ACTA CHEMICA SCANDINAVICA 26 (1972) 624–634

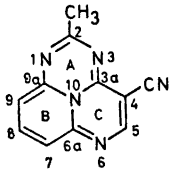
Electrophilic Bromination Studies on 4-Cyano-2-methyl-1,3,6-triazacycl[3.3.3]azine

OLOF CEDER, JOHANNA E. ANDERSSON and LARS-ERIK JOHANSSON

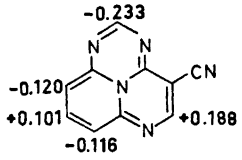
Department of Organic Chemistry, University of Göteborg and Chalmers Institute of Technology, Fack, S-402 20 Göteborg 5, Sweden

Electrophilic bromination of 4-cyano-2-methyl-1,3,6-triazacycl-[3.3.3]azine with *N*-bromosuccinimide and with bromine in glacial acetic acid is described. In accordance with predictions obtained from charge-density calculations, bromination occurred at C-7 and C-9 giving rise to three products, two monobromo isomers, *19* and *20*, and a dibromo compound, *21*. Determination of the position of bromination in the two monobromo isomers was accomplished using a method based on the fact that protons adjacent to an amino group in an aminopyridine undergo a downfield shift upon acylation of the amino group.

In two accompanying papers [1,2] the synthesis and structure determination of compounds belonging to the 1,3,6-triazacycl[3.3.3]azine system have been reported. The charge densities from simple HMO calculations (*cf. 8b*) obtained there predict, in general, electrophilic attack at positions C-7 and C-9. This communication describes electrophilic substitution studies on the easily available 4-cyano-2-methyl-1,3,6-triazacycl[3.3.3]azine, *8c*.* The work was begun in an attempt to verify experimentally the theoretical predictions.



8c



8b

* The compounds in this communication bear the same numbers as in Ref. 1.

Since electrophilic brominations have been performed successfully on similar heterocyclic systems with *N*-bromosuccinimide in carbon tetrachloride [3] and with bromine in glacial acetic acid,[4] in which solvents the azacyclazines are stable and from which they can be recovered unchanged and in quantitative yields, these were the reagents chosen. In the absence of peroxides and light, two blue monobromo derivatives, *19* and *20* (in a 1 : 3 ratio), and a green dibromo compound, *21* (*cf.* Chart 1), resulted. Column chromatography separated *21* from the two monobromocyclazines, while preparative TLC was necessary to separate *19* from *20*. Both monobromo derivatives could be converted to the same dibromo compound, *21*, under conditions similar to those used to prepare the dibromo derivative directly from *8c*.

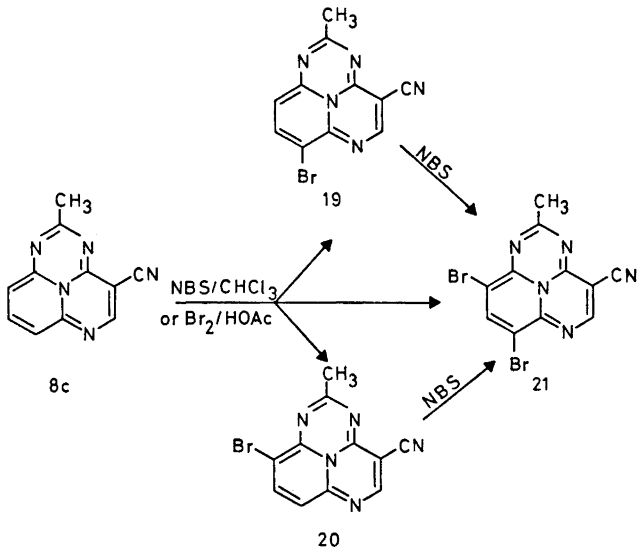


Chart 1.

The monobromo isomers were obtained in optimal yields when the reaction was performed at *ca.* 0° for about 5 h with half an equivalent of *N*-bromosuccinimide. Compounds *19* and *20* exhibit very similar R_F-values (0.51 and 0.58, respectively), but a solubility difference between the two isomers in ethyl acetate makes a fairly complete separation possible. An excess of *N*-bromosuccinimide (*ca.* 3 mol), higher temperature, and longer reaction times (reflux at 65° for *ca.* 72 h) favored the formation of the dibromo derivative. The monobromo and the dibromocyclazines have physical properties which are quite similar to those of the parent compound. They are very insoluble in nonpolar solvents, can be easily sublimed, and their melting points are high (*ca.* 280°).

