NEW 1,4-DISUBSTITUTED PHTHALAZINES: SYNTHESIS, STRUCTURE AND HERBICIDAL EVALUATION

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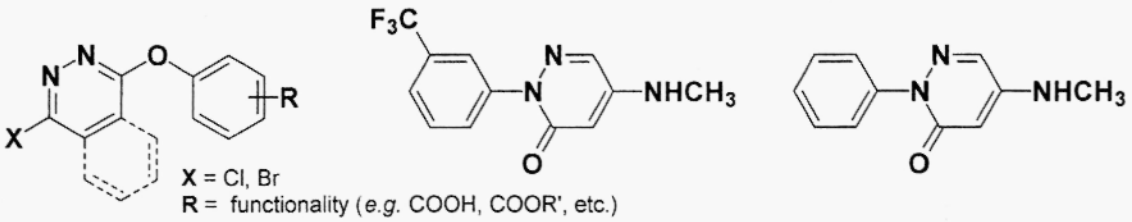
Abstract: the rapid synthesis of eighteen new 1,4-disubstituted phthalazines bearing an aryl or benzyl substituent at C-4 and a variety of aryloxy groups at C-1 is reported; full structural assignments are provided by NMR and MS data together with the biological evaluation for some representative terms of the series.

INTRODUCTION

The agro chemistry of substituted (benzo) pyridazines **I** and pyridazinones is already a classical area of interest for both chemists and biologists (1-4). They exhibit herbicidal activity mainly by inhibiting the biosynthesis of some essential fatty acids (*e.g.* Metflurazon® **II** and Norflurazon® **III**, **Scheme 1**).



Scheme 1

The ether linkage at α-position between the pyridazine ring and aryl groups is a key structural requirement for these compounds and responsible for their phytotoxicity: inhibition by peroxydation of the biochemistry of the fatty acids [*e.g.* the conversion of linoleic (18:2) into linolenic acid (18:3)] (5).

According to our initial findings in functionalisation of (benzo) diazines (6-9), the aim of the present communication consists in the synthesis and biological evaluations of some new 1,4-disubstituted phthalazines of type **I** (**Scheme 1**). We also considered their structure of interest from NMR and Mass Spectrometry points of view.

RESULTS AND DISCUSSION

1. Synthesis

The synthetic pathway we used is depicted in **Scheme 2.**

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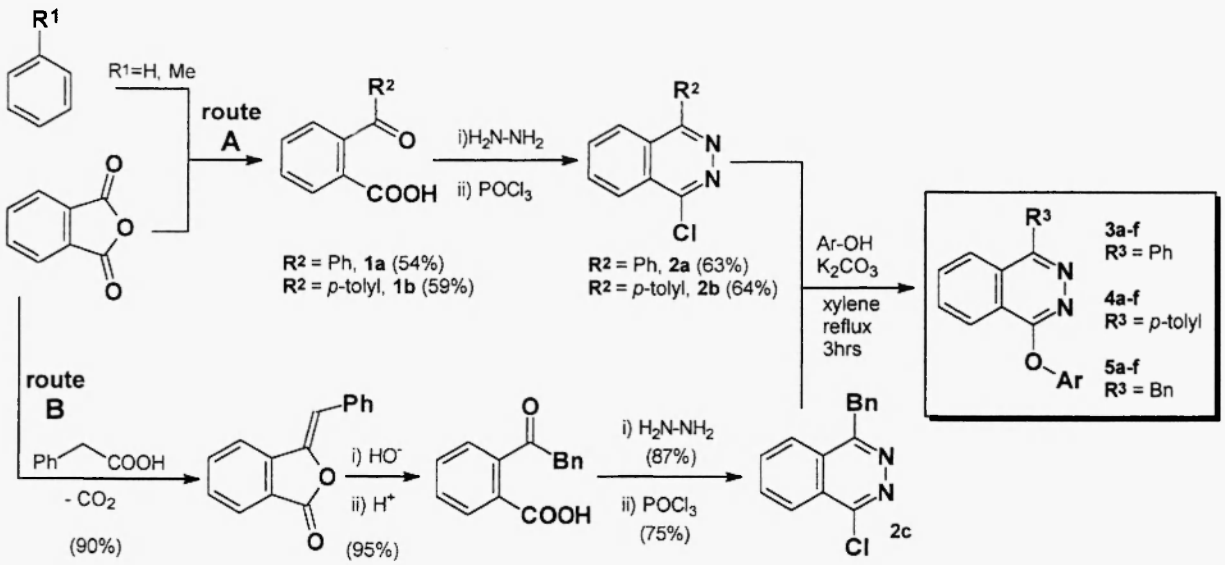


