Synthesis of a series of vicinal diamines with potential biological activity

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**Abstract:** A broad range of vicinal diamines based on styrene oxide are synthesised via mixtures of regioisomeric amino alcohols. The ring opening of the intermediate aziridinium ions by primary amines proceeds with high regioselectivity, leading to the target diamines as single regioisomers for all reaction series. The compounds are of potential biological interest as ligands for cisplatin analogues. Anticancer activity tests of both groups of compounds are in progress.

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*Keywords: Amino alcohols, aziridinium ion, ring opening, vicinal diamines, regioselectivity*

1 Introduction

Vicinal diamines are an important class of organic compounds; they have been widely used as chelating agents in radiopharmaceuticals [1,2], as ligands in analytical chemistry, and for the synthesis of compounds with pharmaceutical importance. Compounds include precursors in the synthesis of azamacrocycles [3] and heterocyclic compounds [4], intermediates in the synthesis of analgesics. Chiral, nonracemic vicinal diamines are of great interest as chiral auxiliaries [5] in important reactions, such as the reduction of prochiral ketones, aldol reactions, etc., which achieve high reaction yields, similar to those of enzyme reactions.

Various natural and synthetic compounds, containing a 1,2-diamine moiety display a broad spectrum of biological activities. The anti-tumour properties of cisplatin were discovered in the mid 1960s [6], and it was successfully used in chemotherapy. Afterward,
many analogous compounds were investigated; among them were several that possess even higher activities [7-12]. Thus, the synthesis of platinum 1,2-diamino complexes has recently received great deal of interest in the search for drugs having greater activities and less toxicity, and to circumvent drug resistance that may develop in certain tumours [13,14].

Among the relevant methods for synthesising vicinal diamines [5], an efficient and expedient one [15-18] is based on the nucleophilic ring opening of epoxides by the action of a secondary amine, followed by substitution of the hydroxyl group on the immediately-formed amino alcohol by a primary amine. The substitution occurs via a tetrahedral aziridinium ion intermediate. The method is a simple, high yield protocol using cheap starting materials. In the case of aziridinium ions having a benzylic position [19], the observed regioselectivity of the transformation presents an additional advantage.

Herein is presented a synthesis of a broad range of vicinal diamines with potential biological activity as ligands for cisplatin analogues.

2 Results and discussion

Mixtures of regioisomeric vicinal amino alcohols (1 and 2) are synthesised from styrene oxide by epoxide ring opening using a series of secondary amines, such as piperidine, pyrrolidine, morpholine and N-phenyl piperazine, according to a known procedure and in high yields (Scheme 1).

Secondary alcohols are the major products, and the relative ratios of the regioisomers

Secondary alcohols are the major products, and the relative ratios of the regioisomers
are similar in all cases (Table 1). Subsequent mesylation of these amino alcohols is carried out using triethyl amine as a base, in order to form aziridinium ions that are not isolated in this procedure. Both regioisomeric amino alcohols give the same aziridinium ion and thus, mixtures of alcohols 1 and 2 can be used in this reaction without preliminary isolation. In situ treatment of the aziridinium ions with various primary amines leads to vicinal diamines (3-10, a-d) as a result of a ring opening reaction at the benzylic center (Scheme 1). The transformation occurs very smoothly, and the target diamines are obtained as the only products in moderate yields, contaminated slightly with impurities of the starting amino alcohols in some cases.

The reaction proceeds with high regioselectivity, and the diamines are formed as single regioisomers in all cases. This observation agrees with general findings, that if the aziridinium ion has a benzylic position it undergoes virtually exclusive ring opening by amines at this position, in contrast to the terminal where the preferential attack is at the least hindered position [19].

As the preferred conformation of the ligand is important in the context of the complexation, a detailed study of the $^1$H and $^{13}$C NMR data of the products is given in Table 2. The assignment of the signals in $^1$H NMR spectra was made based upon the specific chemical shifts and coupling constants, while those of the $^{13}$C NMR signals were based upon DEPT and HMQC techniques. As the proton signals for the methylene and methyne groups of both amino alcohols 1 and 2 are in a region free of other signals, their assignments were made based upon the corresponding integrals and were confirmed by COSY cross peaks. The signals for the phenyl groups, heterocyclic rings, and N-substituents are in a common region, and since some of these signals are partially overlapped in the proton spectra, only the values of the skeleton nuclei are given in Table 1 and Table 2.

