Synthesis of 3,4,5-Triamino-4*H*-1,2,4-triazole (Guanazine) and its 4-Arylideneamino Derivatives

Håkan Emilsson*

Department of Organic Pharmaceutical Chemistry, Biomedical Centre, University of Uppsala, Box 574, S-751 23 Uppsala, Sweden

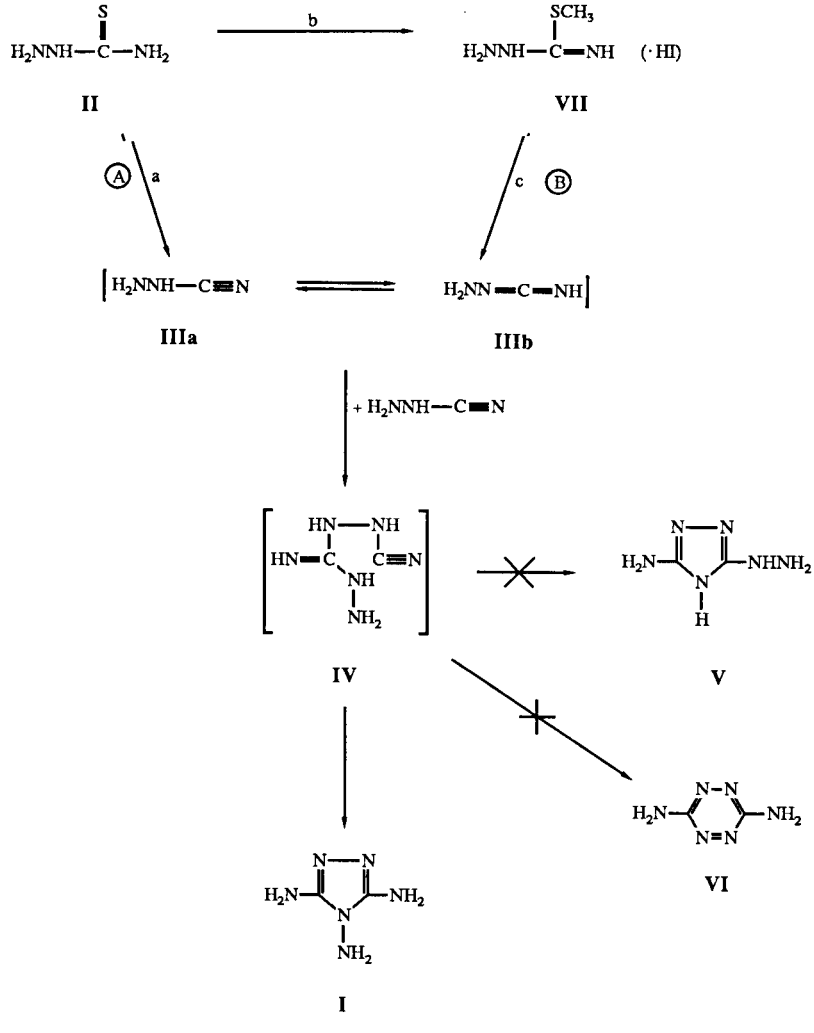
Received December 12, 1988

Synthetic methods for the preparation of 3,4,5-triamino-4*H*-1,2,4-triazole (guanazine) and its 4-arylideneamino derivatives are described. Guanazine, which can be used as an appropriate starting material in the syntheses of different bicyclic heterocycles, was readily obtained from thiosemicarbazide by treatment with mercuric oxide. Guanazine was also obtained from the *S*-methylisothio ether of thiosemicarbazide *via* a pyrolytic reaction. The 4-arylideneamino derivatives were either prepared by treatment of guanazine with an appropriate aromatic aldehyde, or by methods in which 1-arylidene-5-thiocarbamoyldiaminoguanidines are used as starting materials.

J. Heterocyclic Chem., **26**, 1077 (1989).

Guanazine (3,4,5-triamino-4*H*-1,2,4-triazole; I in Scheme 1) is an useful starting material in the preparation of bicyclic heterocycles, such as 1,2,4-triazolo[4,3-*b*]-1,2,4-triazoles [1] and 1,2,4-triazolo[4,3-*b*]-1,2,4-triazines [2]. Guanazine as the free base and its monohydrochloride or monohydrobromide salts, have previously been obtained

Scheme 1



Reagents: a) HgO, S, $MgSO_4$ in dry acetone, reflux 1 hour (-HgS, -H_2O). b) CH_3I in absolute EtOH, reflux 2 hours. c) $KHCO_3$ in absolute EtOH, reflux 3 hours (-CH_3SH, -KI, -H_2CO_3).

by a number of synthetic methods: By treatment of cyanogen bromide with hydrazine hydrate [3], by treatment of cyanogen chloride with hydrazine [4], from cyanogen bromide and diaminoguanidine [5], from thiosemicarbazide and lead oxide [6], and from dimethylcyanamide and hydrazine [7]. The yield of guanazine is poor in most of these methods. The method by Child [7] seems to be the best thus far.