Scheme 2

Thus, following classical methodologies (10-16), three 1-chloro-4-substituted-phthalazines were prepared: **route A** afforded the phthalazines **2a, b** possessing a direct Ar-Ar linkage. **Route B** provided the 1-chloro-4-benzylphthalazine **2c**. Since neat condensation between **2a-c** and our selected phenols resulted in the decomposition of the reaction mixtures, we decided to attempt this key step of the synthesis in a solvent having an enough high boiling point. Indeed, in refluxing xylene (3 hours), we accessed three series of new phthalazine derivatives, **3a-f, 4a-f, 5a-f (Scheme 2)**. The results are presented in **Table 1**. All reactions were monitored by TLC.

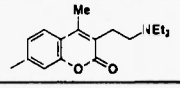
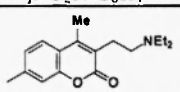
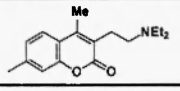
The medium to satisfactory yields we obtained as **2a-c** : K_2CO_3 : phenol 1.00:2.32:1.85 molar ratio (compounds **3-5a, b, e, f**). The synthesis of coumarin derivatives **3-5c** required smaller excess of the base but higher excess of phenol (molar ratio **2a-c** : K_2CO_3 : phenol = 1.00: 1.75:3.50). Finally, the α-naphthyloxy derivatives **3-5d** were prepared with smallest yields despite the excess of base (molar ratio **2a-c** : K_2CO_3 : α-naphthol = 1.0:2.9:3.5). All compounds were isolated simply by direct crystallisation. The yields in **Table 1** refer to compounds of analytical purity (with satisfactory elementary analysis) after supplementary crystallisation from the indicated solvents (see **EXPERIMENTAL** for the typical procedure in the case of compound **4c**).

2. Structural assignments

2.1. NMR analysis

The ^{1}H-NMR spectra fully confirmed the identity of the envisaged structures (**Table 2**). For the present communication, we will restrict our discussion to the benzo-ring in phthalazine moiety (positions **a, b, c, d**). Thus, the protons labelled **H-a, -b, -c, -d** were located, as expected, in the most deshielded zone of the spectra as a typical AA'XX' coupling pattern (17, 18). The unambiguous discrimination between positions **a** - **d** was made by successive NOE-diff. Experiments [*e.g.* irradiation of the signal assigned to **H-b** promoted NOE not only at the adjacent position **d** but also at the *ortho*-positions (with respect to Ar-Ar linkage) of the phenyl R^3 substituent]. These assignments were then confirmed by the 2D ^{1}H-^{1}H COSY Experiments (19, 20). As a general comment, the shielding in the benzo-ring was found throughout as **H-a > H-b > H-c > H-d**. Proton **H-a** was more deshielded than **H-b** presumably because its *peri* position with respect to the lone pairs of the oxygen belonging to C-1 aryloxy fragment. Although ^nJ values ranged the normal magnitude, we note their increase (up to 9.5 Hz) if the substituent ArO was naphthyloxy or *p*-phenyl-phenoxy (compounds **3-5d-f**).

