Selective Amination of Cyanuric Chloride in the Presence of 18-Crown-6

Simona Samaritani,[a] Paola Peluso,[b] Corrado Malanga,[a] and Rita Menicagli*[a]

Keywords: Amination / Heterocycles / Nucleophilic substitution / Phase-transfer catalysis

An interpretation of the role of 18-crown-6 in the selective di- and trialkylamination of 2,4,6-trichloro-1,3,5-triazine is reported, and the usefulness of the procedure is shown.

Introduction

In the context of our interest in new chiral molecules potentially useful both in enantiodiscriminating processes and in the biological and pharmacological fields, we considered the use of the 1,3,5-triazine system, owing to the peculiar reactivity of the commercially available 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride, **1**) towards nucleophiles.[1] With this as a goal, several chiral and achiral 1,3,5-triazine derivatives (Schemes 1 and 2) were prepared[2] by the same experimental methodology as used for selective alkoxylation of **1**,[3] and their biostatic activity was investigated.[2b,4] In this paper the high selectivity observed in the alkylamination of **1** and the presence of 18-crown-6 are for the first time related and interpreted.

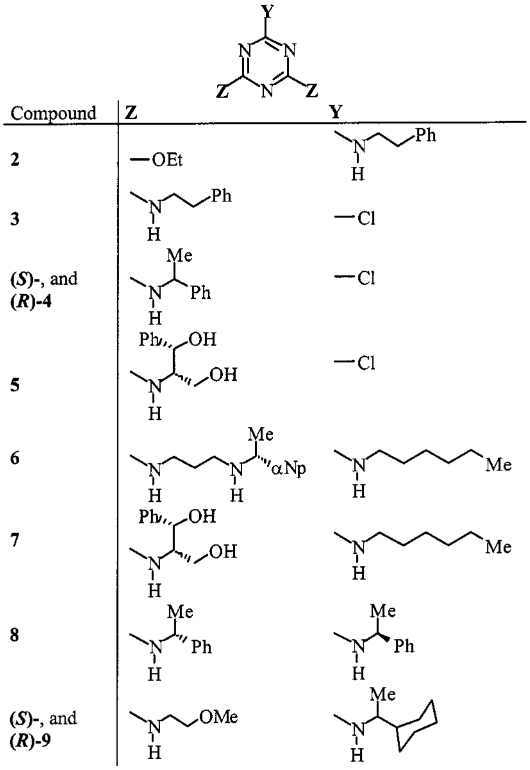
Results and Discussion

The reactivity of **1** with O-,[1b,5a,6] N-[1b,5a] and S-nucleophiles[1b,5a] has been widely studied, and when we started dealing with 1,3,5-triazine derivatives bearing different substituents the following points were well known:

i. selective synthesis of mono-, di- and trialkylamino derivatives of **1** could generally be achieved by following Moffat's rule;[5b]

ii. 2,4,6-trialkoxy-1,3,5-triazines could conveniently be prepared by reported procedures;[1b,5a,6]

iii. the preparation of alkoxyalkylamino-1,3,5-triazines could be carried out only if the correct order of addition of nucleophiles was observed (O-nucleophile followed by N-nucleophiles),[1b,5a] although some problems could arise in the degree of alkoxylation.

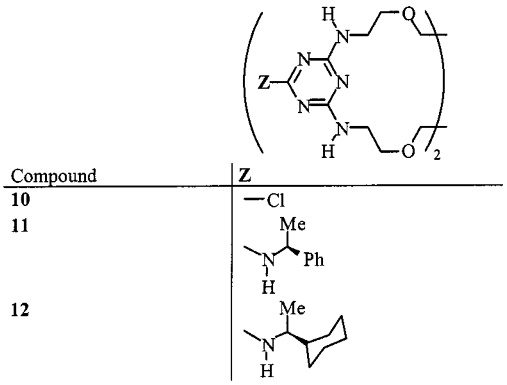


Scheme 1

As a matter of fact, no general procedures for near-quantitative mono- or dialkoxylation of **1** were available; this problem was solved by adoption of phase-transfer catalytic (PTC) reaction conditions.[3] The nearly quantitative derivatization achieved by this procedure allowed us to prepare unsymmetrically trisubstituted derivatives by a one-pot technique, without isolation or purification of the reaction intermediates:[2a,3a] the preparation of 2,4-diethoxy-6-[(2-phenylethyl)amino]-1,3,5-triazine (**2**) was carried out in 92% overall yield by addition of 2-phenylethylamine to the reaction mixture produced by treatment of **1** with 2 mol-equiv. of dry ethanol under PTC reaction conditions.[3a]

---

[a] 'Dipartimento di Chimica e Chimica Industriale dell'Università degli Studi di Pisa and Centro di Studi del CNR per le Macromolecole Stereordinate ed Otticamente Attive,
Via Risorgimento 35, 56126 Pisa, Italy
Fax: (internat.) + 39-050/918260
E-mail: rime@dcci.unipi.it
[b] Dipartimento di Chimica dell'Università Ca' Foscari,
Calle Larga S. Marta 2137, 30123 Venezia, Italy



Scheme 2

The same one-pot approach was successively used for the synthesis of 2-ethoxy-4-hexylamino-6-[(*S*)-1-(1-naphthylethyl)amino]-1,3,5-triazine:[2a] 2,4-dichloro-6-ethoxy-1,3,5-triazine, prepared under PTC reaction conditions, was sequentially treated with 1 mol-equiv. of (*S*)-2-(naphth-1-yl)ethylamine, followed by 1 mol-equiv. of hexylamine.[2a]

