HETEROCYCLES, Vol 22, No 11, 1984

UNAMBIGUOUS SYNTHESIS OF 9-CYANAMINO-ACRIDINE AND 10-CYANO-9-IMINO-ACRIDANE

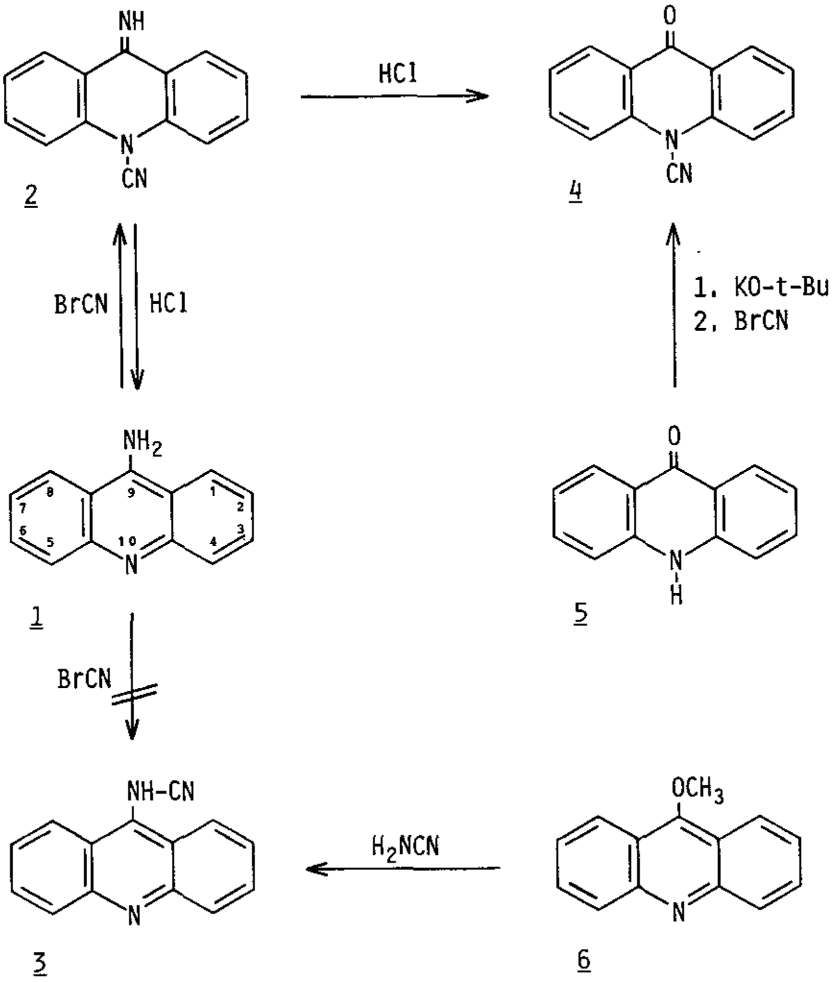
Joachim G. Schantl* and Wolfgang Türk
Institut für Organische und Pharmazeutische Chemie, Universität Innsbruck
Innrain 52a, A-6020 Innsbruck, Austria

Abstract - The reaction of cyanogen bromide with 9-amino-acridine 1 affords 10-cyano-9-imino-acridane 2; the isomeric 9-cyanamino-acridine 3 is formed from 9-methoxy-acridine 6 with cyanamide.

It is well documented that 9-amino-acridine 1 is attacked by electrophilic reagents both at the exocyclic amino group and at the ring-N-atom: Acylation takes place at the 9-amino group leading to 9-acylamino-acridines[1,2] or 9-acylimino-acridanes.[3] Alkylation usually gives rise to substitution at the ring position 10,[4,5] but there are reports[6,7] that mixtures of ring- and exo-N-alkyl derivatives were obtained depending on the reaction condition and on the alkylating reagent used. The reaction of 9-amino-acridine 1 with cyanogen bromide affords a cyanation product in good yield. However, the site of cyanation could not be anticipated nor could the structure of this product be proved by readily available spectroscopic means. Therefore, it was decided to establish the structure by chemical derivatization and by independent synthesis of the respective isomer (Scheme 1).

In an attempt to transform the N-bonded nitrile function, the cyanation product of 9-amino-acridine 1 was treated with ammonium bromide as well as with sodium hydroxide in order to obtain the corresponding guanidino and ureido derivative. However, these procedures merely effected the cyano group to be split off, and 9-amino-acridine 1 was the only product isolated. The reaction with hydrochloric acid furnished an additional compound beside 1: The IR spectrum of this hydrolysis product revealed that the cyano group was retained and, moreover, a carbonyl function was introduced. This led to the conclusion that the structure of the product obtained from the reaction of 9-amino-acridine 1 with cyanogen bromide is 10-cyano-9-imino-acridane 2;[8] hydrochloric acid partly hydrolyzed the imino group of this cyanation product converting it into 10-cyano-9-acridanone 4 which in turn proved identical with the product resulting from the reaction of the potassium salt of 9-acridanone 5 with cyanogen bromide.