Since *N*-bromosuccinimide can effect free-radical substitution, *8c* was also brominated with bromine in glacial acetic acid. Identical products and

similar ratios were obtained with both reagents thus indicating, that in the present case, bromination with *N*-bromosuccinimide is an electrophilic substitution. It should be noticed, however, that the free-valency values [5] predict radical attack at the same positions, C-7 and C-9, as well as at position C-5. In a subsequent paper we will report the results of free-radical substitutions on *8c*.[6]

The correctness of the proposed structures has been supported by spectroscopic data. The mass spectra of the monobromo compounds *19* and *20* both showed molecular ion peaks at $m/e = 287 - 289$, corresponding to the molecular formula $C_{11}H_6N_5Br$. Doublet patterns characteristic of compounds containing one atom of bromine [7] were observed in these spectra (*cf.* Figs. 1 and 2). In the NMR spectra of *19* and *20* (Figs. 3a and 3b), sharp singlets are observed at

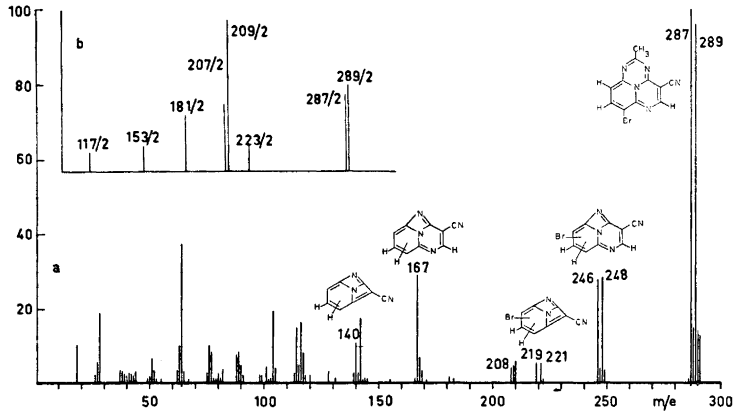


Fig. 1. Mass spectrum of *19*, (a) singly charged ion spectrum; (b) doubly charged ion spectrum.

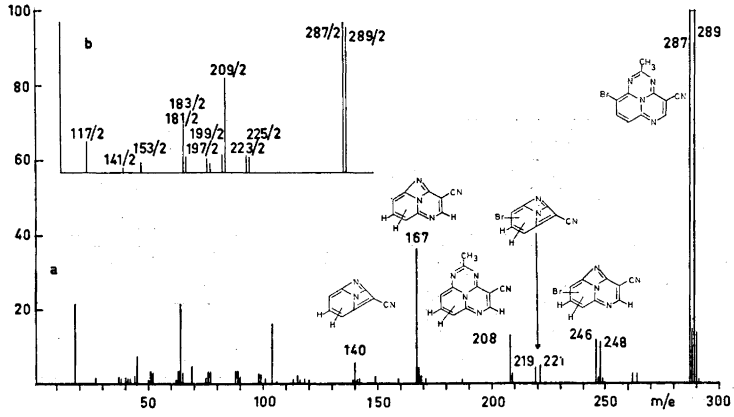


Fig. 2. Mass spectrum of *20*, (a) singly charged ion spectrum; (b) doubly charged ion spectrum.

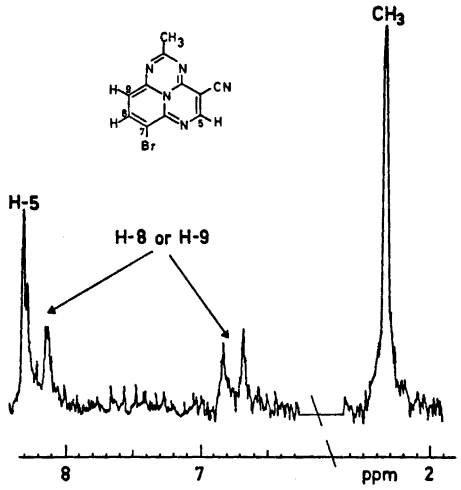


Fig. 3a. NMR spectrum of *19*.

