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Synthesis of a 1,3,6,7-Tetraazacycl[3.3.3]azine*

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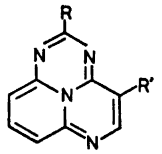
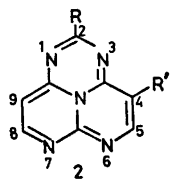
The synthesis and some spectral properties of 4-carbethoxy-1,3,6,7-tetraazacycl[3.3.3]azine, *2a*, are described.

In two preceding communications[1,2] we have reported the synthesis and spectral properties of several members of the 1,3,6-triazacycl[3.3.3]-azine system *1*. This paper describes the preparation of and proof of structure for the 1,3,6,7-tetraazacycl[3.3.3]azine *2a*. The synthesis of this new hetero-



1

R = H and CH_3
R' = H, CN, and COOEt



2

R = CH_3
R' = COOEt

cyclic system was attempted to obtain a compound with the nitrogen atoms in a symmetrical arrangement and thus, if the rings are unsubstituted, suitable for electron spin resonance studies (*cf.* Refs. 3 and 4). So far, however, we have only succeeded in preparing *2a* ($R = CH_3$ and $R' = COOC_2H_5$).

The general synthetic scheme utilized for the synthesis of *1*,[1] namely condensation of 2,4-diaminopyrimidine, *3*, with one mole of ethyl ethoxymethylenecyanoacetate, *4*, in refluxing benzene, was employed. The condensation product, *5*,** was then acetylated with acetic anhydride in refluxing

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** *Cf.* p. 638 and Chart 2 for a discussion of an alternate structure.

p-xylene to yield *6*. The cyclization-dehydration step was finally realized with *p*-toluenesulfonic acid in refluxing diphenyl ether, giving the desired cyclazine *2a* as a bright-red solid in 9 % yield. The sequence of reactions is outlined in Chart 1.

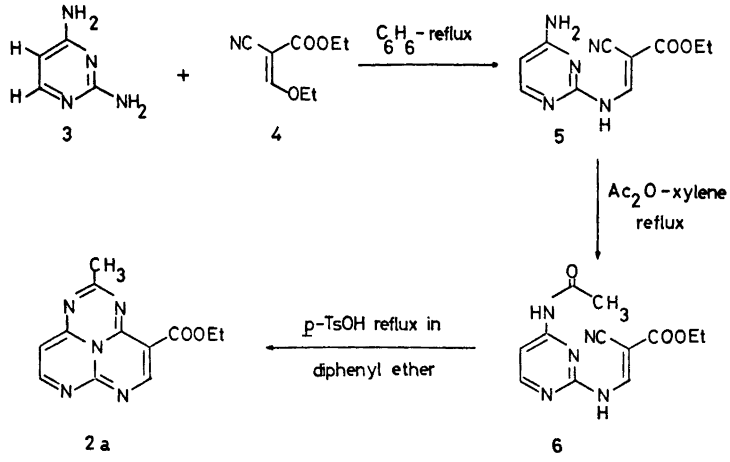


Chart 1

Reaction scheme for the synthesis of *2a*.

The structural proofs of the intermediates and of the final product are based on the following data. The mass spectrum of the monocondensation product *5* showed a molecular ion at $m/e = 233$, and IR spectral bands at 2220 (CN), 3200 – 3400 (NH_2), and 1690 cm^{-1} (ester carbonyl). The NMR spectrum (Fig. 1) displayed the expected types of protons but, surprisingly,

