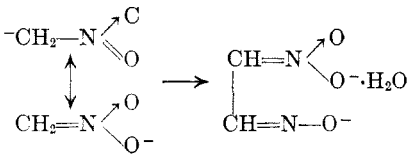
titrated potentiometrically with 0.1*N* sodium hydroxide however, the titration curve (Fig. 1d) showed only one sharp change in *p*H (corresponding to an equivalent of 104) and no other point of inflection.

Methazonic acid therefore normally functions as a monobasic acid $O_2NCH_2CH{=}NO^-H^+$ but in its preparation from nitro methane, an intermediate disodium salt is formed.

Bearing in mind that Drew's kinetic studies showed that the reaction involved two univalent negative ions, a more correct representation of its formation is therefore



although an intermediate compound could well be formed.

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Reaction of 1-Chloroisoquinoline with Peracetic Acid[1]

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As part of an investigation[2,3] of the rearrangement of isoquinoline-*N*-oxides, attempts were made to prepare 1-chloroisoquinoline-*N*-oxide by the reaction of 1-chloroisoquinoline with aqueous peracetic acid. Oxidations of this type have been effected with 2-bromopyridine using 40% peracetic acid[4] and with other α-halo-heterocycles. The desired oxide was not obtained, for the reaction took another course, but since several new isoquinoline derivatives were prepared, and since certain of the transformations were unexpected, the results are reported here.

When 1-chloroisoquinoline[5] was heated with acetic acid and hydrogen peroxide at 65°, a substance with the anticipated composition was obtained in consistently low yield, along with much colored, polymeric material. On treatment of the purified product with acetic anhydride, an acetyl derivative was formed, which, however, reverted to the starting material on hydrolysis. The oxidation product was eventually shown to be 4-chloroisocarbostyril by hydrogenolysis to isocarbostyril and by conversion to the known[5] 1,4-dichloroisoquinoline. Further, 1,4-dichloroisoquinoline, which may be prepared more conveniently by the action of phosphorus pentachloride on isocarbostyril[6] than by the method of Gabriel and Colman, was converted to 4-chloroisocarbostyril by methanolysis of the 1-chloro group and subsequent cleavage of the ether with hydrochloric acid.

It was found that the mode of formation of the unexpected product involved a surprisingly facile hydrolysis of the 1-chloroisoquinoline, followed by chlorination of the resulting isocarbostyril by the free halogen formed from the chloride ion liberated in the oxidizing medium. Although acid-catalyzed nucleophilic substitutions with 1-chloroisoquinoline are well known,[7] the conditions of the attempted oxidation are unusually mild for such a hydrolysis. Convincing evidence was obtained for this reaction course, however: 1. Treatment of 1-chloroisoquinoline with acetic acid and water under conditions identical with those of the oxidation resulted in the formation of a 38% yield of isocarbostyril and the recovery of 52% of the starting material. 2. Treatment of isocarbostyril with a mixture of hydrogen peroxide, hydrochloric acid, and glacial acetic acid produced 4-chloroisocarbostyril rapidly in 87% yield. 3. Prolonged treatment of 1-chloroisoquinoline with acetic acid and water at the reaction temperature before addition of the hydrogen peroxide resulted in an increased yield of 4-chloroisocarbostyril. 4. Addition of bromide ion to a 1-chloroisoquinoline-oxidation mixture resulted in the formation of 4-bromoisocarbostyril.

EXPERIMENTAL[8,9]

4-Chloroisocarbostyril. A mixture of 1.64 g. of 1-chloroisoquinoline,[5] 1 ml. of 30% hydrogen peroxide, and 3 ml. of glacial acetic acid was heated at 65° for a period of 12 hr., 0.8 ml. more hydrogen peroxide being added after 3 hr. The reddish solution, from which crystals separated during the

(1) 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.

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(3) M. M. Robison and B. L. Robison, *J. Am. Chem. Soc.*, in press.

(4) E. Shaw, J. Bernstein, K. Losee, and W. A. Lott, *J. Am. Chem. Soc.*, **72**, 4362 (1950).

