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### OXIDATION OF PRIMARY AMINES BY POTASSIUM

## FERRICYANIDE

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The use of organic amines and aminyl radicals has recently stimulated the development of research on their oxidative transformations during photolysis [1], in electrochemical reactions [2], in reactions with free radicals [3], and in redox systems containing elements with variable valence [4]. The reactions of secondary and tertiary amines were studied in the greatest detail, while those of primary amines characterized by high reactivity and lability in oxidation systems have been studied less.

We studied the oxidative transformations of primary n-alkyl-, sec-alkyl-, and tert-alkylamines by the action of a mild oxidation agent,  $K_3$ Fe(CN)<sub>6</sub>, in an alkaline medium, already used for the oxidative dealkylation of primary and secondary amines [5, 6].

By the action of the  $K_3Fe(CN)_6$ -NaOH system in aqueous solutions at 70-80°C and with equimolar amounts of the reagents, primary n-alkylamines (Ia-c) are oxidized into nitriles (IIa-c) (Table 1):

 $\begin{array}{l} {\rm RCH_2NH_2+4Fe(CN)_6^{3-}+4OH^- \rightarrow RC \equiv N + 4Fe(CN)_6^{4-}+4H_2O} \\ {\rm (Ia-c)} & {\rm (IIa-c)} \\ {\rm R} \ = {\rm C_5H_{11}} \ ({\rm a}), \ {\rm C_6H_{13}} \ ({\rm b}), \ {\rm C_7H_{15}} \ ({\rm c}). \end{array}$ 

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		Reaction products, yield, % based on converted amine (on oxidant)			
	Conversion, %	nitrile	other products		
Hexylamine (Ia) Heptylamine (Ib) Octylamine (Ic)	30 35 30	(IIa), 44 (53) (IIb), 55 (77) (IIc), 45 (54)	(III); <u>12</u> (8,5)		

TABLE 1. Oxidation of Primary n-Alkylamines in K<sub>3</sub>Fe(CN)<sub>6</sub>-NaOH System\*

\* 70-80°C, 7 h, 100 mmoles of amine, 100 mmoles of  $K_3Fe(CN)_6$ . 3H<sub>2</sub>O, 100 mmoles of NaOH, 120 ml of water.

TABLE 2. Oxidation of Primary sec-Alkylamines in  $K_3$ Fe(CN)<sub>6</sub>-NaOH System\*

Amine	Conversion, %	Reaction products, yield, % based on reacted amine (on oxidant)		
Isopropylamine (VIIa) sec-Butylamine (VIIb) Cyclohexylamine (VII¢)	$40 + 28 \\ 25 \\ 25$	(VIIIa), 60 (96) (VIIIb), 76 (85) (VIIIc), 80 (80)		

\* 70-80°C, 7-8 h, 100 mmoles of amine, 100 mmoles of  $K_3Fe(CN)_6 \cdot 3H_2O$ , 100 mmoles of NaOH, 120 ml of water. \*35-40°C.

In the oxidation of heptylamine (Ib), a small amount of n-heptylurea (III) was also identified. Other transformation products of amines (I) were not detected.

Thus, oxidation of primary n-alkylamines by the action of  $K_3$ Fe(CN)<sub>6</sub> · 3H<sub>2</sub>O is a simple method for synthesis of alkyl cyanides.

In analogy with the oxidation of amines into nitriles by the action of  $Pb(OAc)_4$  [7], it can be assumed that the reaction mechanism includes a single-electron oxidation of amines (I) into aminyl radicals (IV), their oxidation into aldimines (V), and a single-electron oxidation of the latter into nitriles (II):

$$\begin{array}{c} R & & \\ \hline R & & \\ \hline (I) & \\ \hline (IV) & \\ \hline (IV) & \\ \hline (IV) & \\ \hline (V) &$$

It is possible that under the reaction conditions, the intermediate aldimines (V) are oxidized fairly rapidly, so that it was impossible to detect the corresponding aldehydes RCHO, products of the hydrolysis of aldimines (V), in an alkaline medium.