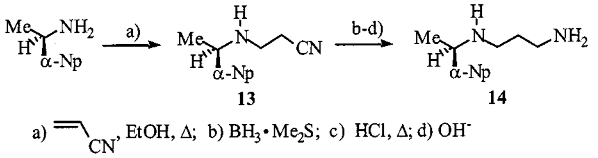
The good yield and complete selectivity of the reaction,[2a] which prompted other authors to use the same synthetic procedure,[7] could not be justified only in terms of the electronic deactivating effect of the ethoxy substituent of 2,4-dichloro-6-ethoxy-1,3,5-triazine towards the further nucleophilic substitution. On the other hand, although the amination of **1** under basic reaction conditions (molar excess of N-nucleophile[5c] or the presence of tertiary amines in organic solvents[5d] or K_2CO_3 in acetone/H_2O mixtures[5e–5l]) is well known, the quantitative amination obtained under our reaction conditions (**1**/N-nucleophile, 1:1 molar ratio, K_2CO_3/toluene) could not be justified without taking an effect of the phase-transfer catalyst into account.

Although 18-crown-6 has been known to complex primary amine groups,[8] the observed selectivity should, in our opinion, arise only in the presence of an almost stoichiometric amount of the crown ether. In order to remove doubt in this respect, **1** was treated under comparable reaction conditions (toluene and 1 mol-equiv. of K_2CO_3) with 2-phenylethylamine (1 mol-equiv.) both in the presence and in the absence of a catalytic amount of 18-crown-6, and the reactions were monitored by GLC and GC-MS (absolute evaluation of the concentrations of the reaction products was carried out with a gas chromatograph equipped with an Atomic Emission Detector, AED, see Exp. Sect.).

After comparable reaction times, while only a slight but appreciable difference in the degree of conversion of **1** into 2,4-dichloro-6-[(2-phenylethyl)amino]-1,3,5-triazine (70 and 90% in the absence and in the presence of 18-crown-6, respectively) was evident after the addition of the first mol-equiv. of the nucleophile, the addition of a further mol-equiv. of the amine resulted in the complete conversion of 2,4-dichloro-6-[(2-phenylethyl)amino]-1,3,5-triazine into 2-chloro-4,6-bis[(2-phenylethyl)amino]-1,3,5-triazine (**3**) only in the mixture containing 18-crown-6. Indeed, only a 2.5% conversion of the intermediate into **3** was observed in the absence of the catalyst, thus showing a key role for 18-crown-6 in the amination process.

With these bases, optically active disubstituted products (*S*)- and (*R*)-**4**, as well as **5** (see Scheme 1; no traces of by-products arising from *O*-substitution were found) were synthesized in high yields (80–86%).

The procedure reported here proved much more convenient in the one-pot preparation of unsymmetrically trialkylamino-substituted compounds **6–9** (Scheme 1); the diamine **14**, precursor of **6**, was prepared according to the reaction sequence depicted in Scheme 3.[9,10] Compounds **6–9** were synthesized and recovered in satisfactory yields (65–92%) by sequential addition of 2 mol-equiv. of the first nucleophile (ZH) and 1 mol-equiv. of the second amine (YH) to **1** dissolved in a suitable solvent. (No by-product arising from nucleophilic substitution by the secondary amino group of **14** was detected along with **6**.)



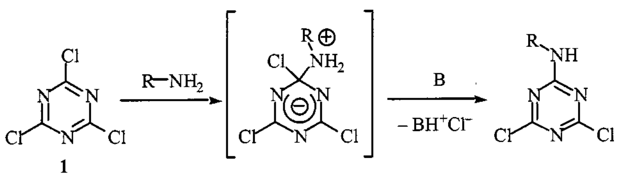
Scheme 3

PTC reaction conditions were eventually used for the successful amination of the previously reported[11] triazine macrocyclic derivative **10** (Scheme 2). In this case the use of high-boiling dimethylacetamide (DMA) was necessary in order to solubilise **10**. The prepared macrocyclic derivative **12** proved very active against some common pathogenic fungi affecting paper.[4b,4c]

Conclusion

The reported data clearly show overall that catalytic 18-crown-6, already successfully used for the selective mono- and dialkoxylation of cyanuric chloride,[3] can also conveniently be employed for the selective amination of the same substrate in the presence of K_2CO_3.

Nucleophilic substitution of the chlorine atoms in cyanuric chloride by amines is a well-known[1b] base-catalysed process (Scheme 4) in which, in the absence of an additional proton scavenger, the formal removal of HCl is carried out by the same amine as used as nucleophile (B = RNH_2): in this case, 2 equiv. of amine is necessary to obtain complete substitution of each chlorine atom in cyanuric chloride.



Scheme 4

By our evidence, only 1 equiv. of amine is sufficient to carry out the same transformation in the presence of a catalytic amount of 18-crown-6 and a stoichiometric amount of K_2CO_3. These findings can be explained by assuming that, under our experimental conditions, i) the K_2CO_3/18-crown-6 system directly carries out the base-catalysed process, preventing the nucleophile from being protonated or ii) the nucleophile works as B (see Scheme 4) and the K_2CO_3/18-crown-6 system regenerates the amine from its hydrochloride, thus allowing the completion of the nucleophilic substitution.