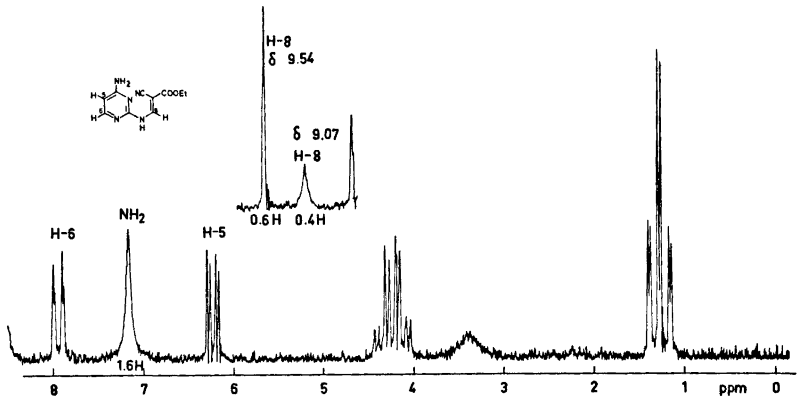
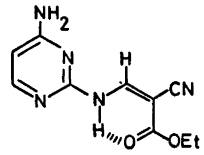


Fig. 1. NMR spectrum of *5*.

the methyl ($\delta = 1.45$), the methylene ($\delta = 4.30$), and the aromatic protons (AX quartet with the doublets centered at $\delta = 6.30$ and 8.03, respectively) were composed of two overlapping sets of bands, separated by *ca.* 2 cps at 60 MHz. The olefinic proton appeared as two bands, one sharp at $\delta = 9.54$ (0.6 H) and one broader at $\delta = 9.07$ (0.4 H). The NH resonances appeared at $\delta = 7.20$ (1.6 H), and on addition of deuterium oxide this band vanished, while all the others, including the olefinic ones, remained. The double pattern is probably due to the presence of a *cis* and a *trans* form of *5* in the solution, even if structure *7* in Chart 2 cannot be excluded. One of them could be stabilized by internal hydrogen bonding, as pictured in *5a*. Since the condensation product, possibly a mixture of *5* and *5a*, was completely homogeneous on



5a

the thin layer chromatograms, it was used after recrystallization for the next step. Treatment of *5* with acetic anhydride in boiling *p*-xylene yielded the *N*-acetyl derivative *6*, which had the expected molecular weight ($M^+ = 275$) and showed a cyano (2230 cm^{-1}) and several carbonyl bands (1648, 1712, and 1728 cm^{-1}) in its IR spectrum. The NMR spectrum displayed, in addition to the bands present in the spectrum of *5*, a CH_3-CO band at $\delta = 2.16$. This resonance, as well as the others, consisted of two sets of bands separated by *ca.* 2 cps (at 60 MHz). Since the spectrum of *6* also showed a double pattern, identical with that in the spectrum of *5*, and with the same ratio between the olefinic proton resonances, we believe that the same mixture of *cis* and *trans* forms was present.

At this stage we wish to point out that the condensation of *3* with *4* could lead to compound *7* rather than to *5*. As outlined in Chart 2, the isomeric cyclazine *9* would then result. It is not possible to distinguish directly between *5* and *7* using NMR or any other conventional spectral methods. We had noticed, however, that in the spectrum of the monocondensation product (*5* or *7*) the chemical shift of H-6, which absorbs at lower field than H-5, since it is adjacent to N-1 in the pyrimidine ring, was drastically altered on acylation of the remaining free amino group, while the corresponding change in chemical shift of H-5 was only about one half as large (*cf.* Chart 3).* The rather large change in δ_{H-6} after acetylation would indicate that the free amino group is adjacent to the proton suffering the larger chemical shift

* This type of effect was first observed in monoamino carbo and heterocyclic aromatic compounds and was then referred to as an *ortho* effect.[5-8] The shifts on acylation were of the same order of magnitude as the ones observed in the present case.

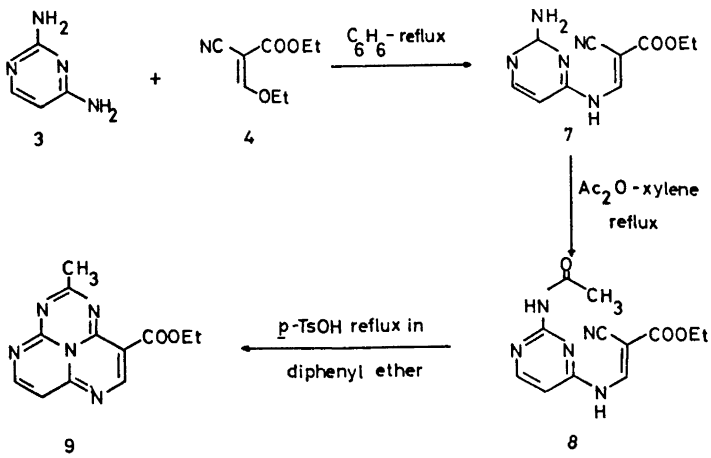


Chart 2

Reaction scheme for the formation of *9*.

