THE JOURNAL OF Organic Chemistry®

Volume 21, Number 12

February 6, 1957

[CONTRIBUTION FROM THE MOORE LABORATORY OF CHEMISTRY, AMHERST COLLEGE]

The Rearrangement of Isoquinoline-*n*-oxides[1]

MICHAEL M. ROBISON AND BONNIE L. ROBISON

Received June 8, 1956

Isoquinoline-N-oxide and 3-methylisoquinoline-N-oxide on treatment with refluxing acetic anhydride rearrange to produce mainly derivatives of the corresponding isocarbostyrils, but also significant quantities of the corresponding 4-hydroxyisoquinoline derivatives. No 3-hydroxy or 3-hydroxymethyl derivatives were isolated from the reactions. Neither isocarbostyril nor 4-acetoxyisoquinoline undergoes isomerization when subjected to the rearrangement conditions, but isocarbostyril is acetylated at the ring nitrogen to form N-acetylisocarbostyril.

Since the report of Katada,[2] in 1947, of the rearrangement of pyridine-N-oxide to 2-acetoxypyridine on treatment with refluxing acetic anhydride, a number of investigations have been carried out on this reaction with related amine oxides. Although pyridine-N-oxide and 3-picoline-N-oxide yield the corresponding 2-acetoxy heterocycles,[2,3] the presence of an alkyl group in the 2 or 4 position of the pyridine ring leads to the formation of the acetyl derivatives of the corresponding 2- or 4-hydroxyalkyl compounds.[3,4] In addition to 4-pyridinemethanol acetate, however, Berson and Cohen[5] isolated a product of substitution at the 3 position of the pyridine ring, 3-hydroxy-4-picoline, from the rearrangement of 4-picoline-N-oxide. Products of β-substitution have apparently also been obtained[5] on treatment of 2-picoline-N-oxide with acetic anhydride[6] and on pyrolysis of the product derived from pyridine-N-oxide and *p*-toluenesulfonyl chloride.[7]

In view of these results it seemed of interest to investigate the course of the rearrangement in the isoquinoline series where the carbon atoms adjacent to the ring nitrogen are not equivalent. Whether the reaction is of a nucleophilic or free-radical nature, substitution at the 1 position would be expected to predominate, since attack at the 3 position would involve disruption of the aromaticity of the benzene ring.

Isoquinoline-N-oxide has been prepared by the action of perbenzoic acid[8] and perphthalic acid[9] on isoquinoline. In this laboratory it was synthesized by the use of peracetic acid according to the method of Ochiai[10] and co-workers for the preparation of pyridine- and quinoline-N-oxides. When the oxide was treated with refluxing acetic anhydride and the reaction mixture was distilled, there was obtained a mixture of products. In most of the experiments the mixture was subjected directly to hydrolysis with aqueous base, no attempt being made to isolate the very easily hydrolyzed acetyl derivatives of the hydroxyisoquinolines. From the basic mixture there was obtained the insoluble isocarbostyril in yields of 50–64%. Identification was based on analysis and

(1) (a) This investigation was supported in part by a research grant, number C-2574, from the National Cancer Institute of the National Institutes of Health, Public Health Service. (b) Presented before the 130th Meeting of the American Chemical Society, Atlantic City, N. J., September 19, 1956.

(2) Katada, *J. Pharm. Soc. Japan*, **67**, 51 (1947).

(3) Boekelheide and Linn, *J. Am. Chem. Soc.*, **76**, 1286 (1954).

(4) Bullitt and Maynard, *J. Am. Chem. Soc.*, **76**, 1370 (1954).

(5) Berson and Cohen, *J. Am. Chem. Soc.*, **77**, 1281 (1955).

(6) Kobayashi and Furukawa, *Pharm. Bull. Japan*, **1**, 347 (1953).

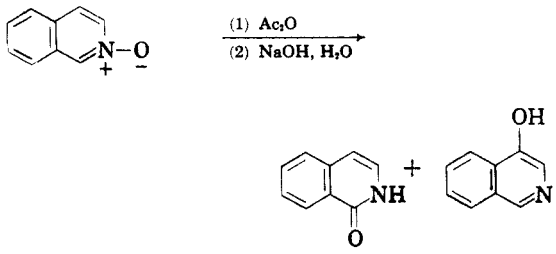
(7) Murakami and Matsumura, *J. Chem. Soc. Japan*, **70**, 393 (1949).