The CH proton appears as a doublet of doublets with different couplings to both protons of the diastereoisotopic CH$_2$ group, giving two sets of signals. This pattern is characteristic of all the products investigated herein. An aromatic N-substituent (products 6-8) shifts the CH-1 proton slightly downfield in its $^1$H NMR spectrum, while the C-1 carbon appears at higher field in its $^{13}$C NMR spectrum with respect to those signals in the other products. The same compounds (6-8) show average and large couplings, while small and large are observed for the rest. The similarity of all other data for the diamines reported here indicate that only the N-substituent slightly affects the preferred conformation of these compounds, while the heterocyclic ring has no influence.

3 Conclusion

A series of vicinal diamines with potential as ligands for cisplatin analogues were synthesised. The target diamines were formed as single regioisomers under these reaction conditions in accordance with the literature data. A detailed analysis of both the $^1$H and $^{13}$C NMR data shows that only an aromatic N-substituent has a slight influence on the preferred conformation of the diamine, while the heterocyclic ring present in the molecule does not affect it.
Anticancer activity tests of the vicinal diamines 3-10, as well as those of the regioisomeric mixtures of vicinal amino alcohols 1 and 2, are in progress.

4 Experimental

All reagents were purchased from Aldrich, Merck and Fluka and were used without any further purification. Diethyl ether was dried over sodium wire. Merck Silica gel 60 (0.040-0.063 mm) was used for column chromatography. Melting points were determined in capillary tubes and were not corrected. The NMR spectra were recorded on a Bruker DRX 250 spectrometer using deuterochloroform as the solvent; chemical shifts were reported in ppm relative to tetramethylsilane (TMS, δ=0 ppm), and the coupling constants were calculated in Hz. Microanalyses were carried out by the microanalyses service of the Institute of Organic Chemistry, Bulgarian Academy of Sciences.

General procedure for the preparation of diamines 3-10a – d:

A solution of styrene oxide (10 mmol) and a secondary amine (20 mmol), piperidine, pyrrolidine, morpholine or N-phenylpiperazine in ethanol (20 ml) was refluxed for 3 h. The solvent was removed in vacuo affording a mixture of regioisomeric amino alcohols 1 and 2 in 92-96 % yield as solid residue, which was used without further purification. The relative ratios of the amino alcohols and their NMR data are given in Table 1.

Triethylamine (30 mmol) was added to a solution of the thus-prepared amino alcohols 1 and 2 (10 mmol) in dry diethyl ether (20 ml) under atmosphere of argon. The reaction mixture was cooled to 0 °C, and methanesulphonyl chloride (MsCl, 12 mmol) was added. After 45 min, triethylamine (20 mmol) was added, and the mixture was warmed to room temperature, followed by addition of the primary amine (20 mmol) and water (20 mmol). Stirring was continued for 10 h at ambient temperature. The ether solution was extracted with brine, aq. NaHCO₃, and again with brine and was dried over MgSO₄. The solvent was evaporated to dryness, and the residue was purified by column chromatography on silica gel using diethyl ether as the mobile phase, affording the 1,2-diamines (3-10a-d). In the case of diamines 3 (R’=H), concentrated NH₃ was used as the reagent, and dioxane was used as the reaction media. The yields of the products and their physical and spectral data are summarised in Table 2.

