Acta Chemica Scandinavica B 31 (1977) 235—238

# Synthesis of the 1,3,4-Triaza- and 1,4-Diazacycl[3.3.3]azine Systems

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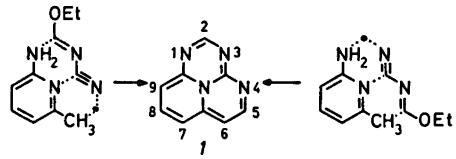
1,3,4-Triazacycl[3.3.3]azine, *1*, and 3-cyano-1,4-diazacycl[3.3.3]-azine, *2a*, have been prepared in low yields from 2-amino-6-methylpyridine by condensation with *N*-cyanoformimidate and ethoxymethylenemalononitrile, respectively. Electrophilic bromination of *1* yielded the three predicted monosubstituted derivatives, but due to *peri* interactions only two di- and no trisubstituted derivatives.

This communication reports synthesis and electrophilic bromination studies of the new unsubstituted 1,3,4-triazacycl[3.3.3]azine, *1*, and the synthesis of 3-cyano-1,4-diazacycl-[3.3.3]azine, *2a*.* The latter system carrying four ring substituents has been prepared earlier [3,4] by different methods. The present work is a continuation of our studies on bridged annulenes,[10,13] which are of considerable theoretical interest.[13]

Condensation of 1 mol of 2-amino-6-methylpyridine, *3*, with 2 mol of ethyl *N*-cyanoformimidate, *4*, gave *1* directly in low yield. It is most reasonable to assume that the first step in the reaction is an attack of the 2-amino group in *3* on *4*. If, instead, the 6-methyl group should react first, the same azacyclazine results. Therefore, no isomers can be formed in the reaction between *4* and a 2,6-disubstituted pyrimidine.[5]

The triazacyclazine *1* is a blue crystalline compound, rather stable both in the solid state and in solution. Its mass spectrum is typical for heteroaromatics with a large molecular ion and abundant doubly charged ions.

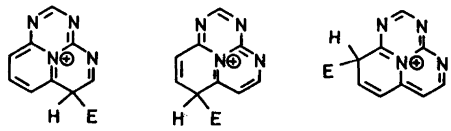



In the mass spectrum of *1* two consecutive losses of HCN are observed. The $^1$H NMR chemical shift values are in the same region ($\delta$ 5.3 – 6.9, *cf.* Experimental) as those of the isomeric 1,3,6-triazacycl[3.3.3]azine ($\delta$ 4.9 – 6.5) [6] and 2,5,8-trimethyl-1,4,7-triazacycl[3.3.3]-azine ($\delta$ 5.5) [4,7] which indicate that they possess a similar degree of aromaticity. In general, physical and chemical properties are very similar for the four known triaza systems.[4–7]

Electrophilic substitution in *1* occurred in positions 6, 7, and 9 as expected (*cf.* structures on Chart 1 and resonance structures in Ref. 6), with approximately the same rate as in the isomeric systems.[4,6] With *N*-bromosuccinimide (NBS), *1* yielded a mixture of three monobromo, two dibromo, but no tribromo derivatives. The most abundant monobromo compound (*ca.* 40 % of total yield of brominated product) is 6-bromo-*1*, *5a*, since its NMR spectrum displays a one-proton singlet signal (H-5) and an ABX-type absorption. The two other monobromo compounds (*ca.* 10 %) could not be separated from each other by thin-layer chromatography. An NMR spectrum of the mixture showed two pairs of AX-type signals from each compound in a 2:1 ratio and they are therefore the 7- and 9-bromo derivatives *5b* and *5c*. Treatment of *5a* with NBS gave only one dibromo compound which

* For definitions and nomenclature of cyclazines, *cf.* Refs. 1 and 2.

*Chart 1.* Some resonance structures for electrophilic substitution intermediates of *1*.

