

STEREOCHEMISTRY OF THE VON BRAUN CYANOGEN BROMIDE REACTION

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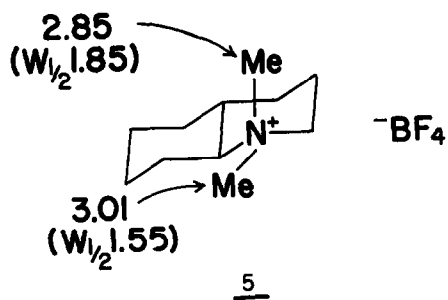
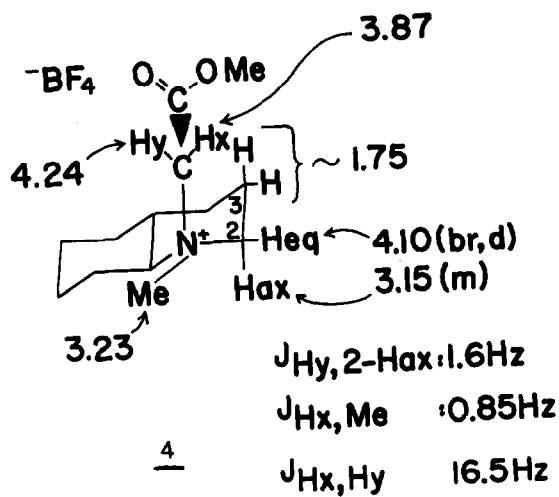
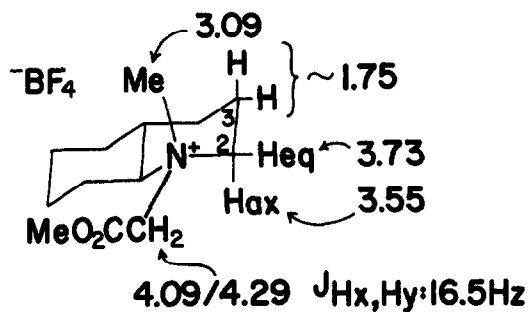
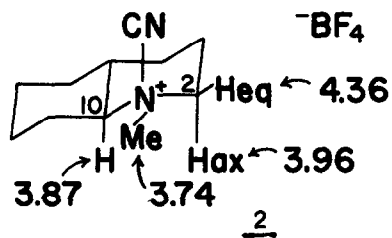
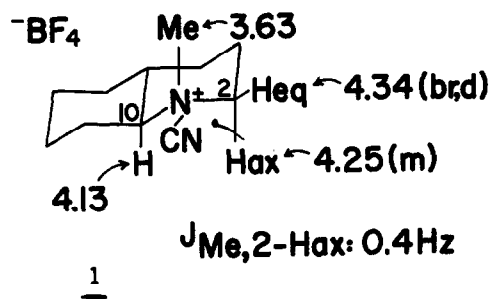
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The intermediate of the von Braun cyanogen bromide reaction of heterocyclic amines was trapped last year¹ and its constitution as an N-cyanoammonium bromide was established by chemical, analytical, and spectral data.^{1,2} Several stabilized^{1,4} cyanoammonium salts have been prepared from the bromides by ion exchange with non-nucleophilic anions. Most recently a low temperature NMR study³ of the intermediate showed that its decomposition followed first order kinetics and is the rate determining step, while the bimolecular reaction of its formation from the amine was immeasurably fast.

Completion of the structural work in terms of configuration and conformation of the intermediates seemed desirable since we regarded the first step of the cyanogen bromide reaction, i.e. cyanation, as a special case of quaternization. Therefore, parallelism to or divergence from the steric course followed by nitrogen alkylations should give a clue concerning the correctness of this assumption.

Now we wish to present for the first time unambiguous evidence for the existence of stereoisomeric N-cyanoammonium bromides. These compounds were precipitated at -20° from ether, and then treated with silver fluoroborate in acetonitrile. The 60 MHz NMR ⁺N-Me peaks at 3.63 and 3.74 ppm showed that the mixture contained the two epimers in a ratio of 9:1. The isomers were separated by fractional crystallization and had m.p.'s 135° and 156°, respectively.⁵ Three independent approaches have been made: (a) PMR studies (b) ¹³C NMR spectroscopy⁸ with both N-epimers as the fluoroborate salts (c) X-ray structure analysis on the major product of cyanation.

(a) Proton magnetic resonance studies. Extensive PMR measurements at 250 MHz and 100 MHz enabled unequivocal determination of the relative configurations at the ammonium chiral center (only pertinent PMR data are given for structures 1-5, measured in CD₃CN) in N-methyl-trans-



