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Synthesis and Biological Studies on Some Different Heterocyclic Nitrogen Nuclei Fused with 1-Phenyl-Naphthcyclopentan-4,9-Dione

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Condensation of 1-phenylnaphthcyclopentan-2,4,9-trione (II) with aromatic aldehydes yielded the corresponding 3-benzylidene derivative (III_{a-f}). Interaction of III_{a-f} with hydrazines, hydroxylamine, urea and thiourea afforded some new (pyrazoline IV_{a-f}, V_{a-f}, isoxazolino VI_{a-f}, pyrimidine and/or pyrimidine-thione, VII_{a-f}, $VIII_{a-f}$) derivatives, respectively.

INTRODUCTION

An efficient strategy for synthesis of new heterocyclics *via* cyclocondensation reaction between different types of α,β-unsaturated ketone compounds with hydrazines, hydroxylamine, urea and thiourea were the subject of our studies[1–5]. In continuation to our previous work on the heterocyclic nitrogen compounds and in view of their various uses as biological and synthetic drugs[6–10], pyrazolines, isoxazolines, pyrimidines and pyrimidine thiones (IV_{a-f}–$VIII_{a-f}$) in conjunction with 1-phenylnaphthcyclopentan-4,9-dione were prepared.

RESULTS AND DISCUSSION

1-Phenylnaphthcyclopentan-2,4,9-trione (II) was prepared through the reaction of 1,4-naphthquinone with benzyl chloride in the presence of ethylene glycol as solvent and sodium bicarbonate as catalyst to give 2-benzyl-1,4-naphthquinone (I), then the cyclocondensation reaction of the previously prepared compound (I) with monochloro-acetic acid proceeded in the presence of triethylamine as catalyst affording the corresponding 1-phenylnaphthcyclopentan-2,4,9-trione (II) (Scheme 1). The structures of I and II were confirmed by the elemental analysis, IR and ^1H NMR spectral data (Tables 1, 2).

Condensation of II with the appropriate aromatic aldehydes proceeded smoothly in absolute alcohol using piperidine as catalyst to yield the cooresponding 3-arylideno-1-phenylnaphthcyclopentan-2,4,9-trione (III_{a-f}).

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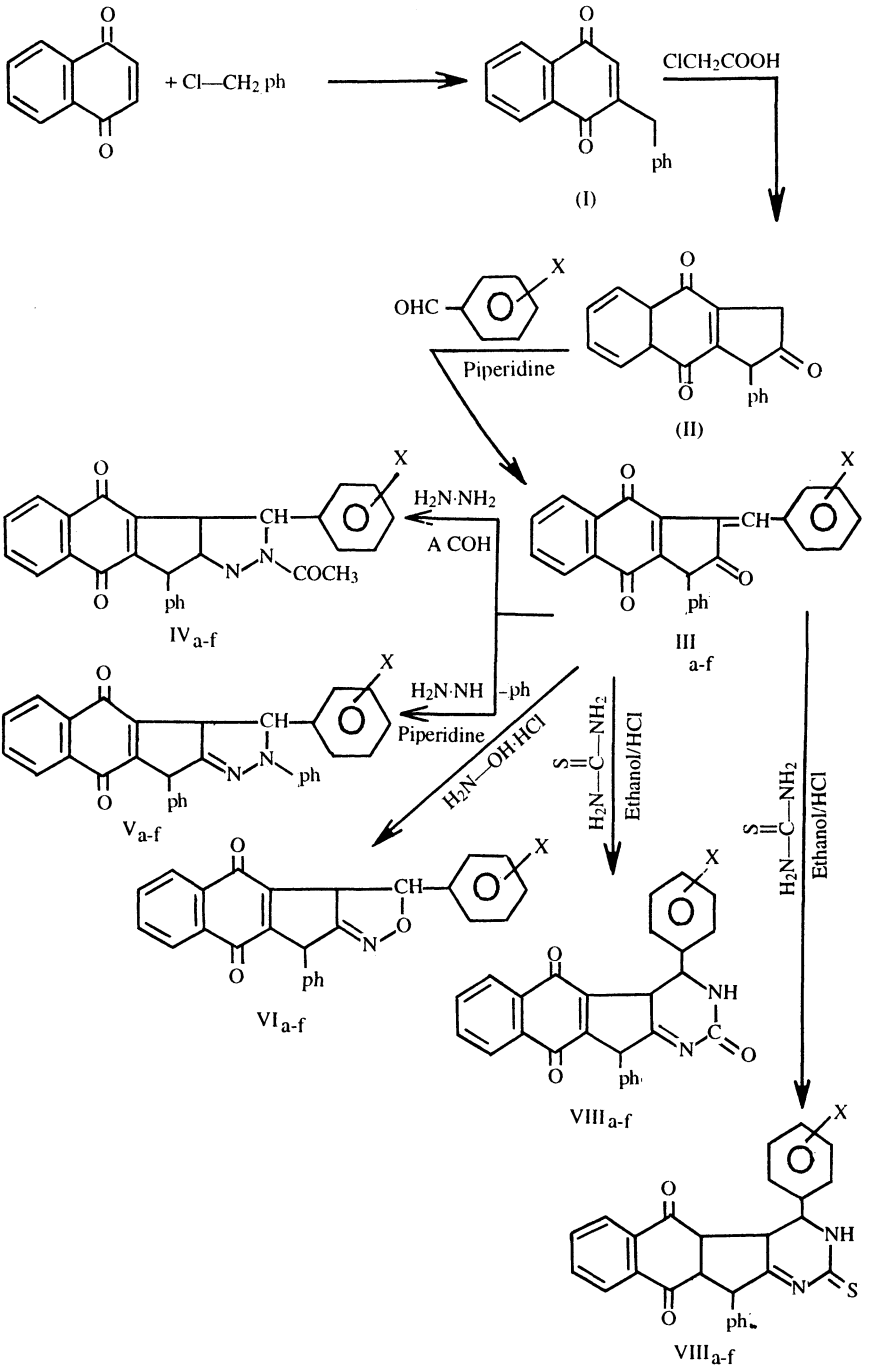
TABLE-1
PHYSICAL DATA OF COMPOUNDS I–VIII