(8) Meisenheimer, *Ber.*, **59**, 1848 (1926).

(9) Ochiai, Ishikawa, and Zai-Ren, *J. Pharm. Soc. Japan*, **65**, 72 (1945) [*Chem. Abstr.*, **45**, 8526^{d} (1951)].

(10) Ochiai, *J. Org. Chem.*, **18**, 534 (1953).

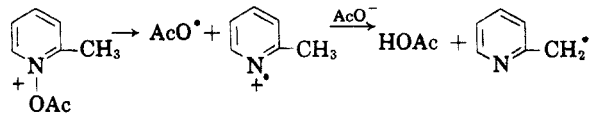
physical properties of the compound and physical properties of its previously reported benzoyl derivative. On neutralization of the alkaline filtrate a second hydroxyisoquinoline, soluble in dilute hydrochloric acid or sodium hydroxide, precipitated. The yield was consistently 8–9%. It was eventually determined that this product was 4-hydroxyisoquinoline. Proof of this structure was achieved by comparison with a sample of known 4-hydroxyisoquinoline, prepared from 4-bromoisoquinoline by the method of Gilman and Gainer.[11] No other products were isolated from the reaction mixture.



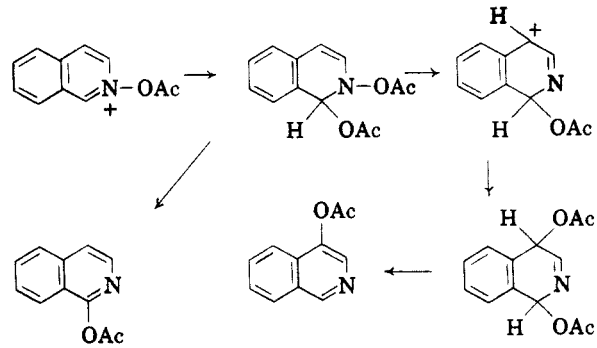
Since, in the pyridine series, the rearrangement apparently proceeds preferentially to an alkyl group in an α-position, rather than to an α-ring position (*vide supra*), it was considered of interest to determine whether the rearrangement of 3-methylisoquinoline-N-oxide would result in substitution at the methyl group or at the 1 position or 4 position of the ring. The 3-methylisoquinoline-N-oxide, which was also prepared by peracetic acid oxidation, on treatment with acetic anhydride yielded products similar to those in the first reaction. Attempted distillation of the reaction mixture resulted in the separation of only a small amount of volatile material, apparently mainly the acetate of 4-hydroxy-3-methylisoquinoline. The ester was again not isolated but was converted directly to the hydroxy compound. By this procedure 4-hydroxy-3-methylisoquinoline was obtained in yields ranging from 8% to 11%. The substance was identified by analysis and by comparison of its ultraviolet spectra with spectra reported for the known compound by Harris and co-workers.[12] Along with the product appeared a small amount of oily, base-insoluble material which could not be purified. Although this fraction appeared to be a mixture, probably containing some 3-methylisocarbostyril, the possibility of the presence of 3-hydroxymethylisoquinoline could not be eliminated. 3-Acetoxymethylisoquinoline, a known compound,[13] is sufficiently volatile to be sublimed and should appear in the distillate by this procedure.

The major product, the isocarbostyril derivative, remained in the residue from the distillation. After hydrolysis 3-methylisocarbostyril was obtained in yields of approximately 40%.

A number of simple mechanisms can be written for the rearrangement to isocarbostyril derivatives, involving either a nucleophilic or free-radical attack at the 1 position. In the case of rearrangement to an α- or γ-alkyl group, for the pyridine series tentative formulations have included an anhydrobase intermediate[3-5,14] or a possible free-radical mechanism including the steps shown below.[15] It may be noted that if an anhydrobase is an intermediate in the process, little or no reaction would be expected



at the alkyl group in the case of 3-methylisoquinoline, since formation of this anhydrobase would result in the disruption of the aromaticity of the benzene ring. One possible mechanism for the substitution at the 4 position of the isoquinoline nucleus is an electronic shift similar to that tentatively proposed by Boekelheide and Harrington for the 2-picoline case, or the process can be formulated as an initial reaction at the 1 position followed by a series of additions and eliminations to produce either the 1- or 4-acetoxy compound, as shown in the following series. To test the latter hypothesis isocarbostyril was subjected to the conditions of the amine oxide