Since only the strictly necessary amount of amine is used under the described PTC reaction conditions, this procedure is particularly convenient for the preparation of symmetrically di- and trisubstituted optically active alkylamino-1,3,5-triazines without loss of expensive materials, as well as for the preparation of asymmetrically di- and trisubstituted alkylamino-1,3,5-triazines by a time-saving one-pot procedure.

Experimental Section

General Remarks: Solvents were purified and dried by standard methods.[12] 2,4,6-Trichloro-1,3,5-triazine (cyanuric chloride, **1**) was purified according to reported procedures[12] and stored under nitrogen. All the amines employed were distilled under nitrogen before use. GLC analyses were performed with a Perkin−Elmer 8500 instrument (both a DB1, 12 m, diameter 0.22 mm or a 25 m, diameter 0.22 mm capillary column was used) equipped with a flame ionization detector and a split-splitless or a PTV injector, with He as carrier gas. GLC analyses for compound **3** were performed with a Hewlett-Packard 6890 instrument (a DB1, 12 m, diameter 0.22 mm capillary column was used) equipped with a selective Hewlett−Packard G2350A Atomic Emission Detector (AED), with He as carrier gas. Analytical HPLC was performed with a Perkin−Elmer series 410 HPLC, equipped with a Perkin−Elmer 785A Programmable Absorbance Detector. TLC analyses were performed on silica gel 60 plates (Fluka) and flash-chromatographic purifications were carried out on silica gel 60 (Fluka, 230−400 mesh) with the solvent eluting mixtures reported for each case. Melting points were determined with a Kofler hot-stage apparatus and are not corrected. Optical rotatory powers were measured with a Perkin−Elmer 142 polarimeter equipped with a temperature control device (±0.1 °C). ^1H and ^{13}C NMR (200 and 50 MHz, respectively) spectra were recorded with a Varian Gemini 200 spectrometer; all NMR-spectroscopic data were obtained in $CDCl_3$ solution if not otherwise stated. Chemical shifts (δ values) are referred to tetramethylsilane (TMS) (^1H NMR) or $CDCl_3$ (^{13}C NMR) as internal standard. Mass spectra [*m*/*z* (%)] were taken with a Perkin−Elmer Q-Mass 910 instrument; IS mass spectra ($[M + 1]^+$) were acquired with a Perkin−Elmer Sciex API III mass spectrometer (Sciex Co., Thornhill, Ontario, Canada); samples were dissolved in methanol and infused into the API source with a Harvard 22 syringe pump; the spectra were acquired in MCA mode by summation of 10 scans. Infrared spectra {$\tilde{\nu}$ [cm^{-1}]} were recorded with a Perkin−Elmer Spectrum GX FT-IR spectrophotometer.

3-{[(1*R*)-1-(Naphth-1-yl)ethyl]amino}propanenitrile (13): According to a reported procedure,[9] an ethanolic solution of (1*R*)-[1-(naphth-1′-yl)ethyl]amine (Aldrich) $[\alpha]_{546}^{20}$ = +65 (*c* = 2.0, EtOH) was heated under reflux (48 h) with dry acrylonitrile (amine/acrylonitrile, 1:1.3 molar ratio). Flash chromatography (ethyl acetate/hexane, 60:40, v/v) of the crude material afforded (2.75 g, 98%) chemically pure **13** as a colourless oil: $[\alpha]_D^{25}$ = +83.90 (*c* = 0.99, $CHCl_3$). MS: *m*/*z* = 225 $[M + 1]^+$. ^1H NMR: δ = 1.50 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$), 1.63 (br. s, 1 H, N*H*), 2.51−2.41 (m, 2 H, CH_2CN), 2.96−2.75 (m, 2 H, CH_2NH), 4.68 (q, *J* = 6.6 Hz, 1 H, CH_3CH), 8.23−7.44 (m, 7 H, Np). ^{13}C NMR: δ = 19.1, 23.8, 43.0, 53.3, 118.8, 122.7, 122.8, 125.4, 125.7, 125.9, 127.5, 129.0, 131.2, 134.0, 140.1. IR (neat): $\tilde{\nu}$ = 3326, 3050, 2967, 2926, 2863, 2247, 1948, 1815, 1596, 1510, 1444, 1418, 1395, 1370, 1258, 1175, 1124, 1007, 863, 802, 780, 739 cm^{-1}. $C_{15}H_{16}N_2$ (224): calcd. C 80.32, H 7.19, N 12.49; found C 80.49, H 7.15, N 12.36.

