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FIRST SYNTHESIS, ROTAMERISM AND HERBICIDAL EVALUATION OF SUBSTITUTED *s*-TRIAZINES WITH SERINOLIC FRAGMENTS (II): AMINO-1,3-DIOXANES OF (1*S*,2*S*)-*p*-NITROPHENYLSERINOLS

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ABSTRACT. Pure enantiomeric amino-1,3-dioxanes, obtained by total diastereospecific ring closure of (1*S*,2*S*)-2-(substituted)amino-1-(4-nitrophenyl)-propane-1,3-diols ("*nitrophenylserinols"*) reacted with cyanuryl chloride to afford *N*-substituted triamino-*s*-triazines (*melamines*) and precursors. Their rotameric behaviour around the C^{sp2}(triazine)-N(1,3-dioxane) bond is discussed in terms of NMR, as steric and electronic influence of the substituents. The herbicidal evaluation of two of the new compounds is also pointed out.

INTRODUCTION

We have previously reported our methodology to prepare pure enantiomeric 5-amino-1,3-dioxanes[1-5] by direct diastereospecific ring closure of (1*S*,2*S*)-2-amino-1-(4-nitrophenyl)-propane-1,3-diol (the so called *"nitrophenylserinol"*) and its *N,N*-dimethyl analogue upon treatment with certain aldehydes in strong acidic media (98 % H_2SO_4, 0 ^oC). These aminodioxanes exhibited useful reactivity upon treatment with typical electrophiles: aryl(di)aldehydes and acid (poly)chlorides[1-3].

For the present preliminary communication, our outstanding attention is dedicated to the reaction between two representative compounds in this class and cyanuryl chloride with a concise stereochemical approach of the products. To the best of our knowledge, amino-1,3-dioxanes were never considered as nucleophiles against cyanuryl chloride though some *N*-subsituted-amino-*s*-triazines bearing an acetal motif are mentioned in the literature to be potential anticancer agents[6].

RESULTS AND DISCUSSION

1. Synthesis

The starting amino-1,3-**D**io**X**anes (DX-NH_2) were prepared from the enantiomerically pure (1*S*,2*S*) serinols S-**1** and S-**2** (**Scheme 1, *p*-N**itro-**Ph**enyl: *p*-NPh). The synthesis and stereochemistry of DX**1**-NH_2 we reported elsewhere[1,4]; the same protocol gave DX**2**-NH_2 in satisfactory optimized yield and total diastereoselectivity

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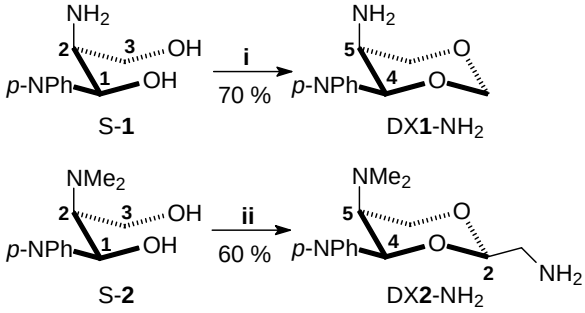
(*R*) with respect to the absolute configuration at C-2. Both compounds are stable solid crystalline and ananchomeric structures, possessing the aromatic group in equatorial position. It is already useful to observe that in DX**1**-NH_2 the amino group is placed in axial position flanked by the preferred bisectional orientation of the aromatic ring (*cis* relationship) whereas in DX**2**-NH_2 the methyleneamino sequence is equatorial.

