Quantitation of the PVA–Borate–Iodine Complex

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While the PVA–borate–iodine complex is shown to be suitable for the qualitative determination of boric acid, attempts to adapt this to a colorimetric procedure were of no avail. A possible explanation is suggested as a dilution phenomenon.

IN A PREVIOUS publication (1), it was reported that the PVA–borate–iodine reaction was suitable for the detection of boric acid in urine. At the same time it was inferred that this test might be adaptable to a quantitative determination of boric acid, on the basis of the fact that the authors were able to detect as little as 0.3 mg. of that substance. The fact that this reaction involved the development of a color as an end point might also lead one to believe that variation in the color produced by different concentrations of boric acid could be used as the basis for a colorimetric assay.

In a series of experiments conducted along those lines in these laboratories, the following facts were ascertained.

(*a*) Simple dilution with water caused the typical blue-black color to be discharged. The resultant color was either yellow or red-brown. The intensity of the dilute color could not be related to differences in the concentration of any of the components of the reaction mixture. Colorimetric determinations were carried out using a Spectronic 20 colorimeter.

(*b*) The discharge of color could not be attributed to alteration in pH. It was determined that an optimum pH of 4.0 was necessary for initial color development, but that subsequent dilution caused the color to discharge even though the optimum pH was maintained throughout the series of dilutions.

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(*c*) A variety of water-miscible, organic solvents was tested to determine whether the discharge of color could be caused by the available excess hydroxyl or hydronium ions. A spectrum of glycols and alcohols caused color discharge. In addition, color loss was also noted with the addition of dioxane, acetone, and ethyl acetate. This seems to indicate that the change in color from blue to yellow is a dilution phenomenon not related to either excess hydroxyl or hydronium ions.

(*d*) In the case of dilution with absolute ethyl alcohol, it was noted that the yellow color which developed could be related to the concentration of boric acid. Using a Beckman model DB recording spectrophotometer, a linear relationship was established for concentrations of boric acid down to 10.0 mg. Below this concentration, only erratic readings were obtained. The developed color was discharged on standing. Decoloration was hastened when heat was applied. It was shown subsequently that the yellow color represented an excess of iodine.

(*e*) The above observations lead us to believe that this test, in all probability, will have to remain qualitative.

It must be concluded that the color developed in the PVA–borate–iodine reaction is dependent upon the optimum concentration of reactants in an optimum volume of solvent. The nature of the solvent is important to the extent that all reactants must be mutually soluble in it. The initial color is probably not due to a production of a color pigment in the complex formation, but rather to the ability of that specific concentration of substances to exhibit spectral absorbance within the blue range.

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Preparation of Some Cyanoalkylpiperidines

By MORRIS FREIFELDER

Selective conversion of the pyridine ring was accomplished without attack of the nitrile group when some alkyl cyanoalkylpyridinium halides were hydrogenated in the presence of platinum oxide or rhodium on carbon catalyst.

CATALYTIC hydrogenation of a ring system is more difficult to achieve than reduction of a functional group. In the pyridine series the difficulty is due to the poisoning effect of the ring nitrogen or more likely to the effect of the resultant more basic piperidine nitrogen atom. Nevertheless, a number of examples have been cited where the ring was preferentially attacked when a methylene bridge separated it from a ketone group (1). In general this took place when the ring was quaternized. There are only a few examples of selective conversion when the carbonyl group is adjacent to the ring. Lyle and Warner converted 3-benzoylpyridine hydrochloride and methyl 3-benzoylpyridinium iodide to the corresponding benzoylpiperidines in 35–40% yield (2); Freifelder obtained 70% of 3-acetyl-1,4,5,6-tetrahydropyridine and 7% of 3-acetylpiperidine

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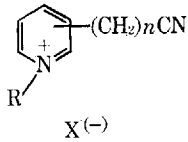
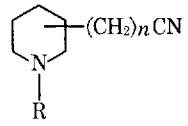
TABLE I.—QUATERNARY SALTS



Compd.	R	n	Position of Side Chain	X	Yield, %	M.p., °C.	Formulas	Anal., % Calcd.	Found
I	CH_3	1	3	I	84.5	119–120	$C_8H_9IN_2$	C, 36.44	36.56
								H, 3.48	3.52
								N, 10.77	10.45
II	$C_6H_5CH_2$[a]	1	3	Cl	74	154–157	$C_{14}H_{13}ClN_2$	C, 68.70	68.69
								H, 5.30	5.20
								N, 11.45	11.58
III	CH_3[b]	2	2	I	61[c]	138–139.5	$C_9H_{11}IN_2$	C, 39.43	39.45
								H, 4.04	3.96
								N, 10.22	10.38

[a] Reaction to form quaternary compound carried out at 100° for 18 hr. [b] Reaction run at 125° for 16 hr. [c] The crystalline mass was admixed with tar. Pure material was obtained by continuous extraction with refluxing isopropyl alcohol.

