SYNTHESIS AND BIOLOGICAL ACTIVITY OF NEW SELECTED DIFFERENT HETEROCYCLIC NITROGEN COMPOUNDS INCORPORATING 1,4-NAPHTHQUINONE

Ali Kamel Khalafallah
Department of Chemistry
Aswan Faculty of Science, Aswan, Egypt.

Abstract:

Condensation of 1-phenylnaphthcyclopentan-2,4,9-trione II with aromatic aldehydes yielded the corresponding 3-benzylidene derivatives 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} pyrimidinone and/or pyrimidinethione, VII_{a-f}, $VIII_{a-f}$ derivatives respectively. Also, a series of some spiro compounds covering 2-lactams and thiazolidinones X_{g-j}, XI_{g-j} incorporating 1-phenylnaphthcyclopentan-2,4,9-trione were prepared.

Introduction:

An efficient strategy for synthesis of new heterocyclics via cyclocondensation reaction between different types of K,2-unsaturated ketone compounds with hydrazines, hydroxylamine, urea and thiourea. Also, this an efficient strategy extended to include a synthesis of some spiro compounds via cycloaddition reaction of monochloroacetyl chloride and thioglycolic acid to the newly synthesised Schiff bases IX_{g-j} were the subject of our studies(1-7). In continuation to our previous work on the heterocyclic nitrogen compounds and in view of their various uses as biological and synthetic drugs (8-12), pyrazolines, isoxazolines, pyrimidines, pyrimidinethiones, 2-lactams and thiazolidinones IV_{a-f} – $VIII_{a-f}$, X_{g-j}, XI_{g-j} in conjunction with 1-phenylnaphthcyclopenan-4,9-dione were prepared.

Results and Discussion:

1-phenylnaphthcyclopentan-2,4,9-trione II was prepared through the reaction of 1,4-naphth- quinone 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 monochloroacetic acid proceeded in the presence of triethylamine as catalyst affording 1-phenylnaphthcyclopentan-2,4,9-trione II (Scheme 1). The structures of I and II were confirmed by the elemental analysis, IR and ^{1}H NMR spectral data (Tables 1,2).

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

The presence of K, 2-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-acetylpyrazolino-4,9-dione IV_{a-f}. However, the reaction of III_{a-f} with phenyl hydrazine gave N-phenylpyrazolino analogues V_{a-f} under the influence of piperidine catalysis.

Also, the activation exerted by the carbonyl group on the exocyclic double bond in III_{a-f} renders them available for the addition of the various amino compounds, e.g., hydroxylamine hydrochloride, 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).

Structure of compounds $I\text{-}VIII_{a-f}$ were confirmed by the elemental analysis, IR and ^{1}H NMR spectral data (13-14) (Tables 1, 2).

Also 1-phenylnaphthcyclopentan-2,4,9-trione II undergo condensation reaction with different aromatic nitroso compounds such as >-nitrosophenol, >-nitroso-N-dimethylaniline, 2-nitroso-K-naphthol and K-nitroso-2-naphthol in the presence of piperidine afforded the corresponding schiff bases compounds IX_{g-i}. Its structures were confirmed by Elemental analysis, IR and ^{1}H NMR spectra (c.f.Tables 1, 2). This schiff bases IX_{g-i} reacted with chloroacetylchloride in the presence of triethylamine in DMF afforded the corresponding spiro 2-lactams X_{g-i}. Its structures were confirmed by Elemental analysis, IR and ^{1}H NMR spectra (c.f. Tables 1, 2).

On the other hand the cycloaddition reaction of thioglycolic acid to the schiff bases IX_{g-i} in DMF give the corresponding thiazolidinone XI_{g-i}. Its structures were confirmed by Elemental analysis, IR and ^{1}H NMR spectra (c.f. Tables 1, 2).

The antibacterial and antifungal activities of some selected compounds, i.e., $III\text{-}VIII_{a,c,f}$ dissolved in ethylene glycol were determined using filter paper disc method (15) against bacteria Bacillus steareth erophil 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 the fused pyrazolines, isoxazolines and pyrimidines $IV_{a,c,f}$ –$VIII_{a,c,f}$ 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 with drawing 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 activity. 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 $VI_{a,c,f}$ - $VIII_{a,c,f}$ to the parent compound $III_{a\,c,f}$ causes a high increase in the biological activity, especially those containing >-N-$(CH_3)_2$ substituent.