(3-Aminopropyl)[(1*R*)-1-(naphth-1-yl)ethyl]amine (14): By a reported procedure,[10] a THF solution of **13** was treated with a 10 M THF solution of $BH_3·SMe_2$ (2.5 mol-equiv.). When the maximum conversion (TLC) was achieved, the reported[10] workup afforded 1.84 g (95%) of chemically pure diamine **14** as a colourless oil: $[\alpha]_D^{25}$ = +20.1 (*c* = 1.65, $CHCl_3$). MS: *m*/*z* (%) = 228 (5) $[M^{+\cdot}]$, 170 (60), 155 (87), 141 (68), 127 (25), 115 (13), 73 (40), 44 (100). ^1H NMR: δ = 1.50 (d, *J* = 6.8 Hz, 3 H, $CHCH_3$), 1.95−1.61 (m, 2 H, $CH_2CH_2CH_2$), 1.96 (br. s, 1 H, CHN*H*), 2.72−2.56 (m, 2 H, CH_2NH_2), 2.76 (t, *J* = 6.9 Hz, 2 H, CH_2NH_2), 3.70−3.52 (m, 2 H, CH_2NH), 4.63 (q, *J* = 6.8 Hz, 1 H, CH_3CH), 8.22−7.44 (m, 7 H, Np). ^{13}C NMR: δ = 23.4, 31.4, 40.2, 45.9, 53.6, 122.5, 122.7, 125.3, 125.6, 125.8, 127.2, 128.8, 131.1, 133.8, 140.5. IR (neat): $\tilde{\nu}$ = 3354, 3047, 2933, 2865, 1596, 1511, 1470, 1447, 1395, 1372, 1327, 1260, 1169, 1125, 1058, 862, 802, 780 cm^{-1}. $C_{15}H_{20}N_2$ (228): calcd. C 78.90, H 8.83, N 12.27; found C 78.99, H 8.78, N 12.23.

General Procedure for the Synthesis of 4,6-Bis(alkylamino)-2-chloro-1,3,5-triazines 3−5: A mixture of **1**, K_2CO_3 and 18-crown-6 (**1**/K_2CO_3/18-crown-6, 1:2:0.02 molar ratio) in a suitable reaction solvent was treated with a solution of the amine (**1**/amine, 1:2 molar ratio) in the same solvent and at the specified temperature. The mixture was stirred until maximum conversion (TLC, GLC and/or GC-MS) was achieved and then filtered through a short pad of Celite. Removal of solvents at reduced pressure and purification of the crude products by flash chromatography afforded the chemically pure compounds. In each case, the reagent, the solvent, the temperature, the time, the conditions used for the flash chromatography, the amount (g) and the yield are reported in parentheses, followed by the chemical and physical properties and the spectroscopic data:

2-Chloro-4,6-bis[(2-phenylethyl)amino]-1,3,5-triazine (3): {2-phenylethylamine, toluene, 0−25 °C, 48 h, 2.10 g, 70%, pale yellow, viscous liquid}. MS: *m*/*z* (%) = 353 (86) $[M^{+\cdot}]$, 262 (39), 207 (47), 170 (4), 158 (10), 105 (100), 91 (43), 77 (10). ^1H NMR: δ = 2.28 (m, 2 H, $NHCH_2CH_2$), 2.95 (br. s, 1 H, N*H*CH_2CH_2), 3.61 (m, 2 H, $NHCH_2$), 7.25−7.05 (m, 5 H, Ph). ^{13}C NMR: δ = 21.2, 40.1 (broad), 125.6, 128.1, 128.9, 141.4, 163.8 (2 C). IR (neat): $\tilde{\nu}$ = 3423, 3452, 3099, 3027, 2964, 1642, 1556, 1453, 1412, 1301, 1133, 988, 805, 695 cm^{-1}. $C_{19}H_{20}ClN_5$ (353): calcd. C 64.49, H 5.70, Cl 10.02, N 19.79; found C 64.57, H 5.72, Cl 9.98, N 19.73.

2-Chloro-4,6-bis{[(1*S*)-1-phenylethyl]amino}-1,3,5-triazine (*S*-4): {[(1*S*)-1-phenylethyl]amine, $[\alpha]_D^{25}$ = −37.8 (neat), optical purity 99%,[13] toluene, 0−25 °C, 24 h, dichloromethane/ethyl acetate, 90:10, v/v, 3.47 g, 96%, white, glassy solid}. $[\alpha]_D^{25}$ = −222.2 (*c* = 0.92, $CHCl_3$). MS: *m*/*z* (%) = 353 (44) $[M^{+\cdot}]$, 354 (15), 355 (12), 338 (17), 248 (17), 234 (51), 120 (100), 105 (75), 77 (39). ^1H NMR: δ = 1.35−1.52 (m, 3 H, $CHCH_3$), 4.90, 5.12, 5.25 (3 dq, *J* = *J′* = 7.5 Hz, 1 H, C*H*CH_3), 5.50, 5.65, 5.72 (3d, *J* = 7.5 Hz, 1 H, N*H*CH), 7.3 (m, 5 H, Ph). ^{13}C NMR: δ = 22.3, 50.0 (broad), 125.9, 127.3, 128.6, 143.4, 164.9 (2 C). IR (neat): $\tilde{\nu}$ = 3400, 3251, 3105, 3028, 1946, 1871, 1803, 1603, 1572, 1533, 1404, 1304, 1135, 986, 807, 698 cm^{-1}. $C_{19}H_{20}ClN_5$ (353): calcd. C 64.49, H 5.70, Cl 10.02, N 19.79; found C 64.36, H 5.62, Cl 10.21, N 19.81.

2-Chloro-4,6-bis{[(1*R*)-1-phenylethyl]amino}-1,3,5-triazine (*R*-4): {[(1*R*)-1-phenylethyl]amine, $[\alpha]_D^{25}$ = +35.9 (neat), optical purity 94%,[13] toluene, 0−25 °C, 24 h, dichloromethane/ethyl acetate, 90:10, v/v, 2.85 g, 80%, white, glassy solid}. $[\alpha]_D^{25}$ = +200.8 (*c* = 0.82, $CHCl_3$). ^1H, ^{13}C NMR and IR spectra were in good agreement with those of ***S*-4**. $C_{19}H_{20}ClN_5$ (353): calcd. C 64.49, H 5.70, Cl 10.02, N 19.79; found C 64.41, H 5.57, Cl 10.20 N 19.82.

