

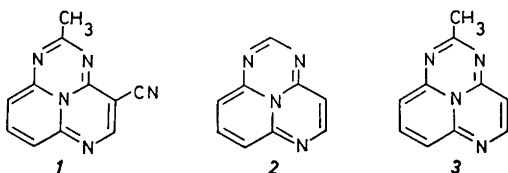
Decyanation of 4-Cyano-2-methyl-1,3,6-triazacycl[3.3.3]azine with Polyphosphoric Acid*

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Decyanation of 4-cyano-2-methyl-1,3,6-triazacycl[3.3.3]azine, **1**, with polyphosphoric acid at 200° yields 2-methyl-1,3,6-triazacycl[3.3.3]azine, **3**. The effect of $\text{Eu}(\text{fod})_3$ on the chemical-shift values of the protons in **3** are reported. The results allow shift assignments to H-7 and H-9.

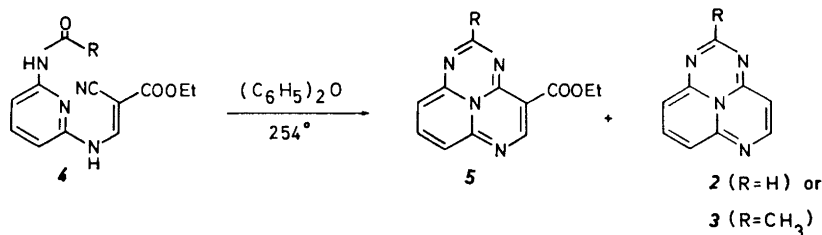
2-Methyl-4-cyano-1,3,6-triazacycl[3.3.3]azine, **1**, can be easily prepared in quantities¹ and our earlier studies on the chemical and spectral properties of the 1,3,6-triazacycl[3.3.3]azine system have been performed with this derivative. The cyano group in **1** causes an extension of the conjugated system, blocks a position susceptible to substitution, and has a directive and deactivating effect in electrophilic substitution reactions.² For these reasons it would be more desirable to carry out such studies on **2**¹ or **3**.¹ Neither of these compounds has been available in amounts sufficient for investigations of this



kind. The present communication describes an improved method of synthesis for 2-methyl-1,3,6-triazacycl[3.3.3]azine, **3**, and reports its NMR spectra in CDCl_3 and CF_3COOH solutions. In addition, the chemical shifts of H-7 and H-9 are assigned with the help of the chemical-shift reagent $\text{Eu}(\text{fod})_3$.³

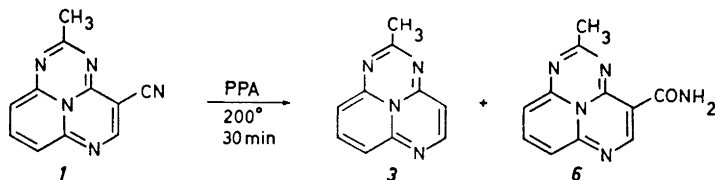
We have earlier obtained minute amounts of **2** and **3** when **4** ($\text{R} = \text{H}$ or CH_3) was ring-closed in diphenylether at 250°.¹ Attempts to increase the yields of **2** or **3** by scaling up or modifying the decarboxylation conditions

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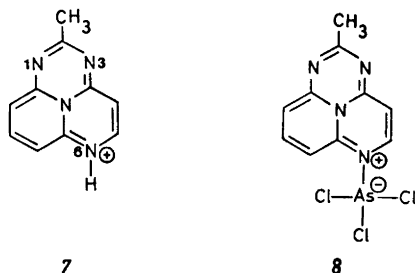
(*e.g.* by varying the reaction time, temperature, concentration, medium, by the use of *p*-toluenesulfonic acid as a catalyst, *etc.*) have not been very successful.

Mosby has reported ⁴ that 2,3,6,7-tetramethylnaphthalene-1,4-dinitrile lost the two cyano groups and gave a "good yield" of 2,3,6,7-tetramethylnaphthalene when the dinitrile was heated to 200° in polyphosphoric acid. Snyder and Elston ⁵ observed that aromatic nitriles were converted to amides when they were heated to *ca.* 100° in polyphosphoric acid for 1–2 h. When *1* was kept in polyphosphoric acid ⁶ at 200° for 30 min, a 25 % yield of *3* and small amounts of the amide *6* were isolated after chromatographic work-up.



At lower reaction temperatures, (100°; 2h), the major product was the amide *6*, which displays physical and spectral properties (*cf.* Experimental) similar to those of the other members of this system. Attempts to prepare *2* from its 4-cyanoderivative by the same method failed, since *2* decomposes in warm polyphosphoric acid.