Experimental:

All melting points are uncorrected. The IR spectra were recorded on a Perkin-Elmer 127 B spectrophotometer and ^{1}H 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 glicol 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 moles of acetic acid; refluxed again for 2h., 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 monochloro- acetic 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-arylideno-1-phenylnaphthcyclopentan-2,4,9-trione III_{a-f}

A mixture of II (0.01 mol) and the aromaric 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 (cf. 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 hydrazinhydrate (0.01 mol) in ethanol (20 ml) containing acetic acid (1ml). 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 the 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 filtered, washed several times with water, dried and crystallised from the proper solvent (cf. Table 1).

Synthesis of 1-phenylnaphthcyclopentan(2,3-c)isoxazolino-4,9-dione derivatives 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 filtered, washed several times with water, dried and crystallised from the proper solvent (cf. Table 1).

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

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 filtered, washed several times with water, dried and crystallised from the proper solvent (cf. Table 1).

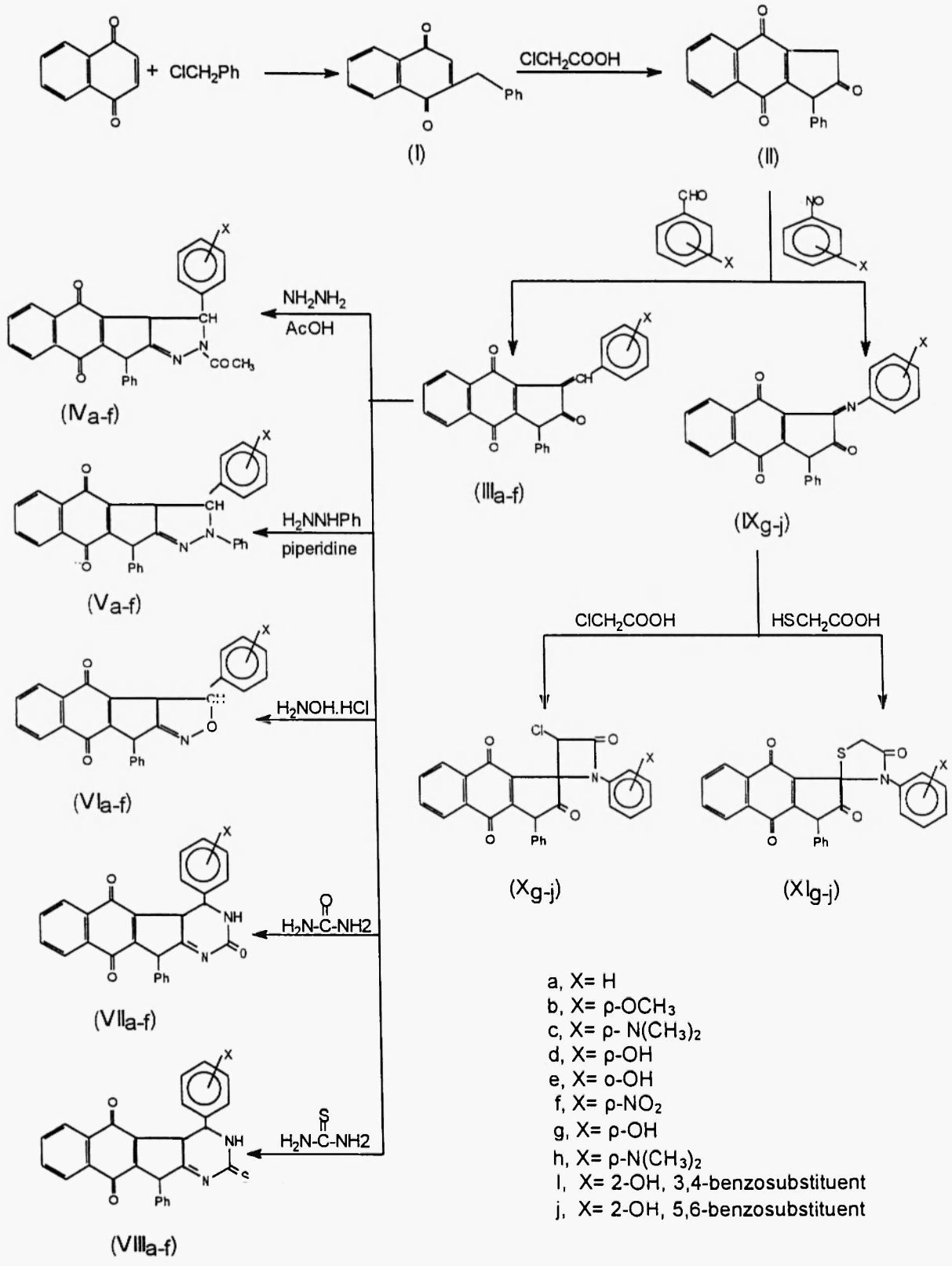

Table 1: Physical Data of Compounds I-XI

Comp. 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	$C_{28}H_{11}O_3N$ (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	$C_{26}H_{15}NO_5$ (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	$C_{34}H_{27}NO_2$ (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)
VI_a	$C_{32}H_{22}NO_3$ (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)