Table 1: Qualitative and quantitative results of the synthesis of the compounds **3-5a-f**

Nr.	R^3	Ar	Yield (%)	m.p. (°C)	R_f
3a	Ph	*o*-Br-C_6H_4-	68	180-1[a]	0.79[c]
3b	Ph	*p*-O_2N-C_6H_4-	70	176-8[a]	0.82[c]
3c	Ph		56	121-3[b]	0.42[d]
3d	Ph	α-naphthyl	35	193-5[a]	0.76[c]
3e	Ph	β-naphthyl	37	168-71[a]	0.82[c]
3f	Ph	*p*-C_6H_5-C_6H_4-	64	193-6[a]	0.85[c]
4a	*p*-tolyl	*o*-Br-C_6H_4-	63	164-5[a]	0.82[c]
4b	*p*-tolyl	*p*-O_2N-C_6H_4-	69	160-2[a]	0.84[c]
4c	*p*-tolyl		55	154-5[b]	0.51[d]
4d	*p*-tolyl	α-naphthyl	34	205-6[a]	0.79[c]
4e	*p*-tolyl	β-naphthyl	37	197-9[a]	0.84[c]
4f	*p*-tolyl	*p*-C_6H_5-C_6H_4-	65	210-12[a]	0.86[c]
5a	Bn	*o*-Br-C_6H_4-	65	139-41[a]	0.80[c]
5b	Bn	*p*-O_2N-C_6H_4-	67	200-3[a]	0.83[c]
5c	Bn		53	130-1[b]	0.47[d]
5d	Bn	α-naphthyl	36	130-2[a]	0.83[c]
5e	Bn	β-naphthyl	35	133-5[a]	0.85[c]
5f	Bn	*p*-C_6H_5-C_6H_4-	66	157-9[a]	0.86[c]

[a]crystallisation from MeOH; [b]crystallisation from toluene; [c]eluent benzene: chloroform : methanol 10:10:1 v/v/v; [d]eluent chloroform : methanol 5:1 v/v.

Surprisingly, in the case of coumarin derivatives **3-5c**, the prochirality of the nitrogen in the Het-CH_2-CH_2-*N*($CH_\alpha H_\beta$-CH_3)$_2$ motif was observed (**Scheme 3**). Indeed, as the substitution test indicates, the methylene protons belonging to the two-*enantiotopic* ethyl ligands are *diastereotopic* one with respect to the other. Accordingly, the NMR appearance for **H-α** (or β) was a doublet of doublets at 2.80 ppm: ^2J=10.5 Hz and ^3J=5.3 Hz. Unfortunately, the full assignment was not possible because of the partially upfield overlapping with the multiplets revealed around 2.60 ppm by the other six methylene protons, including **H-β** (or α). This behaviour might be explained by assuming only the slow pyramidal inversion of the nitrogen on 400 MHz NMR time scale. Obviously, this geminal anisochrony did not apply for the 1,2-ethylene ligand.

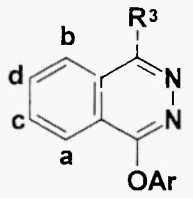
The 2D ^{1}H-^{13}C HMBC (**H**etero **M**ultiple **B**ond **C**orrelation) (21,22) and HSQC (**H**etero **S**ingle **Q**uantum **C**orrelation) (23, 24) experiments were used for location of the carbon atoms **C-a, -b, -c, -d** and allowed also the discrimination between the two methyl groups in the compound **4c** (see full assignments in **EXPERIMENTAL** for the compound **4c**).

2.2. Mass Spectrometry

All Mass Spectra were performed under Electronic Impact (EI 70 eV).

As shown in **Scheme 4**, except the first terms (**3-5a**) in each the series **3-5**, all the other compounds revealed the $[M-1]^+$ peak (*e.g.*: **3b**-69.7 %; **3d**-43.1 %; **3e**-31.5 %; **4b**-69.5 %; **4d**-45.8 %; **4f**-28.7 %). Their proposed structures, according to literature (25), are characteristic for the 1,4-disubstituted phthalazines. In almost all cases, the basic peak $[M]^+$was the molecular ion itself except coumarin derivatives **3-5c** when the classical "onium" cleavage in the aliphatic moiety afforded the stable $H_2C{=}N^+(Et)_2$ ion (m/z = 86) as the basic peak.