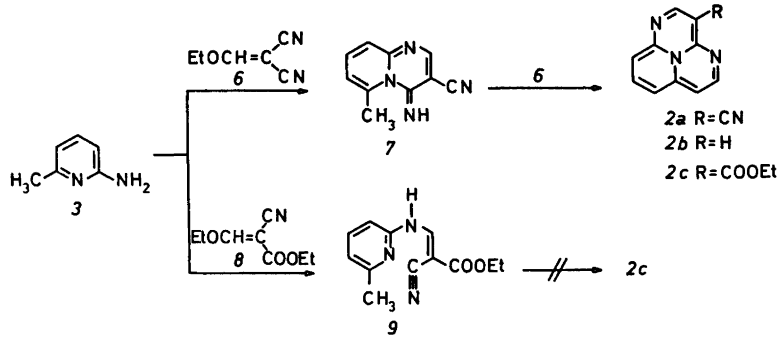


thus is 6,7-dibromo-*1*, *5d*, or 6,9-dibromo-*1*, *5e*. We prefer *5e* since the *peri* relation of bromine atoms in the 6 and 7 positions would cause bond and angle deformations of the ring system.[8] The second dibromo compound isolated (*ca.* 20 %) should the be 7,9-dibromo-*1*, *5f*. Attempts to brominate *5e* or *5f* with NBS resulted in decomposition of the cyclazine system. In other cyclazine systems [4-6] complete bromination has occurred in the positions predicted from resonance structures of the electrophilic substitution intermediates similar to those in Chart 1. The failure to produce a tribromo derivative of *1* is therefore most likely due to the *peri* interaction which would result from two bromine atoms at C-6 and C-7.[8]

The second part will describe experiments directed toward the preparation of 1,4-diazacycl[3.3.3]azine, *2b*, which is one of seven isomers, with non-adjacent, peripheral nitrogen atoms.[5] A tetrasubstituted derivative, dimethyl 3-cyano-2-methylthio-1,4-diazacycl[3.3.3]azine-5,6-dicarboxylate, was reported recently.[3] The possibility of preparing *2b* from this compound by removing as many as four substituents from the not too stable ring system without destroying it seemed rather small. A monosubstituted derivative would therefore be a better precursor for the parent system. Condensation of equimolar amounts of 2-amino-6-methylpyridine, *3*, and ethoxymethylenemalononitril, *6*, at 100 °C for 1 h yielded the bicyclic system *7*. Its structure is in agreement with NMR and mass spectral data (*cf.* Experimental). Ring closure of *7* to *2a* was unusually difficult and it did not succeed with 1 additional mol of *6* under the above-mentioned conditions or in other solvents (*cf.* Experimental). Attempts with acetic formic anhydride or acetic anhydride [9] with or without pyridine as a base were also unsuccessful. Only after careful purification of *7*, followed by the heating of it with 1 mol of *6* for 7 h at 150 °C without solvent, did we obtain *2a*, unfortunately in a yield too low for subsequent preparative decyanation with polyphosphoric acid (PPA) [14] to *2b*. Condensation of *3* with ethoxymethylene cyanoacetate, *8*, which would give *2c* was also tried, but from this reaction only the open intermediate (C≡N, IR) *9* resulted. Ring closure of *9* under the different conditions used to obtain *2a* was totally unsuccessful in the present case.

The structure of *2a* is supported by $^1$H NMR and mass spectral data (*cf.* Experimental). It is a green crystalline compound, fairly stable both in the solid state and in solution. The $^1$H NMR chemical shift values for *2a* ($\delta$ 5.2 – 6.9) are in the same region as those for the isomeric 3-cyano-1,9-diaza system ($\delta$ 5.1 – 6.8).[10] Electron attracting groups seem to stabilize the cycl[3.3.3]azine systems considerably and bring the $\delta$-values for the

*Chart 2.* Schemes for the synthesis of the 1,4-diazacycl[3.3.3]azine system.



ring protons downfield. Therefore it is difficult to evaluate the effect of the relative positions of the peripheral N-atoms in isomeric azacycl-[3.3.3]azine systems on their "aromaticity" [11] from substituted cyclazine systems like *2a*.

## EXPERIMENTAL

*General.* NMR spectra were recorded with a Jeol MH-60 and a Bruker WH 270 spectrometer, using tetramethylsilane (TMS) as internal reference. UV and visible spectra were measured in ethanol solution with a Cary Model 15 spectrophotometer. IR spectra were determined in KBr with a Perkin-Elmer 337 spectrophotometer. Mass spectra were obtained with a GEC-AEI 902 mass spectrometer at the Department of Medical Biochemistry, University of Göteborg. Thin-layer chromatography was performed on silica gel 60F 254 (Merck) and the colorless spots were visualized with short-wave ultraviolet light.