Table 1: Physical Data of Compounds I-XI (continue)

Comp. No.	Mol. Formula (m. wt.)	m.p.* (°C)	Yield (%)	Elemental analysis; Found (Calc.) %			
				C	H	N	S
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)	-
IXg	$C_{25}H_{15}NO_4$ (393.40)	215	60	76.35 (76.33)	3.85 (3.84)	3.58 (3.56)	-
IXh	$C_{27}H_{20}N_2O_3$ (420.47)	225	65	77.14 (77.13)	4.80 (4.79)	6.86 (6.66)	-
IXi	$C_{29}H_{17}NO_3$ (427.46)	240	67	81.50 (81.49)	4.03 (4.01)	3.29 (3.28)	-
IXj	$C_{29}H_{17}NO_3$ (427.46)	250	69	81.51 (81.49)	4.02 (4.01)	3.20 (3.28)	-
Xg	$C_{27}H_{16}NO_5Cl$ (469.89)	230	68	69.03 (69.02)	3.45 (3.43)	2.99 (2.98)	-
Xh	$C_{29}H_{21}N_2O_4Cl$ (496.96)	245	60	70.10 (70.09)	4.27 (4.26)	5.66 (5.64)	-
Xi	$C_{31}H_{18}NO_4Cl$ (503.95)	260	55	73.89 (73.88)	3.62 (3.60)	2.79 (2.78)	-
Xj	$C_{31}H_{18}NO_4Cl$ (503.95)	280	67	73.90 (73.88)	3.63 (3.60)	2.80 (2.78)	-
XIg	$C_{27}H_{17}NO_5S$ (467.50)	265	69	69.39 (69.37)	3.68 (3.67)	3.00 (2.96)	6.88 (6.86)
XIh	$C_{29}H_{22}N_2O_4S$ (494.56)	255	70	70.45 (70.43)	4.49 (4.48)	5.67 (5.66)	6.49 (6.48)
XIi	$C_{31}H_{19}NO_4S$ (501.56)	270	65	74.25 (74.24)	3.83 (3.82)	3.00 (2.79)	6.41 (6.39)
XIj	$C_{31}H_{19}NO_4S$ (501.56)	285	60	74.26 (74.24)	3.84 (3.82)	3.01 (2.79)	6.41 (6.39)

Solvent for crystalllsation: a = ethanol; b = methanol.

Table 2: IR and ^{1}H NMR spectral data of some selected Heterocyclic Compounds I-XI

Comp. No.	IR (KBr ;$_{max}$ cm^{-1})	^{1}H NMR (DMSO) ppm
I	1720 (C=O)	7.06-8.0 (m,9H, aromatic), 3.22 (s, 2H, -CH_2 joined to phenyl).
II	1735 (C=O)	7.06-8.0 (m,9H, aromatic), 4.32 (s, 1H, -CH joined to phenyl), 3.12 (s, 2H, -CH_2 cyclopentanone).
III_a	1735 (C=O), 1610 (C=C)	7.06-8.0 (m,14H, aromatic), 4.8 (s, 1H, ylidene), 4.32(s, 1H, CH joined to phenyl).
IV_a	1745 (C=O), 1575-1520 (C=N)	7.06-8.0 (m,14H, aromatic), 2.2 (s, 3H, -CH-CH_3), 7.1-7.3 (d, 2H, pyrazoline), 4.32 (s, 1H, -CH joined to phenyl).
V_a	1775 (C=O), 1575 (C=N	7.06-8.0 (m,14H, aromatic),7.2-7.5(d, 2H, pyrazoli- ne protons), 4.32(s, 1H, -CH, -CH joined to phenyl).
VI_a	1745 (C=O), 1575 (C=N)	7.06-8.0 (m,14H, aromatic), 6.6-6.8 (d, 2H, isoxazol- ine protons), 4.32 (s, 1H, -CH joined to phenyl).
VII_a	1735 (C=O), 1575 (C=N), 3400-3300 (N-H)	7.06-8.0 (m,14H, aromatic), 3.1 (b, 1H, -NH), 6.4-6.6 (m, 2H, pyrimidine protons), 4.32 (s, 1H, -CH joined to phenyl).
$VIII_a$	1700 (C=O), 1575 (C=N), 3400 (N-H)	7.06-8.0 (m,14H, aromatic), 3.1 (b, 1H, -NH), 5.4-5.6 (m, 2H, pyrimidine thiono protons), 4.32 (s, 1H, -CH joined to phenyl).
IXg	1735 (C=O), 1580 (C=N)	7.01-8.2 (m,14H, aromatic), 4.32 (s, 1H, -CH joined to phenyl).
Xg	1745 (C=O)	7.02-8.1 (m,14H, aromatic), 1.4 (s, 1H)
XIg	1735 (C=O)	7.03-8.1(m,14H, aromatic), 1.2(s,CH of thiazolidinone).

