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Note

Synthesis and biological activity of naphtho[1,2,6,5]pyrano[3,4-*f*]phthalazine-4,14-diones

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The behaviour of pyranone and phthalazinone in naphtho[1,2,6,5] pyrano [3, 4-*f*] phthalazine-4,14-diones **2** towards dimethyl sulphate in different solvents and a mixture of phosphorus pentachloride/phosphorus oxychloride has been described. The structure of the synthesized compounds has been confirmed spectroscopically and chemically.

It has been reported[1] that 3-anisyl-1-benzoyl-2, 3, 12, 12a-tetrahydro-1*H*-12-oxo-naphtho[1, 2, 6, 5]pyrano[3, 4, 6, 5]benzoic acid underwent hydrazinolysis to give 5-anisyl-1-phenyl-3, 4, 4a, 14, 14a, 14b-hexahydro-5*H*-naphtho[1,2,6,5]-pyrano[3,4-*f*] phthalazine-4, 14-diones. In the present note we report the hydrazinolysis of 3-anisyl-/ tolyl-2, 3, 12,12a-tetrahydro-1*H*-12-oxo-naphtho[1, 2, 6, 5]pyrano[3, 4, 6, 5]benzoic acid[1] **1** with hydrazine hydrate, semicarbazide hydrochloride and phenyl hydrazine in alcohol to give 5-anisyl-1-(4-tolyl)-3,4,4a,14,14a,14b-hexahydro-5*H* naphtho [1, 2, 6, 5] pyrano[3, 4-*f*] phthalazine-4, 14-dione **2a**, 5-anisyl-3-carboxamido-1-(4-tolyl)-3, 4, 4a, 14, 14a, 14b-hexahydro-5*H*-naphtho[1, 2, 6,5]pyrano[3,4-*f*] phthalazine-4,14-dione **2b** and 5-anisyl-3-phenyl-1-(4-tolyl)-3, 4, 4a, 14, 14a, 14b-hexahydro-5*H*-naphtho[1, 2, 6, 5]pyrano[3, 4-*f*]phthalazine 4, 14-dione **2c**, respectively. The IR spectra of **2** exhibited absorption bands at 1730-1720 (CO of δ-lactone), 1660-1655 (CO of cyclic amide), and 1630-1620 (C=N). While the IR spectra of **2a,b** showed absorption band in the region 3330-3300cm^{-1} (NH). ^{1}H NMR of **2a** showed signals at δ 2.4 (s, 3H, CH_3), 3.1 (s, 3H, OCH_3), 3.6-3.8 (m, 4H, cyclic), 6.1 (s,1H, NH) 6.7-8 (m, 15H, olefinic and aromatic protons). UV spectra of **2a,c** are given in Table I.

Methylation of **2a,c** with dimethyl sulphate in the presence of anhydrous potassium carbonate[2,3] and dry acetone (lactim form is more predominate) gave 5-anisyl-4,14-dimethoxy-1-(4-tolyl)-4a, 14b-dihydro-5*H*-naphtho[1, 2, 6, 5] pyrano[3, 4-*f*]phthalazine **3**, 5-anisyl-3-carboxamido-14-methoxy-1-(4-tolyl)-3, 4, 4a, 14b-tetrahydro-5*H*-naphtho[1, 2, 6, 5]pyrano[3, 4-*f*] phthalazin-4-one **4a** and 5-anisyl-14-methoxy-3-phenyl-1-(4-tolyl)-3, 4, 4a, 14b-tetrahydro-5*H*-naphtho[1,2,6,5]pyrano-[5]pyrano[3,4-*f*]phthalazin-4-one **4b** (Scheme I). The IR spectra of **4** exhibited absorption band at 1660-1650 (CO of amide), while IR spectrum of **4a** showed absorption band at 3345 cm^{-1} (NH).

The ^{1}H NMR of **3** showed signals at δ 2.5 (s, 3H, CH_3), 3.1 (s, 3H, Ar-OCH_3), 3.25 (s, 3H, N=C-OCH_3), 3.4 (s, 3H,-O-C-OCH_3), 3.6-3.9 (m, 3H, cyclic), 6.5-7.8 (m, 15H, olefinic and aromatic protons).

