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Electrophilic Bromination of 1,3,6-Triazacycl[3.3.3]azine

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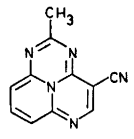
The electrophilic bromination of 1,3,6-triazacycl[3.3.3]azine, *2*, with *N*-bromosuccinimide is described. Under mild conditions, substitution occurs, as predicted by arguments using resonance structures and by HMO-calculations, preferentially (80 %) in position 4. On further bromination, positions 7 and 9 are also attacked.

Electrophilic-substitution studies on the 1,3,6-triazacycl[3.3.3]azine system [1] have earlier been carried out on the 4-cyano-2-methyl derivative *1*, which is available in quantities.[2] As predicted from charge-density values, substitution in this compound occurs in the 7 and 9 positions.[1,2] However, the parent compound *2* [2] is more suitable for such studies than *1* since position 4, which has the lowest charge-density value (*cf.* Table 1), is unsubstituted in *2*.



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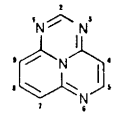

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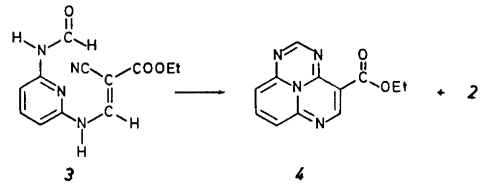
The present communication describes a slight improvement in the preparation of *2* and reports the results of electrophilic-substitution studies on the same compound.

The title compound was prepared as previously described.[2] The last step in this sequence, ring closure of *3* in diphenyl ether at 250°, gave, in low yields, *2* and *4* (0.8 % and 5.4 %, respectively).[2] If instead, a catalytic amount of



3 *4*

p-toluenesulfonic acid was added to the reaction mixture, the yields of *2* and *4* were raised to 5.0 and 7.3 %, respectively. Decarbethoxylation of *4* in the presence of *p*-toluenesulfonic acid gave 16 % of *2*, but the over-all yield of *2* (based on *3*) was still higher in the modified, one-step method.

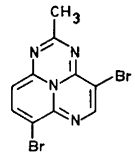
1,3,6-Triazacycl[3.3.3]azine is stable both in the solid state and in solution. It is easily soluble in chloroform, acetic and trifluoroacetic acid. The NMR spectra of *2* (in $CDCl_3$ and in CF_3COOH) contain an ABX-multiplet (H-7, H-8, and H-9), an AX-quartet (H-4 and H-5), and a one-proton singlet (H-2). The coupling constants and chemical-shift values, which show good correlation with the calculated charge-density values [2] on the adjacent carbon atoms, are listed in Table 1.

Table 1. Charge density values,[2] NMR chemical shifts, and coupling constants (in Hz) for *2*.

	H-4	H-9	H-7	H-8	H-5	H-2
Charge-density values	−0.148	−0.136	−0.132	+0.099	+0.164	+0.231
δ_{CDCl_3}	4.86	5.29[a]	5.75[a]	6.68	6.99	6.50
δ_{CF_3COOH}	6.16	6.75	7.13	7.88	8.04	7.40
Multiplicity	doublet	multiplet	multiplet	triplet	doublet	singlet
Coupling constants ($CDCl_3$)		$J_{4-5}=5.2$	$J_{7-8}=7.6$	$J_{8-9}=8.5$	$J_{7-9}=1.3$	

[a] The assignment of chemical-shift values to H-7 and H-9 are based on results of lanthanide-shift-reagent studies on 2-methyl-1,3,6-triazacycl[3.3.3]azine.[3]

The bromination experiments were performed with *N*-bromosuccinimide in chloroform at temperatures between −7° and +25°. Bromination of *2* under mild conditions (*cf.* Experimental) yielded 80 % of *5* and only 7 % of *6* and *7* together (*cf.* Chart 1). Bromination of *5* under slightly more vigorous conditions (*cf.* Experimental) yielded one tri- and two dibromo compounds, *10*, *8*, and *9*, respectively. The number of bromine atoms were determined by mass spectrometry from the element profile in the molecular-ion region. The structure of *5* follows from its NMR spectrum (*cf.* Table 3), which lacks the AX-quartet generated by H-4 and H-5 in the spectrum of *2*. The NMR spectra of the dibromo compounds each display two one-proton singlets and, in addition, AB-type signals; they therefore possess structures *8* and *9*. Bromination of each one separately led to the same tribromo compound as was isolated previously. The NMR spectrum shows three unsplit, one-proton signals (*cf.* Table 3) and thus this compound has structure *10*. The positions of the substituents in *8* and *9* were derived by comparison of the chemical-shift values for their protons with the values for the corresponding protons in the 4,7- and 4,9-dibromo-2-methyl-1,3,6-triazacycl[3.3.3]azine, *11* and *12*.