Synthesis of 3-azoarylmethylene-1-phenyl-2,4,9-trione derivatives IX_{a-j}

A solution of (II) (0.01 mole) in ethanol (30ml) was treated with aromatic nitroso compounds (0.01 mole) in the presence of catalytic amount of piperidine (0.5 ml). The reaction mixture was heated under reflux for 7-9 hr. (monitored by TLC). The solvent was then evaporated under reduced pressure and the residue was treated with ice/water. The solid product was collected and crystallized from ethanol.

Synthesis of 3-spiro(chloro-N-substituted-2-lactam)-1-phenyl-2,4,9-trione derivatives X_{a-j} and 3-spyro-Nsubstituted thiazolidinone-1-phenyl-2,4,9-trione derivatives XI_{a-j}

A solution of (IXg-j) was treated with chloroacetylchloride or mercaptoacetic acid in DMF (30 ml) in the presence of catalytic amount of triethylamine (0.1 ml). The The reaction mixture was heated under reflux for 8-10 hr. (monitored by TLC). The solvent was then evaporated under reduced pressure and the residue was treated with ice/water. The solid product was collected and crystallized from DMF.

References:

(1) A. K. Khalafallah, F. M. Abd El-Latif, M. A. Salim and M. A. El-Maghraby, Asian J. Chem., 5, 988 (1993).

(2) A. K. Khalafallah, A. I. M. Koraiem, M. A. El-Maghraby, and H. A. Shindy, J. Indian Chem. Soc., 66, 398 (1989).

(3) M. A. El-Maghraby, A. K. Khalafallah, M. E. Hassan and H. A. soliman, J. Indian Chem. Soc., 63, 910 (1986).

(4) A. K. Khalafallah, A. Abou El-Ela, E. Elshami and M. A. El-Maghraby, J. Indian Chem. Soc., 62, 676 (1985).

(5) M. A. El-Maghraby, A. I. M. Koraiem, A. K. Khalafallah, Asw. Sci. Tech. Bull., 5, 1 (1984).

(6) A. K. Khalafallah, M. A. Selim, R. M. Abu El-hamd, M. A. El-Maghraby, H. A. Soleiman and M. A. Raslan, Indian J. of Chem., Vol. 34B, December 1995, pp. 1066-1070.

(7) H. A. Soleiman, A. K. Khalafallah and H. M. Abd El-zaher, J. Chine. Chem. Soc., Vol. 47, pp. 1267-1272 (2000).

(8) P. P. Gillman, R. J. Belly, T. K. Kosselok and S. Zigman, U. S. 4, 323, 121 (1980); Chem. Abstr., 94, 97109 (1981).

(9) Y. Makisoumi, Japan, 13, 641 (1960); Chem. Abstr., 60, 531 (1964).

(10) A. Takamizowa and Y. Mamoshima, Japan,14423 (1963); Chem. Abstr., 65, 20144 (1966).

(11) I. Ito, Japan, 7030, 10 (1970); Chem. Abstr., 74, 22827 (1971).

(12) A. Takamizowa and Sato, Japan, 72, 45353 (1972) Chem. Abstr., 78, 58454 (1973).

(13) L. J. Bellamy, The Infrared Spectra of Complex Molecules, 2nd Edn., Methuen, London, (1964).

(14) F. Scheimann, Nuclear Magnetic Resonance and Infrared Spectroscopy, Vol. 1, pp. 41-70 (1970).

(15) Y. H. Loo, P. S. Skell, H. H. Thorabrry, J. L. Megurire, G. M. Savage and J. C. Sylvester, J. Bact., 50, 701 (1945).

Received on May 26, 2001