rearrangement. From the acetic anhydride treatment and subsequent distillation one acetyl derivative was obtained in an apparently pure state. On hydrolysis this produced only isocarbostyril. Since, however, 2-pyridone is not esterified on treatment with acetic anhydride and since the difficultly-prepared 2-acetoxypyridine is exceptionally easily hydrolyzed,[16] a more detailed investigation of the nature of the acetylisocarbostyril was deemed necessary. It was found that the acetyl derivative is insoluble in dilute hydrochloric acid and that its infrared spectrum shows two strong absorption bands in the carbonyl region at 1665 cm.$^{-1}$ and 1705 cm.$^{-1}$ The benzoyl derivative of isocarbostyril, pre-

(11) Gilman and Gainer, *J. Am. Chem. Soc.*, **69**, 1946 (1947).

(12) Harris, Webb, and Folkers, *J. Am. Chem. Soc.*, **62**, 3198 (1940).

(13) Erlenmeyer, Baumann, and Sorkin, *Helv. Chim. Acta*, **31**, 1978 (1948).

(14) Pachter, *J. Am. Chem. Soc.*, **75**, 3026 (1953).

(15) Boekelheide and Harrington, *Chemistry and Industry*, 1423 (1955).

(16) Chichibabin and Szokow, *Ber.*, **58**, 2650 (1925).

pared by reaction with benzoyl chloride in pyridine and reported[17] as 1-benzoxyisoquinoline, also was examined. It was found to exhibit the same solubility behavior and to show the same two carbonyl absorptions in the infrared. These factors indicate that the acyl derivatives are not esters but are, rather, N-acetyl- and N-benzoyl-isocarbostyril. These results are in contrast to findings in the 2-pyridone series where only O-acylation products have been obtained by a variety of methods. As a further check on the infrared data, 2-benzoxypyridine was prepared for investigation by the method of Chichibabin and Oparina.[18] This acid-soluble material was found to exhibit one normal ester absorption band in the carbonyl region at 1740 cm.$^{-1}$ It was therefore apparent that since the N-acetyl compound is readily formed, the attempted rearrangement of isocarbostyril under the N-oxide-rearrangement conditions was without significance with regard to the above mechanism. Attempts were made to prepare authentic 1-acetoxyisoquinoline by the reaction of acetyl chloride with the sodium salt of isocarbostyril and with the silver salt, but from each reaction only the N-acetylation product was obtained. Finally, an attempt was made to separate 1-acetoxyisoquinoline from the mixture of acetyl derivatives obtained on distillation of the N-oxide-rearrangement mixture. From the last fraction of distillate the same N-acylation product was isolated in a relatively pure state. It thus appears that 1-acetoxyisoquinoline, if formed as depicted in the above reaction mechanism, must undergo a facile rearrangement to the amide under the conditions of the reaction or distillation. A similar migration of an acyl group has been observed in the formation of N-benzoyl-1,2,3,4-tetrahydro-8-hydroxyquinoline on catalytic hydrogenation of 8-benzoxyquinoline[17] and a related alkyl-group migration has been reported in the ready rearrangement of 2-methoxyquinoline to N-methylcarbostyril on heating.[19]

After most of the above experiments had been completed there came to our attention a recent investigation of the reaction of isoquinoline-N-oxide with *p*-toluenesulfonyl chloride. Ochiai and Ikehara[20] observed that when the oxide is treated with two equivalents of the acid chloride in refluxing chloroform, substitution at the 4 position predominates, the yields of the 4- and 1-substitution products being 70% and 10%, respectively. These investigators also treated the N-oxide with acetic anhydride, but from this process isolated only isocarbostyril, apparently because of a different procedure employed in working up the reaction mixture. Ochiai and Ikehara also proposed a mechanism involving initial reaction at the 1 position and very similar to that considered above, although they also provided no direct evidence for such a series of transformations. Of particular interest was their observation that 4-hydroxyisoquinoline *p*-toluenesulfonate undergoes rearrangement to isocarbostyril on hydrolysis. The extent of isocarbostyril formation depends on the conditions, rearrangement being most extensive in ethanolic potassium hydroxide and less pronounced in aqueous acid or base. In this laboratory it was found that 4-hydroxyisoquinoline undergoes no rearrangement when subjected to treatment with refluxing acetic anhydride. 4-Acetoxyisoquinoline was isolated from the reaction in a relatively pure state. This ester also failed to rearrange when hydrolyzed in aqueous acid or base under conditions identical with those of the actual rearrangement reactions. Thus, in the acetic anhydride reaction 4-acetoxyisoquinoline is apparently not an intermediate leading to the isocarbostyril derivative.

