THE FACILE SYNTHESIS OF NOVEL SPIRO [INDOLE – PYRAZOLOQUINOLINE] AND SPIRO [INDOLE-PYRAZOLOCYCLOPENTAPYRIDINE] DIONES

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ABSTRACT

A novel spiro system (III) incorporating bioactive indole and pyrazole nuclei has been synthesized exclusively by an elegant procedure, 1, 3-Dihydro-3-(2-oxocycloalkylidene) indol-2-(1H)-ones (II) were synthesized by the reaction of isatin and cycloalkanones, on treatment with 3-amino-1-pheny1-2-pyrazolin-5-one in absolute ethanol/ ethanol + acetic acid yielded 2', 4'a, 5', 6', 7', 8'- hexahydro [3H- indole-3,4'-[4H] pyrozolo [3, 4-b] quinolone]-2,3' (1H, 3' aH) –diones (IIIa-d)/2', 3', 4'a, 5', 6', 7' – hexahydrospiro [3H-indole-3, 4'- [4H] pyrazolo [3,4-b] cyclopenta[b] pyidine]-2 (1H), 3'-diones (IIIe-h) respectively. The reaction appeared interesting in view of the fact that the latter can undergo reactions involving either the double bond and lactam carbonyl group or □, β- unsaturated carbonyl group of the side chain or it can undergo condensation involving both the carbonyl group. All synthesized compound were characterized by their spectral studies.

Keywords: *3-(2-oxocycloalkylidine) indole, 3-aminopyrazolone, pyrazoloquinoline, pyrazolo-pyidine.*

INTRODUCTION

Spiro indole[1-7] derivatives are well recognised for their immense pharmacological and biological activities and are proving to be the most fascinating area of research for organic chemistry. Pyrazoles possess a wide spectrum of pharmacological activities[8-10]. They are also reported to be as potent anthelmintic and acetylcholinesterase inhibitors[11]. Anti-inflammatory, antiallergic and cardiovascular properties are other commonly shown properties of various substituted pyrazolopyridines[12]. The medicinal applications of spiro [indolin-pyrazolines][13-15] and spiro [indolin-pyridines][16-18] have also been reported but spiro indole derivatives incorporating both pyrazolo-quinoline/-cyclopentapyridine and indole moieties have not been synthesized so far. In view of these facts novel 2', 4'a, 5', 6', 7', 8'- hexahydrospiro [3H-indole-3, 4'-[4H] pyrazolo [3, 4-b] quinoline]-2, 3' (1H, 3' aH)-diones (IIIa-d) and 2', 3', 4'a, 5', 6', 7'-hexahydro-spiro[3H-indole-3, 4'-[4H] pyrazolo[3, 4-b] cyclopenta[b] pyridine]-2(1H), 3'-diones (IIIe-h) were synthesized.

The pyrazolone skeleton reacts with various carbonyl compounds and chalcones leading to a mixture of products[19-21]. The title reaction appeared interesting in view of the fact that compound (II) can undergo reactions involving either the double bond and lactam carbonyl group or α, β-unsaturated carbonyl group of the side chain or it can undergo condensation involving both the carbonyl groups, yielding a variety or products (III, IV, V). In the present study, an unusual role of cycloalkane ring was observed leading to the formation of a spiro ring system (III) exclusively (Scheme-1).

The title spiro derivatives (IIIa-h) were prepared in one step by the reaction of 3-amino-1-pheny1-2-pyrazolin-5-one with equimolar amounts

of 1, 3-dihydro-3-[2-oxocycloalkylindine] indol-2(1H)-one (II) in absolute ethanol/ ethanol + acetic acid. The compounds (II) were synthesized by the knoenenagel reaction of indole-2, 3-diones with cyclic ketones (cyclopenta none/ cycloghexanone) in the presence of diethylamine as a basic catalyst followed by dehydration in concentrated hydrochloric acid and glacial acetic acid medium.[1]

Characterization of all the products was done on the basis of their spectral data. The IR spectra of spiro compounds (III) displayed characteristic absorption bands in the region of 3350-3200 (N-H), 2910-2800 (CH_2 ε CH) 1700-1690 (C=O), 1670-1650 (C=O of pyrazolone ring), 1600-1590 (C=N) and 1480-1450 (C=N) cm^{-1}. In PMR spectra, the methylene protons of the cycloalkyl ring appeared as a set of multiplets at δ 1.12 - 1.15 (4H in case of the cyclohexyl ring, 2H in cyclopenty ring), 1.78 – 1.85 (m, CH-C$\underline{H_2}$), triplets at 2.54 – 2.67 (N=C-C$\underline{H_2}$) ε multiplets at 2.95 – 3.02 (C-H) ppm. The presence of two carbonyl absorptions (non conjugated) in IR spectra ruled out the possibility of formation of IV ε V. Similarly, in PMR spectra, presence of C-H proton signal also indicated the formation of III.