Syntheses of 4-arylideneamino derivatives of guanazine have been reported in the literature [5-7]. However, the yield of the desired monoarylideneamino compound is limited by a simultaneous formation of the corresponding 3,4-bis(arylidineamino) derivative.

Synthetic methods for the preparation of guanazine and its 4-arylideneamino derivatives in relatively high yields have now been developed. These methods are described in this paper.

Methods and Discussion.

The synthetic methods developed for the preparation of guanazine and its 4-arylideneamino derivatives, are outlined in Schemes 1 and 2 (methods A-F).

Guanazine has previously been prepared in a low yield from thiosemicarbazide (**II**) and lead oxide [6]. Also in our hands, this reaction resulted in a low yield. The outcome was considerably increased, however, when yellow mercuric oxide (HgO) was used as the desulfurizing agent instead of lead oxide (method A). According to Kurzer and Douraghi-Zadeh, mercuric oxide is by far the most effective agent for desulfurization of thioureas [8]. For optimum results, it is recommended to use an excess of finely divided mercuric oxide, combined with a catalytic amount of sulfur. The presence of sulfur not only catalyzes the desulfurization, but also retards the side reactions [8]. Dry acetone was chosed as a suitable solvent for the reaction, according to a method described by Meakins and Moss [9].

It has been proposed that the conversion of thiosemicarbazide by lead oxide, proceeds *via* the reactive intermediate carbazonitrile (**IIIa**) [7]. It is also possible that the reaction proceeds *via* the carbodiimide **IIIb**, which is an isomer (proton tautomer) to **IIIa**. The same intermediates should be formed when mercuric oxide is used instead of lead oxide.

The water generated in the first step of the reaction, may add to the intermediate (**IIIa** or **b**) to form semicarbazide. The side reaction can, however, be inhibited by the presence of an appropriate dehydrating agent, *e.g.* magnesium sulfate.

The reaction proceeds presumably with a step, in which **IIIa** (or **IIIb**) dimerizes to 1-amino-3-cyanamidoguanidine (**IV**). Guanazine is then formed by cyclization of this compound.

Guanazine was prepared in a relatively good yield (60% after two recrystallizations), when mercuric oxide, sulfur, magnesium sulfate and dry acetone were used (method A).

The pyrolysis of substituted *S*-methylisothioureas into methyl mercaptane and carbodiimides has been known for a long time [8]. This pyrolytic reaction was used in an alternative synthetic method for obtaining guanazine (method B, Scheme 1). The starting material, *S*-methylisothiosemicarbazide hydroiodide (**VII**), was readily obtained from thiosemicarbazide (**II**) by treatment with methyl iodide in ethanol. In method B, compound **VII** was treated with one equivalent of potassium bicarbonate in refluxing ethanol. Carbazonitrile or its carbodiimide-isomer (**IIIa** or **b**) was presumably formed as an intermediate in the reaction, which proceeds in the same way as in method A. The total yield of guanazine was lower when method B was used compared to method A (44% versus 60%).

