in 25 ml of benzene. The mixture was stirred for 16 hr and the precipitate collected and dried to give 49 g of an uncrystallizable solid melting at 80–82° with foaming.

A solution of 21.0 g of the solid in 200 ml of ethanol was shaken with 2 g of a 5% rhodium-on-carbon catalyst for 20 hr at room temperature in an Adams–Parr apparatus under 50 psi of hydrogen. The filtered solution was concentrated to an oil that was dissolved in water; the aqueous solution was treated with solid potassium carbonate and extracted with ether. Evaporation of the ether left 6 g of oil that solidified, mp 91–93°; mixture melting point with pure (mp 96–97°) **21** (see below) was not depressed.

B. *Via* **Hydrogenation of 1.**—To a solution of 40.0 g (0.16 mol) of **1** in 200 ml of ice-cold ethanol was slowly added 37 ml of concentrated hydrochloric acid and the mixture was shaken at room temperature with 1.5 g of platinum oxide catalyst at an initial pressure of 50 psi of hydrogen. Reduction was complete in 10 hr after which the catalyst was filtered off, the filtrate was concentrated *in vacuo*, and the residual oil was dissolved in 200 ml of water. The aqueous solution was made strongly basic with 50% sodium hydroxide and extracted with benzene. Drying and removal of the benzene left an oil that solidified on standing. Recrystallization from pentane gave 36 g (88%) of **3-(4-piperidyl)-2-morpholino-1,1-dimethylcyclobutane** (**19**) as colorless crystals: mp 66–67°; ir ($CHCl_3$) 3220 (NH), pyridine absorption absent; nmr ($CDCl_3$) δ 3.68 (m, 4, morpholine OCH_2), 2.30 (m, 4, morpholine NCH_2), 1.65 (s, 1, NH), 1.07 and 1.05 (two s, 6, *gem*-dimethyl). Other absorptions were unresolved between 3.2 and 1.3 but all protons are accounted for in the total integration.

The catalytic hydrogenation of **1** was also carried out in ethanol solution without any added hydrochloric acid using a 5% rhodium-on-carbon catalyst (8 g of catalyst for 15 g of **1**) at 50° to give a 35% yield of **19**, mp 66–67° undepressed on admixture with **19** prepared with added hyrochloric acid.

An ice-cooled solution of 11.0 g (0.04 mol) of **19** in 150 ml of benzene and 20 ml of triethylamine was treated, dropwise, with 8.5 g (0.06 mol) of benzoyl chloride in 15 ml of benzene. The mixture was stirred for 5 hr at room temperature, washed twice with water, dried, and concentrated to an oil that solidified. Recrystallization from hexane provided 14.5 g (92%) of colorless crystals of **3-(1-benzoyl-4-piperidyl)-2-morpholino-1,1-dimethylcyclobutane** (**20**): mp 102–104°; mp 104–107° after one additional recrystallization; ir ($CHCl_3$) 1625 (amide —C=O), 1585 (phenyl).

The hydrochloride salt of **20**, prepared in ethyl acetate and recrystallized from isopropyl alcohol–hexane, showed mp 268–270°.

The acetyl (**22**) and the 3,4,5-trimethoxybenzoyl (**23**) derivatives (Table III) were similarly prepared.

To a slurry of 2.0 g (0.05 mol) of lithium aluminum hydride in 200 ml of dry tetrahydrofuran was added, dropwise, a solution of 10.0 g (0.03 mol) of **20** in 100 ml of dry tetrahydrofuran. The mixture was stirred for 2 hr at room temperature and then heated at reflux for 2 hr. The cooled mixture was treated with 5 ml of water followed by 25 ml of 20% sodium hydroxide. The coagulated aluminum hydroxide was filtered off and the filtrate was dried and concentrated leaving a solid that was crystallized from pentane to give 5.6 g (58%) of **21**: mp 93–95°; mp 96–97° after further recrystallization; nmr ($CDCl_3$) δ 7.33 (s, 5, phenyl protons), 3.68 (m, 4, morpholine OCH_2), 3.51 (s, 2, benzyl CH_2), 2.35 (m, 4, morpholine NCH_2), 1.08 and 1.05 (two s, 6, *gem*-dimethyl). All other protons were unresolved between 3.1 and 1.3 and accounted for in total integration.