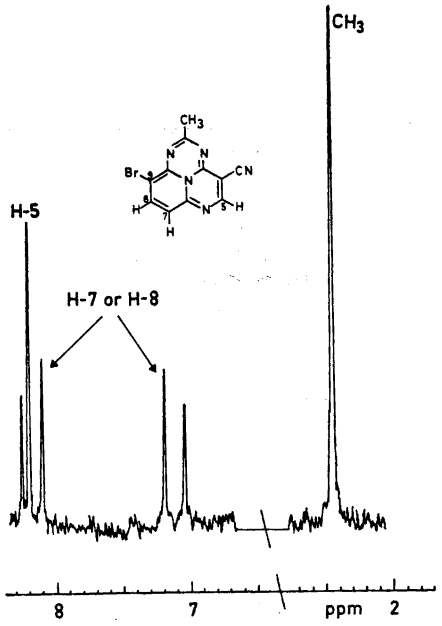


Fig. 3b. NMR spectrum of *20*.

$\delta = 8.33$ and 8.20, respectively. These chemical shift values are very similar to those observed for H-5 in the parent compound and they indicate that substitution has occurred in the *B* ring. Typical AB patterns at $\delta = 6.78$ and 8.24 ($J = 8.75$ Hz), and at $\delta = 7.14$ and 8.19 ($J = 9.25$ Hz), respectively, are characteristic of *ortho* coupling between H-8 and H-9 in *19* and between H-7 and H-8 in *20*. (For IR and UV data see Experimental section.) These observations do not distinguish between *19* and *20*, but they do require that the bromine atom is bound to either C-7 or C-9. The mass spectrum of the dibromo compound *21* shows the molecular weight to be 365 – 367, corresponding to the molecular formula $C_{11}H_5N_5Br_2$. The pattern in the molecular ion region is typical of compounds containing two bromine atoms[7] (*cf.* Fig. 4). As was mentioned above, both *19* and *20* on further bromination give rise to the same

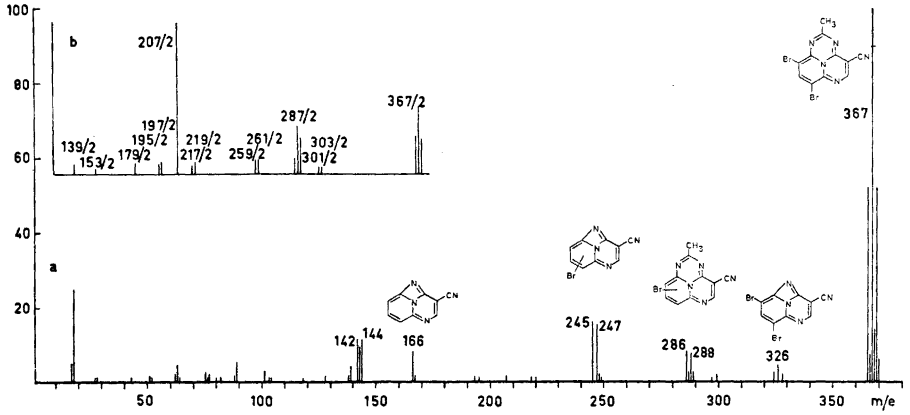


Fig. 4. Mass spectrum of *21*, (a) singly charged ion spectrum; (b) doubly charged ion spectrum.

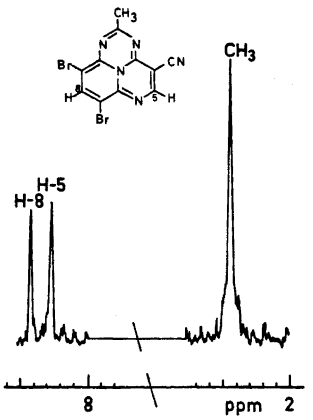


Fig. 5. NMR spectrum of *21*.

dibromo compound. Therefore, *21* must be the 7,9-dibromo derivative. In agreement with this structure, the NMR spectrum (Fig. 5) displays a CH_3-singlet at $\delta = 2.45$ and one-proton singlets at $\delta = 8.30$ for H-5 and at $\delta = 8.45$ for H-8.