Further support was gathered from mass spectra exhibiting the molecular ion peak at m/z 384 and 398 corresponding to their molecular formulae $C_{23}H_{20}N_4O_2$ (IIIa) and $C_{24}H_{22}N_4O_2$ (IIIb). The other intense peaks were observed at 251 $[M-C_7H_5N_2O]^+$ (38%), 224 $[251 – HCN]^+$ (40%), 196 $[224-CO]^+$ (7%) in case of (IIIa) and 265 $[M-C_7H_5N_2O]^+$ (10%), 238 $[265-HCN]^+$ (50%), 210 $[238-CO]^+$ (40%), 196 $[210-CH_2]^+$ (24%), 140 $[196-C_2H_4N_2]^+$ (70%), 138 $[140-2H]^+$ (100%), 110 $[138-CO]^+$ (92%) in case of (IIIb).

Melting points were determined on electrothermal apparatus in open glass capillaries and are uncorrected. IR spectra were recorded on Perkin-Elmer 577 gratting spectrophotometer. The ^1H NMR spectra were taken on a Jeol FX 90Q FT NMR at 90 MHz in TFA + $CDCl_3$. TMS was used as internal standard. Mass spectra were recorded on Kratos-30 and 50 mass spectrometers. The purity of the compounds was checked on TLC plates in various solvent systems.

Synthesis of 2', 4'a, 5', 6', 7', 8'-hexahydrospiro[3H-indole-3, 4'-[4H] pyrazolo[3, 4-b]quinoline]-2, 3' (1H, 3'aH)-dione (IIIa)

A mixture of (IIa) (0.01 mol) and 3-amino-1-pheny1-2-pyrazolin-5-one (0.01 mol) in absolute ethanol was refluxed for 5h. Completion of the reaction was monitored by TLC. The solid thus obtained after cooling the reaction mixture, was filtered, dried and recrystallized from ethanol to give (IIIa). Yield: 40% Rest of the compounds (IIIb-h) were prepared in a similar manner using appropriate compounds (II).

Table 1 : Physical and analytical data of the compounds.

Compound*	R	X	n	Reaction media	Yield (%)	Molecular Formula	Analysis (%) Found/ (Calcd.)		
							C	H	N
IIIa	H	H	2	EtOH	42	$C_{23}H_{20}N_4O_2$	71.45 (71.87)	5.50 (5.20)	14.20 (14.58)
IIIb	CH_3	H	2	EtOH	40	$C_{24}H_{22}N_4O_2$	72.16 (72.36)	5.70 (5.52)	14.05 (14.07)
IIIc	H	5-Cl	2	EtOH	38	$C_{23}H_{19}ClN_4O_2$	66.00 (66.02)	4.05 (4.54)	13.51 (13.39)
IIId	H	5-F	2	EtOH	50	$C_{23}H_{19}FN_4O_2$	68.46 (68.65)	4.56 (4.72)	13.49 (13.93)

