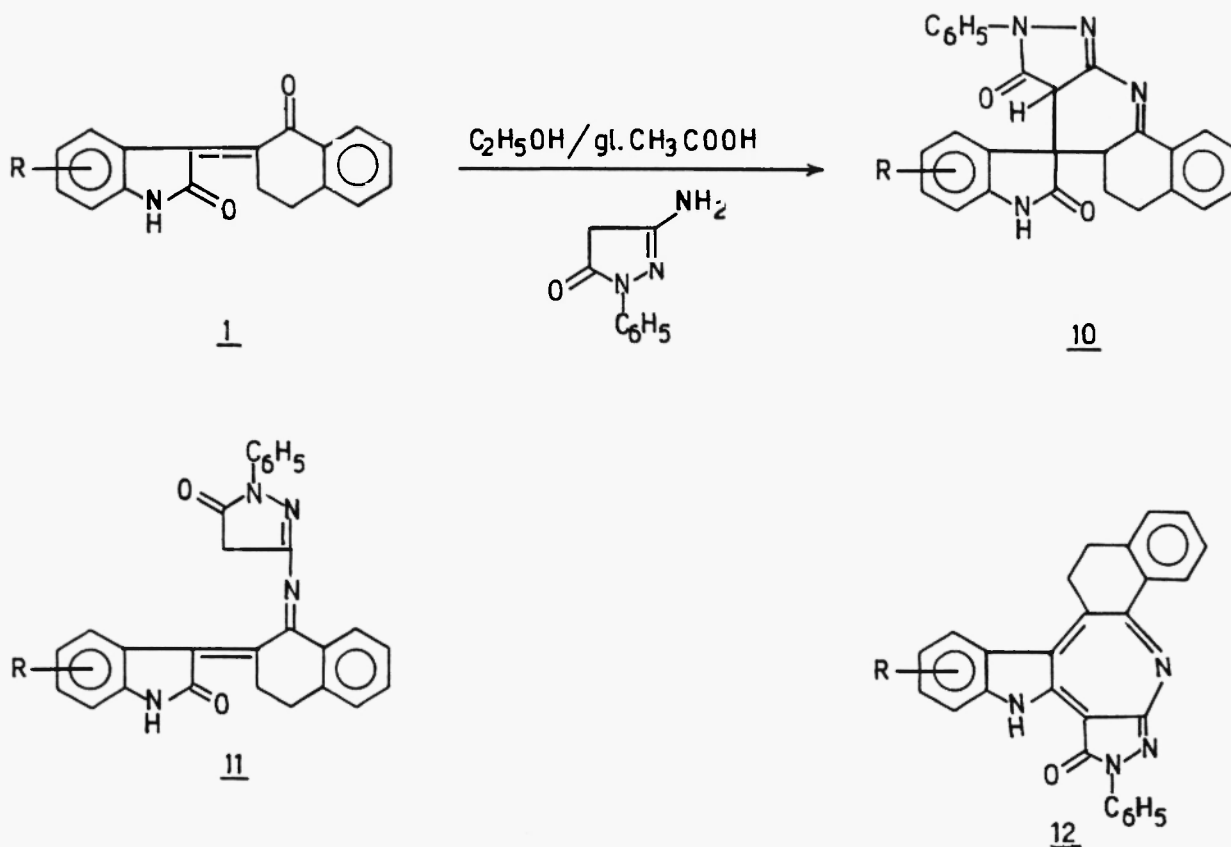
It's IR spectrum exhibits characteristic signals for $\text{C}=\text{N}$ at 1610 cm^{-1} and at 1700 cm^{-1} for $\text{C}=\text{O}$ absorption. It's ^1H NMR showed a characteristic double doublet at δ 3.21 due to methine protons. The ^{13}C NMR spectrum ($\text{DMSO}-d_6$) of **6a** showed characteristic absorption at δ 168.26 ($\text{C}=\text{O}$), 156.23 ($\text{C}=\text{N}$), 111.12 (12-Aromatic carbons), 110.56 (spiro carbon) and 30.13 ppm (2 carbons of naphthalenyl ring).

