

Synthesis, structures, and properties of bis(4,6-disubstituted 1,3,5-triazin-2-yl) ethers

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Reactions of (4,6-disubstituted 1,3,5-triazin-2-yl)trimethylammonium chlorides with glycine sodium salt in the presence of Et₃N afforded bis(triazin-2-yl) ethers instead of the expected triazinylaminoacetic acids. The structures of the resulting compounds were established by the independent synthesis, spectroscopic data, and X-ray diffraction analysis.

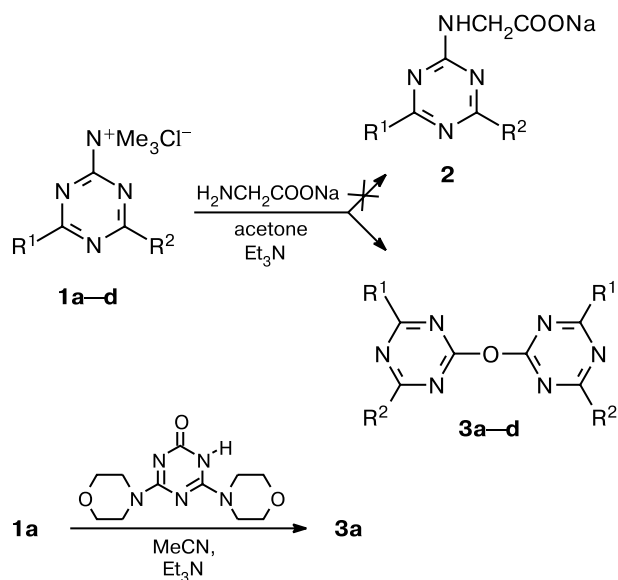
Key words: (4,6-disubstituted 1,3,5-triazin-2-yl)trimethylammonium chlorides, 4,6-dimorpholino-2-oxo-1,2-dihydro-1,3,5-triazine, bis(triazin-2-yl) ethers.

Ethers of *sym*-triazine derivatives containing alkyl and aryl substituents were studied in detail.^{1,2} Generally, these compounds are prepared by the nucleophilic substitution of the chlorine atoms in 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride) under the action of alcohols or phenols in the presence of HCl scavengers. However, the introduction of such electron-donating substituents leads to a decrease in both the electrophilicity of the carbon atoms of the triazine ring and mobility of the remaining chlorine atoms. The chlorine atom in 2-chloro-4,6-disubstituted *sym*-triazines is difficult to replace. However, it is these compounds belonging to trisubstituted *sym*-triazine derivatives that are the most important for the practical use.²

Earlier, we have demonstrated³ that (1,3,5-triazin-2-yl)trimethylammonium chlorides (**1**) are more reactive, and the trimethylammonium group in these compounds is readily replaced under the action of nucleophilic reagents. In the present study, taking into account high growth-regulating activity of triazinetricarboxylic acids,⁴ we attempted to synthesize new monocarboxylic acids of the triazine series by the reactions of salts **1a–d** with amino acids, *viz.*, glycine sodium salt (Scheme 1).

However, it appeared that compound **2** was not formed under these conditions; instead, the reactions unexpectedly afforded bis-triazinyl ethers **3a–d** in 40–47% yields. Presumably, under the reaction conditions the starting salts **1a–d** reacted with water present in glycine sodium salt (the latter was not subjected to additional dehydration), which favors the intermediate formation of the corresponding hydroxy derivatives. The latter, in turn, reacted with salts **1** to form ethers **3**. To confirm this as-

Scheme 1



1, 3: R¹ = R² = morpholino (**a**); R¹ = morpholino, R² = OMe (**b**); R¹ = morpholino, R² = piperidino (**c**); R¹ = pyrrolidino, R² = OMe (**d**)

sumption, we carried out the independent synthesis of ether **3a** by the reaction of (4,6-dimorpholino-1,3,5-triazin-2-yl)trimethylammonium chloride (**1a**) with 4,6-dimorpholino-2-oxo-1,2-dihydro-1,3,5-triazine, the yield of ether **3a** being 62%. Higher yields of the ethers were achieved also in the reactions of other starting salts **1**