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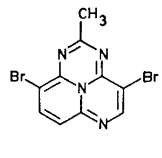

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The structure determinations of *11* and *12* are presented in a separate communication.[4] The chemical-shift values for H-5, H-8, and H-9 in *11* and for H-5, H-7, and H-8 in *12* are very close to the observed values for the corresponding protons in *8* and *9* (*cf.* Table 2).

Table 2. NMR chemical shifts (solvent: trifluoroacetic acid) of *8*, *9*, *11*, and *12*.

	H-5	H-7	H-8	H-9
11	8.45	–	8.07	6.58
8	8.44	–	8.08	6.63
12	8.40	7.12	7.98	–
9	8.37	7.11	7.96	–

Conversion of *6* and *7* to *8* and *9*, respectively, by bromination with NBS ascertained the structures of the monobromoderivates.

Arguments using resonance structures predict that electrophilic substitution in *2* should occur in positions 4, 7, and 9. In Chart 2, the structures of the intermediates for substitutions at C-4 and C-8 are presented. For 4-substitution, structures *13a* – *13d* can be drawn. In *13a*, representing six forms, the positive charge is located on carbon atoms. In the three remaining forms *13b* – *13d* the positive charge is located on the central *N*-atom. Here all atoms possess

Table 3. NMR spectral data (δ-values and coupling constants) for compounds *5*, *8*, *9*, and *10* (solvent: trifluoroacetic acid).

Compound	H-2	H-5	H-7	H-8	H-9	J_{7-8} (Hz)	J_{8-9} (Hz)	J_{7-9} (Hz)
5	7.38	8.32	7.22	7.85	6.73	8.45	8.15	1.0
8	7.36	8.44	–	8.08	6.63	–	9.4	–
9	7.39	8.37	7.11	7.96	–	8.5	–	–
10	7.38	8.48	–	8.26	–	–	–	–

full octets, which is not the case in *13a*. Similar structures can be drawn for electrophilic attack at C-7 and C-9. In *14*, which illustrates the intermediates for substitution on C-8, the charge is located on the peripheral *N*-atoms, and on C-4, C-7, and C-9; no resonance structure exists, where all atoms contain full octets. The predictions are in agreement with the results of the bromination studies.

Compounds *5* – *10* are blue or green and their electronic spectra are similar to those displayed by other brominated derivatives of the 1,3,6-triazacycl[3.3.3]azine system (*cf.* Table 4). The infrared spectra lack characteristic

Table 4. Electronic spectral data in the UV-region for *5* – *10*; nm ($\varepsilon \times 10^{-4}$).

5[a]	233 (1.49)	272 (1.16)	336 (1.22)	351s(0.85)	369 (0.85)	378 (0.67)	387 (0.79)
6[a]	234 (1.69)	266 (1.77)	335 (1.69)	359 (0.84)	376 (1.15)	387 (0.97)	394 (1.01)
7[a]	233 (1.72)	267 (1.50)	334 (1.61)	357 (0.78)	374 (1.00)	389 (0.86)	
8[a]	244 (1.09)	279 (1.29)	342 (1.27)	360 (0.66)	379 (0.76)	388s(0.59)	397 (0.69)
9[a]	241 (2.20)	284 (1.37)	343 (1.73)	349s(1.52)	360s(1.23)	375 (1.03)	392 (0.87)
10[a]	207 (1.72)	247 (0.82)	288 (0.77)	348 (0.88)	367s(0.53)	386 (0.47)	404 (0.42)

Table 4 cont. Electronic spectral data in the visible region for *5* – *10*; nm (ε).

5[b]	560 (125)	605 (186)	663 (177)
6[a]	555 (145)	597 (218)	651 (181)
7[a]	550 (167)	598 (221)	650 (200)
8[b]	566 (83)	616 (134)	673 (134)
9[b]	575 (82)	620 (140)	677 (163)
10[a]	580 (86)	630 (133)	688 (200)

[a] Solvent: ethanol; [b] Solvent: acetone.

absorption in the 4000 – 1200 cm^{-1} region, apart from the C=N band at 1600 cm^{-1}. The solubilities seem to depend on the position of the substituent; compounds *2* and *5* are easily soluble, but *8* and *10* only slightly soluble in chloroform.