Heptylurea (III) is most probably formed as the result of the oxidation of heptylamidyl radical (IVb) by the action of  $K_3$ Fe(CN)<sub>6</sub> by the mechanism of oxidative substitution with a transfer of the CN group to heptylcyana-mide (VI), which under the reaction conditions hydrolyzes into (III):

(Ib) 
$$\xrightarrow{iK_{4}Fe(CN)_{6}} C_{7}H_{15}NH \xrightarrow{iK_{4}Fe(CN)_{6}} C_{7}H_{15}NHCH_{3} \xrightarrow{NaON} H_{2}O C_{7}H_{15}NHCONH_{2}$$
(IVb) (VI) (III)

Potassium ferricyanide is not very effective as a cyanation agent of organic compounds. Only the reaction of C-cyanation of heteroaromatic N-oxides is known [8]. The formation of heptylurea (III) is the first example of N-cyanation by the action of  $K_3Fe(CN)_6$ . The yield of (III) strongly depends on the reaction conditions, because of further hydrolysis into the initial heptylamine (Ib):

$$(III) \xrightarrow[H_2O]{} [C_7H_{15}NHCOOH] \rightarrow C_7H_{15}NH_2 + CO_2$$
(I<sup>b</sup>)

By the action of  $K_3$ Fe(CN)<sub>6</sub>, primary sec-alkylamines RR'CHNH<sub>2</sub> (VII) undergo oxidative dimerization with the formation of hydrazones (VIII) (Table 2):



The mechanism of formation of hydrazones (VIII) most probably includes a single-electron oxidation of a mines (VII) into a minyl radicals (IX), which in the presence of Fe(III)/Fe(II) compounds promoting dimerization of free radicals [9] convert into N,N'-disubstituted hydrazines (X). Under the reaction conditions, the latter oxidize into hydrazones (VIII):



The proposed mechanism is confirmed by the transformation of N,N'-dicyclohexylhydrazine by the action of  $K_3$ Fe (CN)<sub>6</sub> under normal reaction conditions into cyclohexylhydrazone of cyclohexanone (VIIIc) in an 80% yield.

We believe that the difference in the chemical behavior of n-alkylaminyl (IV) and sec-alkylaminyl radicals (IX) is due to steric hindrances to oxidative deprotonation of (IX) into the corresponding ketimines RR'C = NH, and indicates a complex oxidation mechanism of radicals (IV) and (V), possibly with the participation of organoiron compounds.

Aniline, an aromatic amine with no hydrogen atoms in the  $\alpha$ -position to the amino group, by the action of  $K_3Fe(CN)_6$ -NaOH system, and as the result of oxidative dimerization, converts into azobenzene (XI) in an 80% yield, based on the oxidizing agent and on the converted aniline, with aniline conversion of 25%. The reaction mechanism is similar to the one discussed for sec-alkylamines:

$$C_{6}H_{5}NH_{2} \xrightarrow{K_{4}Fe(CN)_{6}} C_{6}H_{5}\dot{N}H \xrightarrow{Fe(III)/Fe(II)} C_{6}N_{5}NH-NHC_{6}H_{5} \xrightarrow{K_{4}Fe(CN)_{6}} C_{6}H_{5}N=NC_{6}$$

The aliphatic analog of aniline, tert-butylamine, is inert under reaction conditions of oxidation by the  $K_3Fe(CN)_6$ -NaOH system.

## EXPERIMENTAL

The GLC analysis was carried out on an LKhM-8MD chromatograph with a flame-ionization detector in a  $N_2$  current, using the following columns (stainless steel):  $300 \times 0.4$  cm with 10% Carbowax 20 M, treated with  $Na_3PO_4$ , on Celite-545 (52-60 mesh);  $300 \times 0.4$  cm with 2% DS-550 on a Chromosorb treated with dimethyldichlorosilane;  $300 \times 0.4$  cm with 10% PEGS on Celite-545 (52-60 mesh). The PMR spectra of the solutions in CDCl<sub>3</sub>, CCl<sub>4</sub>, and (CD<sub>3</sub>)<sub>2</sub>CO were measured on Varian DA-60-IL (60 MHz), Tesla BS-497 (100 MHz), and Bruker WM-250 spectrometers (250 MHz), using HMDS as the internal standard. The mass spectra were run on a Varian MAT CH-6 spectrometer with direct introduction of the sample into the ion source, with an energy of the ionizing electrons of 70 eV. The chromatographic introduction of the sample into the ion source, with energy of the ioniz-ing electrons of 80 eV. The IR spectra were obtained on Perkin-Elmer and Specord 75-IR apparatus in thin layer and in CCl<sub>4</sub> solution. The UV spectra were run on a Specord UV-VIS apparatus, in heptane.

The oxidizing agent  $K_3Fe(CN)_6 \cdot 3H_2O$  (AR grade) and NaOH (pure grade) were used without additional purification. Distilled water was used. Amines (Ia-c) and (VIIIa-c), tert-butylamine, and aniline were purified by distillation at atmospheric pressure in an argon current.