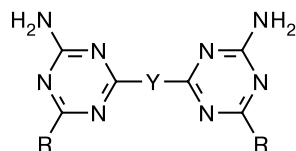
Table 1. Characteristics of bis(triazin-2-yl) ethers **3**

| Com- pound | M.p./°C | Yield* (%) | | <div>Found</div> <div>Calculated</div> (%) | | | Molecular formula | Molecular ion, <i>m/z</i> (<i>I</i> _{rel} (%)) |
|---------------|---------|------------|----------|--|---------------------|-----------------------|--|---|
| | | <i>A</i> | <i>B</i> | C | H | N | | |
| | | | | | | | | |
| 3a | 237—238 | 40 | 62 | <u>51.38</u> 51.15 | <u>6.53</u> 6.24 | <u>27.26</u> 27.12 | C ₂₂ H ₃₂ N ₁₀ O ₅ | 516 (100) |
| 3b | 195—196 | 47 | 70 | <u>47.50</u> 47.28 | <u>5.69</u> 5.47 | <u>27.80</u> 27.57 | C ₁₆ H ₂₂ N ₈ O ₅ | 406 (15) |
| 3c | 187—188 | 45 | 65 | <u>56.46</u> 56.23 | <u>7.27</u> 7.08 | <u>27.59</u> 27.33 | C ₂₄ H ₃₆ N ₁₀ O ₃ | 512 (22) |
| 3d | 180—181 | 43 | 64 | <u>51.32</u> 51.51 | <u>5.92</u> 6.09 | <u>29.93</u> 30.12 | C ₁₆ H ₂₂ N ₈ O ₃ | 374 (100) |

* Methods *A* and *B* are described in the Experimental section.

with 2-oxo-1,2-dihydrotriazines (Table 1). However, an attempt to prepare ether **3a** from 2-chloro-4,6-dimorpholino-1,3,5-triazine under various conditions failed.

It should be noted that data on bis(triazin-2-yl) ethers are lacking in the literature. The only exception is the study⁵ where compounds with the following structures were described:



Y = O, S;

R are residues of secondary aliphatic or cycloaliphatic amines, etc.

Such ethers are prepared by alkaline hydrolysis of 2-alkoxy(alkylthio)-4-amino-6-R-*sym*-triazines in the presence of 2-amino-4-bromo-6-R-*sym*-triazines and MeONa in methanol. These compound exhibit antitumor activities.

Bis(triazin-2-yl) ethers **3a–d** synthesized in the present study are finely crystalline white powders soluble in organic solvents and insoluble in water and aliphatic hydrocarbons. Their compositions and structures were confirmed by elemental analysis, IR and ¹H NMR spectroscopy, and mass spectrometry (Tables 1 and 2).

The IR spectra of compounds **3a–d** have intense narrow absorption bands in the regions of 1590–1500 and 1140–1005 cm^{−1} belonging to stretching vibrations of the conjugated C=N bond and the C–O–C bond, respectively. The ¹H NMR spectra show signals for the protons of all substituents of the 1,3,5-triazine ring, the number of the substituents (based on integral curves) corresponding to the expected value. The mass spectra of ethers **3** have molecular ion peaks, which also confirms their structures.