Compound No.	Mol. formula (m.wt.)	m. p.* (°C)	Yield (%)	Elemental analysis: Found (Calc.) %		
				C	H	N
I	$C_{17}H_{12}O_2$ (248)	140[a]	60	82.30 (82.26)	6.90 (6.85)	—
II	$(C_{19}H_{12}O_3)$ (288)	160[a]	65	79.21 (79.17)	4.20 (4.17)	—
III_a	$C_{26}H_{16}O_3$ (376)	185[a]	55	83.10 (82.98)	4.40 (4.26)	—
III_b	$C_{27}H_{18}O_4$ (406)	205[b]	50	79.90 (79.80)	4.49 (4.43)	—
III_c	$C_{28}H_{21}O_3N$ (419)	195[b]	45	80.20 (80.19)	5.09 (5.01)	3.39 (3.34)
III_d	$C_{26}H_{16}O_4$ (392)	180[b]	52	79.61 (79.59)	4.10 (4.08)	—
III_e	$C_{26}H_{16}O_4$ (392)	230[a]	40	80.10 (79.59)	4.48 (4.08)	—
III_f	$C_{26}H_{15}O_5N$ (421)	170[a]	70	74.20 (74.11)	3.61 (3.56)	3.40 (3.33)
IV_a	$C_{28}H_{20}N_2O_3$ (432)	190[b]	60	77.80 (77.78)	4.68 (4.63)	6.50 (6.48)
IV_b	$C_{29}H_{22}N_2O_4$ (462)	180[b]	50	75.40 (75.32)	4.80 (4.76)	6.10 (6.06)
IV_c	$C_{30}H_{25}N_3O_3$ (475)	195[a]	55	75.80 (75.79)	5.30 (5.26)	8.89 (8.84)
IV_d	$C_{28}H_{20}N_2O_4$ (448)	175[b]	45	75.12 (75.00)	4.50 (4.46)	6.30 (6.25)
IV_e	$C_{28}H_{19}N_2O_4$ (448)	215[a]	35	75.45 (75.00)	4.62 (4.46)	6.45 (6.25)
IV_f	$C_{28}H_{19}N_3O_5$ (477)	170[a]	65	70.49 (70.44)	4.10 (3.98)	8.85 (8.81)
V_a	$C_{32}H_{22}N_2O_2$ (466)	185[a]	50	82.52 (82.40)	4.83 (4.72)	6.08 (6.01)
V_b	$C_{33}H_{24}N_2O_3$ (496)	205[b]	40	79.60 (79.84)	4.98 (4.84)	5.60 (5.65)
V_c	$C_{34}H_{27}N_3O_2$ (509)	205[b]	35	80.27 (80.16)	5.42 (5.30)	8.31 (8.25)
V_d	$C_{32}H_{22}N_2O_3$ (482)	165[b]	40	79.71 (79.67)	4.61 (4.56)	5.86 (5.81)
V_e	$C_{32}H_{22}N_2O_3$ (482)	220[a]	30	79.59 (79.67)	4.48 (4.56)	5.92 (5.81)
V_f	$C_{32}H_{21}N_3O_4$ (511)	185[a]	60	75.20 (75.15)	4.00 (4.11)	8.32 (8.22)