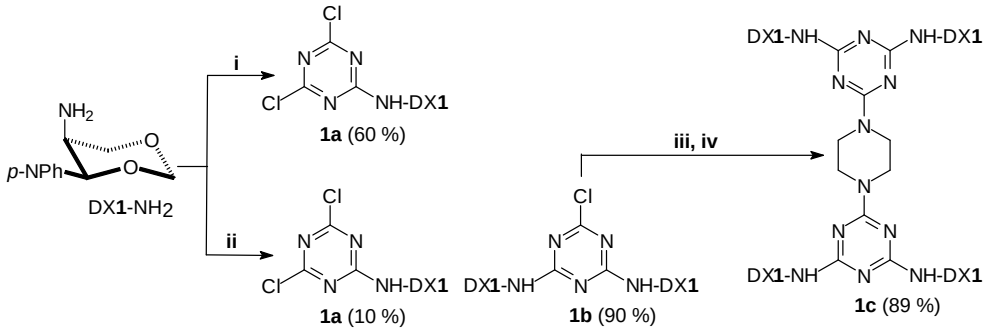


i: 1 eq. CH_2O / 10 eq. H_2SO_4 98 % / 24 hrs. from 0 ^oC to r.t.; **ii:** 1 eq. $H_2N\text{-}CH_2\text{-}CH(OR)_2$ (R = Me, Et) / 10 eq. H_2SO_4 98 % / 24 hrs. from 0 ^oC to r.t.

Scheme 1

The nucleophilicity of DX**1**-NH_2 against chloro-*s*-triazines was first tested (**Scheme 2**, partial conversions of cyanuryl chloride is presented in round brackets).

In a first effort (route **i**) we obtained the expected **1a** with a satisfactory yield; TLC monitoring of the reaction evidenced also the noticeable presence of the unreacted starting materials. Attempting at a melamine based on DX**1**-NH_2 (route **ii**) failed: the successive replacement of chlorine in cyanuryl chloride stopped after the second substitution. Instead, the chloro-diamino-*s*-triazine **1b** was isolated with excellent yield, together with **1a** as side product. They were separated by flash column chromatography. Matching results we reached when the proton scavenger was the “proton sponge” (1,8-bis-dimethylaminonaphthalene). However, if reducing

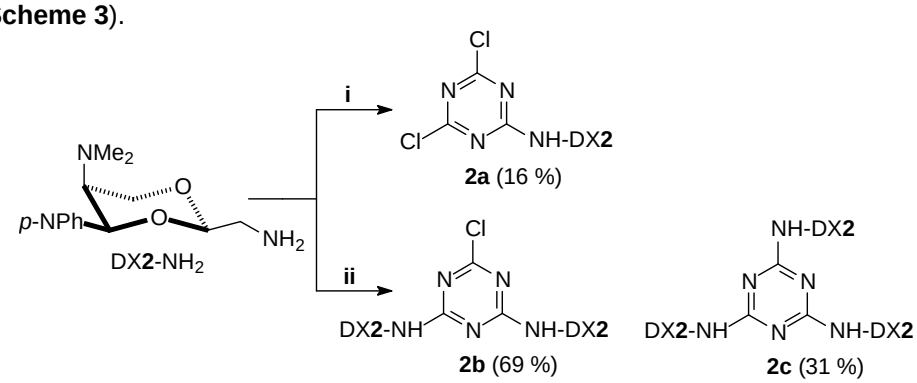


i: 1.05 eq. $C_3N_3Cl_3$ / 1.00 eq. anh. K_2CO_3 / THF / 24 hrs. from 0 ^oC to r.t.; **ii:** 0.33 eq. $C_3N_3Cl_3$ / 1.00 eq. anh. K_2CO_3 / toluene / 24 hrs. at reflux; **iii:** 0.49 eq. piperazine hexahydrate, 1.15 eq. HCl / *i*-PrOH; **iv:** 0.49 eq. piperazine hydrochloride / 2.00 eq. anh. K_2CO_3 / toluene / 12 hrs. at reflux.

Scheme 2

the amount of cyanuryl chloride (0.47 eq., 1.0 eq. K_2CO_3), the partial conversions changed as 47 % (**1a**) and 53 % (**1b**).That is, it was impossible to link three DX**1**-NH units to the triazine ring, presumably because the intimate stereochemistry of the DX**1**-NH_2 which influenced the nucleophilicity of the 5-amino group. Consequently, in order to access melamines based on aminodioxane DX**1**-NH_2, our option focused on a stronger nucleophile, piperazine (**Scheme 2**, routes **iii, iv**). Its hygroscopicity was avoided by preliminary conversion into hydrochloride. The "dimeric" melamine **1c** was prepared in good yield in a very clean reaction.