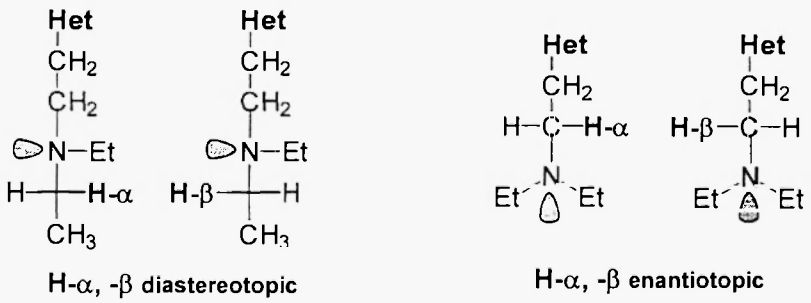
Table 2: Relevant ^{1}H NMR data as δ (ppm) and ^nJ (Hz) for the compounds **3-5a-f** (400 MHz, $CDCl_3$)



3a-f R^3 = Ph **4a-f** R^3 = *p*-tolyl **5a-f** R^3 = Bn

Nr.	R^3	H-a	H-b	H-c	H-d	$^3J_{a-c}$	$^4J_{a-d}$	$^3J_{c-d}$	$^4J_{c-b}$	$^3J_{d-b}$
3a	Ph	8.46	7.97	7.86	7.80	8.8	1.5	7.9	1.5	7.7
3b	Ph	8.40	8.03	7.93	7.86	7.9	1.1	7.5	1.5	7.4
3c	Ph	8.40	7.99	7.89	7.83	6.8	1.1	7.5	1.5	7.7
3d	Ph	8.59	8.02	7.93	7.91	8.1	[a]	-	-	8.1
3e	Ph	8.56	8.07	7.99	7.96	9.1	1.4	10.3	1.0	10.8
3f	Ph	8.53	8.10	7.98	7.91	9.5	2.0	10.0	1.0	11.2
4a	*p*-tolyl	8.49	8.03	7.90	7.83	8.1	1.5	9.0	1.5	8.8
4b	*p*-tolyl	8.37	8.05	7.91	7.85	7.4	1.8	7.3	2.6	7.7
4c	*p*-tolyl	8.39	8.03	7.89	7.83	7.0	1.1	7.5	1.5	8.1
4d	*p*-tolyl	8.68	8.15	8.03	8.03	9.3	2.0	9.4	1.7	10.9
4e	*p*-tolyl	8.56	8.11	7.97	7.95	10.6	1.1	9.7	2.0	10.9
4f	*p*-tolyl	8.53	8.11	7.97	7.90	9.8	1.6	10.2	1.6	10.8
5a	Bn	8.38	7.93	7.78	7.72	7.7	-	7.5	-	7.4
5b	Bn	8.29	8.00	7.82	7.80	8.1	1.5	7.4	1.8	7.9
5c	Bn	8.32	7.97	7.82	7.77	7.5	2.6	7.0	2.6	6.8
5d	Bn	8.61	8.07	7.96	7.92	10.0	1.7	9.8	1.0	10.8
5e	Bn	8.48	8.05	7.92	7.92	9.6	2.2	9.3	2.0	9.3
5f	Bn	8.45	8.04	7.89	7.84	8.8	1.5	9.8	2.4	9.7