2-Chloro-4,6-bis{[(2*S*,3*S*)-1,3-dihydroxy-3-phenylprop-2-yl]amino}-1,3,5-triazine (5): {(1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol, $[\alpha]_D^{25}$ = +26.6 (*c* = 10.0, MeOH),[14] toluene, 0−25 °C, 48 h, acetone/hexane, 70:30, v/v, 4.01 g, 86%, white solid}. M.p. 77 °C. $[\alpha]_D^{25}$ = +18.2 (*c* = 1.0, acetone). MS: *m*/*z* (%) = 446 (100) [M$^+$ + 1], 412 (71), 369 (12). ^1H NMR ([D$_6$]acetone): δ = 3.84−3.52 (m, 4 H, CH*H*OH, C*H*NH), 4.35−4.06 (m, 4 H, N*H*, C*H*HOH), 4.88−4.71 (m, 2 H, CH_2OH), 5.18−5.06 (m, 2 H, ArC*H*), 6.35−6.10 (m, 2 H, ArCHO*H*), 7.52−7.11 (m, 10 H, Ar). ^{13}C NMR ([D$_6$]acetone): δ = 58.8, 62.5, 72.6, 127.1, 127.9, 128.8, 143.8, 167.0 (2 C). IR (KBr): $\tilde{\nu}$ = 3370, 2933, 2882, 1583, 1529, 1415, 1305, 1128, 1040, 985, 803, 701 cm^{-1}. $C_{21}H_{24}ClN_5O_4$ (445): calcd. C 56.57, H 5.43, Cl 7.95, N 15.71; found C 56.48, H 5.60, Cl 8.02, N 15.93.

General Procedure for the Synthesis of Unsymmetrically 2,4,6-Trisubstituted 1,3,5-Triazines 6−9: A mixture of **1**, K_2CO_3 and 18-crown-6 (**1**/K_2CO_3/18-crown-6, 1:3/0.03 molar ratio) in acetonitrile or toluene was treated with a solution of XH (**1**/XH, 1:2 molar ratio) at 25 °C. When complete conversion of **1** was achieved (TLC), a solution of YH in the same solvent was added (**1**/YH, 1:1 molar ratio) and the mixture was heated under reflux until complete conversion of the intermediate (TLC). The usual workup and purification of the crude products by flash chromatography afforded pure compounds. In each case, the reagents XH and YH, the flash chromatography conditions, the amount (g) and the yield are listed in parentheses, followed by the chemical and physical properties and the spectroscopic data.

2,4-Diethoxy-6-[(2-phenylethyl)amino]-1,3,5-triazine (2): {XH = ethanol, YH = (2-phenylethyl)amine, 2.24 g, 92%, white solid}. M.p. 51 °C. MS: *m*/*z* (%) = 288 (55) [M$^{+\cdot}$], 197 (100), 169 (22), 141 (45), 91 (17), 70 (11), 55 (20). ^1H NMR: δ = 1.47−1.32 (m, 6 H, CH_3CH_2O), 2.90 (t, *J* = 7.0 Hz, 2 H, $ArCH_2CH_2$), 3.80−3.66 (m, 2 H, CH_2CH_2NH), 4.55−4.29 (m, 4 H, CH_2O), 5.78 (bt, 1 H, CH_2NH), 7.40−7.10 (m, 5 H, Ar). ^{13}C NMR: δ = 14.1, 14.2, 35.5, 42.0, 63.1, 63.4, 126.6, 128.7, 128.9, 138.9, 167.0, 170.4. IR (KBr): $\tilde{\nu}$ = 3258, 3147, 2985, 2940, 1625, 1573, 1441, 1423, 1382, 1341, 1140, 1103, 1061, 1038, 1019, 813, 748, 697 cm^{-1}. $C_{15}H_{20}N_4O_2$ (288): calcd. C 62.48, H 6.99, N 19.43; found C 62.61, H 6.88, N 19.58.

(*R*)-6-Hexylamino-2,4-bis(3-{[1-(naphth-1-yl)ethyl]amino}propylamino)-1,3,5-triazine (6): {XH = **14**, YH = hexylamine, hexane/2-propanol/25% ammonia, 50:50:3, v/v/v, 0.50, 30%, pale yellow, glassy solid}. $[\alpha]_D^{25}$ = +79.41 (*c* = 0.89, $CHCl_3$). MS: *m*/*z* = 633 [M + 1]$^+$. ^1H NMR: δ = 0.88 (t, 3 H, CH_2CH_3), 1.25 (m, 2 H, CH_2CH_3), 1.45 (2 d, 6 H, $CHCH_3$), 1.85−1.55 (m, 6 H), 2.72−2.45 (m, 10 H), 3.70−3.21 (m, 8 H), 4.65−4.45 (m, 2 H, C*H*), 5.12 (br. s, 1 H, CH_2NH), 8.21−7.25 (m, 14 H, Np). ^{13}C NMR: δ = 14.0, 22.5, 23.5, 26.5, 29.7, 30.2, 31.5, 38.7, 40.6, 45.3, 48.8, 53.6, 122.6, 122.8, 125.2, 125.6 (2 C), 127.0, 128.9, 131.2, 133.9, 141.2, 166.0 (2C). IR (KBr): $\tilde{\nu}$ = 3272, 3048, 2927, 2856, 1512, 1357, 1173, 1127, 801, 778 cm^{-1}. $C_{39}H_{52}N_8$ (632): calcd. C 74.01, H 8.28, N 17.71; found C 74.22, H 8.15, N 17.63.