The dihydrochloride salt of **21** was recrystallized from isopropyl alcohol and showed mp 208–210°.

3-[1-(*n*-Butylcarbamoyl)-4-piperidyl]-2-morpholino-1,1-dimethylcyclobutane (**24**).—To a cold solution of 12.6 g (0.05 mol) of **19** in 25 ml of benzene was added 10.0 g (0.1 mol) of *n*-butyl isocyanate in 15 ml of benzene. The solution was allowed to stand for 16 hr at room temperature and concentrated *in vacuo* and the residual oil was crystallized from hexane to give 16 g (91%) of **24** as glistening plates: mp 105–106°; ir ($CHCl_3$) 3390 (NH), 1635 (urea C=O).

Registry No.—**1**, 28487-22-1; **2**, 28487-23-2; **2** maleate, 28487-20-9; **3**, 28487-24-3; **4**, 28487-25-4; **5**, 28487-26-5; **6**, 28487-27-6; **7**, 28487-28-7; **8**, 28487-29-8; **9**, 28487-30-1; **10**, 28487-31-2; **11**, 28487-32-3; **12**, 28487-33-4; **13**, 28487-34-5; **14**, 28487-35-6; **15**, 28487-36-7; **15** dimaleate, 28487-21-0; **16**, 28487-37-8; **17**, 28487-38-9; **18**, 28487-39-0; **19**, 28487-40-3; **20**, 28487-41-4; **20** HCl, 28487-42-5; **21**, 28487-43-6; **21** 2HCl, 28487-44-7; **22**, 28487-45-8; **22** HCl, 28487-46-9; **23**, 28487-47-0; **23** HCl, 28487-48-1; **24**, 28537-46-4; **25**, 28487-15-2; **26**, 28487-16-3; **27**, 28487-17-4; **28**, 28487-18-5; **29**, 28487-19-6.

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Hydrolysis of Halopyridines at 250–350°. Formation of a Rearranged Product from 3-Halopyridines

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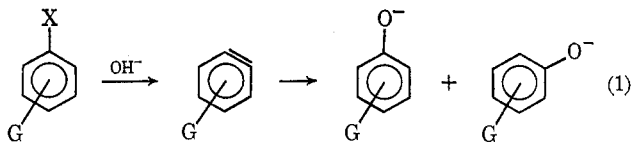
3-Chloro-, 3-bromo-, or 3-iodopyridine when heated with 4 *M* aqueous potassium hydroxide at 250–350° gives mixtures of 3-hydroxypyridine and 4-pyridone. The ratio of the yields of these products as indicated by nmr analysis of the reaction mixtures decreases in the order Cl > Br > I. 3-Iodopyridine gives more rearranged than unrearranged product; it also gives pyridine. Under the same conditions 2- or 4-chloro-, bromo-, and iodopyridines give 2- or 4-pyridone, respectively. 3-Hydroxypyridine is stable under the hydrolysis conditions but 2- and 4-pyridone degrade at the higher temperatures; nonaromatic products were characterized. It is suggested that the hydrolysis reactions of 3-halopyridines may involve competing direct substitution and elimination-addition reactions. The latter involves the formation of 3,4-pyridyne as an intermediate.

It has been known for many years that halobenzenes undergo alkaline hydrolysis at 250–350° to give phenols.[1,2] The mechanisms for this reaction are said to include direct substitution and aryne (elimination–addition) pathways, the aryne route being favored at higher temperatures.[3] The formation of structurally rearranged hydrolysis products is cited as evidence for the aryne route (eq 1). When only aryne formation



(1)

takes place, the ratio of rearranged to unrearranged products is independent of the identity of the leaving

(1) R. W. Hoffmann, "Dehydrobenzene and Cycloalkynes," Academic Press, New York, N. Y., 1967.
(2) W. Hale and E. C. Britton, *Ind. Eng. Chem.*, **20**, 114 (1928).
(3) A. T. Bottini and J. D. Roberts, *J. Amer. Chem. Soc.*, **79**, 1458 (1957).

halide ion. When halobenzenes react by both pathways concurrently, the product ratio is sensitive to the halogen.