On the other hand, methylation of **2a,b** with dimethyl sulphate in the presence of dry pyridine[3,4] (lactam form is more predominate) gave 5-anisyl-3-methyl-1-(4-tolyl)-3,4,4a,14,14a,14b-hexahydro-5*H*-naphtho[1,2,6,5]pyrano[3, 4-*f*]phthalazine-4,14-dione **5a** and 5-anisyl-3-[(N-methyl) carboxamido]-1-(4-tolyl)-3,4, 4a, 14, 14a, 14b-hexahydro-5*H*-naphtho [1, 2, 6, 5]pyrano[3, 4-*f*] phthalazine-4,14-dione **5b**. The IR spectra of **5** showed absorption bands, in the regions 1730-1725 cm^{-1} (CO of δ-lactone) and at 1662-1655 cm^{-1} (CO of amide), while IR spectrum of 5b showed absorption band at 3348 cm^{-1} (NH). UV spectra of 5b are given in Table I.

Treatment of **2c** with a mixture of phosphorus pentachloride/phosphorus oxychloride gave 5-anisyl-14-chloro-3-phenyl-1-(4-tolyl)-3, 4, 4a, 14b-tetrahydro-5*H*-naphtho[1, 2, 6, 5]pyrano[3, 4-*f*]phthalazin-4-one **6**. The IR spectrum of **6** showed absorption band at 1667 cm^{-1} (CO of amide).Amination of **6** with *p*-toluidine and/or benzylamine by fusion gave 5-anisyl-14-arylamino-3-phenyl-1-(4-tolyl)-3, 4, 4a, 14b-

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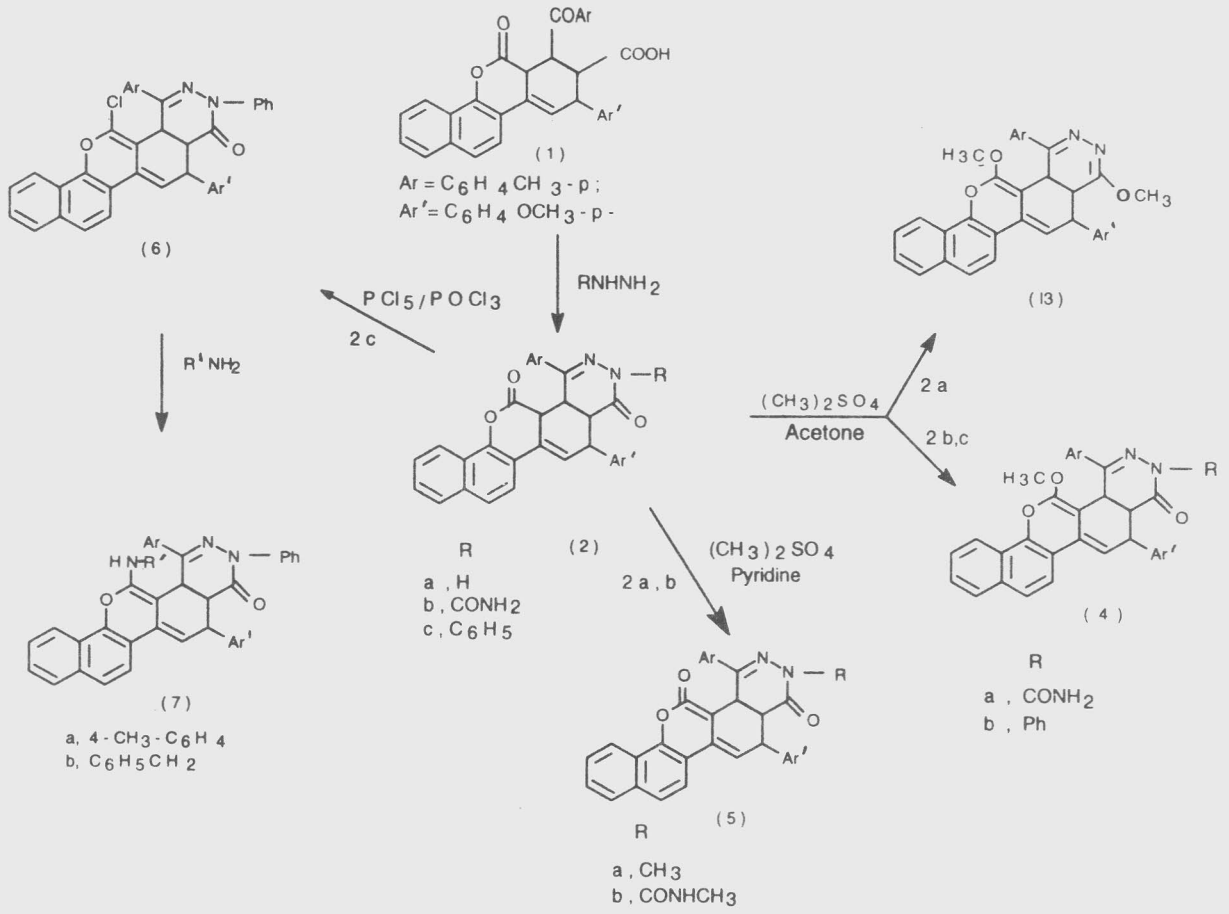