It was not possible to distinguish directly between *19* and *20* with NMR or any other conventional method, and therefore the general principle and results reported in an accompanying communication [8] used to distinguish between a 1,3,6,7- and a 1,3,4,7-tetraazacycl[3.3.3]azine system were utilized. The principle of the method is that the proton adjacent to a free amino group in an aromatic system suffers a considerable shift in δ-value on acylation.* In the 5-bromo compound *22* (*cf.* Chart 3), acylation would therefore cause such a shift for H-3, while in *23*, where the free amino group lacks an adjacent proton, no such shift should be observed. Since the previously used shift values, which were obtained from a pyrimidine system,[8] might possibly differ from those representative for the corresponding pyridine system, we chose as a model compound in the present case 2-amino-6-methylpyridine.** Its NMR spectrum has been reported earlier and all protons have been assigned chemical shift values.[9] In the *N*-acetyl compound, the resonance signal for H-3 has moved 111 Hz downfield (at 60 MHz). The results are summarized in Chart 2. The intermediate *13* (*cf.* Chart 3) was treated

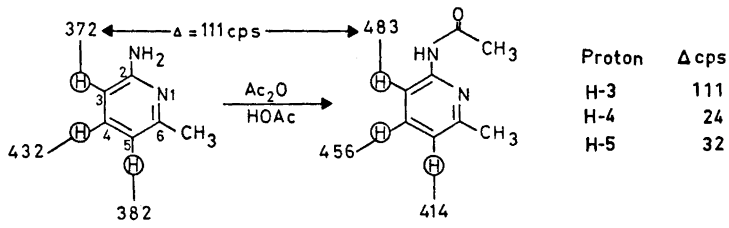


Chart 2.

with *N*-bromosuccinimide in chloroform solution and chromatographic separation of the reaction products yielded a monobromo compound with structure *22* or *23*, containing about 1 % of the other isomer. The ratio was determined from the NMR spectrum (Fig. 6) which contained double sets of signals for all protons. The major component gave rise to two AB doublets, centered at $\delta = 6.30$ and 7.58, resulting from H-3 and H-4 in *22*, or H-5 and H-4 in *23*, a singlet from H-8 at $\delta = 8.58$, and NH_2 and NH resonances at $\delta = 6.37$ and 9.97, respectively. Treatment of this 99 : 1 mixture with acetic anhydride in pyridine gave *24* or *25*. The NMR spectrum (Fig. 7) showed the same isomer ratio and contains a two-proton quartet (derived from the major component) centered at $\delta = 7.92$, produced by H-3 and H-4 in *24* or H-4 and H-5 in *25*, a one-proton singlet at $\delta = 8.53$ due to H-8, an NH signal at $\delta = 10.58$, and a methyl singlet at $\delta = 2.10$. Comparison of the NMR spectra of the non-

* *Cf.* Refs. 4–7 in Ref. 8 and the footnote on p. 637 in the same reference.
** In *Chem. Abstr.* called 6-amino-2-picoline.