TABLE II.—HYDROGENATION PRODUCTS



Compd.	R	n	Ring Position of Side Chain	Yield,[a] %	Constants B.p., mm. °C.		n_D^{25}	M.p. Salt	Formulas	Anal., % Calcd.	Found
IV	CH_3	1	3	59	106	13	1.4654	...	$C_8H_{14}N_2$	C, 69.51	68.91
										H, 10.21	10.21
										N, 20.27	20.30
		...	...	...	...	...	...	120–122[b]	$C_8H_{15}ClN_2 \cdot 1/2H_2O$	C, 52.31	52.47
										H, 8.78	8.62
										N, 15.26	15.28
		...	...	...	...	...	...	93.5–94.5[c]	$C_{12}H_{20}N_2O_4$	C, 56.23	55.94
										H, 7.86	8.00
										N, 10.92	10.71
V	$C_6H_5CH_2$	1	3	56	169	3.8	1.5301	...	$C_{14}H_{18}N_2$	C, 78.46	78.74
										H, 8.46	8.70
										N, 13.07	13.14
VI	CH_3	2	2	54	135	32	1.4710	...	$C_9H_{16}N_2$	C, 71.00	70.96
										H, 10.59	10.81
										N, 18.41	18.51

[a] The bases are easily soluble in water. The yields might be substantially increased by continuous extraction. [b] Hydrochloride salt. [c] Succinate salt.

from the hydrogenation of 3-acetylpyridine (3). Other investigators report selective conversion of the carbonyl group or concurrent reduction in such instances.

1-Methyl-3-cyanomethylpiperidine was obtained from the reduction of methyl 3-cyanomethylpyridinium iodide in the presence of platinum oxide or rhodium on carbon. The instability of 2- and 4-cyanomethylpyridines prevented any work on subsequent quaternization and reduction to obtain the isomeric 2- and 4-cyanomethylpiperidines. 1-Benzyl-3-cyanomethylpiperidine was also prepared and subjected to hydrogenolysis to yield 3-cyanomethylpiperidine.

Attempts were made to reduce 3-cyanomethylpyridine to the piperidine selectively in aqueous alcoholic hydrochloric acid or in glacial acetic acid. In all cases the nitrile group was perferentially attacked.

It had been postulated that the selective conversion of the ring which occurs when a quaternary compound is reduced is due to the existence of a single species incapable of reversibility as compared to the equilibrium existing between the base and the ionic form of an acid salt (1). The unsuccessful conversions in aqueous acidic media were probably due to water competing for protonation. In glacial acetic acid protonation apparently was not complete enough for selective ring reduction. When the hydrogenation of 2-(2-cyanoethyl)pyridine was carried out in trifluoroacetic acid selective conversion of the ring did not take place. On the other hand

reduction of the methiodide in 50% aqueous alcohol yielded 1-methyl-2-(2-cyanoethyl)piperidine in fairly good yield.

EXPERIMENTAL[1]

The following procedure was used to prepare the quaternary salts listed in Table I.

Methyl 3-Cyanomethylpyridinium Iodide (I).—A mixture of 11.8 Gm. (0.1 mole) of 3-cyanomethylpyridine and 21.3 Gm. (0.15 mole) of methyl iodide in 60 ml. of dry benzene was heated in a 183-ml. stainless steel rocker type bomb for 12 hr. at 100°. After cooling, the solid product in the reactor was filtered, washed with anhydrous ether, and dried.

Hydrogenation of the quaternary compounds was carried out in the following manner.