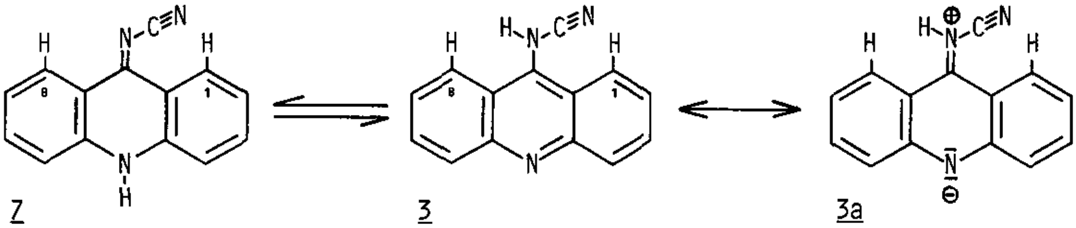
Scheme 1.



The reaction of 9-amino-acridine 1 with cyanogen bromide furnished the ring-N-cyanated compound 2 but no isomeric cyanation product 9-cyanamino-acridine 3 was isolated. This isomer 3 was synthesized in good yield from 9-methoxy-acridine 6: With cyanamide the methoxy substituent of 6 is displaced and the cyanamino group is introduced in position 9, thus providing an unambiguous access to compound 3.

The ^{1}H-NMR spectra of the two isomeric compound 2 and 3 (cf. Experimental Section) need some comments: Both compounds show the signals of their peri-protons (H-1 and H-8) shifted downfield and clearly separated from the multiplets of the other six aromatic protons (H-2 through H-7). In the case of 10-cyano-9-imino-acridane 2 this is attributed to the anisotropic effect of the imine double bond exerted on the 1,8-peri-protons.[9a] - A similar overall signal pattern of the aromatic protons is displayed by 9-cyanamino-acridine 3, and this could suggest the tautomeric structure, 9-cyanimino-acridane 7 (Scheme 2), the downfield shift of H-1,8 being again originated by the anisotropic effect of the imine double bond. However, the substituent attached to the imine-N-atom of 7 is expected to give rise to two separate signals of the syn and anti H-1 and H-8,[9b] but this is not observed. Therefore, this is taken as evidence for the cyanamino-structure 3, H-1 and H-8 being apparently equivalent protons (but a rapidly exchanging tautomeric equilibrium between both forms 3 and 7 cannot be strictly ruled out). As it has been suggested similarly for 9-amino-acridine 1, the mesomeric contribution of zwitterionic structures[10] like 3a lends some double bond character to the C⁹-N bond of 3 (though insufficient to cause observable hindered rotation about it), and this is associated with an appreciable deshielding influence on the resonance of the 1,8-protons.[11] Moreover, the distinct downfield shift of H-1,8 in compound 3 (exceeding that of H-1,8 of 9-amino-acridine 1 by 0.53 ppm, using the same solvent[12]) has to be attributed to the nitrile triple bond[9c] of the cyanamino group which obviously accounts for an additional significant deshielding contribution to the chemical shift of the 1,8-peri-protons of 3.

Scheme 2.



EXPERIMENTAL

Melting points were determined on a Kofler apparatus. The IR spectra were taken on a Beckman AccuLab 6 instrument, the ^{1}H-NMR spectra were recorded on a JEOL C-60-HL spectrometer (60 MHz), and the mass spectra were obtained from an AEI MS 9 spectrometer (250°C, 70 eV). Elemental analyses were performed by Hoffmann-La Roche AG, Basle, Switzerland.

10-Cyano-9-imino-acridane 2: To a solution of 9-amino-acridine 1 (7.76 g, 40 mmol) in boiling acetone (250 ml) a solution of cyanogen bromide (2.12 g, 20 mmol) in acetone (30 ml) was added. The mixture was stirred under reflux for 30 min, the precipitated 1.HBr was filtered off, and the filtrate was evaporated. The residue was treated with boiling ether (50 ml) to give 2 (3.5 g, 80%)

as yellow needles: mp (dec.) 225-232°C (ethanol). MS: m/z 219 (100%), 192 (23), 164 (7); IR (KBr): 2236 cm^{-1} (C≡N), 1655 (C=N); ^{1}H-NMR (DMSO-d_6): δ 7.3-7.9 (m, 6H, H-2 - H-7), 8.42 (dd, J=7.5 and 1.0 Hz, 2H, H-1,8), 10.76 (broad s, 1H, NH). Anal. Calcd. for $C_{14}H_9N_3$ (219.25): C 76.70; H 4.14; N 19.17. Found: C 76.40; H 4.06; N 18.73.