Compound No.	Mol. formula (m.wt.)	m. p.* (°C)	Yield (%)	Elemental analysis: Found (Calc.) %		
				C	H	N
VI_a	$C_{32}H_{22}O_3N$ (468)	170[b]	55	82.09 (82.05)	5.10 (4.70)	3.30 (2.99)
VI_b	$C_{33}H_{24}NO_4$ (498)	160[b]	45	79.61 (79.52)	4.91 (4.82)	2.90 (2.81)
VI_c	$C_{34}H_{27}N_2O_3$ (511)	185[a]	35	79.75 (79.84)	5.19 (5.28)	5.59 (5.48)
VI_d	$C_{32}H_{22}NO_4$ (484)	155[b]	40	79.20 (79.34)	4.41 (4.55)	2.92 (2.89)
VI_e	$C_{32}H_{22}NO_4$ (484)	230[a]	30	79.56 (79.34)	4.67 (4.55)	2.94 (2.89)
VI_f	$C_{32}H_{21}N_2O_5$ (513)	150[a]	70	74.90 (74.85)	4.14 (4.09)	5.51 (5.46)
VII_a	$C_{27}H_{18}N_2O_3$ (418)	185[a]	50	77.60 (77.51)	4.41 (4.31)	6.72 (6.69)
VII_b	$C_{28}H_{20}N_2O_4$ (448)	175[a]	40	75.10 (75.00)	4.56 (4.46)	6.45 (6.25)
VII_c	$C_{29}H_{23}N_3O_3$ (461)	190[b]	35	75.39 (75.49)	4.87 (4.98)	9.21 (9.11)
VII_d	$C_{27}H_{18}N_2O_4$ (434)	180[b]	30	74.76 (74.65)	4.20 (4.15)	6.51 (6.45)
VII_e	$C_{27}H_{18}N_2O_4$ (434)	225[a]	45	74.70 (74.65)	4.21 (4.15)	6.57 (6.45)
VII_f	$C_{27}H_{17}N_3O_5$ (463)	195[b]	60	70.10 (69.98)	3.80 (3.67)	9.08 (9.07)
$VIII_a$	$C_{27}H_{18}N_2O_2S$ (434)	170[a]	50	74.85 (74.65)	4.35 (4.15)	6.59 (6.45)
$VIII_b$	$C_{28}H_{20}N_2O_3S$ (464)	185[a]	40	72.51 (72.41)	4.42 (4.31)	6.07 (6.03)
$VIII_c$	$C_{29}H_{23}N_3O_2S$ (477)	165[a]	30	73.10 (72.96)	5.10 (4.82)	9.10 (8.81)
$VIII_d$	$C_{27}H_{18}N_2O_3S$ (450)	170[a]	45	72.10 (72.00)	4.14 (4.00)	6.31 (6.22)
$VIII_e$	$C_{27}H_{18}N_2O_3S$ (450)	230[b]	30	72.50 (72.00)	4.53 (4.00)	6.50 (6.22)
$VIII_f$	$C_{27}H_{17}N_3O_4S$ (479)	150[b]	70	67.68 (67.64)	3.59 (3.55)	8.91 (8.77)

*Solvent for crystallisation: a = ethanol; b = methanol.

The presence of α,β-unsaturated ketonic system in compounds III_{a-f} led to their reaction with hydrazines according to the reported method[4]. Thus, the interaction of III_{a-f} with hydrazinehydrate in dry alcohol in the presence of glacial acetic acid afforded the corresponding 1-phenylnaphthcyclopentan(2,3-c)-N-


+ Cl—CH2 ph
ClCH2COOH
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(I)
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Piperidine
O
ph
(II)
H2N·NH2
A COH
CH
N
COCH3
IVa-f
III
a-f
H2N·NH
ph
Piperidine
Va-f
H2N—OH·HCl
VIa-f
S=C—NH2
H2N
Ethanol/HCl
NH
VIIIa-f
S
VIIIa-f

acetylpyrazolino-4,9-dione (IV_{a-f}). However, the reaction of III_{a-f} with phenylhydrazine gave N-phenylpyrazolino analogues (V_{a-f}) under the influence of piperidine catalysis.