Although a variety of halogenated carbocyclic aromatic compounds have been hydrolyzed by the high temperature method, curiously, halogenated heteroaromatic compounds have not been treated with aqueous alkali under conditions which might be expected to lead to hetaryne intermediates.[1,4-7]

We report the results of studies with isomeric halopyridines heated at 250–350° with 4 *M* potassium hydroxide. In addition to the nonaromatic degradation products found in all the reaction mixtures, direct substitution products from the reactions of 2- and 4-halopyridines were observed, but 3-halopyridines gave mixtures of 3-hydroxypyridine and 4-pyridone, the ratio depending on the identity of the halogen. In addition, pyridine was formed from 3-iodopyridine.

Results and Discussion

Since halopyridines are expected to hydrolyze to hydroxypyridines, control experiments were carried out to determine the stability of the expected products. The results in Table I show that only 3-hydroxypyridine is completely stable toward 4 *M* KOH at 300–350°. About 19% degradation of 4-pyridone in 4 *M* KOH occurs after 30 min at 350°; almost no degradation results after 1 hr at 300°. 2-Pyridone undergoes extensive fragmentation.[8] After 30 min at 350°, for example, only 23% of 2-pyridone remained; 2 equiv of acetate ion were formed. At lower temperatures the 2-pyridone is more stable. At 300° for 1 hr and at 250° for 4 hr only 30% and ~3% degradation results, respectively. These results indicate that there will be some difficulty in detecting 2-pyridone as a hydrolysis product but that 3-hydroxypyridine and 4-pyridone, owing to their greater thermal stability, can easily be detected.

TABLE I

CONTROL RUNS TO DETERMINE THE STABILITY OF 2- AND 4-PYRIDONE AND 3-HYDROXYPYRIDINE IN 4 *M* AQUEOUS POTASSIUM HYDROXIDE SOLUTION[a]

Pyridine derivative	Furnace *T*, °C	Time, min	% unreacted pyridine[b]
2	350	30	23[c]
2	300	60	70[c]
2	250	240	97[c]
3	350	30	100
3	300	60	100
4	350	30	81[d]
4	300	60	>95[d]

[a] 0.020 mol of the substrate was heated with 25 ml of 4 *M* KOH containing 0.0066 mol of isobutyric acid as internal standard. [b] From nmr analysis of the reaction mixtures. [c] Acetate ion is also present. [d] Formate and acetate ions present as well as acetone.

Also detected (nmr analysis) in the reaction mixture of 4-pyridone showing degradation were formate and acetate ions as well as acetone.[9] These nonaromatic products were commonly found in small, variable quantities in other reaction mixtures where decomposition of the aromatic substrate took place. In control experiments it was shown that formate ion and acetone can survive under the conditions employed for halopyridine hydrolysis. For example, after heating acetone at 300° for 30 min with 4 *M* KOH, 12% could be detected in the mixture. Similarly, 30% of the original formate ion remained after heating for 30 min at 350°. Ammonia and carbon dioxide also were detected when the heteroaromatic substrate decomposed.

In all of our studies reaction mixtures were analyzed by nmr.[10] Isobutyric acid generally was added to reaction mixtures prior to heating to serve as an internal standard. Control runs indicated that the standard was thermally stable and that mixtures could be analyzed quantitatively by this method. The nmr standard had no influence on the ratio of halopyridine hydrolysis products.

In spite of the degradation of 2-pyridone which occurs at 300–350°, we elected to employ these higher temperatures in studies of the hydrolysis of halopyridines. In our systems, dehydrohalogenation reactions are expected to have energies of activation which are greater than those for direct substitution processes. Hence, the higher energy reaction becomes relatively more favorable with increasing temperatures.[3]

Table II summarizes the results of hydrolysis experiments with the 2 and 4 isomers of chloro-, bromo-, and iodopyridines at 300–350° in 4 *M* KOH. The 2-halopyridines gave 22–34% of 2-pyridone. No 3-hydroxypridine or 4-pyridone could be detected. The 4-halopyridines gave rise to 38–62% of 4-pyridone and also 12–17% of 4-aminopyridine. No 2-pyridone or 3-hydroxypyridine products could be found.