10-Cyano-9-acridanone 4: (a) From 2: To a suspension of 2 (0.88 g, 4 mmol) in hot water (100 ml) 36% hydrochloric acid was added just to effect dissolution. Subsequent boiling of the solution induced the precipitation of colourless needles. When this appeared to be complete, the mixture was cooled to 0°C, the precipitated product was filtered off and washed with ethanol (3x 15 ml): Colourless crystals 4 (0.37 g, 42%): mp (dec.) 272-274°C (dimethylformamide). IR (KBr) 2235 cm^{-1} (C≡N, 1655 (C=O). Anal. Calcd. for $C_{14}H_8N_2O$ (220.23): C 76.35; H 3.66; N 12.72. Found: C 76.34; H 3.48; N 12.52. - From the filtrate after addition of sodium hydroxide 9-amino-acridine 1 was isolated.

(b) From 9-acridanone 5: To a solution of 5 (1 g, 5 mmol) prepared in dry dimethylformamide at 70°C a solution of potassium t-butoxide (0.57 g, 5 mmol) in dimethylsulfoxide (5 ml) was slowly added. The mixture was kept at 70°C for 1 h, and then a solution of cyanogen bromide (0.54 g, 5 mmol) in dry dimethylsulfoxide (5 ml) was added. After a further 1.5 h at 70°C the mixture was poured on crashed ice and the crystals formed were collected. This product 4 (0.72 g, 64 %) proved identical with that obtained by the preceeding procedure.

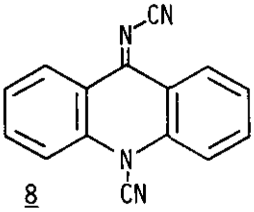
9-Cyanamino-acridine 3: To a boiling solution of cyanamide (2.8 g, 66 mmol; recrystallized from chloroform, mp 43°C) in ethanol (30 ml) 9-methoxy-acridine 6 (7.0 g, 33 mmol) dissolved in dry ethanol (70 ml) was added and the mixture was kept at reflux. After 2 h the precipitated product was filtered off and washed with ethanol (3x 15 ml): Yellow crystals 3 (5.8 g, 80%): mp (dec.) 309-311°C (dimethylformamide; in order to remove this solvent the crystals were washed with ethanol and ether, and subsequently dried at 40°C/0.01 mbar). MS: m/z 244 [M+25],[8] 219 (100%), 192 (37), 164 (5); IR (KBr): 3300-2600 cm^{-1} (broad, with major maxima at 3278, 3242, 2956; N-H), 2148 (C≡N), 1642 (C=N ?); ^{1}H-NMR (DMSO-d_6): δ 7.2-8.1 (m, 6H, H-2 - H-7), 8.97 (dd, J=7 and 1 Hz, H-1,8), 11,5 (very broad s, 1H, NH). Anal. Calcd. for $C_{14}H_9N_3$ (219.25): C 76.70; H 4.14; N 19.17. Found: C 76.54; H 4.03; N 19.16.

ACKNOWLEDGEMENTS

The support of this work by Hoffmann-La Roche AG, Basle, Switzerland is gratefully acknowledged. We wish to thank Dr. W. Vetter for the mass spectra and their discussion. - The authors wish to express their gratitude to Professor Emeritus Dr. H. Bretschneider, University of Innsbruck, for his encouragement and helpful discussions.

REFERENCES AND NOTES

1. J. H. Wilkinson and I. L. Finar, J. Chem. Soc. 1946, 115.
2. A. M. Grigorovskii, C. R. Acad. Sci. USSR, 53 (1946), 229; Chem. Abstr. 41 (1946), 4495.
3. A. I. Gurevich and Y. N. Sheinker, Zh. Fiz. Khim. 36 (1962), 734; Chem. Abstr. 57 (1962), 7231.
4. A. Albert and B. Ritchie, J. Chem. Soc. 1943, 458.
5. I. S. Ioffe and N. A. Seleznewa, Zh. Obshch. Khim. 31 (1961), 50; Chem. Abstr. 55 (1961), 24751.
6. J. P. Galy, J. Elquero, E. J. Vincent, A.-M. Galy and J. Barbe, Heterocycles 14 (1980), 311.
7. R. M. Acheson and E. C. Constable, J. Chem. Soc. Chem. Commun. 1980, 1065.
8. The cyano group of 2 appears to be transferable: The mass spectrum of 2 shows a small peak at m/z 244 (beyond $M^{+\cdot}$ of 2 at 219), which is tentatively attributed to 9,10-dicyano-9-imino-acridane 8, a product of further cyanation presumably formed under the condition of the mass spectrum of 2.



8

9. L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon, London, 2nd ed. 1969, (a) p. 82; (b) p. 226; (c) p. 93.
10. Also other physical properties indicate the polar character of compound 3: Beside the high mp the IR spectrum (strong absorption of N-H streching centered at 3000 cm^{-1} with many subpeaks spread over a broad band) suggests self-association with extended hydrogen bonding.
11. J. G. Schantl and W. Türk, Abstract of the 8th International Congress of Heterocyclic Chemistry, Graz, Austria, 1981, p. 364.
12. R. M. Acheson, "The Chemistry of Heterocyclic Compounds", ed. by A. Weissberger and E. C. Taylor, Wiley, New York, vol. 9, 2nd ed. 1973, p. 697.

Received, 30th July, 1984