The same chemistry starting from DX**2**-NH_2 provided different results (**Scheme 3**).



i: 1.05 eq. $C_3N_3Cl_3$ / 1.05 eq. anh. K_2CO_3 / THF / 24 hrs. from 0 ^oC to r.t.; **ii:** 0.30 eq. $C_3N_3Cl_3$ / 1.00 eq. anh. K_2CO_3 / toluene / 24 hrs. at r.t. / 24 hrs. at 70 ^oC / 24 hrs. at reflux

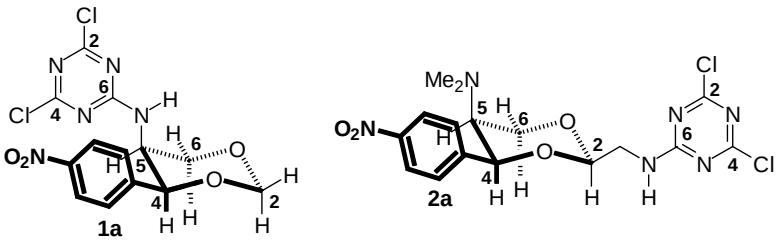
Scheme 3

As depicted in **Scheme 3**, dissimilarity was clearly evidenced. Thus, in route **i**, despite the very slow contact between reagents, the compound **2a** was isolated by flash column chromatography in poor yield. The side product, with complex NMR spectra, appeared to be an oligomeric structure, most probably issued from the competitive replacement of chlorine by both the nucleophilic sites in DX**2**-NH_2. In cyanuryl chloride chemistry (seen as electrophile) this *N*-dealkyl-*N*-acylation of tertiary amines is already very well documented[7]. In route **ii**, we overcame this behaviour by involving, from the beginning, a large excess (300 %) of the aminodioxane. This method allowed obtaining the melamines **2b** and **2c**. No traces of **2a** were found in the crude reaction mixture.

2. Stereochemistry and rotameric behaviour

2.1. *N*-Substituted-2,4-dichloro-6-amino-*s*-triazines with 1,3-dioxane fragments: compounds **1a, 2a** (**Scheme 4**)

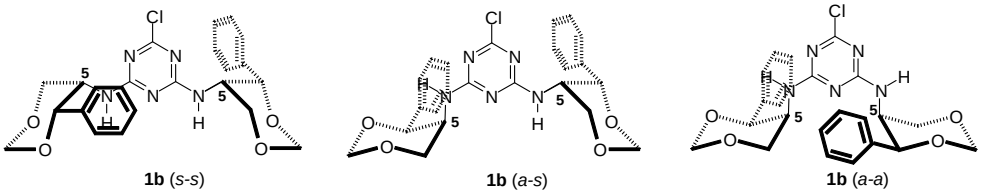
Both the compounds are ananchomeric structures with a double bond character of the linkage C-6(*s*-triazine)-N(1,3-dioxane), hence a restricted rotation in this sequence: in the ^{13}C NMR spectra, the triazine positions 2 and 4 were found diastereotopic (*e.g.* $\Delta\delta$=0.5 ppm, **1a**). The protons N*H* displayed a typical ^3J splitting (*e.g.* ^3J=9.2-9.4 Hz, **1a**) to support a fixed location. In the case of **1a**, one can also anticipate some hindered rotation about the axial C-5-N bond, due to the proximity of the ligands H-6-eq. and *p*-NPh, predicting an *out* orientation of the triazine moiety.



Scheme 4

2.2. *N*-Substituted-2-chloro-4,6-diamino-*s*-triazines with 1,3-dioxane fragments: compounds **1b, 2b**

For the present communication, discussion is limited to assignments at room temperature. The NMR spectra of the compounds **1b**, **2b** revealed the diastereomerism issued from the restricted rotation about the C^{sp2}(triazine)-N(dioxane) bond as mixtures of three blocked rotamers[8,9]: *syn-syn* (*s-s*), *syn-anti* (*s-a*) and *anti-anti* (*a-a*). The dioxane fragments and the triazine chlorine are references for these descriptors (**Scheme 5**, **Table 1**, **Figure 1** and **2**; in **Scheme 5** the *p*-nitro group was omitted for reason of simplicity).