TABLE II

CONDITIONS AND RESULTS OF THE HYDROLYSIS OF 2- AND 4-HALOPYRIDINES WITH 4 *M* POTASSIUM HYDROXIDE

Halopyridine	Furnace *T*, °C	Time, min	% corresponding hydroxypyridine[a]
2-Cl	350	30	22
2-Br	350	30	25
2-I	350	30	34
4-Cl	350	30	60
4-Cl	300	15	62[b]
4-Br	350	30	52
4-Br	300	5	46[b,c]
4-Br	300	10	61[b]
4-I	350	30	38

[a] Nonaromatic products present as well. [b] 12–17% 4-aminopyridine also formed. Amount varies with run. [c] 11% of starting material unreacted.

Although the 4-aminopyridine product could arise from a reaction between 4-halopyridine and liberated

(4) H. J. den Hertog and H. C. van der Plas, "Chemistry of Acetylenes," H. G. Viehe, Ed., Marcel Dekker, New York, N. Y., 1969, Chapter 17.

(5) H. J. den Hertog and H. C. van der Plas, *Advan. Heterocycl. Chem.*, **4**, 121 (1965).

(6) T. Kauffmann, *Angew. Chem., Int. Ed. Engl.*, **4**, 543 (1965).

(7) R. W. Hoffmann, "Chemistry of Acetylenes," H. G. Viehe, Ed., Marcel Dekker, New York, N. Y., 1969, Chapter 16.

(8) By comparison, 2-chloroquinoline is quantitatively converted to 2-quinolone on heating at approximately 300° in 4 *M* KOH for 2.5 hr. Thus, 2-quinolone appears to be more stable than 2-pyridone in aqueous alkali.

(9) The 2,4-dinitrophenylhydrazone derivative of acetone was recovered from a reaction mixture.

(10) Nmr spectra of 2- and 4-pyridones and 3-hydroxypyridine in 4 *M* potassium hydroxide as well as nmr spectra of typical 3-halopyridine hydrolysis reaction mixtures will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth St., N. W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit $3.00 for photocopy or $2.00 for microfiche.

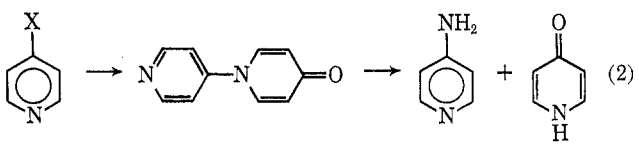
TABLE III

CONDITIONS AND RESULTS OF THE HYDROLYSIS OF 3-HALOPYRIDINES WITH 4 *M* POTASSIUM HYDROXIDE TO 3-HYDROXYPYRIDINE AND 4-PYRIDONE

Halogen	Furnace *T*, °C	Time, min	% hydroxypyridines[a] 3	3:4	4	Other pyridines[b]
Cl	350	30	68	77:23	20	
Cl	350	150	47			
Cl	300	30	63	76:24	20	14% 3-Cl
Cl	300	45	70	78:22	21	9% 3-Cl
Cl	300	60	72	80:20	18	8% 3-Cl
Cl[c]	300	150		80:20		
Cl	250	120	43	89:11	5	36% 3-Cl
Cl	250	240	64	86:14	10	10% 3-Cl
Br	350	30	22	44:56	27	
Br[c]	350	90		59:41		
Br	300	60	27	41:59	39	
Br[c]	300	150		43:57		
Br	250	240	25	45:55	30	
I	350	30	15	32:68	33	25–30% pyridine
I	350	30	18	36:64	32	pyridine
I[c]	350	90		42:58		pyridine
I	300	60	16	33:67	34	11–32% pyridine
I	300	60	17	31:69	39	16–19% pyridine
I	300	60	19	30:70	44	20–27% pyridine
I[c]	300	150		34:66		pyridine
I	250	240	8	40:60	12	pyridine