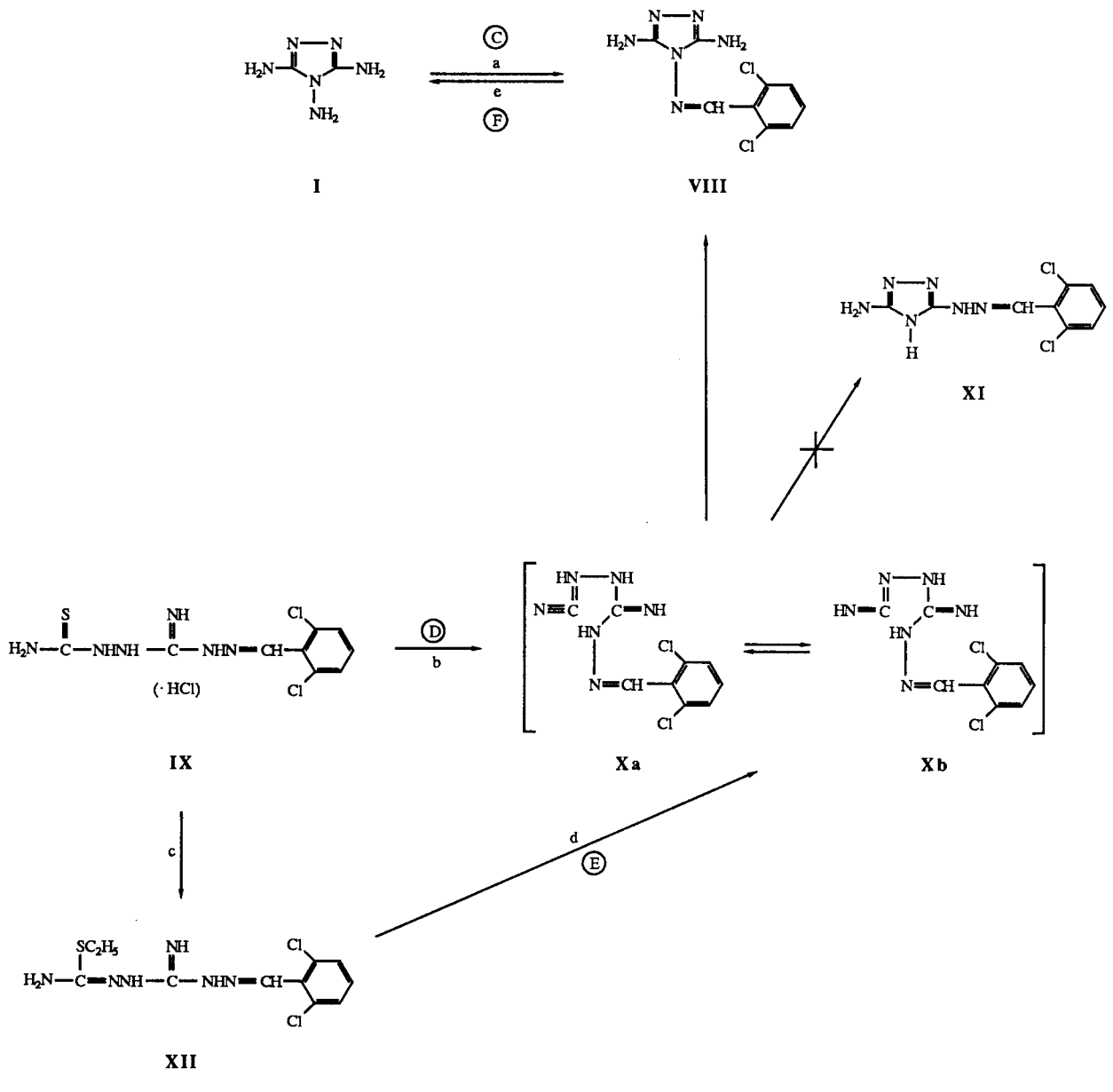
Several by-products can be formed by different ring closure reactions from the intermediate **IV** in methods A and B (*e.g.* **V** and **VI**). Under the conditions used in these methods, the cyclization to guanazine is favoured. However, we have not found the reason for this finding.

The synthesis of 4-benzylideneamino-3,5-diamino-4*H*-1,2,4-triazole has been reported previously [5-7]. This compound was obtained from guanazine by treatment with an excess of benzaldehyde in combination with a catalytic amount of piperidine in an ethanolic solution. However, the yield was limited by a simultaneous formation of 5-amino-3,4-bis-(benzylideneamino)-4*H*-1,2,4-triazole. The same problem with formation of bis-derivatives, was observed when we prepared monoarylidene derivatives of 5-substituted 3,4-diamino-4*H*-1,2,4-triazoles [10-11]. The yields of the desired derivatives were only moderate. However, we found that the yield of the 4-arylideneamino derivative was optimal when the free base of the 5-substituted 3,4-diamino-4*H*-1,2,4-triazole was treated with only one equivalent of an aromatic aldehyde in refluxing ethanol. This method was tried with guanazine and 2,6-dichlorobenzaldehyde (method C, Scheme 2), and the yield of 3,5-diamino-4-(2,6-dichlorobenzylideneamino)-4*H*-1,2,4-triazole (**VIII**) was acceptable (38%).

Different 4-arylideneamino derivatives of guanazine can also be obtained by using the methods D and E in Scheme 2. In our previous search for new antihypertensive agents, different series of substituted 4*H*-1,2,4-triazoles like 3-hydrazino-4*H*-1,2,4-triazoles, 3,4-diamino-4*H*-1,2,4-triazoles and the corresponding hydrazones, have been prepared and tested for antihypertensive properties in spontaneously hypertensive rats [10-12]. The best hypotensive activities were shown for compounds which included a 2,6-dichlorobenzylidene moiety in the 3-position. This finding resulted in the preparation of several new compounds containing this particular moiety.