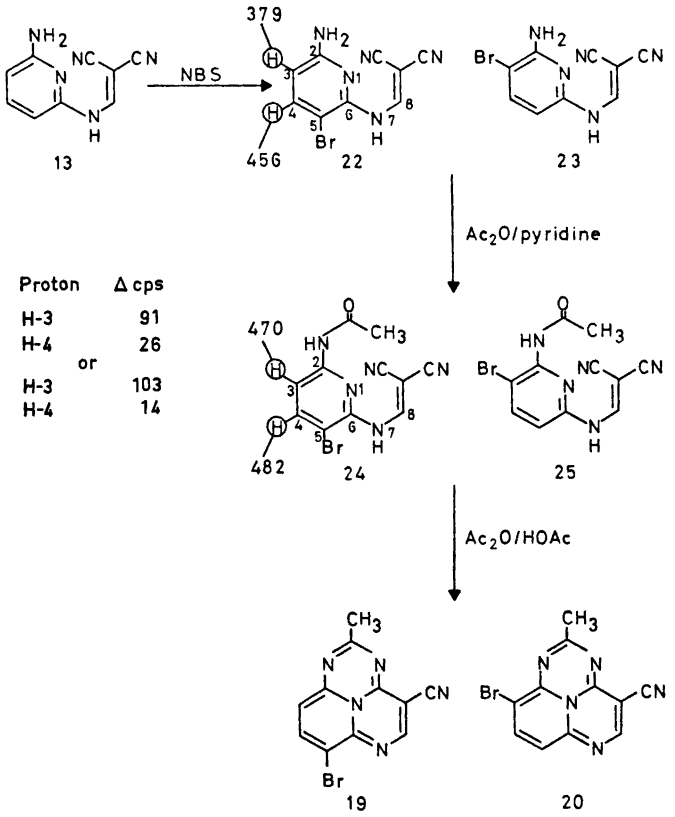


Chart 3.

acylated and acylated compounds shows, that in the major component, one aromatic proton has suffered a downfield shift of 91 Hz, and the other aromatic proton a shift of 26 Hz if, in Fig. 7, the signals at $\delta = 7.83$ and 8.02 are assigned to H-3 and H-4, respectively.* If instead, the signal at $\delta = 7.83$ is assigned to H-4 and that at $\delta = 8.02$ to H-3, shifts of 103 and 14 Hz result for the two aromatic protons. The shift values of 91 or 103 Hz are in good agreement with that obtained for H-3 in the model compound, 2-amino-6-methylpyridine, (and also with values reported in Refs. 4 – 7 in Ref. 8) and indicate that the component isolated in 99 % purity from the bromination product of *13* has a proton on C-3 and therefore should be represented by *22*, which on acetylation yields *24*. Treatment of *24* (containing 1 % of *25*) with acetic anhydride in glacial acetic acid yielded a cyclized product, which therefore is the 7-bromo-4-cyano-2-methyl-1,3,6-triazacycl[3.3.3]azine. By comparing the NMR spectrum of this compound with the spectra of the two monobromo

* The shift values have been obtained with a first approximation AB program.

isomers, obtained from the bromination of *8c* and separated by preparative TLC, we were able to identify the slower-moving isomer as *19*, and the one with the higher R_F-value as *20*.

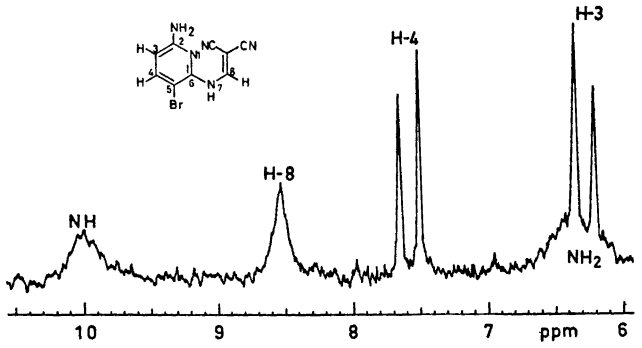


Fig. 6. NMR spectrum of *22*.

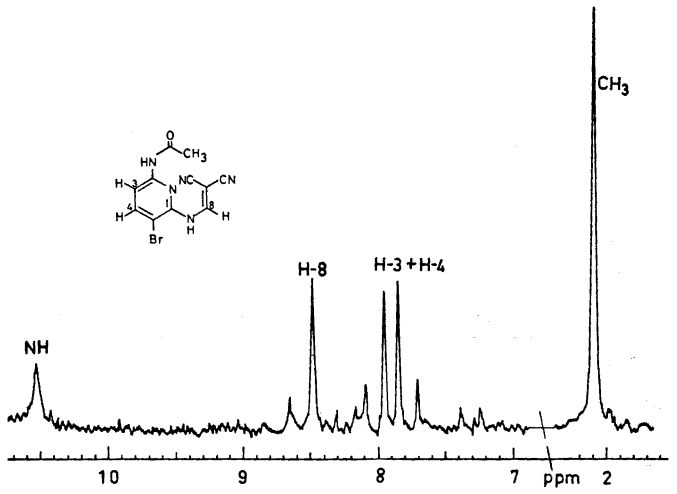


Fig. 7. NMR spectrum of *24*.