[a] This ratio is calculated solely in terms of the amounts of hydroxy pyridines formed. No corrections have been made for the formation of other products. [b] In the case of 3-iodopyridine, the range in the percentage of pyridine formed results from two methods of analysis. [c] No isobutyric acid internal standard present.

ammonia, another route is possible. This involves reaction of the halopyridine to give 1-(4′-pyridyl)-4-pyridone which degrades to 4-aminopyridine and 4-pyridone (eq 2). Treatment of this pyridylpyridone

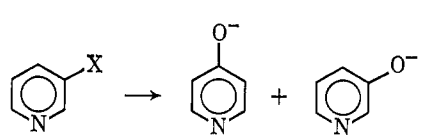


(2)

with 4 *M* KOH at 300° for 15 min resulted in the formation of 28% 4-aminopyridine, 22% 4-pyridone, and nonaromatic products.

4-Aminopyridine is also converted to 4-pyridone in the presence of 4 *M* KOH. After 60 min at 300°, 75% of 4-pyridone was formed; 23% of the amino compound was unchanged.

3-Halopyridines, on the other hand, clearly give rise to both 3-hydroxypyridine and 4-pyridone hydrolysis products (eq 3).[11] It was not possible to detect 2-



(3)

pyridone in the presence of the other two isomers by means of nmr, owing to peak overlap. However, this difficulty was circumvented by analysis using thin layer chromatography; by this means the three hydroxypyridine isomers are clearly separated. No 2-pyridone was detected in 3-chloro- and 3-bromopyridine reaction mixtures, but no conclusion was reached concerning the presence of 2-pyridone in 3-iodopyridine reaction mixtures, owing to streaking of the chromatograms. Note that spots fluorescing under ultraviolet light also were present in the chromatograms. These materials were not identified.

Total yields of pyridines from 3-chloropyridine generally were ~90% but yields from 3-bromo- or 3-iodopyridine mixtures were considerably reduced, owing to extensive decomposition. In spite of the decomposition of 3-iodopyridine reaction mixtures, repeated experiments gave hydroxypyridines in reproducible quantities. Note that, when 3-iodopyridine was heated with 4 *M* potassium chloride in the absence of alkali at 350° for 30 min, extensive carbonization resulted and no pyridine could be detected. This demonstrates the thermal instability of the aryl iodide.

The molar ratio of 3-hydroxypyridine to 4-pyridone products is highly dependent on the identity of the halogen leaving group and only slightly dependent on the reaction temperature in the region 250–350° (Table III). At 350° this ratio increases with reaction time, owing to decomposition of 4-pyridone. Excluding those cases where there is decomposition of this hydrolysis product, the % 3-OH:4-OH ratios and their ranges are for Cl, 76:24–89:11; Br, 41:59–45:55; I, 30:70–40:60. Increasing amounts of rearranged product are formed in the order Cl < Br < I. In addition, unreacted 3-chloropyridine was detected and in the case of 3-iodopyridine pyridine was formed. It is to be noted that pyridine can also undergo degradation reactions. Approximately half the pyridine was destroyed when it was exposed to 4 *M* KOH at 350° for 30 min. A substantial amount of acetate ion was detected by nmr in the mixture.

Before interpreting our results it is worth noting that 3- and 4-halopyridines can be dehydrohalogenated by the action of strong nitrogen bases to give 3,4-pyridyne (I). There is no compelling evidence for the formation

(11) No evidence has been found for the formation of rearranged substitution products in the reactions of 3-chloro- and 3-bromopyridine with sodium methoxide in methanol at 218°.[12]

(12) J. A. Zoltewicz and A. A. Sale, *J. Org. Chem.*, **35**, 3462 (1970).

of 2,3-pyridyne (II) by a dehydrohalogenation route.[4-6,13] Also noteworthy is the occasional formation of reductive dehalogenation products in these reactions.[5]

I

II

In view of these amination results and those from the high temperature hydrolysis of halobenzenes, it may be concluded that 2- and 4-halopyridines on treatment with aqueous alkali only undergo direct substitution reactions. Our results do not provide evidence for the formation of pyridynes. No structurally rearranged product, 3-hydroxypyridine, was detected in reaction mixtures.