change. Consequently, we feel that the first condensation product possesses structure *5*. To support this assumption we studied the change in the chemical

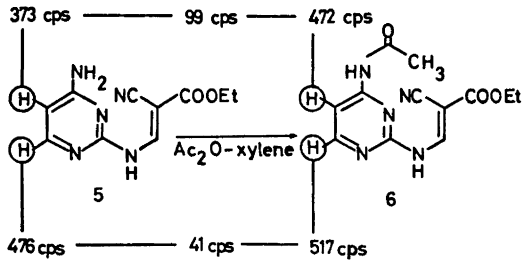


Chart 3

Chemical shift changes on acetylation of *5*.

shifts of the analogous protons in the isomeric 2-amino-4-methylpyrimidine, *10*, and 4-amino-2-methylpyrimidine, *12*, when the amino groups in these compounds were acetylated. As a further correlation, the same shift was determined when 2,4-diaminopyrimidine, *14*, was converted to its *N*,*N*-diacetyl derivative, *15*. For the assignment of chemical shifts to the two aromatic protons in the model compounds, the hydrogen atom adjacent to a ring nitrogen atom was again assumed to resonate at lower field. The results, which are summarized in Chart 4, clearly show that the structure of the condensation product is *5*.

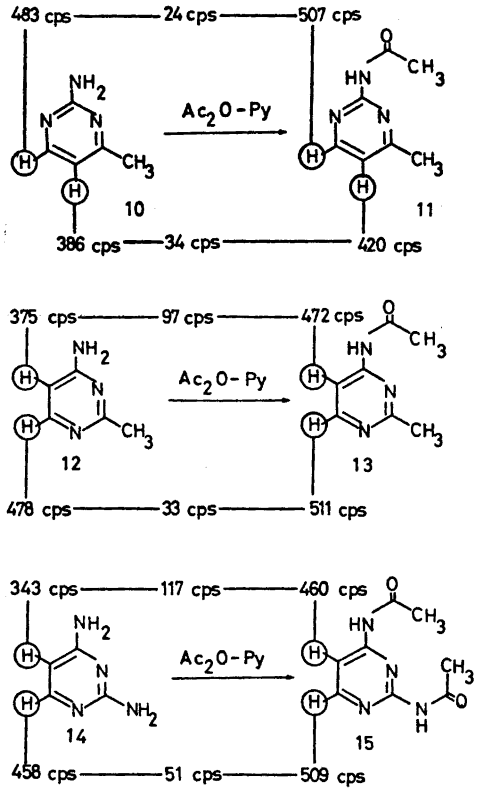


Chart 4

Chemical shift changes on acetylation of model compounds *10*, *12*, and *14*.

The desired cyclazine, *2*, had a molecular weight of 257.0907 ± 0.0013, determined by mass spectrometry, corresponding to the molecular formula $C_{12}H_{11}N_5O_2$ (calc. 257.0913). The IR spectrum lacked amino and cyano absorption, but had a carbonyl band around 1600 cm^{-1}. The UV spectrum (Fig. 2) had maxima at 224, 255, 320, 339 (sh), 346, 355, 410, 455, 490, and 522 nm (log ε: 4.25, 4.19, 4.26, 4.34, 4.32, 4.16, 2.24, 2.17, 2.45, and 2.50, respectively) and was very similar to the spectrum of the corresponding 1,3,6-triazacycl[3.3.3]azine *1* ($R = CH_3$ and $R' = COOEt$).[1] Finally, the NMR spectrum displayed two sets of one-proton doublets of an HX type at $\delta = 7.75$ and 5.76 ($J = 5$ cps), corresponding to H-8 and H-9, respectively, and a one-proton singlet at $\delta = 8.22$, derived from H-5. The spectrum with assignments is reproduced in Fig. 3 and is in complete accord with the proposed structure. The mass spectrum of *2* (*cf.* Fig. 4) shows a fragmentation pattern which is entirely analogous to that of the corresponding cyclazine *1* ($R = CH_3$ and $R' = COOEt$).[2] Strong support for the aromatic nature of this new hetero-