1b (*s-s*) **1b** (*a-s*) **1b** (*a-a*)

Scheme 5

Table 1

Relevant ^{1}H NMR data and contributions of the blocked rotamers for the compounds **1b**, **2b**

	Solvent	Rotamers (%) according to N*H* signals			δ_{NH}, (^3J, Hz)		
		(*s-s*)	(*s-a*)	(*a-a*)	(*s-s*)	(*s-a*)	(*a-a*)
1b	DMSO-d_6	34	53	13	7.55 (8.8)[a]	7.55 (8.8), 7.13 (9.6)	7.10 (11.6)
	C_6D_6	53	24	23	6.48 (8.3)	5.57 (9.1), 5.78 (9.8),	5.85 (9.8)
	$CDCl_3$	26	54	20	6.09 (9.4)	5.88 (9.4), 5.71 (9.8)	6.00 (9.8)
2b	DMSO-d_6	43	47	10	8.15 (8.4)[b]	8.06 (8.0), 8.01 (6.0)	7.79 (6.0)
	C_6D_6	43	46	11	7.45[c]	7.55, 5.49	6.63
	$CDCl_3$	50	41	9	6.36	6.20, 5.62	6.03

[a]doublets; [b]triplets (overlapped doublets of doublets); [c]overlapped doublets of doublets as coalescent triplets

As expected, the "reference" protons were N*H* and used for the calculations (**Table 1**): isochronous in environments (*s*-*s*) and (*a*-*a*) but anisochronous in (*s*-*a*). The rotamerism appeared strongly dependent on the stereochemistry of the linkage dioxane-triazine, axial or equatorial (**Figure 1** and **2**).

Thus, the contributions of the rotamers of **2b** showed the minor occurrence of the most hindered one (*a*-*a*), quite similar with the corresponding open-chain derivatives[8]. The protons N*H* were splitted as overlapped doublet of doublets [(coalescent) triplets] with mediated ^{3}J values (6-8 Hz) with the diastereotopic adjacent methylene group, to prove the free rotation around the >*C*H_2-*N*< bond (**Figure 2**). The A.S.I.S. (***A**romatic **S**olvent **I**nduced **S**hifts*) phenomena[10] had no influence on the content of rotamers.

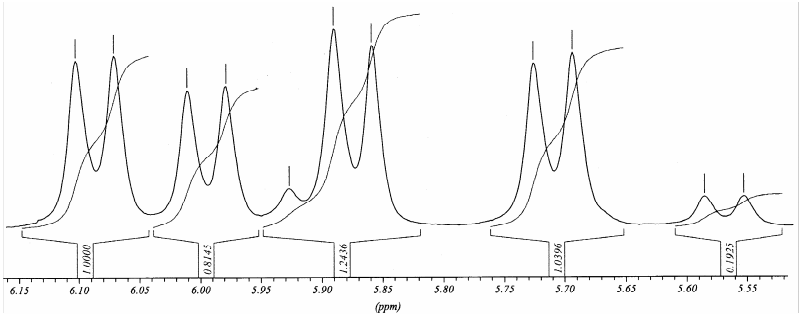


Figure 1: ^{1}H-NMR spectrum of the compound **1b** (300 MHz, $CDCl_3$, 293 K), detail in the region of the protons N*H*.