It may, however, be postulated that the formation of a rearranged product from 3-halopyridines is due to the presence of 3,4-pyridyne (I). Moreover, since the hydroxypyridine product ratio depends on the identity of the leaving halide ion, the presence of concurrent substitution and 3,4-pyridyne pathways also is suggested.

It is interesting to compare our results with those from a series of haloaromatics reacting by concurrent elimination–addition and direct substitution pathways. Halotoluenes when treated with aqueous sodium hydroxide at 250–340° give rise to direct substitution and rearranged products. The amount of direct substitution product increases in the order Cl < Br < I.[3] In the pyridine series the relative amount of direct substitution product increases in the reverse order I < Br < Cl. Both of these orders are compatible with concurrent elimination–addition and direct substitution pathways. Halogen leaving group orders for both types of reactions are markedly dependent on the nature of the reactants as well as the reaction conditions.[14-16]

In addition to the pyridyne hypothesis other mechanisms should be considered. Another possibility includes halogen migration reactions[17] involving the formation of polyhalopyridines which then undergo substitution and reductive dehalogenation. These reactions are not without precedent. Halopyridines are known to undergo base-catalyzed halogen rearrangement reactions.[18] There is an authentic example (thiophene series[19]) of the formation of a rearranged substitution product resulting from a halogen migration sequence. Note that chlorine atoms migrate less readily than bromine or iodine atoms.[17]

The pyridine which is produced in the reaction of 3-iodopyridine could arise by several routes. These include halogen transfer and radical reactions. The radical process could be similar to that involving the reduction of *m*-iodochlorobenzene to chlorobenzene under basic conditions.[20]

Our experiments provide the first examples of the formation of rearranged substitution products in the hydrolysis of hetaryl halides. No doubt, other aromatic heterocyclic halides will give similar results.

Experimental Section

Materials.—2-[21] and 4-iodopyridine,[22] 3-methoxypyridine,[23] and 1-(4′-pyridyl)-4-pyridone[24] were prepared. Other pyridines and 2-chloroquinoline are available from Aldrich Chemical Co.

Calibration Curves for the Rates of Heating–Cooling of the Reaction Bomb.—The Inconel bomb (series 4740, Parr instrument Co.) used in the hydrolysis studies was filled with 25 ml of oil and placed into an electrically heated aluminum furnace. A Honeywell Pyr-O-Vane was used to control temperatures. After the furnace was preheated to the desired temperature, the bomb was added. It took 20–25 min for the bomb and its contents to come to the preset temperature (±5°). On removing the bomb and allowing it to air cool, the temperature rapidly fell about 50° in five min; after 30 min the oil temperature was <150°. Temperatures were measured with a copper-constantan thermocouple.

Control Run Used to Establish the Analytical Method.—Nmr was used to quantitatively analyze reaction mixtures, the signal from the methyl groups of isobutyric acid serving as an internal standard.

A mixture consisting of 0.545 g (0.00500 mol) of 3-methoxypyridine,[23] 0.0145 g (0.00165 mol) of isobutyric acid, and 6.25 ml of 4 *M* KOH was heated at 300° for 1 hr. Methanol was added to the cold mixture to make it homogeneous and the nmr spectrum was recorded. Unreacted 3-methoxypyridine and also 3-hydroxypyridine were present. The ratio of the area of the appropriate peaks of the pyridines (Table IV) to the area of the internal standard were employed to calculate yields: 14% 3-methoxypyridine and 86% 3-hydroxypyridine. The mass balance was quantitative.

TABLE IV

CHEMICAL SHIFTS AND ASSOCIATED PROTONS USED TO IDENTIFY PRODUCTS IN ALKALINE REACTION MIXTURES

Compd	τ[a]	Proton(s)
2-Pyridone[b]	2.6, 3.6	H-4, H-3,5
3-Hydroxypyridine[b]	2.4, 3.0	H-6, H-4,5
4-Pyridone[b]	2.0, 3.5	H-2,6, H-3,5
3-Chloropyridine	1.6	H-2
3-Bromopyridine	1.6	H-2,6
3-Iodopyridine	1.4	H-2
3-Methoxypyridine	2.0, 2.7	H-2,6, H-4,5
4-Aminopyridine	3.4	H-3,5
Pyridine	1.5	H-2,6
Formic acid[b]	1.5–1.6	H
Acetic acid[b]	8.1	CH_3
Acetone	8.0	CH_3

[a] The methyl doublet (τ 9.0) of the isobutyrate ion served as standard. Values refer to alkaline solutions. The approximate center of a multiplet is listed. [b] Exists as its conjugate base in the alkaline solution.