Attempts to introduce more than three bromine atoms in *2* by using higher temperatures and longer reaction times failed. The presence of ethanol in the reaction medium led to the formation of ethoxy derivatives. One of these was shown (mass and NMR spectra) to contain one ethoxy group and three bromine atoms. Since this compound can be obtained from *10*, the bromine atoms are located in positions 4, 7, and 9. The position of the ethoxy group has not been determined. A compound with one chlorine atom, two bromine atoms, and one ethoxy group was observed as an impurity (MS). It has presumably been formed by a radical-induced exchange of chlorine for bromine. This type of reaction has been discussed in a previous communication.[5]

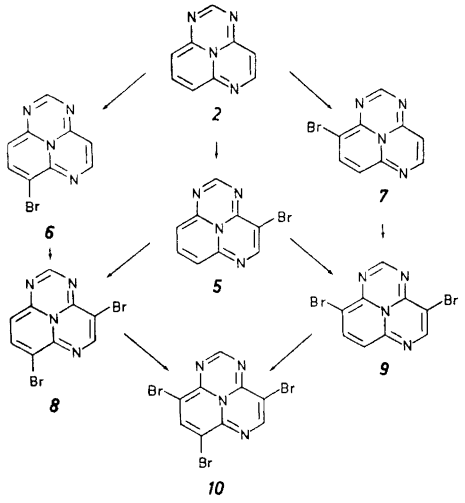

Chart 1. Bromination of *2*; products and interrelation of structures.

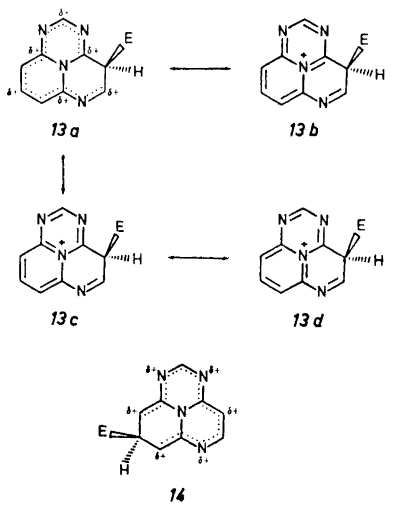

Chart 2. Resonance structures for electrophilic substitution intermediates of *2*.

EXPERIMENTAL

General. The NMR spectra have been measured in $CDCl_3$ or CF_3CO_2H with tetramethylsilane as internal reference using a Varian Model A-60 spectrometer. Mass spectra were recorded with a GEC-AEI 902 mass spectrometer at the Department of Medical Biochemistry, University of Göteborg. The infrared spectra were determined in KBr with a Perkin-Elmer 337 infrared spectrophotometer, and the electronic spectra in ethanol or acetone with a Cary Model 15 spectrophotometer. For column chromatography, neutral aluminium oxide or silica gel ($\phi < 0.08$ mm) was used, and for TLC, Silica Gel GF_{254} (Merck), according to Stahl. *N*-Bromosuccinimide (NBS) was recrystallized from water before use. Compound *3* was prepared by formylation of the condensation product from 2,6-diaminopyridine and ethyl 2-cyano-3-ethoxyacrylate, as earlier described.[2]

Ring closure of 3 *to* 2 *and* 4. A solution of 5.2 g of *3* in 400 ml of diphenyl ether was heated to 250° and 52 mg of *p*-toluenesulfonic acid was added. The mixture was kept at 250° for 2.5 h, then cooled to *ca.* 30° and passed over a column of 50 g of aluminium oxide (activity I). The column was washed with petroleum ether to remove the diphenyl ether. The coloured compounds were eluted with chloroform, the solvent was evaporated, and the residue separated by preparative TLC (EtOAc – MeOH, 3:1). Yield of *2*: 169 mg (5.0 %); of *4*: 352 mg (7.3 %).

Decarbethoxylation of 4 *to* 2. To 47 mg of *4* in 7 ml of diphenyl ether, kept at 250°, was added 5 mg of *p*-toluenesulfonic acid. The reaction mixture was heated for 4 h and then allowed to cool. The solvent was removed and the blue material eluted as described above. Preparative TLC on the residue after evaporation gave 5.2 mg (15.7 %) of *2*; 11.8 mg (25 %) of *4* was recovered unchanged.