The mass spectra of the 7- and of the 9-monobromo compounds, which are virtually identical, and of the 7,9-dibromo derivative, all display molecular ions which are base peaks (*cf.* Figs. 1, 2 and 4). The structures of the major fragments are, in general, analogous to those observed in the spectrum of the parent compound, *8c*, formed by successive losses of CH_3CN and HCN.[2] It is interesting to note, however, that two groups of fragments appear in the spectra of *19* and *20*, one retaining the bromine atoms, easily recognized by the isotope pattern, and another not containing bromine. This behavior is not unexpected since halogen atoms are easily lost from aromatic systems

in the mass spectrometer.[10] Several doubly charged ions are present, as was the case in the spectra of the nonbrominated compounds. The proposed fragmentation schemes, in some cases supported by the occurrence of metastable ions are summarized in Charts 4 and 5.

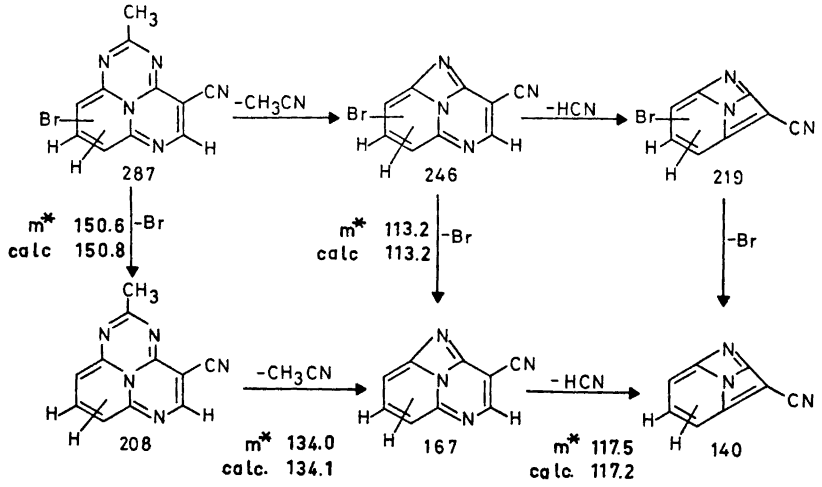


Chart 4. Fragments in the mass spectra of *19* and *20*.

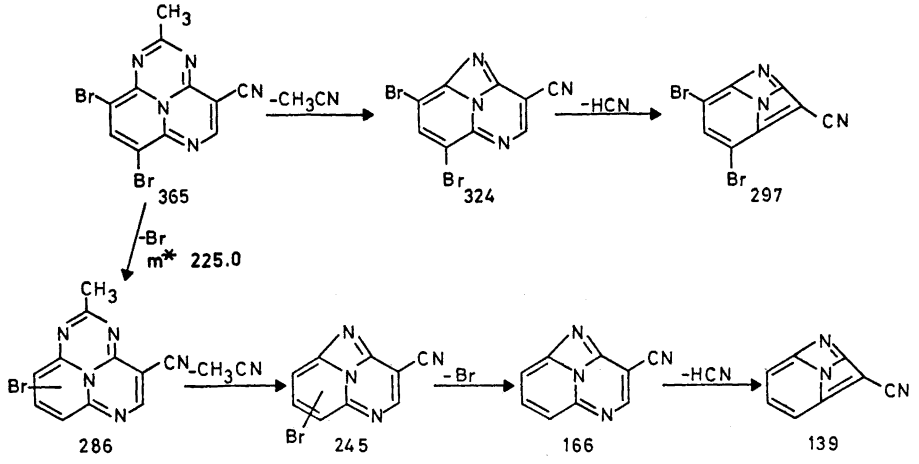


Chart 5. Fragments in the mass spectrum of *21*.

EXPERIMENTAL

General. The NMR spectra have been recorded with a Varian Model A-60 spectrometer with 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 Beckman IR 9 spectrophotometer, and the UV and visible spectra in ethanol with a Cary Model 15 spectrophotometer. For column chromatography, silica gel (0.02 – 0.5 mm) was used, and for TLC, Silica Gel GF_{254} (Merck) according to Stahl, and the spots were visualized with short-wave ultraviolet light and with iodine vapor.