EXPERIMENTAL[21,22]

Isoquinoline-N-oxide. A mixture of 64.5 g. of freshly-distilled isoquinoline, 150 ml. of glacial acetic acid, and 50 ml. of 30% hydrogen peroxide was heated at 60–70° for a period of 12 hours, 40 ml. more hydrogen peroxide being added after 3 hours. Excess volatile reactants were removed under an aspirator vacuum on the water-bath, 50 ml. of water was added to the residue, and volatile materials were again vacuum-distilled. To the red liquid residue was added 300 ml. of chloroform, a large excess of solid potassium carbonate, and sufficient water to form a thick paste with the carbonate. The mixture was allowed to stand overnight, after which the inorganic slurry was separated and washed with additional quantities of chloroform. The combined extracts were dried over potassium carbonate and distilled, the last traces of solvent being removed *in vacuo*. The molten, red liquid residue was poured into 40 ml. of ethyl acetate and allowed to crystallize overnight. The product was separated, washed with ethyl acetate, and dried *in vacuo* over calcium chloride. The heavy yellow blades weighed 48.5 g. (63%, *vide infra*) and had m.p. 105.0–106.0°.

Meisenheimer[8] reported that isoquinoline-N-oxide crystallizes from ethyl acetate as the dihydrate, m.p. 98°, and stated that the water could be removed completely only on drying over sulfuric acid for two weeks in a good vacuum. In this laboratory it was found that air-dried material, prepared as above, melted over a wide range, beginning at about 40°. A sample dried for less than a day *in vacuo* over phosphorus pentoxide also exhibited this wide melting range. Material dried in a vacuum desiccator over $CaCl_2$, however, melted as above. An analytical sample was prepared by recrystallizations from ethyl acetate[8] and dried under these conditions until a constant melting point, 103.5–106.5°, was obtained. The analysis indicated that this material is a hemihydrate.

(17) Cavallito and Haskell, *J. Am. Chem. Soc.*, **66**, 1166 (1944).

(18) Chichibabin and Oparina, *J. Russ. Phys.-Chem. Soc.*, **56**, 153 (1925) [*Chem. Abstr.*, **19**, 3489 (1925)].

(19) Meyer and Beer, *Monatsh.*, **34**, 1173 (1913).

(20) Ochiai and Ikehara, *Pharm. Bull. Japan*, **3**, 454 (1955).

(21) Analyses by Weiler and Strauss Microanalytical Laboratory, Oxford, England, except for some nitrogen analyses which were carried out by a semimicro Kjeldahl technique in this laboratory.

(22) Melting points are corrected and boiling points uncorrected.

Anal. Calc'd for $C_9H_7NO \cdot {}^1/_2H_2O$: C, 70.11; H, 5.24; N, 9.09. Found: C, 70.36; H, 5.36; N, 8.80.

The picrate was prepared by reaction of a solution of the oxide in 1:1 ethanol-water with an excess of picric acid in the same solvent. After one recrystallization from ethanol-water the product melted at 165.5–166.5°. Meisenheimer[8] and Ochiai[9] reported m.p. 165° for this material.

3-Methylisoquinoline-N-oxide. The reaction was carried out on a 0.3-mole scale by the method used for isoquinoline-N-oxide. The solid, colored residue from the chloroform was washed thoroughly with cyclohexane and recrystallized from 1:1 benzene-cyclohexane. There was thus obtained, after drying, in a typical run, 32.8 g. (69%) of small, light-peach needles, m.p. 136–139°. Further recrystallizations from the same solvent (Darco) produced white needles, m.p. 136.0–138.0°.

Anal. Calc'd for $C_{10}H_9NO$: C, 75.44; H, 5.71; N, 8.80. Found: C, 75.12; H, 5.80; N, 8.85.