(5) S. Gabriel and J. Colman, *Ber.*, **33**, 980 (1900).

(6) Cf. S. Gabriel, *Ber.*, **18**, 3470 (1885) for the corresponding reaction with 3-phenylisocarbostyril.

(7) Cf. W. J. Gensler in *Heterocyclic Compounds*, R. C. Elderfield, ed., John Wiley and Sons, Inc., New York, N. Y., 1952, Vol. 4, p. 421.

(8) Melting points are corrected.

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

heating period, was evaporated to dryness *in vacuo*, water was added, and the evaporation was repeated to yield a mixture of red solid and brown tar. This was washed well with ethanol to remove the tarry material and the residue was dissolved as completely as possible in about 15 ml. of boiling butyl acetate (Darco). From the cooled filtrate 4-chloroisocarbostyril was deposited, in yields averaging 20–24%. The analytical sample was prepared by additional recrystallizations from butyl acetate, from benzene, and from acetic acid–water; white needles, m.p. 235.5–237.5° dec.

Anal. Calcd. for C_9H_6NOCl: C, 60.18; H, 3.37; N, 7.80 Found: C, 60.57; H, 3.61; N, 7.60.

The infrared spectrum showed carbonyl absorption at 1680 cm.$^{-1}$ and an additional band at 1650 cm.$^{-1}$ In addition, the usual bands ascribed to ring absorption[2] were observed at 1625 cm.$^{-1}$ and 1600 cm.$^{-1}$

When the reaction was carried out with twice as much acetic acid at steam bath temperature for 6 hr., without the second addition of peroxide, a typical yield of recrystallized product was 38%. When a reaction mixture was prepared as in the first method, but with water instead of hydrogen peroxide, and heated at 65° for 20 hr., further heating and peroxide additions by the usual procedure afforded a 40.5% yield of recrystallized product.

The chloroisocarbostyril was also prepared from a mixture of 1.45 g. of isocarbostyril, 1 ml. of 30% hydrogen peroxide, 3 ml. of glacial acetic acid, and 0.84 ml. of concentrated hydrochloric acid. On gentle warming a vigorous reaction ensued and occasional cooling was necessary for the first hour. After a final period of heating for 1 hr. at 65°, the mixture was cooled and an 87% yield of pale, orange needles, m.p. 230–236.5° dec., was separated. Recrystallization from butyl acetate (Darco) afforded white needles, m.p. 236–238° dec., in 66% yield.

Hydrolysis of 1-chloroisoquinoline. When 0.33 g. of the chloro compound was treated as in the oxidations, except that water was substituted for hydrogen peroxide, an oily solid was obtained on evaporation of most of the solvent. This was washed with warm water and with ether to leave 0.11 g. of undissolved isocarbostyril, m.p. 203–206.5°, undepressed on admixture with an authentic sample. From the filtrate a 52% yield of unchanged starting material was obtained by extraction with ether and evaporation. This had m.p. 33.5–36.5° both alone and on admixture with 1-chloroisoquinoline.

N-Acetyl-4-chloroisocarbostyril. A mixture of 1.35 g. of 4-chloroisocarbostyril and 11 ml. of acetic anhydride was refluxed for 5.5 hr., then cooled to deposit a 62% yield of long, white needles of the acetyl derivative, m.p. 105–107.5°. Evaporation of the anhydride to dryness *in vacuo* afforded an additional 36% of less pure tan solid. The analytical sample, which was recrystallized from hexane, had m.p. 105.5–107°. The compound is formulated as *N*-acetyl-4-chloroisocarbostyril, rather than as the 1-acetoxy compound, on the basis of infrared absorptions at 1723 cm.$^{-1}$ and 1685 cm.$^{-1}$ and ring absorptions at 1625 cm.$^{-1}$ and 1595 cm.$^{-1}$ A similar situation obtains with acyl derivatives of isocarbostyril.[2]

Anal. Calcd. for $C_{11}H_8NO_2Cl$: C, 59.61; H, 3.64; N, 6.32; Cl, 16.00. Found: C, 59.81; H, 3.64; N, 6.39; Cl, 15.75.