6-Hexylamino-2,4-bis{(1*S*)-2-hydroxy-1-[(*S*)-(hydroxy)(phenyl)-methyl]ethyl}amino-1,3,5-triazine (7): {XH = (1*S*,2*S*)-1-phenyl-2-amino-1,3-propanediol, $[\alpha]_D^{25}$ = +26.6 (*c* = 10.0, MeOH),[14] YH = hexylamine, acetone/hexane, 70:30, v/v, 1.60 g, 70%, pale yellow, glassy solid}. $[\alpha]_D^{25}$ = +88.9 (*c* = 1.25, $CHCl_3$). MS: *m*/*z* = 511 [M + 1]$^+$. ^1H NMR: δ = 0.85 (t, 3 H, CH_2-CH_3), 1.50−1.00 (m, 6 H, $3CH_2$), 3.72−2.60 (2 m, 9 H, N*H*, $NHCH_2$, $NHCH_2CH_2$, NHC*H*CH_2OH), 4.25−3.91 (m, 2 H, CH*H*OH), 5.90−4.25 (m, 2 H, C*H*HOH), 6.75−6.00 (m, 4 H, PhCHO*H*, CH_2OH), 7.45−7.00 (m, 10 H, Ph). ^{13}C NMR: δ = 13.9, 22.5, 26.6, 29.4, 31.4, 40.8, 58.2, 62.6, 74.6 (broad), 126.4, 127.5, 128.2, 141.7, 164.7, 165.6. IR (KBr): $\tilde{\nu}$ = 3376, 2928, 2857, 1953, 1562, 1510, 1351, 1169, 1027, 810, 699 cm^{-1}. $C_{27}H_{38}N_6O_4$ (510): calcd. C 63.51, H 7.50, N 16.46; found C 63.67, H 7.53, N 16.44.

2,6-Bis{[(1*R*)-1-phenylethyl]amino}-4-{[(1*S*)-1-phenylethyl]amino}-1,3,5-triazine (8): {XH = [(1*R*)-1-phenylethyl]amine, $[\alpha]_D^{25}$ = +35.9 (neat), optical purity 94%,[13] YH = [(1*S*)-1-phenylethyl]amine, $[\alpha]_D^{25}$ = −37.8 (neat), optical purity 99%,[13] hexane/ethyl acetate, 70:30 v/v, 2.32 g, 80%, pale yellow, glassy solid}. $[\alpha]_D^{25}$ = +62.8 (*c* = 0.88, $CHCl_3$). MS: *m*/*z* (%) = 438 (41) [M$^{+\cdot}$], 423 (11), 318 (6), 214 (36), 120 (69), 105 (100). ^1H NMR (60 °C): δ = 1.48, 1.44 (2 d, *J* = 6.9, *J*′ = 7.2 Hz, 3 H, $CHCH_3$), 5.12, 5.11, 5.03 (2 qd, *J* = 6.9, *J*′ = 7.2 Hz, and m, 2 H, NHC*H*, CHN*H*), 7.31−7.19 (m, 5 H, Ph). ^{13}C NMR: δ = 22.6, 49.9 (broad), 126.0, 126.4, 126.8, 144.7, 165.4. IR (KBr): $\tilde{\nu}$ = 3413, 3257, 3061, 3028, 2969, 2927, 1562, 1493, 1423, 1214, 1161, 812, 698 cm^{-1}. $C_{27}H_{30}N_6$ (438): calcd. C 73.94, H 6.89, N 19.16; found C 73.83, H 6.92, N 19.25.

6-{[(1*S*)-1-Cyclohexylethyl]amino}-2,4-bis[(2-methoxyethyl)amino]-1,3,5-triazine (*S*-9): {XH = (2-methoxyethyl)amine, YH = [(1*S*)-1-cyclohexylethyl]amine, $[\alpha]_{546}^{20}$ = +4.7 (Fluka; neat), ethyl acetate/methanol, 90:10 v/v, 1.01 g, 80%, viscous liquid}. $[\alpha]_{365}^{25}$ = +11.2 (*c* = 0.59, $CHCl_3$). MS: *m*/*z* (%) = 352 (2) [M$^{+\cdot}$], 337 (2), 307 (6), 294 (4), 269 (100), 207 (15), 179 (11), 165 (12), 127 (7), 111 (12), 59 (22). ^1H NMR ([D$_6$]DMSO, 100 °C): δ = 1.70−1.48, 1.50−0.85 (2 m and d, 14 H, $CHCH_3$, cyclohexyl), 3.31 (s, 6 H, OCH_3), 3.50−3.36 (m, 8 H, CH_2CH_2), 3.95−3.75 (m, 1 H, CH_3CH), 5.8 (br. d, N*H*CH), 6.0 (br. s, 2 H, $NHCH_2$). ^{13}C NMR: δ = 17.2, 25.3, 25.4, 25.7, 28.4, 28.7, 39.2, 42.4, 49.1, 57.3, 70.6, 165.2, 165.6. IR (neat): $\tilde{\nu}$ = 3267, 2926, 2853, 1624, 1514, 1449, 1384, 1348, 1197, 1118, 1016, 971, 812, 785 cm^{-1}. $C_{17}H_{32}N_6O_2$ (352): calcd. C 57.93, H 9.15, N 23.84; found C 58.00, H 9.18, N 23.80.

