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Structure Determination of Brominated 1,3,6-Triazacycl[3.3.3]-azines by Polyphosphoric Acid Decyanation of Their 4-Cyano Derivatives

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When the 7- and 9-bromo derivatives of 4-cyano-2-methyl-1,3,6-triazacycl[3.3.3]azine were treated with polyphosphoric acid, the corresponding decyanated derivatives were formed. These compounds were brominated in the 4-position with *N*-bromosuccinimide. We were then able to establish, by analogy, the structures of 4,7- and 4,9-dibromo-1,3,6-triazacycl[3.3.3]-azine.

Polyphosphoric acid (PPA) is a convenient reagent for substitution of a hydrogen atom for a cyano group.[1–3] When the bromocyanoazacyclazines *1*—*3* (*cf.* Chart 1) were treated separately with PPA at 145—185 °C for 15—20 min, low yields of the cyano-free compounds were obtained. Since the structures of *1*—*3* have

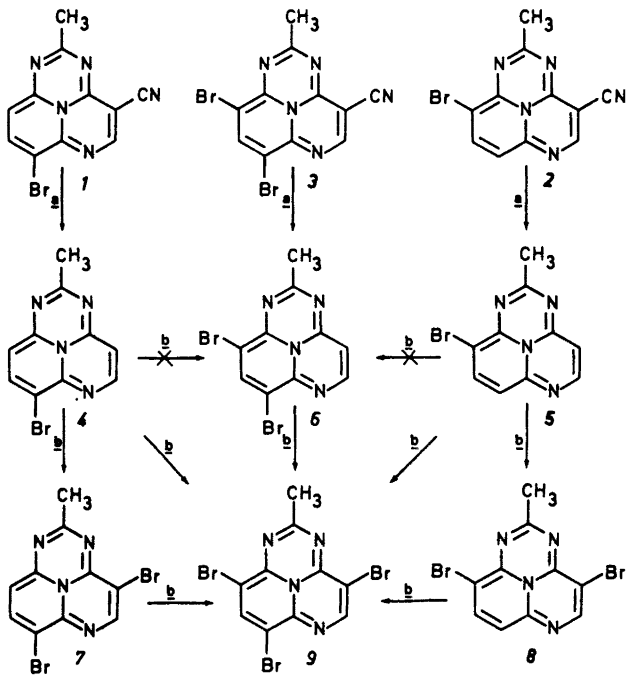
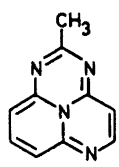


Chart 1. Reagents: *a* PPA; *b* NBS in $CHCl_3$.



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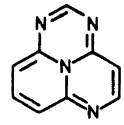

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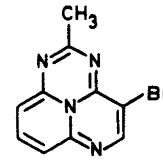

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Table 1. NMR spectral data for *7 – 9*, *12*, and *13 – 16* [5] (solvent: trifluoroacetic acid).

Compound	CH_3	H-2	H-5	H-7	H-8	H-9	Coupling constants (in Hz)
7	2.23	–	8.45	–	8.07	6.58	$J_{8-9}=8.5$
13	–	7.36	8.44	–	8.08	6.63	$J_{8-9}=8.5$
8	2.28	–	8.40	7.12	7.98	–	$J_{7-8}=9.1$
14	–	7.39	8.37	7.11	7.96	–	$J_{7-8}=9.4$
9	2.27	–	8.50	–	8.27	–	
15	–	7.38	8.48	–	8.26	–	
12	2.23	–	8.33	7.19	7.84	6.69	$J_{7-8}=8.6$ $J_{8-9}=7.9$ $J_{7-9}=1.0$
16	–	7.38	8.32	7.22	7.85	6.73	$J_{7-8}=8.5$ $J_{8-9}=8.1$ $J_{7-9}=1.0$

been established independently,[4] the structures for *4 – 6* follow. The PPA-method is so far the only way to obtain the dibromide *6*, since C-4 is the most reactive site in *10* (*vide infra*). Further bromination of *4 – 6* yielded *7 – 9* as indicated in Chart 1. Their structures were deduced from mass and NMR spectra (*cf.* Tables 1 and 2).