The mass spectrum of **6c** showed molecular ion peak at m/z (308) (23.6%) corresponding to its molecular weight with additional peaks at $201(\text{M}^+ - \text{C}_7\text{H}_5\text{F})^+$ (40.4%), $173(201 - \text{CO})^+$ (35.9%), $137(308 - \text{C}_{10}\text{H}_9\text{NO})^+$ (100%), $120(137 - \text{OH})^+$ (87.2%), $109(149 - \text{C}_2\text{OH})^+$ (52.7%), $89(109 - \text{HF})^+$ (79.2%) etc. The presence and position of fluorine was confirmed by ^{19}F NMR spectra. Single fluorine at position -5/6 of indole ring appeared at δ -116.42 and -113.58 ppm respectively.

Presence of only one $\text{C}=\text{O}$ absorption at 1700 cm^{-1} in IR spectrum rules out the possibility of the formation of condensed derivative **9**. The other two possibilities **7**, **8** were ruled out on the basis of characteristic signal for $>\text{CH}$ (double doublet at δ 3.21 ppm) and absence of $-\text{OH}$ proton in ^1H NMR and the product identified as 4,5-dihydro spiro[3H-indol-3,3']-(3aH)-2,1-naphtho[1,2-b]isoxazol-2-one **6**.

The reaction of **1** with 3-amino-1-phenyl-2-pyrazolin-5-one in absolute ethanol/glacial acetic acid mixture yielded dark brown spiro compounds **10** instead of imino compound **11** and/or condensed compounds **12**. (Scheme III)

SCHEME - III



A typical IR spectrum of compound **10** displayed characteristic absorption bands in the region 3200-3480(NH), 2940(CH stretch), 1680 and 1620(two C=O), 1590(C=N) and 1490(C=N). In the ^1H NMR spectrum signals were observed at δ 3.24 ppm due to methine protons along with a multiplet at δ 6.36-8.24 due to aromatic protons. A broad absorption signal due to -NH protons were observed at δ 9.71 ppm.

In a typical mass spectrum of **10a**, the molecular ion peak was not observed but characteristic fragments were observed at 77[M- C₂₁H₁₅N₄O₂]⁺ (21.1%), 133[M-C₂₁H₁₅N₂O]⁺ (46%), 146[M-C₁₉H₁₄N₂O]⁺ (50%), 88[131-CONH]⁺ (48%) etc.

On the basis of the above spectral evidences, the compound has been identified at 3'a, 4'a, 5', 6'-tetrahydro-2'-phenyl spiro[3H- indol-3,4'-benz(h)-[4H]pyrazolo[3,4-b]quinoline-2(1H)-3'-dione **10**.

Experimental

All the melting points are uncorrected. The purity of the compounds synthesized has been checked by TLC. The IR spectra were recorded on a Perkin-Elmer spectrophotometer model 577. The NMR spectra have been recorded at 90 MHz on a Jeol FX 90Q FT-NMR using TMS as an internal

Table 1 : Characteristic data of the synthesized compounds.

Comp. No.	R	Yield (%)	M.P. (°C)	Molecular Formula	Analysis (%) Found/Calcd		
					C	H	N
2a	H	59	230	C ₂₄ H ₁₉ N ₃ O	78.72 78.90	5.16 5.20	11.32 11.49
2b	5F	44	220-222 (d)	C ₂₄ H ₁₈ FN ₃ O	75.16 75.19	4.64 4.69	10.97 10.95
2c	6F	55	235	C ₂₄ H ₁₈ FN ₃ O	75.12 75.19	4.62 4.69	10.92 10.95
6a	H	52	> 360	C ₁₈ H ₁₄ N ₂ O ₂	74.42 74.48	4.60 4.63	8.70 9.05
6b	5F	35	310-312 (d)	C ₁₈ H ₁₃ FN ₂ O ₂	70.10 70.12	4.21 4.22	9.31 9.09
6c	6F	58	308	C ₁₈ H ₁₃ FN ₂ O ₂	70.06 70.12	4.18 4.22	9.20 9.09
10a	H	62	> 360	C ₂₇ H ₂₀ N ₄ O ₂	74.98 75.00	4.58 4.62	12.26 12.95
10b	5F	66	> 360	C ₂₇ H ₁₉ FN ₄ O ₂	71.96 72.00	4.20 4.22	12.40 12.43
10c	6F	64	> 360	C ₂₇ H ₁₉ FN ₄ O ₂	71.98 72.00	4.19 4.22	12.39 12.43