In this synthetic program we prepared also **IX** and **XII**.

Scheme 2



Reagents: a) 2,6-Dichlorobenzaldehyde in EtOH, reflux 3 hours. b) HgO, S, $MgSO_4$ in dry acetone, reflux 0.5 hour (-HgS, $-H_2O$). c) C_2H_5Br, NaOH 2 equiv. in EtOH, 20° 0.1 hour. d) Dry pyridine, 90° 0.25 hour ($-C_2H_5SH$). e) HCl 5M, reflux 3 hours (-2,6-dichlorobenzaldehyde).

These compounds could also be used for the formation of **VIII** according to the methods D and E. We believe that these methods can be used for the preparation of other arylidene derivatives of guanazine.

In method D, the desulfurization of **IX** was performed by use of the same reagents and conditions as in method A (Scheme 1). The reaction went *via* the intermediate **Xa** (or **Xb**), and a relatively high yield (about 50%) of **VIII** was obtained without any concomitant formation of the isomeric compound **XI**.

The formation of compound **VIII** from the *S*-ethyl derivative **XII** has been reported earlier [10,12] (method E, Scheme 2). Ethyl mercaptan was formed in the first step of the pyrolytic reaction, and compound **VIII** was obtained after ring closure of the intermediate **Xa** (or **Xb**). The overall yield of **VIII** was slightly higher when method E was used instead of method D (55% versus 50%).

The hydrochloride salt of guanazine can be prepared in a good yield (73%) when **VIII** is hydrolyzed with 5*M* hydrochloric acid, as previously described [10].

The structures of the different triazole derivatives in this paper, were confirmed by spectroscopic analyses (nmr,

ir and mass spectra). Spectral data have been reported separately [13], and can also be found in the study by Child [7].

In conclusion, guanazine was obtained in relatively high yields from thiosemicarbazide and its *S*-methylisothio ether, using methods A and B, respectively. 4-Arylideneamino derivatives of guanazine were obtained directly from guanazine itself, or from 1-arylidene-5-thiocarbamoyldiaminoguanidines and its *S*-ethylisothio ethers (methods C-E).

EXPERIMENTAL

General.

Melting points (uncorrected) were determined in a heated metal block using open capillary tubes. All compounds were identified by ir, ^{1}H-nmr and mass spectra. The ir spectra were run as potassium bromide pellets on a Perkin-Elmer 157G spectrophotometer. The ^{1}H-nmr spectra were recorded in DMSO-d_6 solution with TMS as the internal standard using a Perkin-Elmer R12B spectrometer. Mass spectra were obtained at 70 eV on an LKB 9000 instrument. Tlc on silica gel plates (Merck 60, F_{254}, precoated 0.2 mm) was used to follow the reactions and to control the purity of the products.

Guanazine (I).

Guanazine was prepared by the following synthetic methods:

Method A.

Finely divided yellow mercuric oxide (HgO, 4.34 g, 0.02 mole) was added in portions to a refluxing mixture of thiosemicarbazide (Merck, 0.91 g, 0.01 mole), magnesium sulfate (6.00 g, 0.05 mole), sulfur (catalytic amount, *ca* 0.05 g), and dry acetone (100 ml). The mixture was boiled for 0.5 hour, then filtered, and the insoluble material was washed with dry acetone (50 ml). The filtrates were combined and the solvent was removed *in vacuo*. The crude residue was recrystallized twice from 95% ethanol, yield 6.85 g (60%) mp 260-261° dec (lit [7] 262-263° dec).

Method B.

The starting material, *S*-methylisothiosemicarbazide hydroiodide (**VII**), was prepared by treatment of thiosemicarbazide (9.10 g, 0.10 mole) with methyl iodide (14.20 g, 0.10 mole) in refluxing absolute ethanol for 2 hours. The mixture was allowed to cool, before filtration and recrystallization from absolute ethanol, yield 18.71 g (80%) mp 138° (lit [14] 140°).

A mixture of **VII** (2.33 g, 0.01 mole) and potassium bicarbonate (1.00 g, 0.01 mole) in 50 ml of absolute ethanol, was refluxed for 3 hours (a slow stream of nitrogen was passed through the reaction mixture in order to trap formed methyl mercaptan in a cooled mixture of sodium hydroxide and hydrogen peroxide). The mixture was allowed to cool during the night. The insoluble potassium iodide was removed by filtration, and the filtrate was concentrated to dryness *in vacuo*. The residue was recrystallized twice from 95% ethanol, yield 6.27 g (55%) mp 260-261° dec (the total yield from thiosemicarbazide was 44%).