REARRANGEMENT OF ISOQUINOLINE-N-OXIDE

In a typical experiment, 18.12 g. of the dried N-oxide, which was thought at the time to be the dihydrate, was added to 150 ml. of acetic anhydride and the mixture was refluxed gently for 5 hours.[23] The liquid soon turned dark red. At the end of the reaction period the acetic anhydride was removed under an aspirator vacuum and the residue was distilled. The volatile portion of the product was collected in one fraction which boiled at approximately 142° (0.9 mm.). An appreciable non-volatile portion remained. The solid distillate was heated on the steam-bath with 4 g. of sodium hydroxide and 75 ml. of water for about 40 minutes, then allowed to stand at room temperature overnight.

Isocarbostyril. By filtration 9.02 g. (53%) of pale yellow isocarbostyril, m.p. 208.0–209.5° was separated. An analytical sample was prepared by sublimation at 150° (0.2 mm.) and recrystallization from water containing a small proportion of ethanol. The pure material had m.p. 208.0–209.0° (reported[24] m.p. 208–209°).

Anal. Calc'd for C_9H_7NO: N, 9.65. Found: N, 9.57.

N-Benzoylisocarbostyril. This derivative was prepared from the isocarbostyril by the method of Cavallito and Haskell.[17] The purified material melted at 145.5–146.5° (reported[17] m.p. 147°). The infrared absorption spectrum showed two very strong bands at 1705 cm.$^{-1}$ and 1670 cm.$^{-1}$ and no absorption in the ester C=O region. Two other strong bands, apparently ascribable to ring vibrations, were observed at 1600 cm.$^{-1}$ and 1630 cm.$^{-1}$ The latter were observed, with relatively slight frequency shifts, in the spectra of all of the isoquinolines studied (*vide infra*).

4-Hydroxyisoquinoline. Carbon dioxide gas was bubbled through the aqueous filtrate from the isocarbostyril to precipitate 1.52 g. (8.9%) of 4-hydroxyisoquinoline, m.p. 209–215° dec. An analytical sample was prepared by recrystallization from acetonitrile. White needles were obtained which browned at about 215° and had m.p. 223–225° dec.

Anal. Calc'd for C_9H_7NO: C, 74.46; H, 4.87; N, 9.65. Found: C, 74.47; H, 4.97; N, 9.53.

On admixture with a sample of authentic 4-hydroxyisoquinoline (m.p. 222.5–224.0° dec., prepared by the method of Gilman and Gainer[11] and also recrystallized from acetonitrile), the compound melted at 222.5–224.0° dec. These authors reported m.p. 223°. The infrared spectra of samples prepared by the two different methods were also identical. The spectra showed OH absorption at 3400 cm.$^{-1}$ and ring absorption at 1580 cm.$^{-1}$ and 1620 cm.$^{-1}$

4-Hydroxyisoquinoline benzoate. This derivative was prepared by the method of Cavallito and Haskell[17] for the isocarbostyril derivative. The product, after recrystallizations from cyclohexane (Darco), melted at 109.0–110.0°. It was obtained in the form of heavy clumps of pale-yellow needles.

Anal. Calc'd for $C_{16}H_{11}NO_2$: N, 5.62. Found: N, 5.41.

4-Hydroxyisoquinoline picrate. This derivative was prepared by reaction of equimolar quantities of the hydroxyisoquinoline and picric acid in 95% ethanol and recrystallization from the same solvent. The picrate had m.p. 242° dec. (reported[11] m.p. 243–244°).

REARRANGEMENT OF 3-METHYLISOQUINOLINE-N-OXIDE

The reaction was carried out by refluxing 15.90 g. of the oxide with 150 ml. of acetic anhydride for 5 hours, after which the dark mixture was allowed to stand at room temperature overnight. The acetic anhydride was removed under an aspirator vacuum and as much material as possible was distilled from the product at 2.5 mm. pressure up to a bath temperature of 220°. The head-temperature rose to 145°. The small, oily distillate and the large residue were then worked up separately as below.

3-Methylisocarbostyril. The dark distillation residue was refluxed 1 hour with 200 ml. of 5% hydrochloric acid, the solution was chilled, and the solid was collected. In a typical run, after washing with water and drying *in vacuo*, the brown solid weighed 6.9 g. (43%) and melted at 196–211°. For analysis a sample was recrystallized from benzene (Darco) and from 1:1 ethanol-water. The white crystals melted at 210.5–212.5° (reported[25] m.p. 211°).