To study the fine structures of the resulting ethers, we carried out X-ray diffraction analysis of compound **3a** whose crystals were grown from an ethanol–CCl₄ mixture. The projection of the three-dimensional structure of

Table 2. Spectroscopic characteristics of ethers **3**

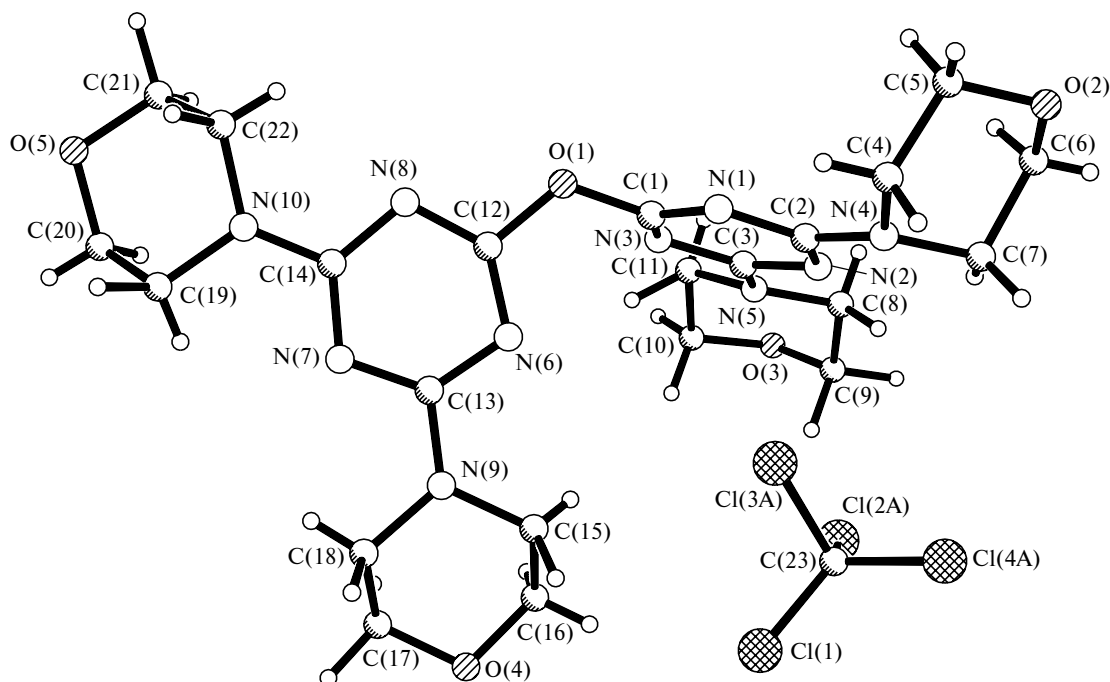
| Compound | IR, ν/cm ^{−1} | | ¹ H NMR, δ |
|-----------|------------------------|------------------|--|
| | C=N, conj. | C–O–C | |
| 3a | 1590, 1560 | 1090, 1050 | 3.55–3.75 (m, 32 H, NCH ₂ , OCH ₂) |
| 3b | 1580, 1540 | 1140, 1070, 1030 | 3.60–3.85 (m, 16 H, NCH ₂ , OCH ₂); 3.90 (s, 6 H, OMe) |
| 3c | 1590, 1570, 1500 | 1120, 1095, 1005 | 3.60–3.75 (m, 24 H, NCH ₂ , OCH ₂); 1.45–1.70 (m, 12 H, CH ₂ piperidine) |
| 3d | 1570, 1510 | 1145, 1080, 1060 | 4.90 (s, 6 H, OMe); 3.45–3.62 (m, 8 H, NCH ₂); 1.93–2.03 (m, 8 H, CH ₂ pyrrolidine) |

compound **3a** is shown in Fig. 1. Selected interatomic distances and bond angles are given in Tables 3 and 4, respectively. The complete tables of atomic coordinates, thermal parameters, bond lengths, and bond angles were deposited with the Cambridge Structural Database.