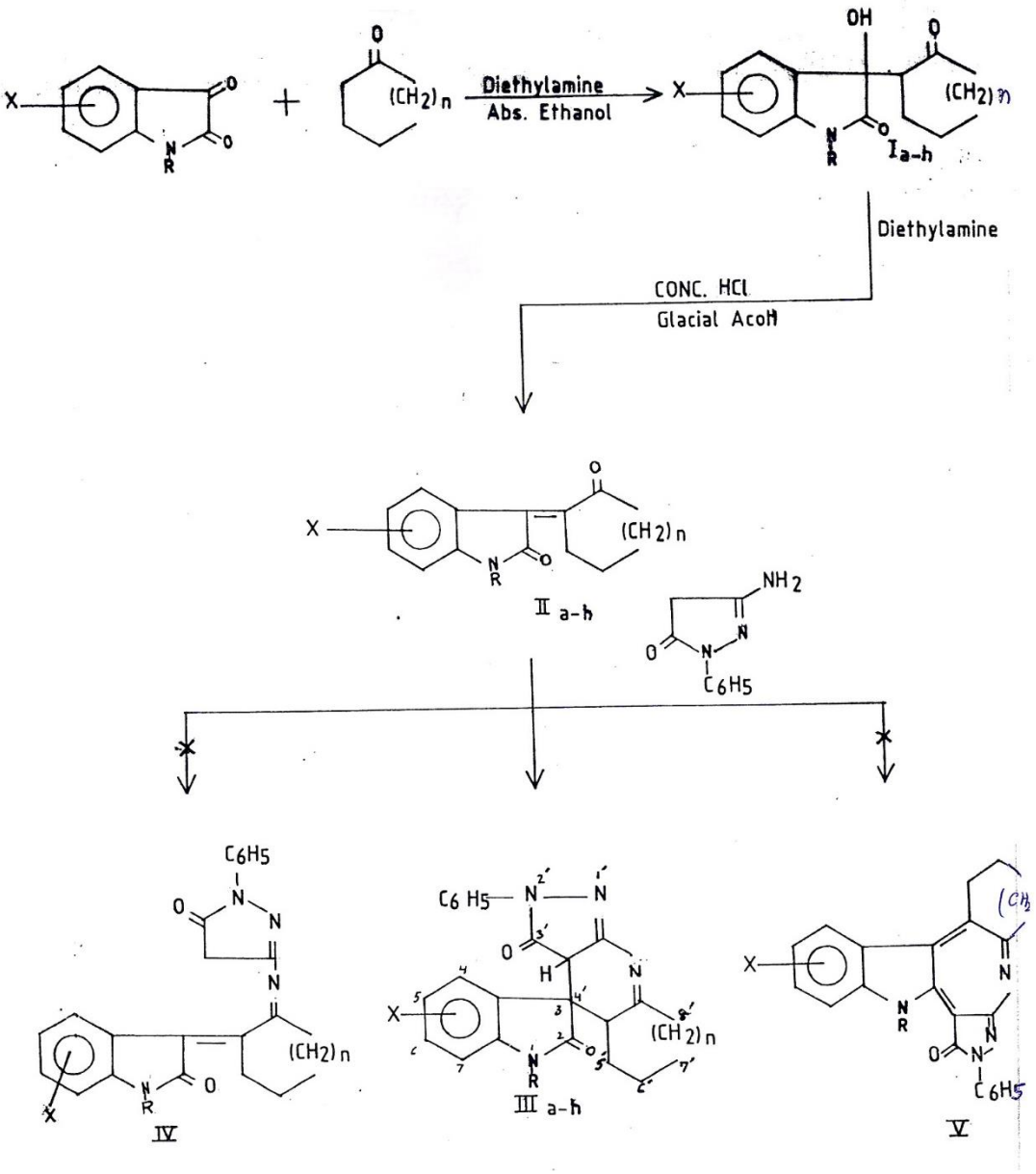
Compound*	R	X	n	Reaction media	Yield (%)	Molecular Formula	Analysis (%) Found/ (Calcd.)		
							C	H	N
IIIe	CH_3	H	1	EtOH + ACOH	50	$C_{23}H_{20}N_4O_2$	71.50 (71.87)	4.90 (5.20)	14.70 (14.58)
IIIf	H	H	1	EtOH + ACOH	55	$C_{22}H_{18}N_4O_2$	71.10 (71.35)	4.40 (4.86)	14.90 (15.13)
IIIg	H	5-Cl	1	EtOH + ACOH	57	$C_{22}H_{17}ClN_4O_2$	65.00 (65.34)	4.38 (4.20)	13.67 (13.86)
IIIh	H	5-F	1	EtOH + ACOH	55	$C_{22}H_{17}FN_4O_2$	67.84 (68.04)	4.05 (4.38)	14.04 (14.43)

*The m.ps. of the compounds IIIa-h are above 360°C.

Table 2 : IR and ^{1}H NMR spectral data of the compounds (IIIa-h)

Compd. No.	IR (cm^{-1})	^{1}H NMR (δ ppm)						
		-C<u>H</u>$_2$-C<u>H</u>$_2$- /	-C<u>H</u>$_2$-C<u>H</u>$_2$-	=C-C<u>H</u>$_2$	2X C-<u>H</u>	N-C<u>H</u>$_3$	Ar-H	NH
IIIa	3300-3200, 2800, 1690, 1670, 1600, 1450, 1300, 1180, 1110, 750	1.13m	1.80m	2.65+	2.95m	–	6.76-7.76m	9.38s br
IIIb	2910, 1690, 1660, 1600, 1480, 1350, 1200, 1040, 760	1.12m	1.82m	2.54t	3.01m	3.37s	6.70-7.77m	–
IIIc	3300-3200, 2810, 1690, 1660, 1600, 1460, 1370, 1200, 1080, 740	1.13m	1.85m	2.67t	3.02m	–	7.15-8.12m	9.70s br
IIId	3350-3200, 2850, 1690, 1670, 1600, 1450, 1300, 1180, 1080, 750	1.12m	1.85m	2.67t	3.01m	–	7.15-8.12m	9.70s br
IIIe	2910, 1690, 1650, 1600, 1460, 1360, 1230, 1080, 750	1.12m	1.78m	2.61t	3.01m	3.31s	6.80-7.79m	–

Compd. No.	IR (cm^{-1})	^{1}H NMR (δ ppm)						
		-C<u>H</u>$_2$-C<u>H</u>$_2$- /	-C<u>H</u>$_2$-C<u>H</u>$_2$-	=C-C<u>H</u>$_2$	2X C-<u>H</u>	N-C<u>H</u>$_3$	Ar-H	NH
IIIf	3350-3220, 2800, 1690, 1650, 1590, 1450, 1350, 1200, 1080, 750	1.14m	1.79m	2.62t	2.98m	–	6.75-7.92m	9.50s br
IIIg	3300-3200, 2840, 1700, 1660, 1590, 1450, 1350, 1210, 1050, 750	1.15m	1.85m	2.60t	3.01m	-	7.20-8.30m	9.70s br
IIIh	3350-3210, 2840, 1690, 1670, 1600, 1450, 1300, 1180, 1080, 760	1.14m	1.85m	2.67t	3.01m	–	7.15-8.12m	9.70s br



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