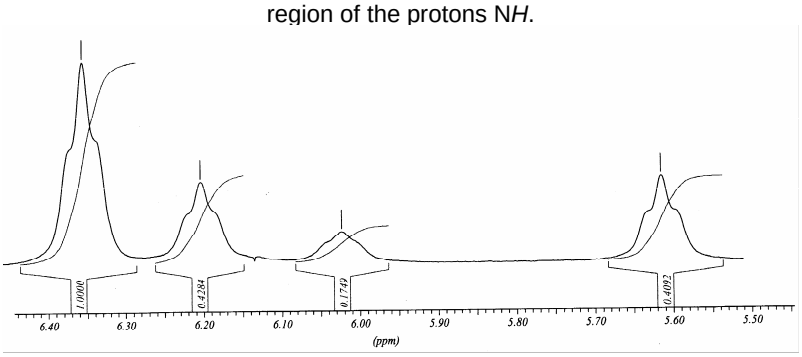


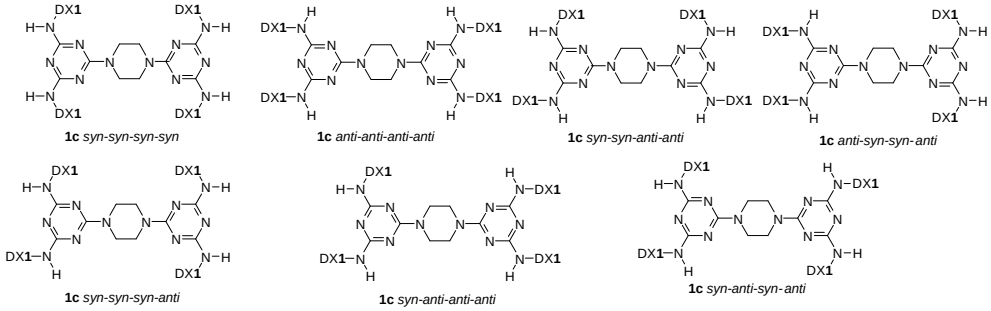
Figure 2: ^{1}H-NMR spectrum of the compound **2b** (300 MHz, $CDCl_3$, 293 K), detail in the region of the protons N*H*.

Surprisingly, the NMR spectra of **1b** clearly indicated that this molecule, arising from a bulky nucleophile, can adopt all possible spatial arrangements (*s*-*s*, *s*-*a*, *a*-*a*) suggested by the manipulation of the Drieding models (**Scheme 5**, **Figure 1**). Moreover, as shown in **Figure 1**, in $CDCl_3$, another pair of doublets was revealed to indicate a fourth minor rotamer which was not assigned. It must be observed that, in all stereoisomers, the coupling pattern as ^{3}J between protons N*H* and H-5-eq. were more significant, in agreement with some hindrance to rotation about the axial *C*-5-*N*H bond (**Table 1**). A major dependence on the solvent was determined

related to the content of rotamers of **1b**: the statistically favoured (*s*-*a*) rotamer was dominant in polar and chelating solvent (DMSO-d_6) or only polar ($CDCl_3$). In contrast, the A.S.I.S. interactions required the rotamer (*s*-*s*) as prevailing.

2.3. *N*-substituted melamines with dioxane fragments: compounds **1c**, **2c**

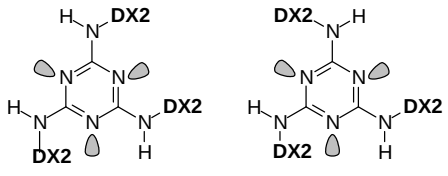
The "dimeric" melamine **1c** can exist as seven distinct rotamers (**Scheme 6**, the 1,3-dioxane and piperazine rings as references; the *syn* and *anti* descriptors are cited clockwise)[8]. At room temperature, the ^{1}H NMR 300 MHz spectra ($CDCl_3$ and DMSO-d_6) were complex and allowed only to identify the type of compound as the envisaged one. The ^{1}H DNMR (400 MHz, DMSO-d_6) recorded by increasing the temperature (ΔT=10 K) provided at 80 ^{o}C a single mediated structure with however some residual coalescence in the aromatic and C-6 methylene regions.



Scheme 6

The melamine **2c** can exist as two distinct rotamers: *asymmetric* and *propeller*[9] (**Scheme 7**) the first being statistically three times favoured.

Indeed, at room temperature, the ^{1}H NMR spectra (300 MHz, DMSO-d_6 and C_6D_6) were consistent with the statistics displaying four equal broad singlets of the best separated protons N*H*: 75 % *asymmetric* and 25 % *propeller*. All other signals were overlapped; however, they permitted, as in the case of **1c**, to confirm the type of structure as the desired one. It is noteworthy that the NMR spectra of compound **2c** performed at room temperature in $CDCl_3$ indicated a single mediated structure on both ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra with some residual coalescence involving the N*H*-CH_2 sequence. The ^{1}H DNMR (400 MHz, DMSO-d_6) experiment of **2c** exhibited progressive coalescence of the signals between 323-353 K and a single mediated rotamer at 353 K (**Figure 3**, labelling of the dioxane position as depicted in **Scheme 4**).