As a check, the reaction mixture then was extracted with methylene chloride and 3-methoxypyridine (79 mg) was recovered, the amount agreeing with that indicated by nmr.

General Method of Hydrolysis.—A mixture of a halo- or hydroxypyridine (0.020 mol), isobutyric acid (0.0066 mol) internal standard, and 25 ml of 4 *M* KOH (0.10 mol) was sealed in an Inconel bomb which then was lowered into the preheated furnace. The reaction times recorded in the tables indicate the

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(24) F. Arndt and A. Kalischek, *Chem. Ber.*, **63**, 587 (1930); F. Arndt, *ibid.*, **65**, 92 (1932).

time the bomb was in contact with the furnace. The bomb was then withdrawn and allowed to air cool.

The contents of the cooled bomb were filtered to remove carbonaceous materials. When unreacted halogenated starting material was present, methanol was added until the reaction mixture became homogeneous. An nmr of the solution was taken using a Varian A-60A spectrometer. Peaks were repeatedly integrated and average areas were employed. Table IV lists the identity of the signals used to calculate the product yields.

In order to determine whether 2-pyridone was present in 3-halopyridine reaction mixtures, the following was employed. 3-Halopyridine reaction mixtures were thoroughly extracted with chloroform and the aqueous phase was acidified to pH 7 with dilute hydrochloric acid. The neutralized phase was extracted with chloroform and dried ($MgSO_4$). (Control runs showed that the hydroxypyridines could be removed from aqueous solutions by this method.) Thin layer chromatography using silica gel plates and acetone containing a small amount of acetic acid as eluent showed that mixtures of the hydroxypyridines could be clearly separated. The order of increasing R_f value is 4-pyridone, 2-pyridone, and 3-hydroxypyridine. No attempt was made to establish the lower limits of detection of 2-pyridone by tlc.

The pyridine content of 3-iodopyridine reaction mixtures was obtained as follows. The nmr spectra of alkaline reaction mixtures were recorded before and after extraction with methylene chloride. Spectra taken before extraction provide a measure of hydroxypyridines as well as of pyridine. Spectra after extraction measure the hydroxypyridines. The amount of pyridine present was obtained by subtraction. In addition the dried ($MgSO_4$) methylene chloride extracts were concentrated and the amount of pyridine present was determined by weight. The two results, Table III, are in reasonable agreement but it is to be noted that both methods assume impurities are not present. These results, then, should be regarded as giving the maximum amounts. The recovered pyridine was distilled and compared with authentic material. Aqueous solutions were neutralized and analyzed for 2-pyridone content as described above.

Isolation of 3-Hydroxypyridine and 4-Pyridone from the Hydrolysis of 3-Bromopyridine.—After 3.16 g (0.20 mol) of 3-bromopyridine was hydrolyzed at 300° for 1 hr with 4 *M* potassium hydroxide (no isobutyric acid), the aqueous solution was acidified to pH 7 with dilute HCl and evaporated to dryness under reduced pressure. The solid was extracted with acetone and then the insoluble portion was dissolved in a minimum amount of water. After adjusting to pH 8, the evaporation–extraction process was repeated. The process was repeated a third time at pH 6. The acetone extracts were dried ($MgSO_4$) and the solvent was removed. The crude mixture of 3-hydroxypyridine and 4-pyridone was sublimed at 140–160° (0.5 Torr). The sublimate was chromatographed on a silica gel column. Elution with 4% methanol in chloroform (v/v) gave 0.40 g (21%) of 3-hydroxypyridine which on recrystallization from benzene showed mp and mmp 127–129° (lit.[25] mp 129°). Elution with 60% methanol in chloroform (v/v) gave 0.48 g (25%) of 4-pyridone which on recrystallization from chloroform–hexane showed mp and mmp 145–149° (lit.[25] 148.5°).