decahydroquinoline derivatives. Structures of the major (80%) and the minor (20%) products, 3 and 4 respectively, resulting from N-methoxycarbonylmethylation of N-methyl-trans-decahydroquinoline were investigated along with the model dimethyl compound 5. In 4, the 3-H's could be located at ca. 1.75 ppm by decoupling of 2-H signals at 4.10 ppm and 3.15 ppm; furthermore, ^{14}N -decoupling resulted in significant change in signal shape around 1.75 ppm, an observation in agreement with the result that β -protons are more extensively coupled to ^{14}N than are α -protons.⁶ Irradiation at 1.75 ppm resulted in a 10% Nuclear Overhauser Effect (NOE) in the 3.87 ppm signal (H_x); therefore, the $-\text{CH}_2\text{COOMe}$ group is axial in 4. The two C-2 proton assignments were made on the basis of their splitting pattern. It should be noted that in accordance with the configuration derived from the NOE, W-type couplings were observed between $\text{H}_y/2-\text{H}_{ax}$, and between $\text{H}_x/\text{N-Me}$; the two couplings show that rotation of the axial $-\text{CH}_2\text{COOMe}$ group is restricted. This restricted rotation of the axial methylene group was also found in the minor isomer of N-benzylation of N-methyl-trans-decahydroquinoline. Thus the benzyl protons of the fluoroborate (4, Ph instead of CO_2Me) appeared as the AB portion (H_x at 4.61 and H_y at 4.16 ppm) of an ABX system with splitting patterns similar to 4: $J_{\text{H}_y/2-\text{H}_{ax}}$ 1.2 Hz; $J_{\text{H}_x/\text{Me}}$ 0.7 Hz; $J_{\text{H}_x/\text{H}_y}$ 13.3 Hz. In the major isomer (3, Ph instead of CO_2Me) they appeared as an AB quartet, H_x at 4.55 and H_y at 4.37 ppm, $J_{\text{H}_x/\text{H}_y}$ 13.3 Hz, which as in 3 was not coupled to other protons. The chemical shifts also provided a suitable means for differentiating the two epimers. In the dimethyl derivative 5, the N-Me peak at higher magnetic field (2.85 ppm) was assigned to the axial Me group as indicated by its larger half-band width (due to W-coupling with $2-\text{H}_{ax}$ and $10-\text{H}_{ax}$). In 3 and 4 also, chemical shifts of the axial Me (3) and $-\text{CH}_2$ groups (4) appeared at a higher field than their equatorial counterparts. This relation holds for a number of other axial and equatorial protons (unpublished) excepting the N-benzyl stereoisomers in which the relation is reversed due to the anisotropic effect of the benzyl group, i.e. axial Me at δ 2.90 and equatorial Me at δ 2.87.

Detailed PMR measurements of the major (1) and minor (2) cyanation products led to the assignment of signals as shown. Again, a clear long-range coupling was present between $2-\text{H}_{ax}$ and Me ($J=0.4$ Hz) in 1, thus indicating the Me group to be axially oriented.⁷ In support of this assignment, the N-Me chemical shift in 1 was also at the higher field of 3.63 ppm (vs. 3.74 ppm in 2.) The mentioned results thus suggested that the preferred steric course of N-cyanation is equatorial in the present case. The same conclusion was drawn for N-methoxycarbonylmethylation and N-benzylation of the tertiary amine.

(b) ^{13}C NMR Spectroscopy. The major product of cyanation of the same base showed N-methyl, C-3 and C-9 signal at higher field ($\Delta\delta$ 8.7, 3.4, and 4.1, respectively⁸) than those of the minor isomer. This is in consonance with known conformational effects of an axial methyl group in the cyclohexane series.⁹

(c) X-ray crystallography. X-ray measurements were made at room temperature using a Picker four-circle diffractometer with Cu K_{α} radiation. The crystals are monoclinic with space group $P2_1/c$ and $a=13.046$, $b=9.222$ and $c=11.382$ Å, $\beta=93.38^\circ$. The structure was solved by the symbolic addition procedure using three-dimensional intensity data and shows the cyano group in equatorial and the methyl substituent in axial position, relative to the piperidine ring (1). The conventional R factor ($R = \frac{\sum |F_o| - |F_c|}{\sum |F_o|}$) is presently 0.140 and least-squares refinement is proceeding. Thus structure 1 for the major product of cyanation was proven.

Details of the X-ray crystallographic work and of chemical and spectral studies¹⁰ on the von Braun cyanogen bromide reaction will be published in full papers separately.

References

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4. J. V. Paukstelis and Moon-gen Kim, *Tetrahedron Lett.* (54) 4731 (1970).
5. Mixed m.p. of the N-stereoisomers was 90-120^o; the lower melting product crystallizes first. Analyses were correct.
6. K. Tori, T. Iwata, K. Aono, M. Ohtsuru and T. Nakagawa, *Chem. Pharm. Bull.* (Tokyo), 15, 329 (1967).
7. No measurable coupling was present between 10-H_{ax}/Me in 1. The reason for this is not known.
8. A joint paper with E. Wenkert, D. Cochran and F. Schell is in preparation on the use of ^{13}C NMR spectra for the determination of N-configurations of certain quaternary ammonium salts inter alia N-cyanoammonium salts of the trans-decahydroquinoline, trans-decahydroisoquinoline and the tropane series.
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10. Thanks are due to National Science Foundation for Grant GP-26558, to the National Research Council of Canada, and to Dr. A. A. Bothner-By, Carnegie-Mellon University, Pittsburgh, Pa., for his permission to use the 250 Mc spectrometer, and his assistance. NIH Grant CA-11572 to one of the authors (K. N.) is also gratefully acknowledged.