Oxidation of Primary Amines by  $K_3Fe(CN)_6$ -NaOH System. A solution of 100 mmoles of  $K_3Fe(CN)_6 \cdot 3H_2O$ in 100 ml of water was added in the course of 2 h at 70-80°C, with vigorous stirring, to a mixture of 100 mmoles of the amine and a solution of 100 mmoles of NaOH in 20 ml of water. The mixture was stirred for another 5-6 h at this temperature, then cooled and extracted with ether (3 × 100 ml). The ether extract was dried over MgSO<sub>4</sub>, and evaporated. The residue was analyzed by GLC. The oxidation products, nitriles (IIa-c) and hydrazones (VIIIa-c), were isolated by distillation. In the case of n-alkylamines (Ia-c), a higher or lower analog of the nitrile formed in the oxidation reaction was used as the standard during the chromatographic analysis of the reaction products. After evaporation of the ether extract from the oxidation reaction of heptylamine (Ib), a solid precipitate separated out. This was filtered, washed on the filter, and dried. Yield, 4.2 mmoles of heptylurea (III), mp 112°C (cf. [10]). The properties and spectral characteristics of the reaction products are listed in Table 3.

	Found/Calculated, %	formula C H N $(\nu, \text{cm}^{-1})$ [ $\beta$ , ppm) [intensity)	- 2250 (vC=N) -	- 2250	- 2250	$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	) $C_{12}H_{32}N_2$ $74,70$ $11,50$ $13,95$ $1635$ $1,30m(4H, CH_2)$ $98(100), 55(80), 136(53), 179(35), 165(10H, CH_2)$ $74,23$ $74,23$ $11,34$ $14,43$ $15,43$ $15,43$ $15,44$ $15,44$ $15,14$ $15,$	
	Found /Calcul	υ	 			60,28 1 1		67,23 67,61 1	74,23	
u)		formula	 1	I	I	C <sub>8</sub> H <sub>18</sub> N <sub>2</sub> O	1	C <sub>8</sub> H <sub>18</sub> N <sub>2</sub>	C <sub>12</sub> H <sub>22</sub> N <sub>2</sub>	
	ہ۔ <sub>م</sub> ر رہ	mm Hg)	68(10)	82-84(12)	85 - 86(10)	1	60(45) *	70(40)	115-116(10)	•
zones (VII		Compound	(11a)	(IIb)	(IIc)	(111)	(VIIIa)	(dIIIV)	(VIIIc)	

TABLE 3. Physicochemical Properties and Spectral Characteristics of Nitriles (II), Heptylurea (III), and Hydra-

<u>Behavior of tert-Butylamine in  $K_3Fe(CN)_6$ -NaOH System.</u> A solution of 100 mmoles of  $K_3Fe(CN)_6 \cdot 3H_2O$ in 100 ml of water was added at 45°C, with vigorous stirring, to a mixture of 100 mmoles of tert-butylamine and a solution of 100 mmoles of NaOH in 20 ml of water. The mixture was stirred for another 6 h at this temperature, cooled, and extracted with ether (3 × 100 ml). The ether extract was dried over MgSO<sub>4</sub>, and evaporated. In the residue, 85% of unreacted tert-butylamine was detected by GLC.

Oxidation of Aniline in  $K_3Fe(CN)_6 - NaOH$  System. A solution of 60 mmoles of  $K_3Fe(CN)_6 \cdot 3H_2O$  in 60 ml of water was added in the course of 2 h at 50°C, with vigorous stirring, to a mixture of 60 mmoles of aniline and a solution of 60 mmoles of NaOH in 10 ml of water. The mixture was stirred at this temperature for another 5 h, cooled and extracted with benzene (4×150 ml). The extract was dried over MgSO<sub>4</sub> and evaporated. In the residue 35 mmoles of aniline and 12 mmoles of azobenzene (XI) were found by GLC. Distillation gave 10 mmoles (75% based on reacted aniline) of azobenzene; bp 118-120°C (1 mm), mp 66-68°C (cf. [12]). UV spectrum ( $\lambda$ , nm): 450 ( $\epsilon$  342), 317 ( $\epsilon$  21,670), 230 ( $\epsilon$  18,670), identical with the spectrum of pure grade azobenzene.

<u>Transformation of Heptylurea (III) by Action of NaOH (control experiment).</u> An 8 mmole portion of heptylurea was added at 70-80°C to a solution of 20 mmoles of NaOH in 15 ml of water, and the mixture was stirred at this temperature for 3 h. The reaction mixture was cooled and extracted with ether  $(3 \times 50 \text{ ml})$ . The extract was dried over MgSO<sub>4</sub>, and evaporated. By distillation, 7 mmoles (90%) of heptylamine (Ib) were isolated.