Scheme 7

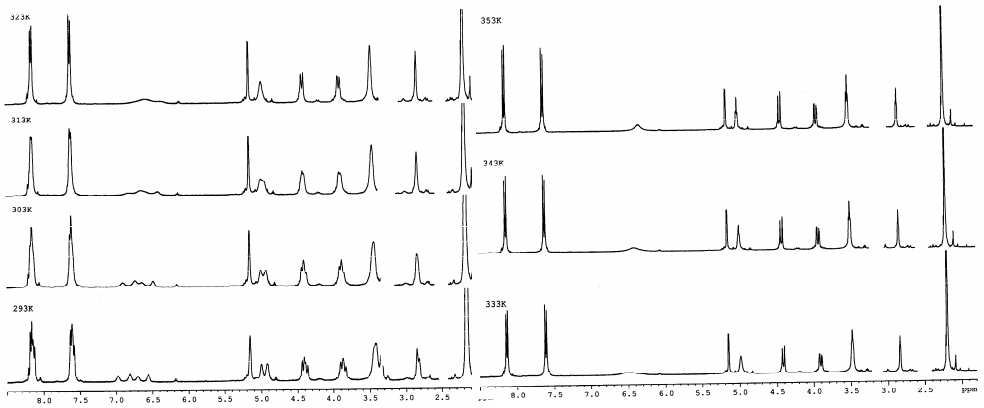


Figure 3: ^{1}H DNMR of the compound **2c** [400 MHz, DMSO-d_6, 353 K, from left to right, δ (ppm), ^{n}J (Hz)]: 8.13 (6 H, d, ^{3}J=8.8 Hz, H-Ar); 7.62 (6 H, d, ^{3}J=8.8 Hz, H-Ar); 6.32 (3 H, bs, N*H*); 5.15 (3 H, d, ^{3}J=3.6 Hz, H-4-ax.); 5.00 (3 H, dd as t, ^{3}J=4.6 Hz, H-2-ax.); 4.42 (3 H, d, ^{2}J=12.4 Hz, H-6-eq.); 3.92 (3 H, dd, ^{2}J=12.4 Hz, ^{3}J=3.2 Hz, H-6-ax.); 3.50 (6 H, dd as t, ^{3}J=5.2 Hz, CH_2-NH); 2.83 (3 H, dd as t, ^{3}J=2.6 Hz, H-5-eq.); 2.23 (18 H, s, CH_3).

3. Herbicidal evaluation

Compounds **1b** and **2b** were in addition tested as potential herbicides on seeds of *Cucumis sativus* and *Raphanus sativus*. Literature methods were straightforward[11]. The results, as mean (±SD) percentage values of germination inhibition and root length are collected in **Table 2**.

Table 2

Percent inhibitions of seeds germination and root length of *Cucumis sativus* and *Raphanus sativus* in response to different concentrations of the compounds **1b** and **2b** compared to control

Tested species	**Germination**		**Root Length**	
Conc.	**1b**	**2b**	**1b**	**2b**
Cucumis 0.50 mM	59 ± 4.8	60 ± 3.9	65 ± 5.4	67 ± 6.5
sativus 0.75 mM	87 ± 2.3	89 ± 2.5	88 ± 3.2	92 ± 3.8
1.00 mM	100 ± 0.0	100 ± 0.0	-	-
Raphanus 0.50 mM	64 ± 7.3	66 ± 5.3	70 ± 4.6	73 ± 6.7
sativus 0.75 mM	88 ± 3.5	90 ± 2.7	91 ± 3.9	93 ± 5.6
1.00 mM	100 ± 0.0	100 ± 0.0	-	-

Our introductory data evidenced an important inhibition in germination seeds of the tested species, even complete (c. 1mM). The root length was also significantly reduced. Although no reference compound was used along with the synthesised **1b**, **2b**, they already appeared active at 5×10^{-4} M in comparison with Atrazine® (>> 10^{-4} M), in the same conditions[11a].