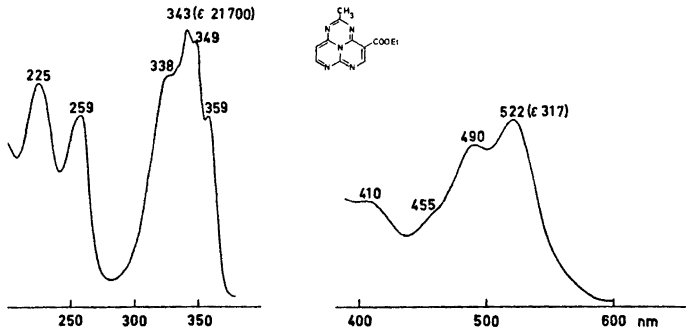


Fig. 2. UV spectrum of *2*.

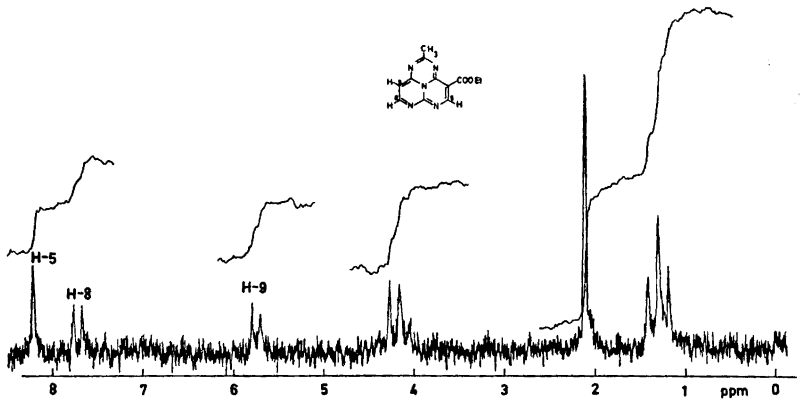


Fig. 3. NMR spectrum of *2*.

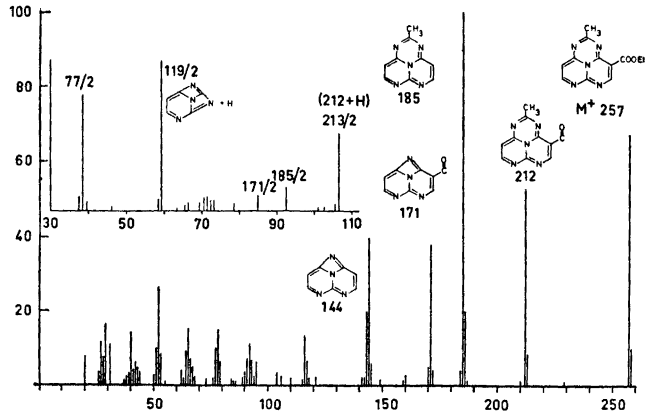


Fig. 4. Mass spectra (singly and doubly charged ions) of *2*.

Table 1. Charge densities.

Position / Compound	1	2	3	3a	4	5	6	6a	7	8	9	9a	10	11	12	13
2	−0.321	+0.329	−0.322	+0.229	−0.136	+0.210	−0.322	+0.222	−0.321	+0.168	−0.120	+0.201	+0.438	+0.346	−0.613	+0.102
2a	−0.339	+0.223	−0.339	+0.188	−0.136	+0.152	−0.339	+0.195	−0.339	+0.152	−0.136	+0.188	+0.530	–	–	–

Table 2. Free valences.

