J. Indian Chem. Soc.,
Vol. 66, June 1989, pp. 398-400

Synthesis and Studies on some Heterocyclic Nitrogen Compounds

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Manuscript received 21 July 1988, revised 10 March 1989, accepted 12 April 1989

Condensation of 4,9-dioxopiperidine[2,3-*g*]-1,2,3,4 6,7,8,9-octahydroquinolinoquinone (1) with aromatic aldehydes yielded the corresponding 3,3-bis-benzylidene derivatives (2a – f). Interaction of 2a – f with hydrazines, hydroxylamine, urea and thiourea afforded a new bis(pyrazolino-, 4a – f, 5a – f ; isoxazolino- 6a – f ; pyrimidine and/or pyrimidine-thione, 7a – f, 8a – f) derivatives, respectively.

IN continuation to our previous work on the heterocyclic nitrogen compounds[1-4] and in view of their various uses[5], bis-pyrazolines, isoxazoline, pyrimidine and pyrimidine-thiones (3 – 7a-f) in conjunction with 4,9-dioxopiperidino[2,3-*g*]hydroquinolinoquinone were prepared.

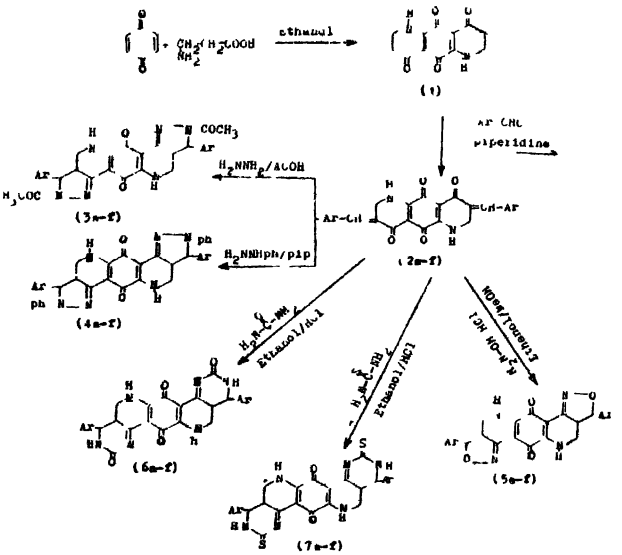
Results and Discussion

4,9-Dioxopiperidino[2,3-*g*]-1,2,3,4,6,7,8,9-octahydroquinolinoquinone (**1**) was prepared by 1,4-cyclocondensation reaction of *p*-benzoquinone with *β*-alanine in ethanol[6] (Scheme 1). The structure of **1** was confirmed by the elemental analysis, ir and pmr spectral data.

Condensation of **1** with the appropriate aromatic aldehydes proceeded smoothly in dry alcohol using piperidine as catalysis to yield the corresponding 3,3-bis-arylideno[2,3-*g*]-1,2,3,4,6,7,8,9-octahydroquinolinoquinone (**2a – f**).

The presence of *α,β*-unsaturated carbonyl group in compounds **2a – f** led to their reaction with hydrazines according to the reported methods[3]. Thus, the interaction of **2a – f** with hydrazine hydrate in dry alcohol in the presence of glacial acetic acid afforded the corresponding bis-*N*-acetylpyrazolino[3,4-*c*, 3,4-*c*]piperidino[2,3-*g*]-1,2,3,4,6,7,8,9-octahydroquinolinoquinone (**3a – f**). However, the reaction of **2a – f** with phenyl hydrazine gave bis-*N*-phenylpyrazolino analogues (**4a – f**) under the influence of piperidine catalysis.

Also, the activation exerted by the carbonyl group on the exocyclic double bond in **2a – f** renders them available for the addition of various amino compounds, e.g. hydroxylamine hydrochloride, urea and thiourea. Thus, interaction of **2a – f** with two mole-equivalent of hydroxylamine hydrochloride in ethanolic sodium hydroxide solution gave the corresponding bis-isoxazolino[3,4-*c*, 3,4-*c*]-piperidino[2,3-*g*]-1,2,3,4,6,7,8,9-octahydroquinolinoquinone (**5a – f**), whereas the interaction of **2a – f** with bimolar ratios of urea and/or thiourea in ethanol containing hydrochloric acid gave the corresponding bis-pyrimidine(pyrimidinethione)[3,4-*c*, 3,4-*c*]piperidino[2,3-*g*]-1,2,3,4,6,7,8,9-octahydroquinolinoquinone **6a – f** and **8a – f** respectively (Scheme 1).