CONCLUSIONS

As demonstrated by our preliminary findings, the amino-1,3-dioxanes built on some *p*-nitrophenyserinols skeleton react with cyanuryl chloride to yield amino-*s*-triazines in medium to good yields. The substitution of the second and third chlorine depends on the orientation of the amino group (C-5-axial or C-2-equatorial). At room temperature, all *N*-substituted-amino-*s*-triazines with a 1,3-dioxane group are distinct type of rotamers due to the partial double bond character of the C^{sp2}-N(serinol) site. The content of rotameric species is dependent on the orientation of this bond with respect to the 1,3-dioxane ring: axial or equatorial and the solvent. The herbicidal activity in this class of *s*-triazines was tested. The full report of our complete results is under consideration for the near future.

EXPERIMENTAL

General

Melting points were uncorrected; they were carried out on Electrothermal® instrument. Current NMR spectra were recorded on Brucker® AM 300 instrument operating at 300 and 75 MHz for ^{1}H and ^{13}C nuclei respectively. The ^{1}H DNMR spectra were run on Brucker® AM 400 instrument operating at 400 MHz for ^{1}H nuclei with each step 10 K increasing the temperature. No $SiMe_4$ was added; chemical shifts were measured against the solvent peak. All chemical shifts (δ values) are given throughout in ppm; all coupling patterns ($^{n}J_{H,H}$ values) are given throughout in Hz. TLC was performed by using aluminium sheets with silica gel 60 F_{254} (Merck®); flash column chromatography was conducted on Silica gel Si 60 (40–63 μm, Merck®). IR spectra were performed on a Perkin- Elmer® 16 PC FT-IR spectrometer. Only relevant absorptions are listed in cm^{-1}[weak (w), medium (m) or (s) strong]. Mass spectrum (MS) was recorded on an ATI-Unicam Automass® apparatus, fitted (or not) with a GC-mass coupling (high-resolution J&W column, 30 m, 0.25 mm ID, flow rate: 1.2 mL min^{-1}).

For the present preliminary communication, only the synthetic pathway **1a → 1b→1c** is listed below:

2,4-Dichloro-6-[(4*S*,5*S*)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]-amino-*s*-triazine (1a): (60 %) yellowish crystalline powder; m.p.=194-195 ^{o}C (Et_2O); [Found: C, 42.11; H, 2.77; N, 19.09. $C_{13}H_{11}N_5Cl_2O_4$ requires C, 41.96; H, 2.98; N, 18.82 %]; IR (ν_{max}, KBr) 3305 (s), 2875 (m), 1585 (s), 1556 (s), 1510 (s), 1410 (s), 1346 (s), 1325 (s), 1240 (m), 1183 (s), 1167 (s), 1103 (s), 1043 (m), 1028 (m), 964 (m), 842 (m), 798 (m), 713 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): 8.18 (2 H, d, ^{3}J=8.7 Hz, H-Ar), 7.51 (2 H, d, ^{3}J=8.7 Hz, H-Ar), 6.65 (1 H, d, ^{3}J=9.4 Hz, N*H*), 5.35 (1 H, d, ^{2}J=6.4 Hz, H-2eq.), 5.11 (1 H, s, H-4-ax.), 5.02 (1 H, d, ^{2}J=6.4 Hz, H-2-ax.), 4.56 (1 H, d, ^{3}J=9.8 Hz, H-5-eq.), 4.24 (1 H, d, ^{2}J=12.1 Hz, H-6-eq.), 4.14 (1 H, d, ^{2}J=11.3 Hz, H-6-ax.); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): 171.1 (1 C, C-Cl), 170.6 (1 C, C-Cl), 165.8 (1 C, C-N), 148.0 (1 C, Cq.-Ar), 144.4 (1 C, Cq.-Ar), 126.8 (2 C, CH-Ar), 124.0 (2 C, CH-Ar), 94.9 (1 C, C-2), 78.9 (1 C, C-4), 70.6 (1 C, C-6), 50.2 (1 C, C-5); MS (EI, 70 eV); m/z (rel. int. %): 371 (40) [M^{+}-1], 341 (25), 311 (100), 277 (18), 218 (39), 190 (25), 164 (27).