[a] overlapped signals



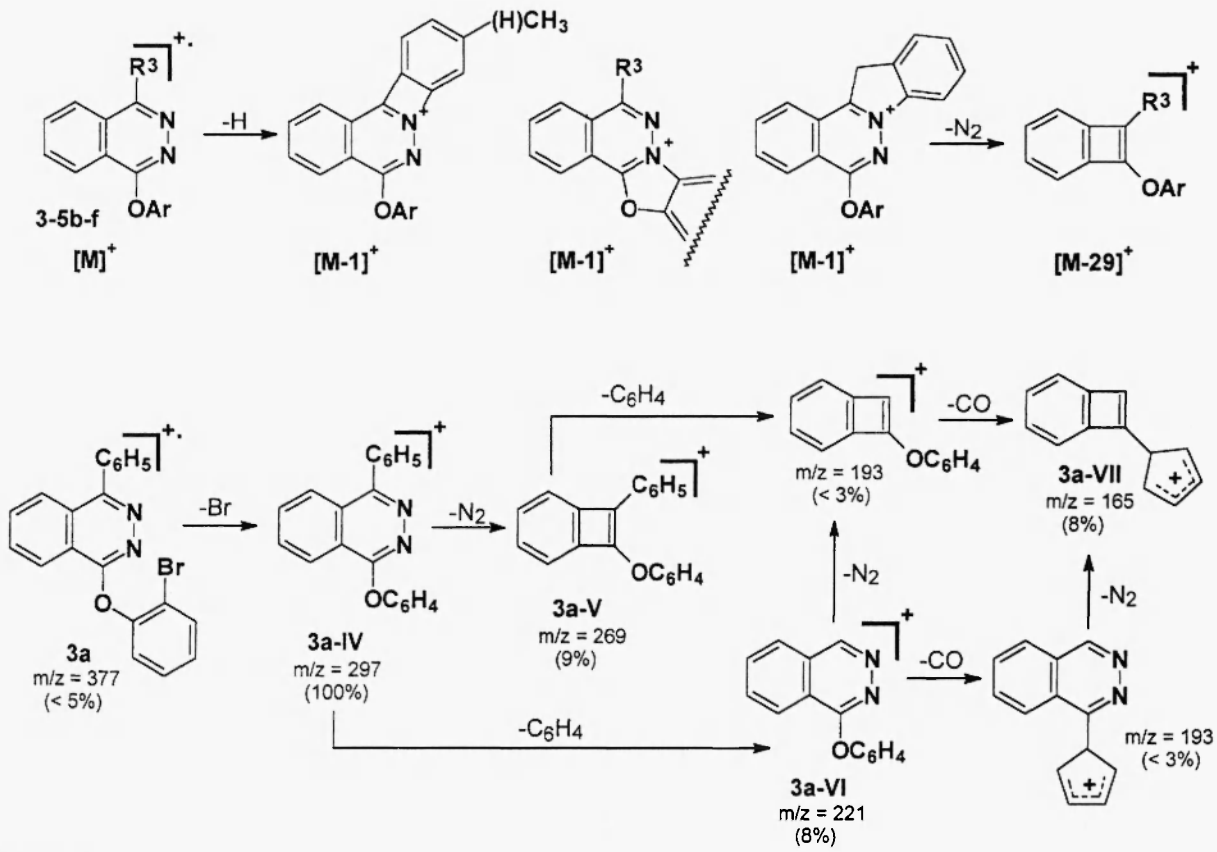
Scheme 3

In the case of 2-bromophenoxy derivatives **3-5a**, the abundance of the molecular peak was less than 5%. That is, the main fragmentation route started by the loss of the halogen, to provide the basic peaks of type **3a-IV** (**Scheme 4**). The fragmentation of the compound **3a** (given as typical example) also exhibited detectable ions possessing m/z values consistent with benzocyclobutene skeletons (**3a-V**, **3a-VII**). This fragmentation pathway appeared to us quite similar to the other compounds **3-5b-f** since in their Mass Spectra stable cations of type benzocyclobutene **3a-VII** were also observed.

No peak possessing higher mass than the molecular peak was detected throughout, to indicate the monomer structure in gas phase for all investigated compounds.

3. Herbicidal evaluation

For preliminary tests, we investigated the biological activity of the prochiral coumarin compounds **3-5c**. They were used as



Scheme 4

aqueous solutions and hydrochlorides (1000 ppm). The effect on following seedlings were examined: radish (*Raphanus sativus*), cucumber (*Cucumis sativus*), pode beans (*Phaseolus vulgaris*) and tomatoes (*Solanum lyopersicum)*. So, upon foliar treatement, the content of the main types of acyl lipids (glyco- and phospholipids) decreased affecting directly the integrity of cell membranes: up to 25% was the decrease of foliar lipids together with an siginificant increase of the saturated fatty acids content (up to 30%). Thus, as predicted, the compounds **3-5c** inhibited the biosynthesis of the unsaturated fatty acids.