*Preparation of 1,3,4-triazacycl[3.3.3]azine*, 1. A mixture of 500 mg (4.6 mmol) of 2-amino-6-methylpyridine, *3*, and 900 mg (9.2 mmol) of ethyl *N*-cyanoformimidate,[12] *4*, was kept at 140 °C for 4 h and then cooled to room temperature. The product was dissolved in EtOAc. The insoluble material was filtered off and the solution evaporated to dryness. The residue was purified first by column chromatography on silica gel (EtOAc-MeOH; 9:1), then by preparative TLC (EtOAc-MeOH; 3:1). Yield: < 5 % of a blue solid *1*, m.p. 191–194 °C. UV: $\lambda_{max}$ ($\varepsilon$) 217 (9470), 247 (18 720); 332 sh. (14 450), 337 (15 150), 356 sh. (8870), 368 sh. (5470), 375 sh. (5280), 525 sh. (220), 569 (420), 617 (570), 672 (380) nm, NMR ($CDCl_3$): $\delta$ 5.31 (1H, d, H-6), 5.53 (1 H, d, H-7 or H-9), 5.60 (1 H, d, H-7 or H-9), 6.69 (1 H, d, H-5), 6.75 (1 H, t, H-8), 6.85 (1 H, s, H-2), $J_{5,6}=6.0$, $J_{7,8}=J_{8,9}=8.0$ Hz, MS: M+ = 170.0585. Calc. for $C_9H_6N_4$: 170.0592.

*Bromination of* 1. (a) To a solution of 32 mg (0.18 mmol) of *1* in 3 ml of $CH_2Cl_2$, 33 mg (0.18 mmol) of NBS was added. The mixture was applied directly to preparative TLC plates (EtOAc-MeOH; 5:1). Three bands, two blue ($R_F=0.10$, $R_F=0.52$) and one blue-green ($R_F=0.30$) were scraped off and eluted. The latter and the blue with the largest $R_F$ value contained the dibrominated compounds *5f* and *5e*, respectively. Yield: 4 mg of *5f*, m.p. 260 °C and 5 mg of *5e*, m.p. 265–267 °C. The blue zone ($R_F=0.10$), on the other hand, consisted of three components, all monobrominated *1*. One of them, *5a*, could be separated from the others on preparative TLC plates developed three times in EtOAc. Yield: 7 mg, m.p. 235–237 °C, of a green solid, *5a*, and 2 mg of a green solid, *5b*+*5c*. *5a:* NMR ($CDCl_3$) $\delta$ 5.63 (1 H, d, H-7 or H-9), 5.83 (1 H, d, H-7 or H-9), 6.75 (1 H, t, H-8), 6.76 (1 H, s, H-2 or H-5), 6.81 (1 H, s, H-2 or H-5), $J_{7,8}=J_{8,9}=8.0$ Hz, MS: M+ = 247.9690 ± 0.003. Calc. for $C_9H_5N_4{}^{79}Br$: 247.9698. *5b*+*5c*: NMR ($CDCl_3$) $\delta$ 5.36 (1 H, d, H-7 or H-9), 5.52 (1 H, d, H-6), 6.70 (1 H, d, H-5), 6.73 (1 H, s, H-2), 6.78 (1 H, d, H-8), $J_{5,6}=6.0$, $J_{7,8}$ or $J_{8,9}=9.2$ Hz and 5.20 (1 H, d, H-6), 5.30 (1 H, d, H-7 or H-9), 6.61 (1 H, d, H-5), 6.85 (1 H, s, H-2), 6.86 (1 H, d, H-8), $J_{5,6}=6.3$, $J_{7,8}$ or $J_{8,9}=8.7$ Hz. The integrals indicate a 2:1 ratio of *5b* and *5c*. MS:M+ = 247.9680 ± 0.003. Calc. for $C_9H_5N_4{}^{79}Br$: 247.9698. *5e:* NMR (acetone-$d_6$) $\delta$ 6.01 (1 H, d, H-7), 7.05 (1 H, s, H-2 or H-5), 7.07 (1 H, s, H-2 or H-5), 7.45 (1 H, d, H-8), $J_{7,8}=8.7$ Hz, MS: M+ = 327.876 ± 0.003. Calc. for $C_9H_4N_4{}^{79}Br^{81}Br$: 327.8784. *5f:* NMR ($CDCl_3$) $\delta$ 5.77 (1 H, d, H-6), 6.95 (1 H, d, H-5), 7.07 (1 H, s, H-2 or H-8), 7.29 (1 H, s, H-2 or H-8), $J_{5,6}=6.6$ Hz, MS: M+ = 327.878 ± 0.003. Calc. for $C_9H_4N_4{}^{79}Br^{81}Br$: 327.8784.