2-Chloro-4,6-bis[(4*S*,5*S*)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]-amino-s-triazine (1b): (90 %) yellow crystalline powder; m.p.=154-155 ^{o}C (flash column chromatography, eluent ligroine : acetone 1.5:1 v/v); [Found: C, 48.97; H, 4.14; N, 17.99. $C_{23}H_{22}N_7ClO_8$ requires C, 49.34; H, 3.96; N, 17.51 %]; IR (ν_{max}, KBr) 3404 (m), 3314 (m), 2859 (s), 1573 (s), 1518 (s), 1510 (s), 1346 (s), 1240 (m), 1174 (s), 1167 (s), 1094 (s), 1026 (s), 1028 (s), 987 (s), 851 (m), 805 (m), 711 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): 8.12-8.05 (12 H, m, H-Ar), 7.45-7.39 (12 H, m, H-Ar), 6.09 (2 H, d, ^{3}J=9.4 Hz, N$H_{s\text{-}s}$), 6.00 (2 H, d, ^{3}J=9.8 Hz, N$H_{a\text{-}a}$), 5.88 (1 H, d, ^{3}J=9.4 Hz, N$H_{s\text{-}a}$), 5.71 (1 H, d, ^{3}J=9.8 Hz, N$H_{s\text{-}a}$), 5.35-5.30 (3 H, m, H-2eq.), 5.25-5.20 (3 H, m, H-2eq.), 4.99-4.91 (12 H, m, H-2-ax., H-4-ax.), 4.41-3.88 (18 H, m, H-5-eq., H-6-eq., H-6-ax.); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): 169.5 (3 C, C-Cl), 165.8, 165.4, 165.3, 165.2 (6 C, C-N), 147.9, 147.7 (6 C, C-q.-Ar), 145.2, 145.0 (6 C, Cq.-Ar), 126.9, 126.73, 126.66 (12 C, CH-Ar), 123.80, 123.77, 123.73 (12 C, CH-Ar), 94.9, 94.8 (6 C, C-2), 79.33, 79.27, 79.21, 79.1 (6 C, C-4), 71.1, 70.8, 70.7, 70.5 (6 C, C-6), 49.6, 49.5, 49.3, 49.2 (6 C, C-5); MS (ESI, 35 eV); m/z (rel. int. %): 559 (100) [M^{+}], 541 (27), 529 (22), 511 (10).

1,4-Bis{4,6-bis[(4*S*,5*S*)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]-amino-s-triazine-2-yl}-piperazine (1c): (89 %) yellow crystalline powder; m.p.=224-225 ^{o}C (flash column chromatography, eluent ligroine : acetone 1.25:1 v/v); [Found: C, 53.37; H, 5.02; N, 19.69. $C_{50}H_{52}N_{16}O_{16}$ requires C, 53.00; H, 4.63; N, 19.78 %]; IR (ν_{max}, KBr) 3414 (m), 2855 (m), 1576 (s), 1548 (s), 1520 (s), 1442 (s), 1346 (s), 1244 (w), 1173 (s), 1095 (m), 1027 (m), 985 (m), 852 (w), 810 (m), 742 (w), 711 (w) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, 353 K): 8.06 (8 H, bs, H-Ar), 7.59 (8 H, d, ^{3}J=7.6 Hz, H-Ar), 5.58 (4 H, d, ^{3}J=7.6 Hz, N*H*), 5.22 (4 H, d, ^{2}J=6.0 Hz, H-2eq.), 5.20 (4 H, s, H-4-ax.), 4.99 (4 H, d, ^{2}J=6.0 Hz, H-2-ax.), 4.37 (4 H, d, ^{3}J=7.6 Hz, H-5-eq.), 4.10 (4 H, d, ^{2}J=10.4 Hz, H-6-eq.), 3.94 (4 H, bs, H-6-ax.), 3.36 (8 H, s, CH_2 piperazine); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): 165.7 (4 C, C-N), 165.5 (2 C, C-N), 147.6 (4 C, Cq.-Ar), 146.0 (4 C, Cq.-Ar), 127.0 (8 C, CH-Ar), 123.4 (8 C, CH-Ar), 94.7 (4 C, C-2), 79.8 (4 C, C-4), 71.4 (4 C, C-6), 49.0 (4 C, C-5), 42.8 (4 C, CH_2-piperazine); MS (FAB^{+}); m/z (rel. int. %): 1132 (95) [M^{+}-1], 952 (20), 663 (33), 551 (33), 459 (100).

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