Position / Compound	2	3a	4	5	6a	8	9	9a	10	11
2	0.444	0.190	0.168	0.463	0.166	0.433	0.455	0.170	0.445	0.245
2a	0.428	0.156	0.463	0.419	0.147	0.419	0.463	0.156	0.335	–

Table 3. Bond orders.

Bond / Compound	1–2	1–9a	2–3	3–3a	3a–4	3a–10	4–5	5–6	6–6a	6a–7	6a–10	7–8	8–9	9–9a	9a–10	4–11	11–12	11–13
2	0.655	0.545	0.634	0.572	0.541	0.430	0.612	0.658	0.548	0.586	0.433	0.614	0.685	0.592	0.424	0.411	0.708	0.368
2a	0.652	0.531	0.652	0.531	0.582	0.462	0.687	0.626	0.557	0.557	0.472	0.626	0.687	0.582	0.462	–	–	–

cyclic system is the occurrence of fairly abundent doubly charged ions in the mass spectrum (*cf.* Fig. 4).*

Before the synthesis of system *2* was attempted, we carried out simple HMO calculations on the unsubstituted compound (*2a:* R = R′ = H) and the one actually prepared (*2:* R = CH_3 and R′ = COOEt) using the same parameters as chosen for the triazacyclazine *1* (*cf.* Table 2 in Ref. 1). The resonance energies obtained, 5.6748β for *2* and 4.9684β for *2a*, are of the same order of magnitude as those for the 1,3,6-triazacycl[3.3.3]azines,[1] and the highest negative charge densities (at the carbon atoms) are found in position 9, as was the case in *1* and its derivatives.[1] The values for charge densities, free valences, and bond orders are listed in Tables 1, 2, and 3.

Finally we wish to point out that the various steps in the present synthesis usually required more vigorous conditions to overcome the higher degree of inertness of the 2,4-diaminopyrimidine compared to the corresponding pyridine analog.

EXPERIMENTAL

Molecular orbital calculations were performed with a program, which incorporated the ω-technique of Streitwieser, on an IBM Model 360 – 50 digital computer at the Computing Center of Göteborg. The program, Hückel II (author: Dr. S. Weckherlin), was obtained through the courtesy of the "Deutsches Rechenzentrum", Darmstadt. Nuclear magnetic resonance spectra were recorded with a Varian Model A-60 spectrometer with tetramethylsilane as internal reference. Ultraviolet and visible spectra were measured in ethanol with a Cary Model 15 spectrophotometer. Mass spectra were determined with an LKB 900 mass spectrometer at the Laboratory for Mass Spectrometry, Karolinska Institutet, Stockholm, and the exact measurements were obtained with a GEC-AEI MS 902 instrument at the Department of Medical Biochemistry, University of Göteborg. Thin layer chromatography was performed on Silica Gel GF_{254} (Merck), according to Stahl, developed with chloroform – methanol (85 : 15) and visualized with short-wave ultraviolet light. For column chromatography, silica gel, 0.05 – 0.2. mm (Merck) was used.

Condensation of 2,4-diaminopyrimidine with ethyl ethoxymethylenecyanoacetate to 5. To a suspension of 11.0 g (0.10 mol) of 2,4-diaminopyrimidine in 1.3 l of benzene was added 16.9 g (0.10 mol) of ethyl ethoxymethylenecyanoacetate. The reaction mixture was heated under reflux for 48 h. After the reaction mixture had cooled to room temperature, it was filtered to remove a small amount of brown, solid material, and the benzene was evaporated under reduced pressure. The residual yellow solid was recrystallized five times from methanol to yield 4.5 g (21 %) of a pale-yellow, homogeneous (TLC) solid; IR (KBr) 3200 – 3400 (NH), 2200 (CN), and 1690 (C=O) cm^{-1}; NMR (d_6-dimethyl sulfoxide) aromatic doublet, centered at 6.30 (1H), vinyl singlets at 9.54 (0.4H) and 9.07 (0.6H), amino NH at 7.20 (3H) ppm; MS: $M^+ = 233$. Chromatography of this material, for the purpose of obtaining a higher yield, was not attempted because of its extreme insolubility in most solvents.