By the above sequence of reactions all expected * bromo derivatives of *10*, except *12*, have been obtained. Compound *12* was formed (77 %) along with *4* and *5* (18 % together) by mild bromination of *10*. Bromination of *12* with NBS gave two dibromo compounds, identical with those obtained from *4* and *5*; they therefore have structures *7* and *8*. Compounds *7* and *8* are more conveniently obtained in this way, or from *10*, than *via* the routes outlined in Chart 1. Further bromination of *7* and *8* gave the tribromide *9*.

In the decyanation procedure we always observed considerable amounts of 4-carboxamido derivatives having almost the same chromatographic mobilities as the corresponding decyanated compounds. These amides could be solvolysed in boiling ethanol in the presence of catalytic amounts of acid; the ethoxycarbonyl derivatives of the respective bromides then formed were easily separated from the decyanated compounds. Attempts to increase the yields of *4 – 6* were unsuccessful. Higher temperatures resulted in degradation of the cyclazine system, and treatment of *1 – 3* with PPA at lower temperatures gave only the respective carboxamides in good yields.

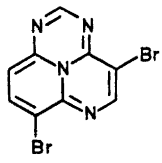
The chemical shifts for the aromatic protons in *7* and *8* have been used to establish, by analogy, the structures of two dibromo derivatives of *11*, reported earlier.[5] From theoretical considerations and from NMR data these compounds were predicted to be the 4,7- and 4,9-dibromides, but they could not be conveniently differentiated. One of them displayed chemical-shift values for the aromatic protons identical

Table 2. Mass spectral data for *7 – 9* and *12*.

	M+	Rel. intensities
7	340, 342, 344	1:2:1
8	340, 342, 344	1:2:1
9	418, 420, 422, 424	1:3:3:1
12	262, 264	1:1

* Simple HMO-calculations, performed on *11*,[6] and arguments using resonance structures [5] seem to exclude electrophilic substitution at C-5 and C-8 in the 1,3,6-triazacycl[3.3.3]azine system.

with those of *7* and the other one, values identical with those of *8* (Table 1); therefore they can now be assigned structures *13* and *14*, respectively.



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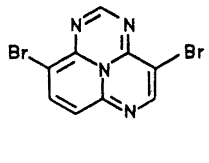

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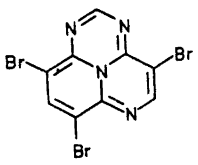

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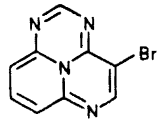

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EXPERIMENTAL

General. NMR spectra were obtained with a Varian Model A-60 spectrometer and chemical shifts are reported in δ-values, using tetramethylsilane as internal reference. Mass spectra were recorded with a GEC-AEI 902 mass spectrometer at the Department of Medical Biochemistry, University of Göteborg. The IR spectra were determined in KBr with a Perkin-Elmer 337 infrared spectrophotometer. For TLC, Silica Gel GF_{254} (Merck) was used. Compounds *1*, *2*, *3*, and *10* were prepared as previously described.[2,4]

Decyanation of 1 *with PPA.* Freshly prepared PPA [7] (*ca.* 0.5 ml) was heated to 145°, 5 mg of *1* was added, the mixture was stirred at this temperature for 15 min, then cooled to 25°, and diluted with water. This solution was neutralized with 10 % aqueous sodium bicarbonate and extracted with chloroform. The organic layer was dried over magnesium sulfate and the solvent evaporated *in vacuo*. On the TLC-plate only one coloured band was observed ($R_F = 0.10$; EtOAc). This was shown to contain, in addition to *4*, the 4-carboxamido derivative of *4* (IR). The crude product was dissolved in 5 ml of ethanol, one drop of perchloric acid (70 %) was added, and the solution was heated under reflux for 1 h. The solvent was evaporated, the residue dissolved in chloroform, the organic layer washed with water, and then dried over magnesium sulfate. TLC showed that a new product ($R_F = 0.53$), which we believe is the ethoxycarbonyl derivative of *4*, had formed. Compound *4* was separated from this product and from small amounts of still unreacted amide by preparative TLC (EtOAc; the chromatogram was developed three times). M.S.: $M^+ = 262$, 264 (intensities 1:1). M.p.: decomposed above *ca.* 240 °C.