CONCLUSIONS

Eighteen new 4-substituted-1-aryloxyphthalazines were prepared with medium to satisfactory yields. Although not optimised, the quantitative results for the insertion of the selected phenols were possible only in milder conditions than previously reported in the literature. NMR and MS data were in complete agreement with the desired structures: Under electronic impact, the fragmentation schemes depended on the substitution in the aryloxy group. Three terms of the series, bearing at C-1 a prochiral 7-coumarinyloxy motif, inhibited the biosynthesis of unsaturated fatty acids in both glyco- and phospholipids.

EXPERIMENTAL

Preparation of 1-[3-(2-diethylaminoethyl)-4-methylcoumarin-7-oxi]-4-tolylphthalazine, 4c.

1-Chloro-4-tolylphthalazine (1.57 g, 6.2 mmol), 3-(2-diethylaminoethyl)-4-methylcoumarin-7-ol (3.00 g, 10.9 mmol) and potassium carbonate (3.00 g, 21.7 mmol) in refluxing xylene (25 mL) were vigorously stirred for 3 hrs (TLC monitoring, **Table 1**). At r.t., water (50 mL) was added with stirring. After separation, the organic solution was washed with water to neutrality (x 10 mL) then

dried over magnesium sulphate and filtered off. The xylene solution was evaporated in vacuum to afford the crude product, which was preliminarily isolated by crystallisation from ligroin. A second crystallisation from hot toluene afforded the pure title compound **4c** as yellowish crystalline powder; yield 55 % (1.68 g) with respect to 1-Chloro-4-tolylphthalazine. ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm, *J* Hz); *phthalazine moiety* 8.39 (1H, dd, *J*=7.0 and 1.1), 8.03 (1H, dd, *J*=8.1 amd 1.5), 7.89 (1H, dd, *J*=7.5 and 1.8), 7.83 (1H, dd, *J*=7.5 and 1.8); *p-tolyl moiety* 7.54 (2H, dd, *J*=7.2 and 1.8), 7.28 (2H, dd, *J*=8.5 and 2.2), 2.38 (3H, s); *coumarin moiety* 7.60 (1H, d, *J*=8.8), 7.31 (1H, d, *J*=2.2), 7.27 (1H, dd, *J*=9.2 and 2.2), 2.80 (2H, dd, *J*=10.5 and 5.3), 2.59 (6H, m), 2.40 (3H, s), 1.05 (6H, d, *J*=7.2). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm); *phthalazine moiety* 155.2 (1C, Cq), 132.7 (1C, -CH=), 132.2 (1C, -CH=), 128.4 (1C, Cq), 126.6 (1C, -CH=), 125.4 (1C, Cq), 123.1 (1C, -CH=); ; *p-tolyl moiety* 139.2 (1C, Cq), 138.2 (1C, Cq), 129.9 (2C, -CH=), 129.2 (2C, -CH=), 21.4 (1C, $-CH_3$); *coumarin moiety* 163.6 (1C, >C=O), 161.7 (1C, Cq), 158.1 (1C, Cq), 153.1 (1C, Cq), 146.6 (1C, Cq), 133.1 (1C, Cq), 125.4 (1C, -CH=), 118.0 (1C, -CH=), 109.9 (1C, -CH=), 46.9 (2C, $-CH_2-$), 50.8 (1C, $-CH_2-$), 24.9 (1C, $-CH_2-$), 15.1 (1C, $-CH_3$), 11.8 (2C, $-CH_3$). Anal calcd. for $C_{31}H_{31}N_3O_3$: C 75.41, H 6.33, N 8.55 %; found: C 75.71, H 5.99, N 8.54 %.

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Received on September 7, 2003.