Anal. Calc'd for $C_{10}H_9NO$: N, 8.80. Found: N, 8.91.

1-Chloro-3-methylisoquinoline. For identification the methylisocarbostyril was converted to the chloro compound by the method of Gabriel and Neumann.[25] After purification by two steam-distillations and an evaporative distillation at a bath temperature of 70° (1.5 mm.), the white product had m.p. 34–35° (reported m.p. 35–36°).

4-Hydroxy-3-methylisoquinoline. The small, oily distillate from the reaction mixture was refluxed 1 hour with 20 ml. of 5% hydrochloric acid, filtered to remove traces of insoluble material, and neutralized with solid sodium bicarbonate. From the pink solution an oil was deposited which solidified partially on scratching. The solid was separated by filtration and washed with water and the small quantity of oil was discarded. After drying and washing with cyclohexane, the solid weighed 1.35 g. (8.5%) and melted over the range 163–175°. An analytical sample was prepared by recrystallizations from benzene; pale yellow needles, m.p. 178.5–180.0° dec. (reported[12] m.p. 180°). A convenient proof of the identity of the compound was obtained by comparison of the ultraviolet spectra of aqueous solutions at *p*H 2.1 and *p*H 14 with the curves published by Harris, Webb and Folkers.[12] The general shapes and frequencies of absorption for the two characteristic curves were in excellent agreement, though intensities of absorption differed slightly at some minima. These differences were apparently due to the presence of a small amount of impurity which could not be separated. It was noted that when samples of the compound were recrystallized from water a green color usually developed, even when the material had previously been purified by recrystallization from benzene. The nature of the impurity was not determined.

Anal. Calc'd for $C_{10}H_9NO$: N, 8.80. Found: N, 9.05.

When the hydrolysis was carried out in aqueous base part of the organic material did not dissolve but remained as an insoluble oil from which no pure compound could be obtained. In the basic hydrolysis, further, a green color developed which remained in the product. Accordingly, most of the hydrolyses were carried out in dilute acid, by the above procedure.

(23) In one case the reflux period was shortened to 2 hours. The yields of the two products were not significantly altered.

(24) Bamberger and Kitschelt, *Ber.*, 25, 1138 (1892).

(25) Gabriel and Neumann, *Ber.*, 25, 3563 (1892).

TREATMENT OF ISOCARBOSTYRIL WITH ACETIC ANHYDRIDE

N-Acetylisocarbostyril. A mixture of 7.25 g. of isocarbostyril and 75 ml. of acetic anhydride was refluxed for 1 hour and the acetic anhydride was evaporated under an aspirator vacuum. The tan residue after drying *in vacuo* weighed 9.32 g. (99.7%) and had m.p. 85–88°. Recrystallizations from cyclohexane (Darco) produced large white needles, m.p. 84–86°. The infrared spectrum showed strong absorption bands at 1665 cm.$^{-1}$ and 1705 cm.$^{-1}$ attributable to carbonyl absorptions and ring absorption bands at 1597 cm.$^{-1}$ and 1625 cm.$^{-1}$

Anal. Calc'd for $C_{11}H_9NO_2$: N, 7.48. Found: N, 7.69.

The purified acetyl compound (5.49 g.) was added to 44 ml. of acetic anhydride and the mixture was refluxed 5 hours. Removal of the acetic anhydride followed by distillation of the product produced 4.10 g. of unchanged amide, b.p. 127–139° (2 mm.) and m.p. 80–85°. As in the N-oxide reactions, there was an appreciable, non-volatile, tarry residue. Hydrolysis of the acetyl compound by the usual procedure with sodium hydroxide produced 2.98 g. of isocarbostyril, m.p. 208.0–210.5°. On neutralization of the alkaline filtrate with carbon dioxide a small additional amount of solid precipitated. This was more isocarbostyril, m.p. 207.0–209.5°, undepressed on admixture with an authentic sample.