Bromination of 2. A solution of 124 mg (0.73 mmol) of *2* and 130 mg (0.73 mmol) of NBS in 35 ml of chloroform was stirred for 30 min at −7°. The reaction mixture was then filtered to remove succinimide and the solvent evaporated. The following compounds were isolated from the residue by preparative TLC (EtOAc): *5* (145 mg; 80 %) and *6* + *7* (13 mg; 6.7 %). Minute amounts of *8* and *9* were observed (TLC). The mixture of *6* and *7* was separated by preparative TLC (CH_2Cl_2; the chromatogram was developed twice). NMR data for *5* are presented in Table 3, UV data for *5* – *7* in Table 4, mass-spectral data, melting points, and chromatographic mobilities in Table 5.

Table 5. Mass spectral data, melting points, and chromatographic mobilities of *5*–*10*.

	M.S. (M^+ and intensities)		M.p., °C	R_F (TLC)
5	248, 250	1:1	189–191	0.20[a]
6	248, 250	1:1	233–234	0.15[a]
7	248, 250	1:1	186–188	0.15[a]
8	326, 328, 330	1:2:1	251–253	0.36[b]
9	326, 328, 330	1:2:1	199–200	0.42[b]
10	404, 406, 408, 410	1:3:3:1	308–310	0.61[b]

[a] Solvent: EtOAc; [b] solvent $CHCl_3$–EtOAc, 3:1.

Bromination of 5. To a solution of 145 mg (0.58 mmol) of *5* in 20 ml of chloroform was added 100 mg (0.56 mmol) of NBS and the mixture was stirred at −7°. A sample taken after 20 min still contained starting material (TLC). An additional 30 mg of NBS was added and the temperature was allowed to rise to +5°. After another 10 min, the mixture was filtered, the solvent evaporated, and the residue analyzed by TLC. Compounds *8*, *9*, and *10* had formed with *9* as the main component. The crude product was suspended in 10 ml of chloroform, filtered, and analyzed (TLC). The filtrate contained almost pure *9* and the solid residue mainly *8* and *10*. Further purification was performed by TLC ($CHCl_3$–EtOAc, 1:3). No yields were determined, since substantial amounts of material were lost during the purification procedure. NMR and UV data for *8*–*10* are presented in Tables 3 and 4; mass-spectral data, melting points, and chromatographic mobilities are summarized in Table 5.

Bromination of 8 *to* 10. Equivalent amounts of *8* (12 mg, 0.037 mmol) and NBS (6.5 mg, 0.037 mmol) were dissolved in 3 ml of chloroform and stirred for 1 h at 25°. TLC showed, that *ca.* 50 % of *8* had reacted to give *10*.

Bromination of 9 *to* 10. Compound *9* was treated as described for *8* above. TLC showed, that *10* had been formed and that no starting material remained.

Bromination of 6 *to* 8 *and* 10. One crystal each of *6* and of NBS, dissolved in 0.5 ml of chloroform, were shaken for 1 min and the solution was then analyzed by TLC. Two products, *8* and *10*, were observed.

Bromination of 7 *to* 9 *and* 10. Compound *7* was treated as described for *6* above. According to TLC, *9* and *10* had formed.

Formation of ethoxyderivatives of 10. A solution of 30 mg of *10* and 15 mg of NBS in 20 ml of chloroform (stabilized with *ca.* 1 % of ethanol) was stirred for 2 weeks at 25°. After evaporation of the solvent, the residue was separated by preparative TLC (EtOAc). Compound *10* was the main component, but *ca.* 2 mg (6 %) of another blue product was isolated. Since a mass spectrum of the latter compound suggested the presence of an ethoxy group, 30 mg of *2* and 95 mg of NBS (3 equivalents) dissolved in 30 ml of chloroform containing 10 % ethanol was stirred for 3 days at 25°. Preparative TLC (CH_2Cl_2; the chromatogram was developed twice) yielded the same blue compound as isolated above. M.S.: 448, 450, 452, 454 (intensities 1:3:3:1). NMR ($CDCl_3$): singlets at $\delta =$ 7.60 (1 H) and 7.72 (1 H), quartet at 4.33 (2 H), and triplet at 1.33 (3 H).

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