d = decomposes

standard in CDCl₃. Mass spectra were recorded on Kratos-30 and -50 mass spectrometer. 'C' and 'H' analyses of compounds have been done on Coleman 'C' and 'H' analyzer. Nitrogen analyses has been done using Carlos Ebra N- analyzer 1106 at CDRI, Lucknow.

Preparation of 3,3a,4,5-tetrahydro spiro[2H-benz(g)indazole-3,3'-(3H)-indol]-2'-(1H)-one (2a-c)

A mixture of compound 1 (0.01 mole, 2.75 gm) and phenyl hydrazine (0.012 mole, 1.29 gm) in absolute ethanol (30 ml) was refluxed for 5-6 hours. On cooling, a bright yellow compound separated out which was filtered, dried in air and recrystallized from ethanol. Physical data of the compounds synthesized are given in Table 1.

Preparation of 4,5-Dihydro spiro[3H-indol-3,3'(3aH)-2,1-naphthisoxazol]-2(1H)-one (6a-c)

A mixture of 1 (0.01 mole, 2.75 gm), hydroxylamine hydrochloride (0.01 mole, 6.95 gm) and potassium hydroxide (1 gm) in aqueous ethanol (25 ml) was refluxed for 3-4 hours and kept overnight

at room temperature (24°C). The solid obtained was recrystallized from ethanol. Physical data of the compounds synthesized are given in Table 1.

Preparation of 3'a,4'a,5',6'-tetrahydro-2'-phenyl spiro[3H-indol- 3,4'--benz(h)-[4H]-pyrazolo[3,4-b]quinoline]-2(1H),3'-dione (10a-c)

A mixture of 1 (0.01 mole, 2.75 gm) and 3-amino-1-phenyl-2- pyrazolin-5-one (0.011 mole, 1.92 gm) in absolute ethanol and glacial acetic acid mixture was refluxed for 32-34 hours. On cooling, the reaction mixture, a blackish solid separated out. It was filtered, dried and recrystallized from ethanol. Physical data of the compounds synthesized are given in Table 1.

Acknowledgement

The authors thank Dr. Vishnu Ji Ram, Scientist, CDRI, Lucknow for providing mass spectral data. Financial assistance from U.G.C. and C.S.I.R., New Delhi is gratefully acknowledged.

References

- (1) K.C. Joshi, A. Dandia and S. Khanna, Indian J. Chem. 29B, 1125 (1990)
- (2) A.Dandia, V. Kaur and P. Singh, Phosphorus, Sulfur and Silicon 69, 277 (1992).
- (3) K.C. Joshi, A. Dandia, and S. Sanan, J. Fluorine Chem. 44, 59 (1989).
- (4) K.C. Joshi, A. Dandia and S. Khanna, Indian J. Chem. 29B, 933 (1990).
- (5) K.C. Joshi, A. Dandia, R.T. Pardasani and C.S. Sharma, Indian J. Chem. 33B, 483 (1994)
- (6) K.C. Joshi, A. Dandia and S. Sanan, J. Indian Chem. Soc. 67, 404 (1990)
- (7) K.C. Joshi, R. Jain, S. Garg and S. Arora, J. Indian Chem. Soc. 66, 176 (1989)
- (8) K.C. Joshi, A. Dandia and S. Khanna, Indian J. Chem. 30B, 469 (1991)
- (9) K.C. Joshi, A. Dandia and S. Sanan, J. Heterocyclic Chem. 26, 1397 (1989)
- (10) K.C. Joshi, A. Dandia, R. Jain and V. Sharma, J. Heterocyclic Chem. 23, 97 (1986)
- (11) A. Dandia, Rahul Joshi, C.S. Sharma and Varinder Sehgal, Communicated, 1995

Received October 12, 1995