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ACTION OF POTASSIUM AMIDE ON 3-FLUOROPYRIDINE IN LIQUID AMMONIA[1,2]

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3-Chloro, 3-bromo and 3-iodopyridine react with potassium amide in liquid ammonia[3,4] and the first two halogeno compounds with lithium piperidide and piperidine in ether[5,6] via 3,4-pyridyne as an intermediate yielding mixtures of 3- and 4-substituted reaction products, i.e. aminopyridines and piperidinopyridines. 3-Fluoropyridine was shown to react with lithium piperidide nearly exclusively according to the addition-elimination mechanism, 3- and 4-piperidinopyridine being formed in yields of 88 and 4% respectively. Now we have found that in the reaction of 3-fluoropyridine (I) with the equimolecular amount of potassium amide in liquid ammonia, for 7 hrs at -33°,

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[1] 10th communication on hetarynes from this Laboratory.

[2] The present investigation has been carried out under the auspices of the Netherlands Foundation for Chemical Research (S.O.N.) and with financial aid from the Netherlands Organization for the Advancement of Pure Research (Z.W.O.).

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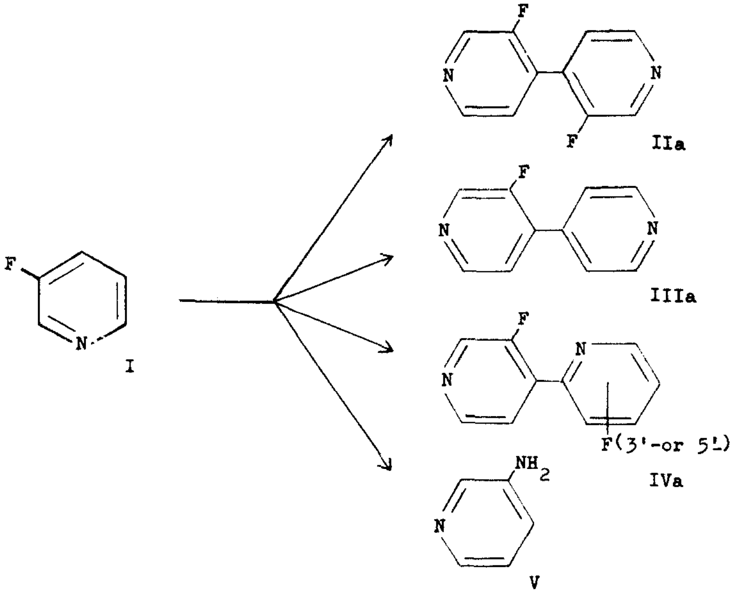
[4] M.J.Pieterse, Thesis, Amsterdam 1962.

[5] T.Kauffmann and F.P.Boettcher, Angew.Chem. 73, 65 (1961).

[6] T.Kauffmann and F.P.Boettcher, Ber. 95, 1528 (1962).

neither 3- nor 4-aminopyridine was formed, but a reaction mixture from which three fluoro derivatives of bipyridines could be isolated by G.L.C. using a column with Polywachs and sodium carbonate on Chromosorb W as stationary phase and hydrogen as carrier gas at 180°. From microanalyses, molecular weight determinations and N.M.R. data these substances were proved to be: 3,3'-difluoro-4,4'-bipyridine (IIa, m.p. 172-173°), 3-fluoro-4,4'-bipyridine(IIIa, m.p. 139-141°) whereas it seems probable that IVa (m.p. 103-105°) is 3,3'- or 3,5'-difluoro-2',4-bipyridine. The yields were established to be 25%, 15-20% and 5-10% respectively.

When I was reacted with 4 times the equimolecular amount of potassium amide, together with the substances IIa, IIIa and IVa (yields: 15, 15 and 5%), some 3-aminopyridine (V, yield 5%) was formed.



In connection with the proof of the structures, IIa and IVa were converted into the corresponding ethoxy compounds IIb (m.p. 110-111°) and IVb (m.p. of monopicrate 162°). IIIa was transformed into both the ethoxy derivative IIIb (m.p. 67-69°) and *via* the hydrazino compound into a bipyridine which was established by mixed melting point determination and by comparing the I.R. and U.V.spectra to be the 4,4'-isomer.

As for the mechanism of the conversion of 3-fluoropyridine (I) by potassium amide, it appears that this reaction occurs only to a slight extent according to a simple addition-elimination process (formation of 3-aminopyridine in the presence of an excess of the reagent) and that just as little a hetaryne type mechanism plays a rôle. It is likely that first a hydrogen ion is abstracted from the 4-carbon atom and that, thereupon, the carbanion formed adds to positively charged carbon atoms in the nucleus of a second molecule of I producing intermediates which yield the difluorobipyridines IIa or IVa by splitting off a hydride ion. The formation of IIIa seems to be a more complicated process. We do not exclude that in this process 3,4-pyridyne is involved as an intermediate.