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| Pr. | Relative ratio (%) | Formula, MW | Analysis (%)<sup>a</sup>, Found (Calcd) | H-1/C-1 | H-2/C-2 |
|-----|-------------------|-------------|----------------------------------------|---------|---------|
| 1a  | 64                | C<sub>13</sub>H<sub>19</sub>NO           | 4.718; J 3.8,10.4, 2.383; J 10.4,12.4 | 4.718; J 3.8,10.4 | 2.383; J 10.4,12.4 |
|     |                   | H<sub>1</sub>/C<sub>1</sub> 2.383; J 10.4,12.4 | C 75.87 (76.05), 68.575 | 68.575 | 66.890 |
| 2a  | 36                | C<sub>12</sub>H<sub>17</sub>NO           | 3.965; J 8.8,9.1 | 3.965; J 8.8,9.1 | 59.795 | 70.213 |
|     |                   | H<sub>2</sub>/C<sub>2</sub> 3.965; J 8.8,9.1 | H 9.51 (9.33), 6.63 (6.82), 3.600; J 5.2,9.1 | 3.600; J 5.2,9.1 | 3.672; J 5.2,8.8 |
| 1b  | 68                | C<sub>12</sub>H<sub>17</sub>NO           | 4.697; J 3.3,10.6, 2.456; J 3.3,12.2 | 4.697; J 3.3,10.6 | 2.456; J 3.3,12.2 |
|     |                   | H<sub>1</sub>/C<sub>1</sub> 2.456; J 3.3,12.2 | C 75.53 (75.35), 70.668 | 70.668 | 64.106 |
| 2b  | 32                | C<sub>12</sub>H<sub>17</sub>NO<sub>2</sub> | 3.851; J 5.8,10.7 | 3.851; J 5.8,10.7 | 64.294 | 70.010 |
|     |                   | H<sub>2</sub>/C<sub>2</sub> 3.851; J 5.8,10.7 | H 8.82 (8.96), 7.57 (7.32), 3.778; J 5.8,10.7 | 3.778; J 5.8,10.7 | 3.407; J 5.8 |
| 1c  | 62                | C<sub>12</sub>H<sub>17</sub>NO<sub>2</sub> | 4.724; J 5.7,8.1, 2.463; J 8.1,12.6 | 4.724; J 5.7,8.1 | 2.463; J 8.1,12.6 |
|     |                   | H<sub>1</sub>/C<sub>1</sub> 2.463; J 8.1,12.6 | C 69.32 (69.54), 68.386 | 68.386 | 66.435 |
| 2c  | 38                | C<sub>12</sub>H<sub>17</sub>NO<sub>2</sub> | 3.906; J 8.5,10.2 | 3.906; J 8.5,10.2 | 60.750 | 70.545 |
|     |                   | H<sub>2</sub>/C<sub>2</sub> 3.906; J 8.5,10.2 | H 8.43 (8.27), 6.92 (6.76), 3.754; J 5.7,10.2 | 3.754; J 5.7,10.2 | 3.505; J 5.7,8.5 |
| 1d  | 65                | C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>O | 4.767; J 5.6,8.3, 2.529; J 8.3,12.4 | 4.767; J 5.6,8.3 | 2.529; J 8.3,12.4 |
|     |                   | H<sub>1</sub>/C<sub>1</sub> 2.529; J 8.3,12.4 | C 76.82 (76.56), 68.705 | 68.705 | 66.112 |
| 2d  | 35                | C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>O | 4.026; J 10.5,12.0 | 4.026; J 10.5,12.0 | 60.469 | 69.975 |
|     |                   | H<sub>2</sub>/C<sub>2</sub> 4.026; J 10.5,12.0 | H 7.71 (7.85), 9.68 (9.92), 3.735; J 5.0,12.0 | 3.735; J 5.0,12.0 | 3.724; J 5.0,10.5 |

<sup>a</sup> Determined as mixtures of regioisomers.

**Table 1** Relative ratios (as determined by <sup>1</sup>H NMR) and analytical and NMR data (CDCl<sub>3</sub>, δ referenced to TMS as an internal standard, J in Hz) of the skeleton nuclei of amino alcohols 1 and 2.
| Pr. | Yield (%) | Mp (°C) | Formula, MW | Analysis (%), Found (Calcd) | H-1/C-1 | H-2/C-2 |