Bromination of 8c with N-bromosuccinimide in chloroform. (a) Preparation of 19 and 20. To a solution of 100 mg (0.48 mmol) of *8c* in 15 ml of chloroform, cooled in an ice – ethanol bath to *ca.* −7°, 43 mg (0.24 mmol) of *N*-bromosuccinimide was added and the reaction was followed continuously with TLC (EtOAc). After 5 min, the two monobromo isomers, *19* and *20*, appeared and after 5 1/4 h, the dibromo compound, *21*, was visible. The reaction mixture was then filtered to remove unreacted *N*-bromosuccinimide, the solution concentrated *in vacuo* and column chromatographed on 10 g of silica gel using $CHCl_3$ – EtOAc, 9 : 1, as the eluent. A yield of 52 mg (40 % based on *8c*) of a mixture of *19* and *20* was obtained, m.p. 269 – 274°. Two products with $R_F = 0.58$ and 0.51 were visible with TLC (EtOAc). The size of the reaction could be scaled-up without difficulty.

(b) Preparation of 21. A mixture of 500 mg (2.4 mmol) of *8c* and 1.25 g (7.0 mmol) of *N*-bromosuccinimide in 25 ml of chloroform was refluxed for 72 h. The reaction mixture was worked up as described above, and a green product with $R_F = 0.74$ (TLC, EtOAc) was obtained. Yield: 545 mg (62 %), m.p. 307 – 309°; IR: 2220 cm^{-1} (CN); UV: λ_{max} at 245, 288, 347 ($\varepsilon = 21\,535$), 385, 405, 580, 625 ($\varepsilon = 922$), and 680 nm; mass spectrum: $M^+ = 365 - 367$.

Separation of 19 and 20. To 150 mg of a mixture of *19* and *20*, 15 ml of ethyl acetate was added. The resulting suspension was filtered after 15 min, and the crystals which were not soluble in ethyl acetate were washed with petroleum ether, collected, and dried at 60°/15 torr. Thin layer chromatography (EtOAc) showed $R_F = 0.51$. A yield of 31 mg of *19* with m.p. > 360° (after sublimation at 200°/1 torr) was obtained. IR 2210 cm^{-1} (CN); UV λ_{max} at 243, 275, 338 ($\varepsilon = 13\,630$), 375, 395, 565, 605 ($\varepsilon = 448$), and 660 nm; mass spectrum: $M^+ = 287 - 289$. Concentration of the ethyl acetate solution *in vacuo* and column chromatography on 20 g of silica gel ($CHCl_3$ – EtOAc, 9 : 1) yielded 90 mg of the second isomer, *20*, m.p. > 360°, $R_F = 0.58$ (TLC, EtOAc); IR: 2220 cm^{-1} (CN); UV: λ_{max} at 242, 282, 335 ($\varepsilon = 15\,930$), 378, 395, 570, 609 ($\varepsilon = 710$), and 660 nm; mass spectrum: $M^+ = 287 - 289$.

Bromination of 19 and of 20 to 21. (a) To a solution of 1.5 mg (0.005 mmol) of *19* in 0.5 ml of glacial acetic acid, 1 drop (0.03 mmol) of bromine in 0.25 ml of glacial acetic acid was added. A red precipitate, the hydrobromide of the cyclazine, formed almost immediately, indicating a very rapid electrophilic substitution. Analytical TLC on a sample taken after 5 min showed the presence of a green product with $R_F = 0.74$ (EtOAc), as well as unreacted starting material. The mixture was allowed to stand at R.T. for *ca.* 1 h and was then evaporated to dryness *in vacuo* leaving a green solid with m.p. > 360°. Upon evaporation, the red cyclazine hydrobromide is converted to the free cyclazine. This can also be accomplished by washing the red salt with ethanol. Analytical TLC on the green solid showed the presence of only one product, *21*, with $R_F = 0.74$ (EtOAc).

(b) To a solution of 5 mg (0.017 mmol) of *20* in 1 ml of glacial acetic acid was added 2 drops (0.06 mmol) of bromine in 1 ml of glacial acetic acid. The experimental procedure used under (a) was followed. Analytical TLC on the green solid obtained showed the presence of only one product, *21*, with $R_F = 0.74$ (EtOAc).