Scheme I

Table I— Electronic spectra of some compounds (ethanol)

Compd.	λ (nm)	ε
2a	205	48300
	246	69400
	350	15800
	370	10100
2c	210	54800
	245	53600
	355	13500
	372	7500
5b	210	63200
	248	57000
	358	10500
	372	7500
7b	214	72800
	250	51000
	355	18800
	370	12500

tetrahydro-5*H*-naphtho[1, 2, 6, 5] pyrano[3, 4-*f*] phthalazin-4-one **7a,b**. The IR spectra of **7** showed absorption bands at 1665-1660 (CO of amide), and at 3340-3320 cm^{-1} (NH). UV spectra of **7b** are given in Table I.

Antimicrobial Activity*

The antimicrobial activity of synthesized compounds **1-4** were tested using the hole plate and filter paper disc method[5].

Naphthopyranobenzoic acid **1** showed slight activity by the effect of inhibition zone which has mean diameter equal to 0.7 mm at minimum inhibitory concentration (MIC) (120 μg/mL) against *Aspergillus flavus* but inactive against the remainder of the tested microorganisms. Phthalazinone derivative **2c** showed moderate activity of inhibition zone which has mean diameter equal to 1.7 mm at MIC (200 μg/mL) against *Aspergillus flavus* and *Penicillium notatum* but low activity of inhibition zone which has mean diameter equal to 1.0 mm against *Bacillus cereus*

*Origin of cultures:
Botany Dept., Faculty of Science, Benha University, Benha, Egypt.
Mereen collection, Ain Shams University, Cairo, Egypt.

and inactive against *Bacillus circulans*. Dihydrophthalazine derivative **3** showed different grades of activity at MIC of inhibition zone which has mean diameter equal to (0.8-1.6 mm) at MIC (125-200 μg/mL) against *Aspergillus flavus* and *Penicillium notatum* but inactive against *Bacillus cereus* and *Bacillus circulans*.

Chlorophthalazinone 6 was inactive against all the tested microorganisms.

Experimental Section

All melting points are uncorrected. IR spectra were measured in KBr on a UNICAM SP-1200 spectrophotometer (lambda 3B) and ^{1}H NMR spectra (DMSO-d_6) on a Varian 360-60 MHz spectrometer using TMS as internal standard. The micro-analyses were performed by the micro analytical center at Cairo University.

Action of hydrazines on 3-(substituted)-2, 3, 12, 12a-tetrahydro-1*H*-12-oxonaphtho[1, 2, 6, 5]pyrano[3, 4, 6, 5]benzoic acid 1: Formation of 5-anisyl-3-(substituted)-1-(4-tolyl)-3, 4, 4a, 14, 14a, 14b-hexahydro-5*H*-naphtho[1, 2, 6, 5]pyrano[3, 4-*f*] phthalazine-4, 14-dione 2a-c. A solution of **1** (0.01 mole), hydrazine hydrate, semicarbazide hydrochloride and/or phenyl hydrazine (0.03 mole) in ethanol (50 mL) was refluxed for 5hr. The reaction mixture was poured into ice-dilute hydrochloric acid. The solid obtained was filtered off and crystallized from the proper solvent to give **2a-c** (cf. Table II).