Molecule **3a** is nonplanar and the triazine rings are inclined to one another. The morpholine rings of the substituents adopt chair-like conformations and are also inclined to the triazine ring. As a result, the molecule

Table 3. Selected interatomic distances in molecule **3a**

| Atom | <i>d</i> /Å | Atom | <i>d</i> /Å |
|------------|-------------|-------------|-------------|
| O(1)–C(12) | 1.370(6) | N(5)–C(11) | 1.465(9) |
| O(1)–C(1) | 1.376(6) | N(6)–C(12) | 1.306(7) |
| N(1)–C(1) | 1.305(7) | N(6)–C(13) | 1.347(7) |
| N(1)–C(2) | 1.362(7) | N(7)–C(13) | 1.332(7) |
| N(2)–C(2) | 1.332(7) | N(7)–C(14) | 1.350(7) |
| N(2)–C(3) | 1.335(7) | N(8)–C(12) | 1.317(7) |
| N(3)–C(1) | 1.317(7) | N(8)–C(14) | 1.343(7) |
| N(3)–C(3) | 1.351(7) | N(9)–C(13) | 1.368(7) |
| N(4)–C(2) | 1.349(7) | N(10)–C(14) | 1.338(7) |
| N(5)–C(3) | 1.345(7) | | |

Fig. 1. Crystal structure of **3a**.

contains a cavity, which can readily accommodate a carbon tetrachloride molecule. This is responsible for instability of the crystals formed. Thus, evaporation of the solvent from the inner cavity leads apparently to a sharp increase in the internal strain in the crystals and the latter decompose within several hours on storage in air. Hence, the crystals of **3a** must be stored under a solvent layer.

As can be seen from Table 3, the bond lengths in the triazine rings are distorted only slightly and vary from 1.306 (N(6)—C(12)) to 1.362 Å (N(1)—C(2)), which is somewhat different from the bond lengths in unsubstituted

sym-triazine⁶ (1.337 Å). By contrast, the bond angles (see Table 4) at the nitrogen atoms in these rings are distorted (they vary from 111.6° (N(6)) to 115.2° (N(2))) and differ substantially from the bond angles at the carbon atoms (124.6° (C(2))—130.6° (C(12))). The bond lengths and bond angles in the morpholine fragments of the molecule are only slightly distorted and agree well with the average values observed in cyclic nonaromatic amines (see Tables 3 and 4).

To summarize, procedures were developed for the synthesis of bis-triazinyl ethers, which are potentially biologically active compounds, and new ethers were prepared based on (4,6-disubstituted 1,3,5-triazin-2-yl)tri-methylammonium chlorides.

Experimental

The IR spectra were recorded on a Specord-75 IR spectrophotometer in Nujol mulls. The ¹H NMR spectra were measured on a Bruker WM-500 radiospectrometer in DMSO-d₆. The mass spectra were obtained on a Finnigan MAT INCOS50 instrument; the energy of ionizing electrons was 70 eV. Elemental analysis was carried out on a Carlo-Erba 1106 analyzer. The course of the reactions and the purities of the products were monitored by TLC on Silufol UV-254 plates in a 1 : 1 acetone—hexane mixture.

Starting ammonium salts **1** and 4,6-disubstituted 2-oxo-1,2-dihydro-1,3,5-triazines were prepared according to procedures described earlier.^{3,7} The solvents and triethylamine were purified and dried according to known procedures.⁸ Glycine was purified by crystallization from methanol before use.