2 – 7 ; a, Ar = C_6H_5, **b**; Ar = *p*-OCH_3-C_6H_4, **c** ; Ar = *p*-$N(CH_3)_2$-C_6H_4, **d**, Ar = *p*-OH-C_6H_4, **e** ; Ar = *o*-OH-C_6H_4, **f**, Ar = *p*-NO_2-C_6H_4.

Scheme 1

Structures of compounds **1 – 7** (Table 1) were confirmed by elemental analysis, ir and pmr spectra.

The antibacterial and antifungal activities of some of the selected compounds, i.e. **2 – 7** (**a, c, f**) dissolved in ethylene glycol, were determined using filter paper disc method[6] against bacteria *Bacillus stearetherophil* and *serratia* and fungi *Aspergillus* and *Penicillium* species. The inhibition zones of all the compounds were found in the range 6 – 16 mm.

Structure-biological activity relationship of fused pyrazolines, isoxazolines and pyrimidines (**3 – 7**)

TABLE 1—PHYSICAL DATA OF COMPOUNDS 2–7*

Compd. no.	M.p.** °C	Yield %	Mol. formula	Colour
2a	168	28	$C_{26}H_{16}N_2O_4$	Pale brown
2b	150	20	$C_{28}H_{22}N_2O_6$	Deep brown
2c	80	69	$C_{30}H_{26}N_4O_4$	Shiny deep brown
2d	250	32	$C_{26}H_{18}N_2O_6$	Deep brown
2e	140	25	$C_{26}H_{18}N_2O_6$	Shiny brownish violet
2f	113	67	$C_{26}H_{16}N_4O_6$	Shiny deep brown
3a	230[a]	62	$C_{28}H_{26}N_6O_4$	Intense brown
3b	205[b]	23	$C_{30}H_{30}N_6O_6$	Pale brown
3c	212[a]	33	$C_{32}H_{30}N_6O_4$	Pale yellowish green
3d	213[b]	42	$C_{28}H_{26}N_6O_6$	Pale brown
3e	195[b]	25	$C_{28}H_{26}N_6O_6$	Deep brown
3f	270[a]	28	$C_{28}H_{26}N_6O_8$	Deep yellowish green
4a	200[b]	55	$C_{34}H_{30}N_6O_2$	Deep brown
4b	188[b]	62	$C_{40}H_{34}N_6O_4$	Shiny deep brown
4c	215[b]	33	$C_{42}H_{40}N_6O_2$	Pale brown fine
4d	180[b]	60	$C_{38}H_{30}N_6O_4$	Deep brown
4e	190[a]	45	$C_{38}H_{30}N_6O_4$	Deep brown fine
4f	150[a]	25	$C_{38}H_{28}N_6O_6$	Reddish fine
5a	260[a]	50	$C_{26}H_{20}N_4O_4$	Intense brown
5b	250[a]	35	$C_{28}H_{24}N_4O_6$	Pale brown
5c	280[a]	22	$C_{30}H_{30}N_6O_4$	Intense brown
5d	310[a]	25	$C_{28}H_{20}N_6O_6$	Deep brown
5e	245[a]	27	$C_{26}H_{20}N_4O_6$	Shiny pale brown
5f	200[a]	20	$C_{26}H_{18}N_6O_8$	Deep brown
6a	280[a]	33	$C_{28}H_{22}N_6O_4$	Deep brown
6b	225[a]	27	$C_{30}H_{26}N_6O_6$	Intense brown
6c	240[b]	22	$C_{32}H_{32}N_6O_4$	Shiny brown
6d	190[a]	37	$C_{30}H_{22}N_6O_6$	Pale brown
6e	212[a]	35	$C_{28}H_{22}N_6O_6$	Grey
6f	230[b]	23	$C_{28}H_{20}N_8O_8$	Pale brown
7a	290[a]	25	$C_{28}H_{28}N_6S_2O_2$	Intense brown
7b	220[a]	22	$C_{30}H_{26}N_6S_2O_4$	Intense brown
7c	227[a]	20	$C_{32}H_{28}N_6S_2O_2$	Pale brown
7d	200[a]	23	$C_{28}H_{22}N_6S_2O_4$	Deep brown
7e	233[a]	29	$C_{28}H_{22}N_6S_2O_4$	Shiny brown
7f	250[a]	20	$C_{28}H_{20}N_8S_2O_6$	Yellowish green