ATTEMPTED PREPARATIONS OF 1-ACETOXYISOQUINOLINE

Reaction of acetyl chloride with the sodium salt of isocarbostyril. A solution of 1.45 g. of isocarbostyril and 0.40 g. of sodium hydroxide in 60 ml. of 95% ethanol was evaporated to dryness *in vacuo* and the residue was dried to constant weight *in vacuo* at 100° over phosphorus pentoxide. To a slurry of 1.41 g. of the resulting sodium salt in 10 ml. of anhydrous ether a solution of 0.66 g. of acetyl chloride in 10 ml. of dry ether was added dropwise with stirring over a ten-minute period. The resulting suspension was stirred and refluxed for 1 hour. Separation of the sodium chloride by filtration and evaporation of the ether afforded 1.25 g. of N-acetylisocarbostyril, m.p. 86.0–87.0°, undepressed on admixture with a sample prepared by the acetic anhydride method.

Reaction of acetyl chloride with the silver salt of isocarbostyril. A solution of 0.56 g. of acetyl chloride in 10 ml. of dry ether was added dropwise with stirring over a 20-minute period to a suspension of 1.82 g. of the silver salt of isocarbostyril in 15 ml. of dry ether. The salt was prepared by the method of Fernau.[26] The mixture was refluxed with stirring for 1 hour, the solid was separated by filtration, and the solvent was evaporated. The resulting crude N-acetylisocarbostyril weighed 0.63 g. and melted at 79.5–85.0°. After recrystallization from *n*-hexane it had m.p. 83.0–86.5°, undepressed on admixture with authentic amide.

(26) Fernau, *Monatsh.*, **14**, 59 (1893).

Attempted isolation from amine-oxide rearrangement. When the mixture of products from a typical isoquinoline-N-oxide rearrangement was distilled as usual, the last fraction of distillate was found to melt at 74–81° alone and at 73–83° on admixture with authentic amide. After recrystallization from cyclohexane the material had m.p. 83.0–85.5°, undepressed on admixture with authentic N-acetylisocarbostyril.

TREATMENT OF 4-HYDROXYISOQUINOLINE WITH ACETIC ANHYDRIDE

4-Acetoxyisoquinoline. A mixture of 2.54 g. of purified hydroxy compound and 26 ml. of acetic anhydride was refluxed 5 hours and distilled as usual. The 4-acetoxyisoquinoline distilled at 135–139° (1 mm.) and weighed 2.17 g. (66.3%). The light-yellow oil crystallized on cooling to form pale-yellow crystals, m.p. 47.5–52.5°. After several recrystallizations from low-boiling petroleum ether the product was obtained as large white needles, m.p. 55.0–55.5°. The infrared spectrum showed absorption at 1740 cm.$^{-1}$ (ester C=O) and at 1585 cm.$^{-1}$ and 1625 cm.$^{-1}$

Anal. Calc'd for $C_{11}H_9NO_2$: N, 7.48. Found: N, 7.71.

Acid hydrolysis. One millimole of the acetoxy compound was heated with 2 ml. of 5% hydrochloric acid for 2 hours on the steam-bath, then allowed to stand at room temperature overnight. White crystals were deposited from the solution, m.p. 208–210°. On admixture with isocarbostyril this product melted at 125–160°. The material was a salt of 4-hydroxyisoquinoline for on dissolution in a few milliliters of water and addition of solid sodium bicarbonate, ebullition ensued and 98 mg. of 4-hydroxyisoquinoline (m.p. 220.5–223.5° dec.) precipitated. On admixture with authentic 4-hydroxy compound the material melted at 220.0–222.5° dec. From the hydrochloric acid filtrate an additional 30 mg. of unrearranged phenol was precipitated by addition of sodium bicarbonate. This had m.p. 221.0–222.0° dec., undepressed on admixture with authentic material. The total recovery was thus 88.3%.

Alkaline hydrolysis. One millimole of acetoxy compound was added to 2 ml. of 5% sodium hydroxide solution. Dissolution, indicating saponification, took place within a few minutes at room temperature. The mixture was heated on the steam-bath 1 hour, then allowed to stand overnight at room temperature. Saturation of the clear yellow solution with carbon dioxide precipitated 135.5 mg. (93.4%) of unchanged 4-hydroxyisoquinoline, m.p. 221.5–224.5° dec., undepressed on admixture with authentic material.

Absorption spectra. Ultraviolet spectra were determined on a Beckman model DU quartz spectrophotometer at a concentration of 10^{-4} M. Infrared spectra were determined with a Baird spectrophotometer (KBr disc) by Dr. Stephen M. Nagy and associates at the Microchemical Laboratory, Massachusetts Institute of Technology.

AMHERST, MASSACHUSETTS