Also, the acivation exerted by the carbonyl gorup on the exocyclic double bond in III_{a-f} renders them available for the addition of various amino compounds, *e.g.*, hydroxylaminehydrochloride, urea and thiourea. Thus, interaction of III_{a-f} with one mole equivalent of hydroxylamine hydrochloride in ethanolic sodium hydroxide solution gave the corresponding 1-phenylnaphthcyclopentan(2,3-c)isoxazolino-4,9-dione (VI_{a-f}), whereas the interaction of III_{a-f} with equimolar ratios of urea and/or thiourea in ethanol containing hydrochloric acid gave the corresponding 1-phenylnaphthcyclopentan(2,3-c)pyrimidine (pyrimidinethione)-4,9-dione (VII_{a-f} and $VIII_{a-f}$), respectively (Scheme 1).

Structures of compounds I–VIII were confirmed by elemental analysis, IR and ^1H NMR spectral data[11, 12] (Tables 1, 2).

TABLE-2
IR AND ^1H NMR SPECTRAL DATA OF SOME SELECTED HETEROCYCLIC COMPOUNDS I–VIII

Compound No.	IR (KBr ν_{max} cm^{-1})	^1H NMR (DMSO) ppm
I	1720 (C=O)	7.2–7.9 (m, 9H, aromatic), 0.7–1.3 (s, 2H, —CH_2 joined to phenyl)
II	1735 (C=O)	7.2–7.8 (m, 9H, aromatic), 0.5–1.1 (s, 1H, —CH joined to phenyl), 0.6–1.2 (s, 1H, —CH_2 cyclopentanone)
III_a	1735 (C=O) 1610 (C=C)	7.1–7.9 (m, 14H, aromatic), 4.8 (s, 1H, ylidene), 0.5–1.2 (s, 1H, —CH joined to phenyl)
IV_a	1745 (C=O) 1575–1520 (C=N)	7.2–8.4 (m, 14H aromatic), 2.2 (s, 3H, (—CH—CH_3), 5.1–5.4 (d, 2H, pyrazoline), 0.5–1.1 (s, 1H, —CH joined to phenyl)
V_a	1745 (C=O) 1575 (C=N)	7.1–8.6 (m, 14H, aromatic), 6.80–6.91 (d, 2H, pyrazoline protons), 0.5—1.1 (s, 1H, —CH joined to phenyl)
VI_a	1745 (C=O) 1575 (C=N)	7.1–8.3 (m, 14H, aromatic), 5.1–5.2 (d, 2H, isoxazoline protons), 0.5–0.7 (s, 1H, —CH joined to phenyl)
VII_a	1735 (C=O) 1575 (C=N) 3400–3300 (N—H)	7.2–8.7 (m, 14H, aromatic), 3.1 (b, 1H, —NH), 3.5 (m, 2H, pyrimidine protons), 0.5–1.1 (s, 1H, —CH joined to phenyl)
$VIII_a$	1700 (C=O) 1575 (C=N) 1200–1050 (C=S) 3400 (N—H)	7.1–8.6 (m, 14H, aromatic), 3.1 (b, 1H, —NH), 3.4 (m, 2H, pyrimidine thiono protons), 0.5–0.9 (s, 1H, —CH joined to phenyl)

The antibacterial and antifungal activities of some of the selected compounds, *i.e.*, III–$VIII_{a, c, f}$ VIII (a, c, f) dissolved in ethyleneglycol were determined using

filter paper disc method[13] against bacteria *Bacillus stearetherophil* and *Serratia* and fungi *Aspergillus* and *Penicillium* species. The inhibition zones of all the compounds were found in the range of 6–14 mm.

Structure-biological activity relationship of fused pyrazolines, isoxazolines and pyrimidines (IV–VIII) was demonstrated relative to the parent compound III. Thus, the parent compounds $III_{a, c, f}$ are slightly potent against bacteria and fungi. It is quite obvious that the presence of electron-donating or withdrawing groups (III_c or III_f) increases the activity more than the unsubstituted III_a. Also, inserting a pyrazolino moiety to the parent III_a to give IV_a causes, to some extent, an increase in the biological activities. Thus, N-acetylpyrazolino derivatives ($IV_{a, c, f}$) slightly increase the biological activity, but those of N-phenylpyrazolino analogues ($V_{a, c, f}$) increase the activity. On the other hand, insertion of isoxazolino and/or pyrimidino moieties $(VI–VIII)_{a, c, f}$ to the parent compound ($III_{a, c, f}$) causes a high increase in the biological activity, especially those containing *p*-N-$(CH_3)_2$ substituent.