Method F.

Guanazine was isolated as hydrochloride salt when **VIII** was hydrolyzed with 5*M* hydrochloric acid for 3 hours, yield 73% (95% ethanol) mp 242-243° dec [12].

4-Arylideneamino-3,5-diamino-4*H*-1,2,4-triazoles.

Method C.

3,5-Diamino-4-(2,6-dichlorobenzylideneamino)-4*H*-1,2,4-triazole (VIII).

A mixture of 0.01 mole of guanazine (**I**) and 2,6-dichlorobenzaldehyde (1.75 g, 0.01 mole) in 50 ml of absolute ethanol, was heated under reflux for 3 hours. The light yellow solution was evaporated to dryness *in vacuo*. The residue was washed with dry ether in order to remove the side product 5-amino-3,4-bis(2,6-dichlorobenzylideneamino)-4*H*-1,2,4-triazole and unreacted 2,6-dichlorobenzaldehyde, before recrystallization from the absolute ethanol, yield 1.03 g (38%) mp 196-198° dec (lit [12] 196-197° dec).

Method D.

Compound VIII.

A mixture of 1-(2,6-dichlorobenzylidene)-5-thiocarbamoyldiaminoguanidine hydrochloride (**IX**, 3.05 g, 0.01 mole) [10,12], magnesium sulfate (6.00 g, 0.05 mole), sulfur (catalytic amount, *ca* 0.5 g), and dry acetone (150 ml) was heated under reflux for 0.25 hour. Finely divided yellow mercuric oxide (4.34 g, 0.02 mole) was added in portions, and the mixture was boiled for 1 hour. The precipitate was collected and washed with dry acetone (50 ml). The combined filtrates were evaporated to dryness and the light yellow residue was recrystallized from absolute ethanol, yield 1.36 g (50%) mp 196-197° dec.

Method E.

The starting material, 1-(2,6-dichlorobenzylidene)-5-(*S*-ethylthiocarbamoyl)diaminoguanidine (**XII**), was prepared from **IX** as we have reported earlier, yield 72% (ethanol/water) mp 135-137° [10,12].

Compound VIII.

A mixture of **XII** (3.33 g, 0.01 mole) and 100 ml of dry pyridine was heated at 90° for 0.25 hour. The solvent was then removed under reduced pressure, and the residue was washed with dry ether before recrystallization from absolute ethanol, yield 2.10 g (77%) mp 196-198° dec (lit [12] 196-197° dec).

Acknowledgements.

I wish to thank Mr. Peter Jahnke, Biomedical Centre, Uppsala, for recording the mass spectra and Dr. Hans Selander for valuable discussions. This work was supported by grants from AB Hässle, Mölndal, Sweden, and from the Swedish Academy of Pharmaceutical Sciences.

REFERENCES AND NOTES

* Correspondence should be addressed to: Ph.D. Håkan Emilsson, Apoteksbolaget AB, S-105 14 Stockholm, Sweden.

[1] R. G. Child and A. S. Tomcufcik, *J. Heterocyclic Chem.*, **2**, 302 (1965).

[2] R. I. Trust, J. D. Albright, F. M. Lovell and N. A. Perkinson, *J. Heterocyclic Chem.*, **16**, 1393 (1979).

[3] G. Pellizzari and A. Cantoni, *Gazz. Chim. Ital.*, **35** I, 291 (1907).

[4] G. Peters, private communication.
[5] G. Pellizzari and A. Ripetto, *Gazz. Chim. Ital.*, **37** II, 317 (1907).
[6] R. Stollé and W. Dietrich, *J. Prakt. Chem.*, **139**, 193 (1934).
[7] R. G. Child, *J. Heterocyclic Chem.*, **2**, 98 (1965).
[8] F. Kurzer and K. Douraghi-Zadeh, *Chem. Rev.*, **67**, 107 (1967).
[9] G. D. Meakins and R. J. Moss, *J. Chem. Soc.*, 993 (1957).
[10] H. Emilsson, K. Luthman and H. Selander, *Eur. J. Med. Chem.-Chim. Ther.*, **21**, 235 (1986).
[11] H. Emilsson, J. Gaarder and H. Selander, *Eur. J. Med. Chem.-Chim. Ther.*, **20**, 333 (1985).
[12] H. Emilsson, A. Lewisson and H. Selander, *Acta Pharm. Suec.*, **20**, 161 (1983).
[13] H. Emilsson and H. Selander, *J. Heterocyclic Chem.*, **25**, 565 (1988).
[14] Kirsten and Smith, *J. Am. Chem. Soc.*, **58**, 800 (1936).