Alkylation of 2a-c in K_2CO_3/acetone: Formation of 5-anisyl-4, 14-dimethoxy-1-(4-tolyl)-4a, 14b-dihydro-5*H*-naphtho[1, 2, 6, 5] pyrano [3,4-*f*] phthalazine 3 and 5-anisyl-3-(substituted)-14-methoxy-1-(4-tolyl)-3, 4, 4a, 14b-tetrahydro-5*H*-naphtho[1, 2, 6, 5]pyrano[3, 4-*f*] phthalazin 4a,b. A solution of **2a-c** (0.01 mole), dimethyl sulphate (0.01 mole) and anhydrous potassium carbonate (0.04 mole) in dry acetone (50 ml) was refluxed for 24hr. The excess acetone was removed by distillation, and the reaction mixture poured on water and extracted with ether. After evaporation of the dried ethereal solution, the product obtained was filtered off and crystallized from the proper solvent to give compounds **3** and **4a,b** (cf. Table II).

Alkylation of 2 in pyridine: Formation of 5-anisyl-3*N*-(substituted)-1-(4-tolyl)-3, 4, 4a, 14, 14b-hexahydro-5*H*-naphtho-[1, 2, 6, 5]pyrano[3, 4-*f*] phthalazine-4, 14-dione 5a,b. A solution of **2a,b** (0.01 mole), dimethyl sulphate (0.01 mole) in dry pyridine (10 mL) was refluxed for 24 hr. The reaction mixture was poured on ice-dilute hydrochloric acid, the solid obtained was filtered

Table II—Physical data of the compounds **2a-c, 3, 4a,b, 5a,b, 6** and **7a,b**

Compd	m. p. °C	Yield (%)	Mol. Formula (Mol. wt.)	Found % (Calc.) C	H	N
2a	240	67	$C_{33}H_{26}N_2O_4$ (514)	77.2 (77.0	5.2 5.1	5.7 5.5)
2b	271-72	69	$C_{34}H_{27}N_3O_5$ (557)	73.0 (73.3	4.8 4.9	7.4 7.5)
2c	228	64	$C_{39}H_{30}N_2O_4$ (590)	79.0 (79.3	5.0 5.1	4.6 4.8)
3	>280	64	$C_{35}H_{30}N_2O_4$ (557)	77.3 (77.5	5.2 5.5	5.1 5.2)
4a	>280	66	$C_{35}H_{29}N_3O_5$ (571)	73.4 (73.6	5.0 5.1	7.3 7.4)
4b	215-17	65	$C_{40}H_{32}N_2O_4$ (604)	79.6 (79.5	5.2 5.3	4.4 4.6)
5a	148-50	66	$C_{34}H_{28}N_2O_4$ (528)	77.5 (77.3	5.1 5.3	5.1 5.3)
5b	223-25	65	$C_{35}H_{29}N_3O_5$ (571)	73.3 (73.6	5.0 5.1	7.3 7.4)
6	238	62	$C_{39}H_{29}N_2O_3Cl$ (608.5)	76.7 (76.9	4.8 4.8	4.5 4.6)
7a	121-23	65	$C_{46}H_{37}N_3O_3$ (679)	81.0 (81.3	5.5 5.5	6.0 6.2)
7b	205-7	68	$C_{46}H_{37}N_3O_3$ (679)	81.0 (81.3	5.4 5.5	6.1 6.2)

off and crystallized from the proper solvent to give **5a,b** (cf. Table II).

Action of phosphorus pentachloride/phosphorus oxychloride on 2c: Formation of 5-anisyl-14-chloro-3-phenyl-1-(4-tolyl)-3, 4, 4a, 14b-tetrahydro-5*H*-naphtho[1, 2, 6, 5]pyrano-[3, 4-*f*]phthalazin-4-one 6. A mixture of **2c** (0.01 mole) phosphorus pentachloride (0.01 mole) and phosphorus oxychloride (0.1 mole) was refluxed for 3hr, then poured slowly into ice-cold water. The solid obtained was washed several times with water, filtered off, dried, and crystallized from the proper solvent to give **6** (cf. Table II).

Treatment of 6 with amines under fusion : Formation of 5-anisyl-14-arylamino-3-phenyl-1-(4-tolyl)-3, 4, 4a, 14b-tetrahydro-5*H*-naphtho[1, 2, 6, 5]pyrano[3, 4-*f*]phthalazin-4-one 7a,b. A mixture of **6** (0.01 mole) and *p*-toluidine or benzylamine (0.01 mole) was heated at 160°C for 4hr, and poured into ice-dilute hydrochloric acid. The solid obtained was filtered off and crystallized from the proper solvent to give **7a,b**. (cf. Table II).

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