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded on a Perkin-Elmer 127 B spectrophotometer and ^1H NMR spectra on an EM 390 (90 MHz) spectrometer.

Synthesis of 2-benzyl-1,4-naphthquinone (I)

A mixture of 1,4-naphthquinone (0.01 mol) and benzyl chloride (0.01 mol) in ethylene glycol 30 mL containing 5 mL sodium bicarbonate 20%, was refluxed for 8 h. The hot reaction mixture was filtered; to the filtrate were added 10 mL ethanol and a few mols of acetic acid; refluxed again for 2 h, then to the hot reaction mixture cold water was added, whereby the product I separated out; it was filtered off, washed several times with water, dried and crystallised from the proper solvent (*cf.* Table-1).

Synthesis of 1-phenylnaphthcyclopentan-2,4,9-trione (II)

A mixture of 2-benzyl-1,4-naphthquinone (I, 0.01 mol) and monochloroacetic acid (0.01 mol) in 30 mL ethanol containing 2 mL triethylamine was refluxed for 10 h. The hot reaction mixture was filtered, concentrated and boiling water was added. The product (II) precipitated out and was filtered off, washed several times with water, dried and crystallised from the proper solvent (*cf.* Table-1).

Synthesis of 3-arylidino-1-phenylnaphthcyclopentan-2,4,9-trione ($III_{a–f}$)

A mixture of II (0.01 mol) and the aromatic aldehyde (0.01 mol) was dissolved in ethanol (20 mL) containing piperidine (1 mL) and refluxed for 25–30 h. The reaction mixture was then filtered while hot, concentrated and allowed to cool at room temperature for overnight. On addition of petroleum ether 60–80°C, a resinous material was separated and triturated with water. The resulting solid was filtered, washed several times with water, dried and crystallised from the proper solvent (*c.f.* Table-1).

Synthesis of 1-phenylnaphthcyclopentan(2,3-c)-N-acetylpyrazolino-4,9-dione (IV_{a-f})

A mixture of III_{a-f} (0.01 mol) and hydrazinohydrate (0.01 mol) in ethanol (20 mL) containing acetic acid (1 mL) was refluxed for 15–20 h. The reaction mixture was then filtered while hot, concentrated to one-third of its volume, poured in ice-water mixture with vigorous stirring and left overnight at room temperature. The resulting solid was filtered, washed several times with water, dried and crystallised from proper solvent (*cf.* Table-1)

Synthesis of 1-phenylnaphthcyclopentan(2,3-c)-N-phenylpyrazolino-4,9-dione (V_{a-f})

A mixture of III_{a-f} (0.01 mol) and phenylhydrazine (0.01 mol) was dissolved in ethanol (20 mL) containing piperidine (1 mL) and refluxed for 18–26 h. The reaction mixture was then filtered while hot, concentrated to one-third of its volume, poured in ice-water mixture with stirring for 40 min and left overnight at room temperature. The resulting solid was washed several times with water dried and crystallised from the proper solvent (*c.f.* Table-1).

Synthesis of 1-phenylnaphthcyclopentan(2,3-c)-isoxazolino-4,9-dione (VI_{a-f})

A mixture of III_{a-f} (0.01 mol) and hydroxylamine hydrochloride (0.01 mol) in ethanol (20 mL) containing 2% sodium hydroxide (1 mL) was refluxed for 20–25 h. The reaction mixture was then filtered while hot, the filtrate concentrated to one-third of its volume, poured in ice-water mixture with stirring for 20 min and left overnight at room temperature. The resulting solid was washed several times with water, dried and crystallised from the proper solvent (*cf.* Table-1).

Synthesis of 1-phenylnaphthcyclopentan(2,3-d) pyrimidine and/or pyrimidinethiono-4,9-dione (VII_{a-f}, $VIII_{a-f}$)

A mixture of an ethanolic solution of (III_{a-f}) (0.01 mol), urea and/or thiourea (4 g) and concentrated hydrochloric acid (20 mL) was refluxed for 15–22 h. The reaction mixture was then filtered while hot, allowed to cool and neutralised with 5NaOH. The resulting solid was washed several times with water, dried and crystallised from the proper solvent (*cf.* Table-1).

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