The NMR spectra earlier reported were mostly recorded in AsCl_3 and CF_3COOD , where the solubility of the cyclazines is sufficient. These solutions are red, while the solutions in nonacidic, organic solvents are dark-blue. In CF_3COOH and AsCl_3 , where the shifts for the corresponding protons are the same, we propose that cyclazinium ions of, *e.g.*, types *7* and *8* are formed. This



assumption is supported by the observation⁷ that a red hydrochloride is formed when dry HCl is passed through a chloroform solution of *1*. The δ -values for the protons in *3* are listed in Table 1. Good correlation is observed between them and the charge-density values¹ at the sp^2 -hybridized carbon atoms to which the protons are attached. On this basis H-7 and H-9 are assigned the chemical shift values 5.81 and 5.35 ppm, respectively. These assignments agree with the results of lanthanide-shift reagent studies on *3* (*vide*

Table 1. Charge densities^a and chemical-shift values (ppm) for the protons in *3* in CDCl₃ and CF₃COOH.

	Charge densities	CDCl ₃	CF ₃ COOH	$\Delta\delta$
H-5	+0.164 (C-5)	7.07	8.15	1.08
H-8	+0.099 (C-8)	6.77	7.97	1.20
H-7	-0.132 (C-7)	5.81	7.23	1.42
H-9	-0.136 (C-9)	5.35	6.81	1.46
H-4	-0.148 (C-4)	4.97	6.28	1.31
CH ₃	-	1.67	2.27	0.60

^a The charge-density values quoted in Table 1 have been calculated¹ for *2*, but they are assumed to be applicable also to the corresponding atoms in *3*.

infra). The displacement of the ring-proton resonances 1.0–1.4 ppm to lower field (*cf.* Table 1) when the medium is changed from CDCl₃ to CF₃COOH indicates that the 12π -electron periphery becomes protonated in the acid medium. The NMR spectrum of *3* in CF₃COOH or in H₂SO₄ displays no CH₂ signal and the five aromatic proton signals show a 1:1:1:1:1 ratio. The same spectrum of *3* recorded in D₂SO₄ displays an identical ratio for the aromatic proton signals, which indicates that none of these protons have been exchanged for deuterium.* Although we cannot localize the >NH⁺ signal in the NMR spectrum, we conclude that protonation has occurred on nitrogen. Three sites of protonation are possible (N-1, N-3, and N-6; *cf.* structure 7), but it is not possible to predict from the NMR and electronic spectral data, or from the charge-density values for N-1, N-3, and N-6 (-0.352, -0.354, and -0.341, respectively),¹ if one of these atoms is preferentially protonated. Alkylation of *3*, however, results in three *N*-alkyl derivatives,⁹ with one of them predominating. When the NMR spectrum of *3* was recorded in CF₃COOD or D₂SO₄, the 2-methylprotons were completely exchanged in *ca.* 20 min. The reactivity of this methyl group will be discussed in a subsequent communication.⁹

It has proved difficult to assign chemical-shift values to H-7 and H-9 in the 1,3,6-triazacycl[3.3.3]azine system.** We have therefore studied the effect of Eu(fod)₃-*d*₂₇³ on *3*, where the peripheral *N*-atoms represent three possible sites of coordination. The charge-density values for these *N*-atoms are very

* *Cf.* the *C*-protonation of cycl[3.2.2]azine.⁸

** The assignment for H-7 and H-9 in Ref. 1, Figs. 3–5, should have the order indicated on those spectra.

close (*cf.* footnote to Table 1), but since N-1 and N-3 are sterically shielded by the 2-methyl group, N-6 should be the most likely site of coordination. Consequently, the chemical shifts for H-5 and H-7 should be more affected by the shift reagent than those of H-4 and H-9. When the Eu-ion is placed 5.0 Å from N-6, good, linear correlation between the Δ_{Eu} -values¹⁰ (Table 2) and $(3 \cos^2 \theta_i - 1)/r_i^3$ ¹¹ (*cf.* Fig. 1) is obtained for H-4, H-5, H-7, and H-8 in 3.

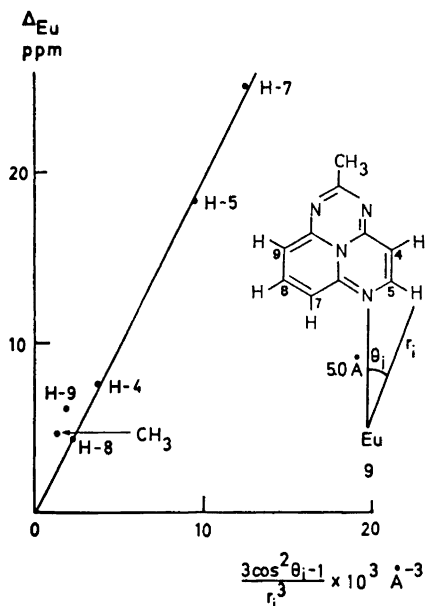


Fig. 1. Δ_{Eu} -values for the protons in 9 as a function of $(3 \cos^2 \theta_i - 1)/r_i^3$ for $r = 5.0$ Å.

We therefore assign the signal at 5.81 ppm with the highest Δ_{Eu} -value (Table 2) to H-7 and the signal at 5.35 to H-9. The points for H-9 and the 2-methyl protons deviate and show larger Δ_{Eu} -values than expected. We believe that this deviation is caused by Eu-coordination also at N-1 and N-3.