(b) To a solution of 8 mg (0.04 mmol) of *1* in 2 ml of $CH_2Cl_2$ 25 mg (0.14 mmol) of NBS was added. As performed above, the mixture was applied to preparative TLC plates. This time dibrominated *5e* resulted and only traces of *5f*.

*Preparation of* 7. A mixture of 5.0 g (46.3 mmol) of 2-amino-6-methylpyridine, *3*, and 5.7 g (46.7 mmol) of ethoxymethylenemalononitrile, *6*, was kept at 100 °C for 15 min. The reaction product was air-dried overnight; 9 g of crude material was obtained. Chromatographic purification on $Al_2O_3$ ($CH_2Cl_2$) yielded 7 g (82 %) of a white solid *7*, m.p. 180 °C. IR: 3310, 3250 (NH), 2220 $cm^{-1}$(C≡N), UV: $\lambda_{max}$ ($\varepsilon$) 266 sh. (10 190), 273 (11 600), 326 (28 780) nm, NMR (DMSO-$d_6$): $\delta$ 2.43 (3 H, s, $CH_3$), 7.01 (2 H, d, H-7 and H-9), 7.67 (1 H, t, H-8), 8.62 (1 H, s. H-2), $J_{7,8}=J_{8,9}=7.6$ Hz, MS: M+ = 184.

*Ring closure of* 7 *to* 2a. (a) An attempt to synthesize *2a* from *7* by using one additional mol of *6* at 100 °C was not successful. The result was also negative when a small amount of base (pyridine or NaOEt) was present. The use of hexamethylphosphoric triamide (HMPA) or *o*-dichlorobenzene as solvents and varying the temperature from 100 °C to 170 °C also failed to give *2a*. The reactions were followed by analytical TLC.

(b) Formylation ($HCOOH/Ac_2O$) or acetylation ($Ac_2O$) of *7* with or without pyridine present as a base, at different temperatures 20 to 140 °C) and different reaction times (up to 2 days) gave no ring closure.

(c) A mixture of 1.0 g (5.4 mmol) of *7* and 0.7 g (5.7 mmol) of *6* was heated at 150 °C for 7 h. The work-up procedure was the same as for *1*, yielding < 1 % of a green solid *2a*. IR: 2220 $cm^{-1}$ (C≡N), NMR ($CDCl_3$): $\delta$ 5.18 (1 H, d, H-6), 5.31 (1 H, d, H-7 or H-9), 5.66 (1 H, d, H-7 or H-9), 6.45 (1 H, d, H-5), 6.62 (1 H, t, H-8), 6.83 (1 H, s, H-2), $J_{5,6}=6.3$, $J_{7,8}=J_{8,9}=8.2$ Hz, MS: M+ = 194.058 ± 0.003. Calc. for $C_{11}H_6N_4$: 194.0592.

*Preparation of* 9. A mixture of 5.0 g (46.3 mmol) of 2-amino-6-methylpyridine, *3*, and 7.8 g (46.2 mmol) of ethoxymethylenecyanoacetate, *8*, was kept at 100 °C for 15 min. The sample was air-dried overnight and purified on $Al_2O_3$ ($CH_2Cl_2$). Yield: 9 g (84 %) of a white solid *9*, m.p. 117–118 °C. IR: 3290, 3240 (NH), 2210 (C≡N), 1670 $cm^{-1}$ (C=O), UV: $\lambda_{max}$ ($\varepsilon$) 268 sh. (6410), 274 (8980), 326 (34 000) nm, NMR ($CDCl_3$): $\delta$ 1.37 (3H, t, ester protons), 2.50 (3 H, s, $CH_3$), 4.30 (2 H, q, ester protons), 6.64 (1 H, d, H-3 or H-5), 6.92 (1 H, d, H-3 or H-5), 7.56 (1 H, t, H-4), 8.75 (1 H, d, vinyl proton), $J_{7,8} = J_{8,9} = 7.7$ Hz, MS: $M^+ = 231$.

*Acknowledgements.* Financial support from the Swedish Natural Science Research Council and from the grant "Främjande av ograduerade forskares vetenskapliga verksamhet" to the University of Göteborg is gratefully acknowledged. We thank Mrs. Gun Engström for technical assistance.

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Received October 6, 1976.