Isolation of 4-Aminopyridine from the Hydrolysis of 4-Bromopyridine.—A mixture of 3.89 g (0.092 mol) of 4-bromopyridine hydrochloride and 25 ml of 4 *M* potassium hydroxide was heated at 300° for 10 min. The cold mixture was extracted with methylene chloride and dried ($MgSO_4$). Removal of the solvent gave 0.226 g (12%) of 4-aminopyridine, mp and mmp 158–159° (lit.[25] mp 158°). Nmr analysis of the aqueous solution indicated that 61% of 4-hydroxypyridine was present.

Registry No.—2-Chloropyridine, 109-09-1; 2-bromopyridine, 109-04-6; 2-iodopyridine, 5029-67-4; 3-chloropyridine, 626-60-8; 3-bromopyridine, 626-55-1; 3-iodopyridine, 1120-90-7; 4-chloropyridine, 626-61-9; 4-bromopyridine, 1120-87-2; 4-iodopyridine, 15854-87-2.

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Independent Syntheses of the Products of Acid- and Base-Catalyzed Rearrangements of 2-(1-Isoquinolyl)-3,3,5-triarylpyrrolenines

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2-(1-Isoquinolyl)-3,4,5-triphenylpyrrole (**4**) and 2-(1-isoquinolyl)-3-*p*-anisyl-4,5-diphenylpyrrole (**6**) have been synthesized by unambiguous methods. The synthetic samples are identical with the products of the acid- or base-catalyzed isomerization of 2-(1-isoquinolyl)-3,3,5-triphenylpyrrolenine (**3**) and the base-catalyzed isomerization of 2-(1-isoquinolyl)-3-*p*-anisyl-3,5-diphenylpyrrolenine (**21**), respectively. By inference, 2-(1-isoquinolyl)-4-*p*-anisyl-3,5-diphenylpyrrole (**7**) is the product of the acid-catalyzed isomerization of **21**. These facts provide additional support for the mechanisms of the isomerization reactions proposed in previous papers.

Mainly by a series of tracer studies, but also on the basis of other evidence, it has been established that the acid-catalyzed condensation of 2-benzoyl-1,2-dihydroisoquinaldonitrile (**1**) with 1,1-diphenylethylene (**2**) affords a mixture of 2-(1-isoquinolyl)-3,3,5-triphenylpyrrolenine (**3**) and 2-(1-isoquinolyl)-3,4,5-triphenylpyrrole (**4**).[1] It was also established that **3** can be isomerized to **4** by the action of acid or by fusion with potassium hydroxide. Mechanisms were suggested for the formation of **3** and its isomerization to **4**. It was also pointed out in a footnote of a previous paper[1] that 2-(1-isoquinolyl)-3-*p*-anisyl-3,5-diphenylpyrrolenine (**21**), obtained by the acid-catalyzed condensation of **1** with 1-*p*-anisyl-1-phenylethylene (**5**), gives two isomeric pyrroles, one predominating in the acid-catalyzed isomerization and the other in the potassium hydroxide fusion. It was suggested that the two pyrroles are 2-(1-isoquinolyl)-3-*p*-anisyl-4,5-diphenylpyrrole (**6**) and 2-(1-isoquinolyl)-4-*p*-anisyl-3,5-diphenylpyrrole (**7**). Based on mechanistic considerations, it was further suggested that **6** should be the product of the alkali fusion reaction and **7** that of the acid-catalyzed isomerization. We have now developed unambiguous syntheses of **4** and **6**, and these results serve to complete the proofs of structure of the compounds and to provide a firm foundation for the mechanistic considerations.

2,3,4-Triphenylpyrrole (**8**), prepared by the procedure of Pollak and Tisler,[2] was the principal starting material in the unambiguous synthesis of **4**. The key step

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(2) A. Pollak and M. Tisler, *Tetrahedron Lett.*, 253 (1964).