Bromination of 8c with bromine in glacial acetic acid. To a solution of 100 mg (0.48 mmol) of *8c* in 10 ml of glacial acetic acid, 160 mg (1.0 mmol) of bromine in 5 ml of acetic acid was added dropwise. The reaction mixture was stirred for 2 h at 15° and the acetic acid was then evaporated *in vacuo*. The resulting blue crystalline solid was column chromatographed on 10 g of silica gel with $CHCl_3$ – EtOAc, 9 : 1. Three fractions of 30 ml each were taken; the first was shown with TLC (EtOAc) to contain 10 mg (6 %) of *21* with $R_F = 0.74$, and the other two fractions were shown to contain 38 mg (28 %) of a mixture of *19* and *20*, with $R_F = 0.51$ and 0.58, respectively.

Acetylation of 2-amino-6-methylpyridine. To a solution of 500 mg (4.6 mmol) of 2-amino-6-methylpyridine in 1 ml of glacial acetic acid was added 1 ml (10.6 mmol) of acetic anhydride. The mixture was refluxed for 90 min and then evaporated to dryness *in vacuo* yielding 655 mg (95 %) of a white solid which was shown to be pure by analytical TLC. NMR ($CDCl_3$): δ 2.20 (singlet, 3H, CH_3), 2.45 (singlet, 3H, CH_3), 6.90 (doublet, 1H, H-5), 7.60 (triplet, 1H, H-4), 8.01 (doublet, 1H, H-3), and 9.23 (broad singlet, 1 H, NH).

Bromination of 13 to 22. To a solution of 2 g (10.8 mmol) of *13* in 1 l of ethyl acetate, cooled in an ice – ethanol bath to *ca.* $-5°$, was added 960 mg (5.4 mmol) of *N*-bromosuccinimide. The solution was allowed to stand at 0° for 48 h, then filtered to remove unreacted starting materials, and evaporated to dryness *in vacuo*. Column chromatography on 150 g of silica gel, using chloroform as the eluent, gave 225 mg (8.5 %) of *22*, m.p. 178 – 180°. The NMR spectrum (DMSO-d_6) is reproduced in Fig. 5.

Acetylation of 22 to 24. To a solution of 200 mg (0.76 mmol) of *22* in 3.6 ml of pyridine was added 0.4 ml (4.2 mmol) of freshly distilled acetic anhydride and the mixture was allowed to stand at R.T. for 4 days. It was then poured into 20 ml of water and the white precipitate formed was collected and dried *in vacuo* at R.T. over P_2O_5. The white solid was then column chromatographed on 7 g of silica gel, using ethyl acetate as the eluent, whereupon 114 mg of a white solid was obtained. Further purification by preparative TLC (silica gel, EtOAc) gave 80 mg (38 %) of *24*, m.p. 242 – 245°. The NMR spectrum (DMSO-d_6) is reproduced in Fig. 6.

Ring closure of 24 to 19. To a solution of 40 mg (0.14 mmol) of *24* in 4.5 ml of glacial acetic acid, 0.48 ml (5.1 mmol) of acetic anhydride was added, the mixture was refluxed for 90 min and then evaporated to dryness *in vacuo*, yielding a blue product, $R_F = 0.51$ (EtOAc), having an NMR spectrum identical with that of *19* (*cf.* Fig. 3a).

Acknowledgements. We are indebted to Mrs. Inger Nilsson for technical assistance and to the *Swedish Natural Science Research Council* for financial support.

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. Paudler, W. W. and Blewitt, H. L. *J. Org. Chem.* **30** (1965) 4081.
4. Mariella, R. P. and Belcher, E. P. *J. Am. Chem. Soc.* **74** (1952) 1916.
5. *cf.* Ref. 1 p. 606.
6. Ceder, O. and Samuelsson, M. L. *To be published.*
7. Biemann, K. *Mass Spectrometry*, McGraw, New York 1962, p. 66.
8. Ceder, O. and Witte, J. F. *Acta Chem. Scand.* **26** (1972) 635.
9. Bell, C. L., Egan, R. S. and Bauer, L. *J. Heterocycl. Chem.* **2** (1965) 420.
10. Budzikiewiez, H., Djerassi, C. and Williams, D. H. *Interpretation of Mass Spectra of Organic Compounds*, Holden-Day, San Francisco 1964, p. 190.

Received April 19, 1971.