Acetylation of 5 to 6. A suspension of 1.0 g (0.004 mol) of *5* in 70 ml of *p*-xylene was heated under reflux for 24 h with 3 ml of acetic anhydride. The resulting solution was allowed to cool to room temperature, and the white, crystalline solid, which had precipitated, was filtered and dried to yield 0.9 g (77 %) of pure *6* (TLC); IR (KBr) 3280 (NH), 2230 (CN), 1772 and 1788(C=O) cm^{-1}; NMR (d_6-dimethyl sulfoxide) broad NH at 10.83 (2H), vinylic singlet at 8.92 (1H), two methylene quartets, centered at 4.22 (2H), and two methyl triplets, centered at 1.30 (3H) ppm; MS: $M^+ = 275$.

Cyclization of 6 to 2a. To a solution of 1.0 g (0.004 mol) of *6* in 150 ml of refluxing diphenyl ether was added 10 mg of *p*-toluenesulphonic acid. The solution immediately

* For a discussion of doubly charged ions in nitrogen-heterocyclic aromatic systems, *cf.* Ref. 2 and references therein.

became deep red-brown. Refluxing was continued for 15 min. The now turbid reaction mixture was allowed to cool and was poured onto a column of 150 g of silica gel, which had been packed in ethyl acetate. The diphenyl ether was removed by elution with *ca.* 1 l of ethyl acetate. Further elution with *ca.* 1 l of ethyl acetate containing 2 % of methanol produced a bright-red band. The eluate containing this material was collected and evaporated under reduced pressure to yield a red solid. The solid was redissolved in cold benzene and the solution filtered. The benzene was removed *in vacuo* to yield 90 mg of *2*, which was judged homogeneous by means of TLC. The NMR spectrum ($CDCl_3$) and other spectral data are reported above.

2-Acetamido-4-methylpyrimidine, 11. 2-Amino-4-methylpyrimidine, *10*, (Fluka) was acetylated to *11* by the procedure used to prepare *6*. The compound melted at 151 – 154°; lit. m.p. 152 – 154°.[9]

4-Amino-2-methylpyrimidine, 12, was prepared from 4-amino-6-chloro-2-methylpyrimidine [10] by the method of Budesinsky [11] and acetylated as described above; m.p. 145 – 146°, lit. m.p. 140 – 141°.[12]

2,4-Diaminopyrimidine, 14, was prepared by the method of Brown,[13] and acetylated as described above to 2,4-bisacetamidopyrimidine, *15*, m.p. 240 – 243°.

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REFERENCES

1. Ceder, O. and Andersson, J. E. *Acta Chem. Scand.* **26** (1972) 596.
2. Ceder, O. and Andersson, J. E. *Acta Chem. Scand.* **26** (1972) 611.
3. Atherton, N. M., Gerson, F. and Murrell, J. N. *Mol. Phys.* **6** (1963) 265.
4. Gerson, F. and van Voorst, J. D. W. *Helv. Chim. Acta* **46** (1963) 2257.
5. Ribera, A. and Rico, M. *Tetrahedron Letters* **1968** 535.
6. Brown, R. F. C., Radom, L., Sternhell, S. and Rae, I. D. *Can. J. Chem.* **46** (1968) 2577.
7. Zanger, M., Simons, W. W. and Gennaro, A. R. *J. Org. Chem.* **33** (1968) 3673.
8. Andrews, B. D., Rae, I. D. and Reichert, B. E. *Tetrahedron Letters* **1969** 1859.
9. Whitlock, B. J., Lipton, S. H. and Streng, F. M. *J. Org. Chem.* **30** (1965) 115.
10. Whitehead, C. W. and Traverso, J. J. *J. Am. Chem. Soc.* **80** (1958) 2185.
11. Budesinsky, S. *Collect. Czech. Chem. Commun.* **14** (1949) 223.
12. Den Hertog, H. J., Van Der Plas, H. C., Pieterse, M. J. and Streef, J. W. *Rec. Trav. Chim.* **84** (1965) 1569.
13. Brown, D. J. *J. Soc. Chem. Ind. (London)* **69** (1950) 353.

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