Bromination of 4 *to* 7 *and* 9. Five mg of *1*, treated with PPA, yielded a mixture of *4* and the 4-carboxamide of *4*. This mixture was dissolved in 5 ml of chloroform, 1 mg of NBS was added, and the solution was shaken for 5 min. The solvent was then evaporated and the residue was subjected to preparative TLC (EtOAc). *Ca.* 0.5 mg (7 %) of *7* + *9* (mainly *7*) and 1.5 mg (25 %) of the 4-carboxamido derivative* of *4* (IR, NMR) were isolated. TLC (EtOAc): $R_F = 0.37$ (*7*) and 0.57 (*9*).

Decyanation of 2 *with PPA.* Compound *2* (5 mg) was treated with 0.5 ml of PPA at 185 °C for 20 min and the reaction mixture was worked up and analysed as described for *1* above. Compound *5* was separated from the 4-carboxamido derivative of *5* on a TLC-plate (EtOAc; the chromatogram was developed five times). TLC: $R_F = 0.10$. M.S.: $M^+ = 262$, 264. M.p.: 193 – 195 °C.

Bromination of 5 *to* 8 *and* 9. A mixture of *5* and the 4-carboxamide of *5* (from 5 mg of *2*) was brominated as described for *4* above. Compounds *8* and *9* (mainly *8*; TLC) were isolated along with the 4-carboxamido derivative* (IR) of *5*. Yield of *8*: *ca.* 0.5 mg (7 %). TLC (EtOAc): $R_F = 0.45$ (*8*).

Decyanation of 3 *with PPA and bromination of* 6 *to* 9. A solution of 25 mg of *3* in 1 ml of PPA was stirred at 165 °C for 15 min. The reaction mixture was worked up as described for *1*. TLC (EtOAc): $R_F = 0.42$ (*6*) and 0.47 (4-carboxamide of *6*). The crude reaction product was dissolved in 5 ml of chloroform, 2 mg of NBS was added, and the solution was shaken for 10 min. Compound *9* and the 4-carboxamido derivative of *6* (IR, MS) were isolated by preparative TLC (EtOAc). Yield of *9*, *ca.* 1.5 mg (5 %) and of amide, 4 mg (15 %).

Bromination of 10 *to* 12 *with NBS.* A solution of 43 mg (0.23 mmol) of *10* and 41 mg (0.23 mmol) of NBS in 15 ml of chloroform was stirred at 25 °C for 20 min. The solution was filtered to remove succinimide and then evaporated. The residue was separated by preparative TLC (EtOAc, the chromatogram was developed twice). Yield of *12*: 43 mg (77 %); of *4* + *5*: 10 mg (18 %). Small amounts of *7* – *9* were also obtained. TLC: $R_F = 0.13$ (12). NMR and mass spectral data for *12* are presented in Tables 1 and 2, respectively.

Bromination of 10 *to* 7, 8, *and* 9 *with NBS.* A solution of 80 mg (0.44 mmol) of *10* and 150

* The possibility that the 4-carboxamido derivatives are converted to 4-brominated products can be eliminated, since the pure amides do not give *7* and *8* when treated with NBS under similar conditions.

mg (0.81 mmol) of NBS in 50 ml of chloroform was stirred for 15 min at −10 °C. The solution was filtered and the filtrate evaporated to dryness. From the residue, three products were isolated by preparative TLC (EtOAc): *7* (89 mg; 60 %), *8* (26 mg; 17 %), and *9* (17 mg; 9 %). NMR and mass spectral data for *7*–*9* are summarized in Tables 1 and 2, respectively.

Addendum: In Table 3, Ref. 5, two coupling constants have been exchanged. J_{8-9} (in *8*) should be 8.5 Hz and J_{7-8} (in *9*) should be 9.4 Hz.

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