Table 4. Bond angles in molecule **3a**

| Angle | φ/deg | Angle | φ/deg |
|-------------------|----------|------------------|----------|
| C(12)—O(1)—C(1) | 118.7(4) | N(2)—C(2)—N(1) | 124.6(5) |
| C(1)—N(1)—C(2) | 112.8(5) | N(4)—C(2)—N(1) | 116.8(5) |
| C(2)—N(2)—C(3) | 115.2(5) | N(2)—C(3)—N(5) | 117.5(5) |
| C(1)—N(3)—C(3) | 112.4(5) | N(2)—C(3)—N(3) | 125.2(5) |
| C(8)—N(5)—C(11) | 114.2(6) | N(5)—C(3)—N(3) | 117.3(5) |
| C(12)—N(6)—C(13) | 111.6(5) | N(6)—C(12)—N(8) | 130.6(5) |
| C(13)—N(7)—C(14) | 113.9(4) | N(6)—C(12)—O(1) | 117.3(5) |
| C(12)—N(8)—C(14) | 112.1(4) | N(8)—C(12)—O(1) | 112.1(5) |
| C(13)—N(9)—C(15) | 122.2(6) | N(7)—C(13)—N(6) | 126.4(5) |
| C(13)—N(9)—C(18) | 122.5(5) | N(7)—C(13)—N(9) | 116.4(5) |
| C(15)—N(9)—C(18) | 113.7(6) | N(6)—C(13)—N(9) | 117.2(5) |
| C(14)—N(10)—C(22) | 123.7(5) | N(10)—C(14)—N(8) | 117.6(5) |
| C(14)—N(10)—C(19) | 122.8(5) | N(10)—C(14)—N(7) | 117.1(5) |
| C(22)—N(10)—C(19) | 113.1(5) | N(8)—C(14)—N(7) | 125.3(5) |
| N(2)—C(2)—N(4) | 118.5(5) | | |

X-ray diffraction study. Crystals of compound **3a** were grown from a 5 : 1 ethanol—carbon tetrachloride mixture. Prismatic crystals of **3a**: C₂₃H₃₂N₁₀O₅; unit cell parameters at $T = 293$ K: $a = 8.277$ (1), $b = 10.877$ (2), $c = 17.290$ (2) Å, $\alpha = 75.96$ (3)°, $\beta = 81.93$ (3)°, $\gamma = 84.67$ (3)°, $Z = 2$, $d = 1.492$ mg m⁻³, $V = 1492.3(2)$ Å³. The space group is $\bar{P}1$. The X-ray data were collected on an automated Enraf-Nonius CAD-4 diffractometer (MoK α radiation, β filter) using the $\theta/2\theta$ scanning technique. A total of 2378 reflections with $I > 2\sigma(I)$ were measured. The structure of **3a** was solved by direct methods using the SHELXTL program package^{8,9} and refined with anisotropic thermal parameters (isotropic thermal parameters for H atoms) to the reliability factors $R = 0.0642$, $R_w = 0.1798$.

Bis(4,6-dimorpholino-1,3,5-triazin-2-yl) ether (3a). **A.** (4,6-Dimorpholino-1,3,5-triazin-2-yl)trimethylammonium chloride (1.2 mmol) was added portionwise with stirring to a suspension of glycine sodium salt (1.2 mmol) and freshly distilled dry triethylamine (1.2 mmol) in anhydrous acetone (10 mL) at 20–25 °C. The reaction mixture was stirred at 30 °C for 12 h. The solvent was removed *in vacuo*. The dry residue was thoroughly washed with water and dried. After purification by crystallization from ethanol, ether **3a** was obtained in a yield of 0.25 g (40%).

B. (4,6-Dimorpholino-1,3,5-triazin-2-yl)trimethylammonium chloride (**1a**) (1.5 mmol) was added portionwise with stirring to a mixture of 4,6-dimorpholino-2-oxo-1,2-dihydro-1,3,5-triazine (1.5 mmol) and freshly distilled dry triethylamine (1.5 mmol) in anhydrous acetonitrile (9 mL) at 20 °C. The reaction mixture was stirred at this temperature for 10 h. The solution was concentrated *in vacuo* to 2/3 of the initial volume and poured into cold water (50 mL). The precipitate that formed was filtered off, washed with water, and dried. After purification by crystallization from ethanol, ether **3a** was obtained in a yield of 0.48 g (62%).

Bis-triazinyl ethers **3b–d** were prepared analogously and purified by crystallization from ethanol. Their yields, selected constants, and spectroscopic characteristics are given in Tables 1 and 2.

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