Conclusions from N.M.R. data (by M.van Ammers).

1. From the F^{19} magnetic resonance spectra [7] of IIa, IIIa and IVa it was concluded that in all compounds the fluorine atoms occupy the β-position, as sharp peaks were observed in a region where 3-fluoropyridine shows absorption, whereas 2-fluoropyridine gives

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[7] F^{19} and proton N.M.R.spectra were taken on a J.E.O.L. J.N.M.-C-60 N.M.R.spectrometer. For F^{19} a frequency of 56.4 MHz was used. All compounds were dissolved in $CDCl_3$. Proton shifts are reported in τ-values, referred to the internal standard TMS.

a broad band situated about 59 ppm lower than the absorption of 3-fluoropyridine.[8]

Apart from some coupling with hydrogen the spectrum of both the difluoro compound IIa and the monofluoro compound IIIa consisted of a singulet, which proved that in IIa the fluorine atoms are equivalent. The F^{19} spectrum of IVa showed two doublets, spaced 8 ppm, J^{FF}: 34 cps, thus indicating two nonequivalent fluorine atoms.

2. In the proton N.M.R.spectra of pyridine and derivatives of this substance the lowest field signals, due to the α-protons are always clearly separated from those of the β- and γ-protons. Depending on substituent effects, the signals from β- and γ-protons sometimes overlap[9].

Structure of IIa. The proton N.M.R.spectrum of IIa consisted of a multiplet around 2.70 τ due to protons in β- and/or γ-position and a multiplet around 1.40 τ due to α-protons. As the ratio of the integrated areas amounted to ~ 1 : 2. IIa might be either 3,3'-difluoro-4,4'-bipyridine or 3,3'-difluoro-5,5'-bipyridine. To avoid H-F coupling the fluorine atoms were substituted by ethoxy groups. The N.M.R.spectrum of the aromatic protons of the diethoxy compound IIb clearly showed the ABX-pattern to be expected for a 3,4-disubstituted pyridine derivative (a doublet at 2.85τ(J : 5 cps) due to the 5- and 5'-protons and a broadened

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[8] c.f. K.Ito, K.Inukai and T.Isobe. *Bull.Chem.Soc. Japan,* **33**, 315-19 (1960); C.A. **54**, 18080d (1960).

[9] W.Brügel, Z.Electrochem. **66**, 159 (1962).

doublet at 1.8 τ due to 6- and 6'-protons, overlapped by a singulet at 1.75 τ due to 2- and 2'-protons). Thus, it appears that IIb is 3,3'-diethoxy-4,4'-bipyridine and consequently IIa 3,3'-difluoro-4,4'-bipyridine.

Structure of IIIa. The proton N.M.R.spectrum of IIIa showed two multiplets at 2.50 and 1.30 τ respectively (ratio of areas $= \sim 3 : 4$) which proved that all α-positions are unsubstituted. The N.M.R.spectrum of the ethoxy compound IIIb obtained by replacing the fluorine atom of IIIa by ethoxyl, showed the ABX-pattern of a 3,4-disubstituted pyridine just as that of IIb (doublets at 2.80 τ and 1.70 τ, singulet at 1.65 τ), and at the same time the A_2X_2-pattern of a 4-substituted pyridine (seen as a quartet at 2.55 τ (J_{AX}: 5.5 cps; $J_{AX'}$: 1 cps) and a broadened doublet at 1.35 τ). This substance gave separate proton signals of each ring, due to the shielding effect of the ethoxy group on the protons of one of the rings. Thus, IIIb is 3-ethoxy-4,4'-bipyridine and IIIa 3-fluoro-4,4'-bipyridine.

Structure of IVa. The proton N.M.R.spectrum of IVa showed two multiplets at 2.45 τ and 1.4 τ (relative areas $= \sim 1 : 1$) proving that IVa is either a α-β- or a α-γ-bipyridine. The diethoxy compound IVb obtained by replacing the fluorine atoms in IVa by ethoxy groups showed a N.M.R.spectrum with multiplets at 2.7 τ and 1.6 τ respectively. From these data it could not be concluded which structure must be attributed to IVa, since the possible difluorobipyridines can give the same type of absorption pattern, the absorptions from both rings being not separated as is the case with compound IIIb.

From considerations on the course of the reaction of potassium amide with 3-fluoropyridine given before it seems probable, however, that IVa is the 3,3'- or 3,5'-difluoro derivative of 2',4-bipyridine.

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