|-----|-----------|---------|-------------|------------------------------|---------|---------|
| 3a  | 74 oil    | 204.319 | C$_{13}$H$_{20}$N$_2$ | C 76.45 (76.42), H 9.63 (9.87), N 13.58 (13.71) | 2.200; J 3.4,10.8 | 67.242   |
|     |           |         |             | H 2.567; J 10.8,12.6        |         |         |
| 4a  | 76 oil    | 218.346 | C$_{14}$H$_{22}$N$_2$ | C 76.87 (77.01), H 10.32 (10.16), N 12.74 (12.83) | 2.241; J 3.4,10.8 | 66.625   |
|     |           |         |             | H 2.418; J 11.0,12.4        |         |         |
| 5a  | 81 oil    | 232.373 | C$_{15}$H$_{24}$N$_2$ | C 77.68 (77.53), H 10.57 (10.41), N 11.83 (12.06) | 2.289; J 3.4,10.5 | 66.070   |
|     |           |         |             | H 2.765; J 10.7,12.6        |         |         |
| 6a  | 93 80-81° | 280.417 | C$_{19}$H$_{24}$N$_2$ | C 81.22 (81.31), H 8.81 (8.63), N 9.73 (9.99) | 2.456; J 5.7,9.9 | 66.061   |
|     |           |         |             | H 2.473; J 9.9,11.4         |         |         |
| 7a  | 92 98-99° | 294.444 | C$_{20}$H$_{26}$N$_2$ | C 81.43 (81.58), H 8.78 (8.90), N 9.71 (9.51) | 2.415; J 5.7,12.0 | 66.082   |
|     |           |         |             | H 2.465; J 9.9,12.0         |         |         |
| 8a  | 86 81-82° | 310.444 | C$_{20}$H$_{26}$N$_2$O | C 77.57 (77.38), H 8.13 (8.44), N 9.31 (9.02) | 2.432; J 5.4,10.2 | 66.144   |
|     |           |         |             | H 2.454; J 10.2,12.3        |         |         |
| 9a  | 82 40-41° | 294.444 | C$_{20}$H$_{26}$N$_2$ | C 81.73 (81.58), H 8.97 (8.90), N 9.36 (9.51) | 2.205; J 3.4,11.2 | 66.379   |
|     |           |         |             | H 2.450; J 11.2,12.3        |         |         |
| 10a | 93 65-66° | 368.525 | C$_{23}$H$_{32}$N$_2$O$_2$ | C 74.73 (74.96), H 8.91 (8.75), N 7.81 (7.60) | 2.220; J 3.6,12.3 | 66.244   |
|     |           |         |             | H 2.249; J 10.9,12.3        |         |         |
| 4b  | 82 oil    | 204.319 | C$_{13}$H$_{20}$N$_2$ | C 76.57 (76.42), H 9.83 (9.87), N 13.68 (13.71) | 2.226; J 3.4,11.9 | 63.840   |
|     |           |         |             | H 2.831; J 10.9,11.9        |         |         |
| 6b  | 91 73-74° | 266.390 | C$_{18}$H$_{22}$N$_2$ | C 80.97 (81.16), H 8.51 (8.32), N 10.67 (10.52) | 2.561; J 5.6,10.6 | 63.349   |
|     |           |         |             | H 2.978; J 5.6,12.0         |         |         |
| 7b  | 93 64-65° | 280.417 | C$_{19}$H$_{24}$N$_2$ | C 81.23 (81.38), H 8.58 (8.63), N 10.13 (9.99) | 2.504; J 10.5,12.0 | 63.418   |
|     |           |         |             | H 2.944; J 6.3,12.0         |         |         |