*All compounds gave satisfactory C, H and N analyses.
**Solvent for crystallisation : [a]ethanol : [b]methanol.

was demonstrated relative to the parent 3,3-bis-arylideno-4,9-dioxopiperideno[2,3-*g*]-1,2,3,4,6,7,8,9-octahydroquinolinoquinones (**2a, c, f**). Thus, the parent compounds (**2a, c, f**) are more potent against bacteria (7–16 mm) and fungi (6–10 mm). It is quite obvious that the presence of electron-donating or -withdrawing groups (**2c** or **2f**) increases the activity more than the unsubstituted (**2a**). Also, inserting a pyrazolino moiety to the parent **2a** to give **3** causes lowering in the biological activities. Thus, bis-*N*-acetylpyrazolino derivatives (**3a, c, f**) destroy completely the biological activity, but those of bis-*N*-phenylpyrazolino analogous (**4a, c, f**) slightly inhibit the activity. On the other hand, insertion of bis-isoxazolino and/or pyrimidino moieties (**5–7a, c, f**) to the parent compound (**2a, c, f**) completely destroys the biological activity, while pyrimidinethiono analogous slightly inhibit the activity especially those containing *p*-NO_2 substituent (**7f**).

Experimental

All melting points are uncorrected. The ir spectra were recorded on a Perkin-Elmer 127 B spectrophotometer and pmr spectra on a EM 390 (90 MHz) spectrometer.

4,9-Dioxopiperideno[2,3-g]-1,2,3,4,6,7,8,9-octahydroquinolinoquinone (**1**) : A mixture of *p*-benzoquinone (3.2 g, 3 mol) and β-alanine (1.7 g, 2 mol) was refluxed in ethanol (40 ml) for 50 h on a water-bath. The reaction mixture was then filtered while hot to remove the unreacted materials. The filterate was poured in ice-water mixture with stirring vigrously for 15 min and left aside for 3.5 h at room temperature. The resulting deep brown solid was filtered, washed several times with water, dried and crystallised from ethanol, (11%), m.p. 210° (Found : C, 58.6 ; H, 4.1 ; N, 11.4 . $C_{12}H_{10}N_2O_4$ requires : C, 58.5 ; H, 4.1 ; N, 11.4%) ; ν_{max} (KBr) 3 490 (NH), 1 735 (C=O) and 1 610 cm^{-1} (C=C conj.) ; δ(DMSO) 5.65 (2H, s, 2NH exchangeable with D_2O), 3.6 (4H, t, $2CH_2$ joined to nitrogen) and 3.75 (4H, t, $2CH_2$ joined to C=O)[9].

Bis-arylideno-4,9-dioxopiperideno[2,3-g]-1,2,3,4,6,7,8,9-octahydroquinolinoquinone (**2a–f**) : A mixture of **1** (0.2 g, 0.01 mol) and the aromatic aldehyde (2 mol) was dissolved in ethanol (20 ml) containing piperidine (1 ml) and refluxed for 29–35 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°, a resinous material was separated and triturated with water. The resulting solid was filtered, washed several times with water, dried and crystallised from methanol : **2c**, ν_{max} (KBr) 3 240–3 500 (NH), 1 600–1 665 (C=C conj. with C=O), 1 720 (C=O) and 700 cm^{-1} (Ar-disubstituted)[8] ; δ (DMSO) 6.8–9.8 (8H, m, ArH), 6.5 (2H, s, 2×NH exchangeable with D_2O), 3.6 (4H, s, 2×CH_2 joined to nitrogen), 6.8 (2H, s, 2×CH olefinic) and 3.1 (12H, s, 4×CH_3 joined to nitrogen)[9].