6-{[(1*R*)-1-Cyclohexylethyl]amino}-2,4-bis[(2-methoxyethyl)amino]-1,3,5-triazine (*R*-9): {XH = (2-methoxyethyl)amine, YH = [(1*R*)-1-cyclohexylethyl]amine, $[\alpha]_{546}^{20}$ = −4.7 (Fluka; neat), ethyl acetate/methanol, 90:10 v/v, 0.93 g, 90%, viscous liquid}. $[\alpha]_{365}^{25}$ = −11.4 (*c* = 0.49, $CHCl_3$). ^1H, ^{13}C NMR and IR spectra were in good agreement with those of ***S*-9**. $C_{17}H_{32}N_6O_2$ (352): calcd. C 57.93, H 9.15, N 23.84; found C 58.05, H 9.08, N 23.72.

General Procedure for the Synthesis of Macrocyclic 1,3,5-Triazine Derivatives: A mixture of 14,29-dichloro-5,8,20,23-tetraoxa-2,11,13,15,17,26,28,30,31,32-decaazatricyclo[25.3.1.1^{12,16}]dotriaconta-1(31),12,14,16(32),27,29-hexaene (**10**),[11] anhydrous K_2CO_3, 18-crown-6 (**10**/K_2CO_3/18-crown-6, 1:2:0.02 molar ratio) and 25 mL of *N*,*N*-dimethylacetamide (DMA) was treated with a solution of the appropriate amine (**10**/amine, 1:2 molar ratio) in the same solvent and heated under reflux until the complete conversion of the precursor was achieved (HPLC, C_{18} Bondclone, MeOH/H_2O/CH_3COOH, 7:4:1, v/v/v). After the mixture had been filtered through a short pad of Celite (eluent $CHCl_3$), the solvent was removed at reduced pressure. The residue was dissolved in the minimum quantity of $CHCl_3$, and hexane was added to effect the precipitation of the product, which was filtered, washed with small portions of cold hexane and finally dried. For each of the isolated, chemically pure compounds, the amine used, the column and eluting mixture for the HPLC analysis, the amount (g), the yield, the chemical and physical data and the spectroscopic characterisation are reported (see below).

14,29-Bis{[(1*S*)-1-phenylethyl]amino}-5,8,20,23-tetraoxa-2,11,13,15,17,26,28,30,31,32-decaazatricyclo[25.3.1.1^{12,16}]-dotriaconta-1(31),12,14,16(32),27,29-hexaene (11): {[(1*S*)-1-phenylethyl]amine, $[\alpha]_D^{25} = -37.8$ (neat), optical purity 99%,[13] C_{18} Bondclone column, $MeOH/H_2O$/acetic acid, 7:4:1, v/v/v, 0.75 g, 60%, pale yellow, glassy solid}. $[\alpha]_D^{25} = -13.75$ ($c = 0.88$, $CHCl_3$). MS: m/z = 689 $[M + 1]^+$, 711 $[M + 23]^+$. ^{13}C NMR (C_6D_6, 75 °C): δ = 22.6, 41.4, 50.4, 71.2, 71.3, 126.2, 126.6, 127.3, 134.0, 166.1, 166.7. IR (KBr): $\tilde{\nu}$ = 3332, 3264, 3112, 3029, 2928, 2865, 1619, 1571, 1530, 1501, 1443, 1344, 1144, 1108, 1025, 812, 701 cm^{-1}. $C_{34}H_{48}N_{12}O_4$ (688): calcd. C 59.28, H 7.02, N 24.40; found C 59.43, H 7.05, N 24.28.

14,29-Bis{[(1*S*)-1-cyclohexylethyl]amino}-5,8,20,23-tetraoxa-2,11,13,15,17,26,28,30,31,32-decaazatricyclo[25.3.1.1^{12,16}]-dotriaconta-1(31),12,14,16(32),27,29-hexaene (12): {[(1*S*)-1-cyclohexylethyl]amine, $[\alpha]_{546}^{20} = +4.7$ (Fluka; neat), C_{18} Bondclone column, $MeOH/H_2O$/acetic acid, 7:4/1, v/v/v, 0.83 g, 60%, pale yellow, glassy solid}. $[\alpha]_D^{25} = +2.15$ ($c = 1.00$, $CHCl_3$). MS: m/z = 701 $[M + 1]^+$, 723 $[M + 23]^+$. ^{13}C NMR: δ = 13.4, 17.8, 26.5 (broad), 29.3 (broad), 40.8, 43.4, 50.2, 71.0, 71.3, 165.6, 166.8. IR (KBr): $\tilde{\nu}$ = 3359, 3266, 2925, 2852, 1570, 1505, 1447, 1345, 1109, 1075, 811 cm^{-1}. $C_{34}H_{60}N_{12}O_4$ (700): calcd. C 58.26, H 8.63, N 23.98; found C 58.37, H 8.65, N 24.00.

Acknowledgments

The authors wish to thank Dr. L. Bonfanti (ENEL Produzione-Ricerca) for her kind help in AED GLC analyses and Mr. G. Vergamini for the accurate acquisition of IR spectra. This work was supported, in part, by the Ministero della Ricerca Scientifica e Tecnologica (MURST, Rome) and by the C.N.R. (Comitato Nazionale Scienza e Tecnologia Beni Culturali).