<u>Preparation of N,N'-Dicyclohexylhydrazine (Xc).</u> A 0.3 mole portion of hydrazine hydrate was added dropwise, with stirring, to a mixture of 0.9 mole of cyclohexanone and 1 mole of CaO. As the reaction mixture thickened, absolute ethanol was added. The mixture was boiled for 2 h and then cooled. The precipitate was filtered and washed with alcohol. By distillation of the filtrate in vacuo, 0.24 mole (80%) of cyclohexanone azine (XII) was obtained, bp 165-175°C (15 mm) (cf. [13]). A solution of 0.1 mole of (XII) in 30 ml of absolute ether was added dropwise to a suspension of 0.15 mole of LiAlH<sub>4</sub> in 150 ml of absolute ether with vigorous stirring and cooling (~0°C). The mixture was stirred for 1 h at 25°C. The excess of LiAlH<sub>4</sub> was decomposed with alcohol, and 200 ml of water were added to the reaction mixture. The mixture was centrifuged, and the organic layer was separated. By distillation in vacuo, 0.05 mole (50%) of N,N'-dicyclohexylhydrazine (Xc), bp 140-142°C (10 mm), were obtained (cf. [14]).

<u>Oxidation of N,N-Dicyclohexylhydrazine (Xc) in  $K_3Fe(CN)_6$ -NaOH System</u>. A solution of 100 mmoles of  $K_3Fe(CN)_6 \cdot 3H_2O$  in 100 ml of water was added at 70-80°C in the course of 2 h, with vigorous stirring, to a mixture of 50 mmoles of (Xc) and a solution of 100 mmoles of NaOH in 20 ml of water. The mixture was stirred for another 5 h at this temperature, then cooled, and extracted with ether (3 × 100 ml). The ether extract was dried over MgSO<sub>4</sub> and evaporated. The residue was distilled in vacuo to yield 40 mmoles (80%) of (VIIIc), bp 115-116°C (10 mm) (cf. [15]).

#### CONCLUSIONS

1. By the action of the  $K_3Fe(CN)_6$ -NaOH system, primary alkylamines RCH<sub>2</sub>NH<sub>2</sub> are oxidized into alkanoic acid nitriles RCN. The action of the  $K_3Fe(CN)_6$ -NaOH system on heptylamine also leads to its N-cyanation with the formation of N-heptylurea, which is readily hydrolyzed under the reaction conditions.

2. By the action of the  $K_3Fe(CN)_6$ -NaOH system, primary sec-alkylamines R,R'CHNH<sub>2</sub> convert into alkylhydrazones of alkanones RR'C=N-NHCHRR' as the result of oxidative dimerization.

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# NITROXYL DERIVATIVES OF PYRAZOLO[3,4-d]PYRIMIDINE

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Pyrazolo[3,4-d]pyrimidines are "irreversible" xanthine oxidase inhitibors and are widely used in research into this enzyme [1-3]. Paramagnetic pyrazolopyrimidine derivatives which are capable of binding strongly with xanthine oxidase may be a useful tool for elucidating the topography of the active center of the enzyme.

We have prepared pyrazolopyrimidine derivatives of formula (IIIa-c), which are the first of their kind, by reacting 4-chloropyrazolopyrimidine (I) with amino radicals (IIa-c):



The reaction was performed in boiling ethanol (1-1.5 h), the HCl formed in the reaction being bound with triethylamine. The consumption of the bases was monitored by TLC and by potentiometric titration with 0.1 N HCl. The yield of (IIIa-c) under these conditions is 95-97% (Table 1).

A mino radical (IIc) was prepared by reducing the amide (IV) in THF and then oxidizing the resulting hydroxypiperidine (VI). The reduction of (IV) was monitored on the basis of  $H_2$  evolution and LiAlH<sub>4</sub> consumption, indicating that the reaction is practically complete by the time (IV) is extracted into the solution, and that 5 moles of LiAlH<sub>4</sub> are consumed and 5 moles of  $H_2$  are released for every 2 moles of (IV). The resulting colorless, THF-insoluble complex (V) releases  $H_2$  and is converted to (VI) when decomposed with water:



The oxidation of (VI) to (II) is effected in an alkaline aqueous methanol medium in the presence of  $Cu^{2+}$ . This method of preparing (IIc), which gives a yield of ~60%, is considerably simpler than the methods of [4, 5] since it avoids protection of the amino group during oxidation.

Pyrazolopyrimidines (IIIa-c) are high-melting substances colored in different shades of red. They are readily soluble in alcohols, sparingly soluble in alkanes and water, and moderately soluble in medium-polarity solvents.

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