Table 2. Δ_{Eu} -values for the protons in 3.⁷

H-4	H-5	H-7	H-8	H-9	2-CH ₃
7.5	18.3	25.0	4.3	6.1	4.6

EXPERIMENTAL

General. NMR spectra were recorded with a Varian A-60 spectrometer, using TMS as internal reference. Chemical shifts are given in δ -values. 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 GF₂₅₄ (Merck) according to Stahl and the colorless spots were visualized with short-wave, ultraviolet light. Elemental analyses were carried out at "Mikroanalytisches Laboratorium, Institut für Physikalische Chemie, Universität Wien".

Preparation of 2-methyl-1,3,6-triazacycl[3.3.3]azine, 3. To 7 ml of freshly prepared polyphosphoric acid,⁶ kept at 200°, 1 g (5.3 mmol) of **1** was added and the solution was stirred for 35 min. After having been cooled to room temperature, 10 ml of water was added and the deep-red solution was neutralized with 10 % aqueous NaHCO₃ and then extracted with chloroform. The extract was dried (MgSO₄) and evaporated to dryness, yielding 300 mg (30 %) of **3**, which was purified by column chromatography on 9 g of neutral alumina (Fluka, activity I). Chloroform eluted 207 mg of pure **3** with properties earlier described.¹ NMR data for **3** in CDCl₃ and in CF₃COOH are summarized in Table I.

Preparation of 4-amido-2-methyl-1,3,6-triazacycl[3.3.3]azine, 6. To 1.6 ml of freshly prepared polyphosphoric acid,⁵ kept at 100°, 200 mg (0.97 mmol) of **1** was added and the solution was stirred for 2 h. The reaction mixture was worked up as described above and 200 mg of a crude mixture of **6** and **1** was obtained. Chromatography on 9 g of silica gel gave (CHCl₃-EtOAc; 9:1) 102 mg (51 %) of pure, crystalline **6**, m.p. 294–296°C (decomp.). IR: 3310, 3150 (NH), 1690 cm⁻¹ (amide C=O), UV: λ_{\max} at 237 ($\epsilon=18\,011$), 260 ($\epsilon=11\,990$), 332 ($\epsilon=14\,310$), 352 ($\epsilon=7650$), 370 ($\epsilon=9380$), 388 ($\epsilon=7770$), 545 ($\epsilon=347$), 586 ($\epsilon=400$) and 633 ($\epsilon=197$) nm; NMR (AsCl₃): singlet at 2.31 (3 H, CH₃), doublet ($J=8$ Hz) at 6.82 (1 H, H-9), doublet ($J=8$ Hz) at 7.12 (1 H, H-7), triplet ($J=8$ Hz) at 7.82 (1 H, H-8), doublet ($J=6$ Hz) at 8.41 (1 H, H-5) ppm, *Anal.*: (Found: C 58.30; H 4.09; N 30.53. Calc. for C₁₁H₉N₅O: C 58.15; H 3.99; N 30.82), MS: M⁺=227.

Lanthanide-shift-measurements. The shifts induced by Eu(fod)₃.d₂ were measured in a ca. 0.3 M solution of **3** in CDCl₃, dried over Linde 4A molecular sieve for 1 day. After each addition of shift reagent the solution was left for ca. 5 min before the spectrum was determined. The Δ_{Eu} -values for **3** were calculated as the slope of the straight, first part of the curve obtained when the induced shifts (in ppm) were plotted against [Eu(fod)₃]/[**3**]. The curve is linear up to a molar ratio of ca. 0.6 for H-5 and H-7 and to ca. 1.0 for the remaining protons in **3**. The straight line passing through the origin in Fig. 1 is calculated by the least-squares method excluding the values for H-9 and 2-CH₃. The distances r_i and angles θ_i were estimated from structure **9**. The bond-lengths and angles quoted in **9** have been obtained from X-ray studies.*

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REFERENCES

1. Ceder, O. and Andersson, J. E. *Acta Chem. Scand.* **26** (1972) 596.
2. Ceder, O., Andersson, J. E. and Johansson, L.-E. *Acta Chem. Scand.* **26** (1972) 624.
3. Rondeau, R. E. and Sievers, R. E. *J. Am. Chem. Soc.* **93** (1971) 1522.
4. Mosby, W. L. *J. Am. Chem. Soc.* **75** (1953) 3600.
5. Snyder, H. R. and Elston, C. T. *J. Am. Chem. Soc.* **76** (1954) 3039.
6. Uhlig, F. and Snyder, H. R. *Advan. Org. Chem.* **1** (1960) 35.
7. Ceder, O. and Samuelsson, M. L. *Acta Chem. Scand.* **27** (1973) 2095.
8. Boekelheide, V., Gerson, F., Heilbronner, E. and Meuche, D. *Helv. Chim. Acta* **46** (1963) 1951.
9. Ceder, O. and Vernmark, K. *To be published.*
10. Demarco, P. V., Elzey, T. K., Lewis, R. B. and Wenkert, E. *J. Am. Chem. Soc.* **92** (1970) 5734.
11. McConnell, H. M. and Robertson, R. E. *J. Chem. Phys.* **29** (1958) 1361.

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* An X-ray structure determination, which will be published elsewhere, has been carried out on **1** by Professor Iain C. Paul, University of Illinois, Urbana, Ill.