*Bis-*N*-acetylpyrazolino[3,4-c ; 3',4'-c]piperideno-[2,3-g]-1,2,3,4,6,7,8,9-octahydroquinolinoquinone* (**3a–f**) : A mixture of **2a–f** (0.01 mol) and hydrazine hydrate (0.02 mol) in ethanol (20 ml) containing acetic acid (1 ml) was refluxed for 19–23 h. The reaction mixture was then filtered while hot, concentrated to one-third of its volume, poured in ice-water mixture with vigrous stirring and left overnight at room temperature. The resulting solid was filtered, washed several times with water, dried and crystallised from proper solvent : **3c**, ν_{max} (KBr) 3 300–3 450 (NH), 1 520–1 575 (C=N), 1 735–1 745 (C=O) and 700 cm^{-1} (Ar-disubstituted)[8] ; δ (DMSO) 6.95 8.6 (8H, m, ArH), 1.4 (4H, s, 2×CH_2 joined to nitrogen), 3.65 (2H, br, 2×NH exchangeable with D_2O), 3.15 (18H, s, 2×$COCH_3$, 4×CH_3 joined to nitrogen) and 6.85–6.90 (4H, m, pyrazolone protons)[9].

*Bis-*N*-phenylpyrazolino[3,4-c ; 3',4'-c]piperidino-[2,3-g]-1,2,3,4,6,7,8,9-octahydroquinolinoquinone* (**4a–f**) : A mixture of **2a–f** (0.01 mol) and phenylhydrazine (0.02 mol) was dissolved in ethanol (20 ml) containing piperidine (1 ml) and refluxed for 17–25 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 : **4f**, ν_{max} (KBr) 3 300–3 450 (NH), 1 520–1 575 (C=N), 1 735–1 745 (C=O) and 700 cm^{-1} (Ar-substitution)[8] ; δ (DMSO) 6.95–8.6 (18H, m, ArH), 1.4 (4H, s, 2×CH_2 joined to nitrogen), 3.65 2H, br, 2×NH exchangeable with D_2O) and 6.85–6.90 (4H, m, pyrazolone protons)[9].

Bis-isoxazolino[3,4-c ; 3',4'-c]piperideno[2,3-g]-1,2,3,4,6,7,8,9-octahydroquinolinoquinone (**5a–f**) *:* A mixture of **2a–f** (0.01 mol) and hydroxylamine hydrochloride (0.02 mol) in ethanol (20 ml) containing 2% sodium hydroxide (1 ml) was refluxed for 21–23 h. The reaction mixture was then filtered while hot, the filterate concentrated to one-third of its volume, poured in ice-water mixture with stirring for 15 min and left overnight at room temperature. The resulting solid was washed several times with water, dried and crystallised from ethanol : **5f**, ν_{max} (KBr) 3 350–3 400 (NH), 1 540 (C=N), 1 680–1 630 (C=O) and 700 cm^{-1} (Ar-substitution)[8] ; δ (DMSO) 8.35–8.75 (8H, m, ArH), 7.8 (4H, m, isoxazolone protons), 3.5 (2H, br, 2×NH exchangeable with D_2O), 1.2–2.1 (4H, s, 2×CH_2 joined to nitrogen)[9].

Bis-pyrimidino and/or pyrimidine thiono[3,4-c ; 3'4'-c]piperideno[2,3-g]-1,2,3,4,6,7,8,9-octahydroquinolinoquinone (**6a–f, 7a–f**) *:* A mixture of an ethanolic solution of **2a–f** (0.02 mol), urea and/or thiourea (4 g) and concentrated hydrochloric acid (20 ml) was refluxed for 12–18 h. The reaction mixture was then filtered while hot, allowed to cool and neutralised with 5*N* NaOH. The resulting solid was washed several times with water, dried and crystallised from the proper solvent : **6f** and **7f**, ν_{max} (KBr) 3 390–3 450 (NH), 1 540 (C=N), 1 720 (C=O for pyrimidine) and 1 350 cm^{-1} (C=S for pyrimidine thione)[8] ; δ (DMSO) 6.9–8.4 (8H, m, ArH), 3.1–4.2 (4H, br, 4×NH exchangeable with D_2O), 0.6–2.1 (4H, s, 2CH_2 joined to nitrogen) and 3.5 (4H, m, pyrimidine protons)[9].

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