---

[1] [1a] *Cyanuric Chloride*, American Cyanamid Company, New York, **1955**. [1b] W. L. Mur, *Russ. Chem. Rev.* **1964**, *33*, 92−103. [1c] K. Venkataraman in *The Chemistry of Synthetic Dyes*, Academic Press, New York, **1952**, and refs. therein.

[2] [2a] G. Uccello-Barretta, A. Iuliano, R. Menicagli, P. Peluso, E. Pieroni, P. Salvadori, *Chirality* **1997**, *9*, 113−121. [2b] S. Samaritani, PhD Dissertation, University of Pisa, **1999**.

[3] [3a] P. Peluso, Thesis Dissertation, University of Pisa, **1993**. [3b] R. Menicagli, C. Malanga, P. Peluso, *Synth. Commun.* **1994**, *24*, 2153−2158.

[4] [4a] C. Fanelli, A. A. Fabbri, S. Monti, R. Menicagli, D. Pini, S. M. Rapaccini, S. Samaritani, P. Salvadori, "Effect of some Novel Antifungals of Different Pathogenic Fungi", *7th International Congress of Plant Pathology*, Edinburgh, August, 9−13, **1998**. [4b] S. Samaritani, A. A. Fabbri, C. Fanelli, R. Menicagli, P. Salvadori, "Sintesi ed attività biostatica di nuovi derivati 1,3,5-triazinici", *XXV Convegno Nazionale della Divisione di Chimica Organica*, Folgaria (TN), September, 8−12, **1998**. [4c] A. Ricelli, A. A. Fabbri, C. Fanelli, R. Menicagli, S. Samaritani, D. Pini, S. M. Rapaccini, P. Salvadori, *Restaurator* **1999**, *20*, 97−107.

[5] [5a] J. M. E. Quirke, "1,3,5-Triazine" in *Comprehensive Heterocyclic Chemistry* (Ed.: W. Rees), Ed. A. A. J. Boulton McKillop, Pergamon Press, **1984**, vol. 3, p. 459. [5b] W. W. Cuthberson, J. S. Moffatt, *J. Chem. Soc.* **1948**, 561−564. [5c] A. Dhainaut, G. Régnier, G. Atassi, A. Pierré, S. Léonce, L. Kraus-Berthier, J.-F. Prost, *J. Med. Chem.* **1992**, *35*, 2481−2496. [5d] G. R. Gustafson, C. M. Baldino, M-M. E. O'Donnell, A. Sheldon, R. J. Tarsa, C. J. Verni, D. L. Coffen, *Tetrahedron* **1998**, *54*, 4051−4065. [5e] N. Ohi, K. Moriguchi, M. Muramatsu, *Japan Kokai* 76 99, 096 [*Chem. Abstr.* **1977**, *86*, 37316j]. [5f] N. Oi, M. Horiba, H. Kitahara, *J. Chromatogr.* **1980**, *202*, 299−301. [5g] N. Oi, T. Doi, H. Kitahara, Y. Inda, *J. Chromatogr.* **1981**, *208*, 404−408. [5h] N. Oi, M. Nagase, Y. Sawada, *J. Chromatogr.* **1984**, *292*, 427−431. [5i] J.-Y. Lin, M.-H. Yang, *J. Chromatogr.* **1993**, *644*, 277−283. [5j] C.-E. Lin, C.-H. Lin, *J. Chromatogr. A* **1994**, *676*, 303−309. [5k] H. Brückner, M. Wachsmann, *J. Chromatogr. A* **1996**, *728*, 447−454. [5l] C.-E. Lin, F. K. Li, C.-H. Lin, *J. Chromatogr. A* **1996**, *722*, 211−220.

[6] [6a] H. Koopman, J. H. Uhlenbroek, H. H. Haeck, J. Daams, M. J. Koopmans, *Recl. Trav. Chim. Pays-Bas* **1959**, *78*, 967−980. [6b] G. Kay, E. M. Crook, *Nature* **1967**, *216*, 514−515. [6c] R. Fornasier, F. Montanari, G. Podda, P. Tundo, *Tetrahedron Lett.* **1976**, *17*, 1381−1384.

[7] [7a] A. Iuliano, I. Voir, P. Salvadori, *J. Org. Chem.* **1999**, *64*, 5754−5756. [7b] A. Iuliano, I. Voir, P. Salvadori, *Eur. J. Org. Chem.* **2000**, 1767−1772.

[8] A. G. M. Barrett, J. C. A. Lana, *J. Chem. Soc., Chem. Commun.* **1978**, 471−472.

[9] R. Kinas, K. Pankiewicz, W. J. Stec, *J. Org. Chem.* **1977**, *42*, 1650−1652.

[10] H. C. Brown, Y. M. Choi, S. Narasimhan, *Synthesis* **1981**, 605−606.

[11] H. Graubaum, G. Lutze, F. Tittelbach, M. Bartoszek, *J. Prakt. Chem.* **1995**, *337*, 401−404.

[12] D. D. Perrin, W. L. F. Armarego, D.R. Perrin, in *Purification of Laboratory Chemicals*, Pergamon Press, New York, **1983**.

[13] W. Theilacker, H.-G. Winkler, *Chem. Ber.* **1954**, *87*, 690−691.

[14] A. I. Meyers, G. Knaus, K. Kamata, M. E. Ford, *J. Am. Chem. Soc.* **1976**, *98*, 567−576.

Received November 26, 2001
[O01561]