1-Methyl-3-cyanomethylpiperidine (IV).—A solution of 20.8 Gm. (0.08 mole) of I in 200 ml. of 90% aqueous alcohol was hydrogenated (3 Atm.) in the presence of 0.6 Gm. of platinum oxide.[2] Uptake for 0.24 mole was complete in 4 hr. The catalyst was removed by filtration. It was washed with 25 ml. of water and the combined filtrate and washings concentrated to dryness under reduced pressure. The residue was dissolved in a small amount of water and the solution, kept below 15°, was made strongly basic with 40–50% sodium hydroxide solution. The mixture was extracted thoroughly with benzene and the extract dried over anhydrous magnesium sulfate. The solution was then concentrated and the residue distilled. Gas-liquid chromatography of the distilled product as well as the other amines (V and VI) showed each to be a single component. Infrared examination gave no evidence of the presence of primary or secondary amine but did show the characteristic C≡N band at 4.46–4.48 μ. It was difficult to get good carbon, hydrogen, and nitrogen values unless the bases were analyzed immediately after distillation because they absorbed carbon dioxide so rapidly. Some were additionally characterized as salts. (See Table II.)

3-Cyanomethylpiperidine (VII).—A solution of 32.8 Gm. (0.153 mole) of V in 100 ml. of 95% ethanol containing 0.153 mole of dry hydrogen chloride was hydrogenated in the presence of 5.0 Gm. of 5% palladium on carbon at room temperature and 2 Atm. pressure. Hydrogen uptake was interrupted at 90% of theory to insure selectivity. After removal of catalyst, the solution was concentrated to dryness under reduced pressure. The residue was dissolved in 50–75 ml. of water and cooled to about 10–15° and kept cold while adding an excess of 50% sodium hydroxide solution. The oily layer was extracted with benzene, dried over anhydrous magnesium sulfate, and concentrated after filtration from the drying agent. The residue was distilled, b.p. 125° (15 mm.); n_D^{25} 1.4791; yield, 53%.

Anal.—Calcd. for $C_7H_{12}N_2$: C, 67.69; H, 9.74. Found: C, 67.79; H, 9.95.

The base picks up carbon dioxide rapidly and must be analyzed immediately. The found nitrogen value continued to drop after each analysis.

A hydrochloride melted at 140–142°. It was found to be a hemihydrate.

Anal.—Calcd. for $C_7H_{13}ClN_2 \cdot 0.5H_2O$: C, 49.55; H, 8.35; N, 16.52. Found: C, 49.39; H, 8.00; N, 16.58.

On further drying at 100° under reduced pressure for 8 hr. the salt appeared to stabilize at 0.25 H_2O.

Anal.—Calcd. for $C_7H_{13}ClN_2 \cdot 0.25H_2O$: C, 50.90, H, 8.24; Cl, 21.45; N, 16.96; O, 2.45. Found: C, 50.75; H, 8.35; Cl, 20.79; N, 16.98; O, 1.87.

Attempts to dry the salt at 130° *in vacuo* caused loss of hydrogen chloride.

Hydrogenation of 3-Cyanomethylpyridine in Acidic Media.—A solution of 11.8 Gm. (0.1 mole) of 3-cyanomethylpyridine in 50–75 ml. of water containing 1.0 to 1.2 moles of hydrogen chloride was hydrogenated in the presence of 0.350 Gm. of platinum oxide. Only 2 molar equivalents of H were absorbed. After removal of catalyst, concentration of the filtrate and basification, as in previous experiments, the crude product on infrared examination showed that the C≡N band was no longer present. The presence of the pyridine ring C=N, and the presence of primary or secondary amine was noted. On distillation about a 10% yield of 3-(2-aminoethyl)pyridine was obtained. The residue was a tarry formation.

In a reduction in glacial acetic acid containing 0.1% of concentrated sulfuric acid, 30% of the same amine was obtained. We never were able to show more than trace amounts of VII by gas-liquid chromatography in these or other experiments in various acidic media.

[1] Microanalyses were carried out by O. F. Kolsto and his group, infrared examination by A. Kammer and W. Washburn, gas-liquid chromatography by Mrs. Taimi Anderson. The author is grateful to these people for their assistance and to Miss Evelyn Schuber for the preparation of 2-(2-cyanoethyl)pyridine.

[2] A 15–20% ratio of 5% rhodium on carbon to substrate may be substituted. Both catalysts are available from Engelhard Industries, Newark, N. J.

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