When the acetyl derivative was hydrolyzed in refluxing 10% hydrochloric acid, it was converted to 4-chloroisocarbostyril in essentially quantitative yield.

Hydrogenolysis of 4-chloroisocarbostyril. A mixture of 135 mg. of the chloro derivative, 0.1 g. of 5% palladium-on-charcoal, 0.3 g. of potassium acetate, and 20 ml. of 95% ethanol was stirred with hydrogen until slightly more than the theoretical volume had been absorbed. The catalyst was separated and the solution evaporated to dryness *in vacuo*. The isocarbostyril, after washing with water, weighed 71 mg. (65%) and had m.p. 202.5–205.5°, undepressed on admixture with the known compound.

1,4-Dichloroisoquinoline. When 0.01 mole of the chloroisocarbostyril was heated with 6 ml. of phosphorus oxychloride in a sealed tube at 120° for 4 hr., and the mixture poured onto ice, a quantitative yield of 1,4-dichloroisoquinoline, m.p 93–94°, separated. Steam-distillation and recrystallizations from ethanol-water produced the analytical sample, long, white needles, m.p. 92–92.5° (reported[5] m.p. 88–89°).

Anal. Calcd. for $C_9H_5NCl_2$: C, 54.58; H, 2.54; N, 7.07. Found: C, 54.65; H, 2.92; N, 7.04.

The melting point was undepressed on admixture with an authentic sample prepared by the method of Gabriel.[5] A preparation more convenient than the latter involved heating a mixture of 2.90 g. of isocarbostyril and 7 g. of phosphorus pentachloride at 140° for 6 hr. The mixture was poured onto ice and the crude product recrystallized from ethanol-water; yield 50%, m.p. 92–94°.

Independent preparation of 4-chloroisocarbostyril. A solution of 1 g. of sodium and 0.6 g. of the dichloro compound in 15 ml. of methanol was heated in a sealed tube at 100° for 1.5 hr. The solvent was evaporated and the residue was washed with water to produce the crude methyl ether, m.p. 48–50°. This was not investigated further but was heated in a sealed tube with 6 ml. of concentrated hydrochloric acid at steam bath temperature for 2 hr. Addition of water allowed the separation of 4-chloroisocarbostyril, m.p. 238–238.5° dec., undepressed on admixture with material from the oxidation. The infrared spectra of the two samples were also identical. The over-all yield was 91%.

4-Bromoisocarbostyril. A mixture of 1.45 g. of isocarbostyril, 1 ml. of 30% hydrogen peroxide, and 3 ml. of glacial acetic acid was maintained at 20–25° while a solution of 1.69 g. of 48% hydrobromic acid in 1 ml. of acetic acid was added dropwise. The mixture was allowed to stand for 3 hr., then heated to 40° for 1 hr. Dilution with water afforded a 78% yield of crude 4-bromo compound, m.p. 233–237° dec. The analytical sample was recrystallized from benzene, from butyl acetate, and from 1:1 acetic acid–water; m.p. 248–249° dec.

Anal. Calcd. for C_9H_6NOBr: N, 6.25. Found: N, 6.18.

The substance was also obtained when one equivalent of potassium bromide was added to a 1-chloroisoquinoline–oxidation mixture. Initial cooling was necessary. The reaction mixture was worked up in the usual manner to produce the crude bromo compound in approximately 7% yield. After two recrystallizations the material melted at 246–248° dec.

Absorption spectra. Infrared spectra were determined with either a Perkin-Elmer or Baird spectrophotometer (KBr disk) by Dr. S. M. Nagy and associates at the Massachusetts Institute of Technology.

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Reactions of Alkyl Phosphites with Diethyl Azodicarboxylate[1]

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The reaction of diethyl phosphite with azodicarboxylic acid diethyl ester under alkaline catalysis was studied in the hope that the phosphite would add to the double bond of the azo group, forming a phosphoric hydrazide compound. This appeared to take place and a product was isolated which gave

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