Table 2: Analytical and NMR data (CDCl$_3$, δ referenced to TMS as an internal standard, J in Hz) of the skeleton nuclei of diamines 3–10.
### Table 2 (continue) Analytical and NMR data (CDCl₃, δ referenced to TMS as an internal standard, J in Hz) of the skeleton nuclei of diamines 3–10.

| Pr. | Yield (%) | Mp (°C) | Formula, MW | Analysis (%), Found (Calcd) | H-1/C-1 | H-2/C-2 |
|-----|-----------|---------|-------------|-----------------------------|--------|--------|
| 8b  | 92        | 56-57°  | C₁₅H₂₄N₂O   | 296.417                     | 4.146; 2.387; J 10.2,12.0 | 2.845; J 5.8,12.0 |
|     |           |         | 296.417     | H 8.32 (8.16)               | N 9.63 (9.45)   | 58.117  |
|     |           |         |             |                             | 63.418  |        |
| 9b  | 90        | oil     | C₁₉H₂₄N₂    | 280.417                     | 3.685; J 3.3,11.4 | 2.198; J 3.3,12.0 |
|     |           |         | 280.417     | H 8.49 (8.63)               | N 9.73 (9.99)   | 60.421  |
|     |           |         |             |                             | 63.625  |        |
| 10b | 76        | 43-44°  | C₂₂H₃₀N₂O₂   | 354.498                     | 3.669; J 3.6,10.9 | 2.225; J 3.6,11.9 |
|     |           |         | 354.498     | H 8.71 (8.53)               | N 7.69 (7.90)   | 62.093  |
|     |           |         |             |                             | 63.432  |        |
| 3c  | 76        | oil     | C₁₂H₁₈N₂O    | 206.292                     | 4.099; J 3.9,9.8 | 2.342; J 3.9,12.3 |
|     |           |         | 206.292     | H 8.92 (8.80)               | N 13.55 (13.58) | 51.812  |
|     |           |         |             |                             | 66.916  |        |
| 4c  | 78        | oil     | C₁₃H₂₀N₂O₂   | 220.319                     | 3.721; J 3.4,9.3 | 2.340; J 3.4,12.5 |
|     |           |         | 220.319     | H 9.39 (9.15)               | N 12.87 (12.72) | 61.575  |
|     |           |         |             |                             | 65.976  |        |
| 5c  | 73        | oil     | C₁₄H₂₂N₂O    | 234.346                     | 3.788; J 3.6,10.9 | 2.325; J 3.6,12.4 |
|     |           |         | 234.346     | H 9.51 (9.46)               | N 11.68 (11.95) | 59.421  |
|     |           |         |             |                             | 66.006  |        |
| 6c  | 95        | 94-95°  | C₁₄H₂₂N₂O    | 282.390                     | 4.301; J 5.5,10.0 | 2.528; J 10.0,12.5 |
|     |           |         | 282.390     | H 7.81 (7.85)               | N 9.71 (9.92)   | 55.054  |
|     |           |         |             |                             | 65.612  |        |
| 7c  | 76        | 103-104°| C₁₉H₂₄N₂O    | 296.417                     | 4.263; J 5.4,9.7 | 2.492; J 5.4,12.3 |
|     |           |         | 296.417     | H 8.31 (8.16)               | N 9.38 (9.45)   | 55.267  |
|     |           |         |             |                             | 65.646  |        |
| 8c  | 74        | 99-100° | C₁₉H₂₄N₂O₂   | 312.417                     | 4.238; J 5.0,8.3 | 2.491; J 5.0,12.4 |
|     |           |         | 312.417     | H 7.85 (7.74)               | N 8.82 (8.97)   | 55.674  |
|     |           |         |             |                             | 65.737  |        |
| 9c  | 86        | 65-66°  | C₁₉H₂₄N₂O    | 296.417                     | 3.684; J 3.4,11.0 | 2.203; J 3.4,12.4 |
|     |           |         | 296.417     | H 8.23 (8.16)               | N 9.58 (9.45)   | 57.266  |
|     |           |         |             |                             | 65.734  |        |
| 10c | 72        | 82-83°  | C₂₂H₃₀N₂O₃   | 370.498                     | 3.712; J 3.5,10.9 | 2.279; J 3.5,12.1 |
|     |           |         | 370.498     | H 8.31 (8.16)               | N 7.72 (7.56)   | 59.435  |
|     |           |         |             |                             | 65.723  |        |
| Pr. | Yield (%) | Mp (°C) | Formula | Analysis (%) | H-1/C-1 | H-2/C-2 |
|-----|-----------|---------|---------|--------------|---------|---------|
| 4d  | 83        | 78-79°  | C_{19}H_{25}N_{3} | C 77.17 (77.25) | 3.671; J 3.4,10.8 | 2.383; J 3.4,12.4 |
|     |           |         |         | H 8.49 (8.53)  |         | 2.547; J 10.8,12.4 |
|     |           |         |         | N 14.47 (14.22) | 362.183 | 65.814 |
| 6d  | 81        | 134-135°| C_{24}H_{27}N_{3} | C 80.42 (80.63) | 4.328; J 4.7,10.5 | 2.537; J 4.7,12.3 |
|     |           |         |         | H 7.83 (7.61)  |         | 2.644; J 10.5,12.3 |
|     |           |         |         | N 11.91 (11.75) | 55.440 | 65.165 |
| 7d  | 72        | 97-98°  | C_{25}H_{29}N_{3} | C 80.91 (80.82) | 4.275; J 4.7,10.9 | 2.501; J 4.7,12.3 |
|     |           |         |         | H 7.68 (7.87)  |         | 2.565; J 10.9,12.3 |
|     |           |         |         | N 11.45 (11.31) | 55.593 | 65.096 |
| 8d  | 74        | 128-129°| C_{25}H_{29}N_{3}O | C 77.62 (77.48) | 4.266; J 4.8,10.7 | 2.541; J 4.8,12.4 |
|     |           |         |         | H 7.33 (7.54)  |         | 2.661; J 10.7,12.4 |
|     |           |         |         | N 10.67 (10.84) | 55.690 | 65.271 |
| 9d  | 76        | 110-111°| C_{25}H_{29}N_{3} | C 80.62 (80.82) | 3.833; J 3.4,11.2 | 2.364; J 3.4,12.4 |
|     |           |         |         | H 7.98 (7.87)  |         | 2.622; J 11.2,12.4 |
|     |           |         |         | N 11.45 (11.31) | 57.709 | 65.414 |
| 10d | 73        | 116-117°| C_{28}H_{33}N_{3}O_{2} | C 75.62 (75.47) | 3.733; J 3.4,10.8 | 2.326; J 3.4,12.2 |
|     |           |         |         | H 7.78 (7.92)  |         | 2.472; J 10.8,12.4 |
|     |           |         |         | N 9.52 (9.43)  | 59.934 | 65.250 |

Table 2 (continue) Analytical and NMR data (CDCl₃, δ referenced to TMS as an internal standard, J in Hz) of the skeleton nuclei of diamines 3–10.