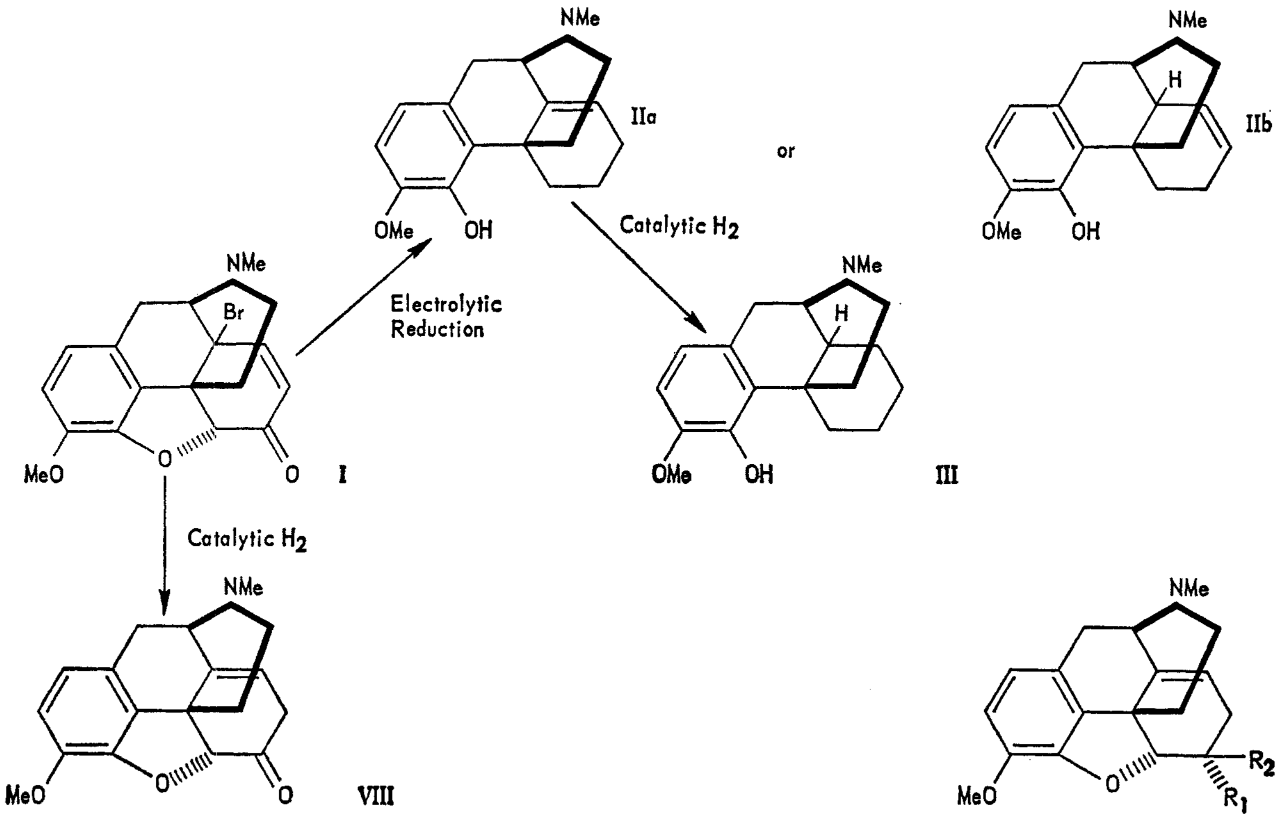
SCHEME I



IV: $R_1 = OH$, $R_2 = H$
V: $R_1 = H$, $R_2 = OH$
VI: $R_1 = R_2 = H$
VII: $R_1 = OMe$, $R_2 = H$

matographed on alumina. Elution with benzene-methylene chloride (1:1) yielded first unchanged I, 19%, followed by II, 31%. Subsequent elution with chloroform and chloroform-methanol 6:1 gave additional, more polar fractions, which were not identified; they were nonketonic (no ν (CO) between 1700 and 1721 cm^{-1}). The melting point and nmr spectrum of the sample of II obtained in this way agreed completely with those of the old samples.

Registry No.—I, 5140-31-8; IIa, 16808-39-2.

Laboratory Application of a Chemical Reactor Column. The Synthesis of Perdeuteriotropilidene

PAUL MÜLLER AND JAN ROČEK

Department of Chemistry, University of Illinois at Chicago Circle, Chicago, Illinois 60680

Received February 13, 1968

Perdeuteriotropilidene, which was required in larger quantities in our program of investigations of mechanisms of oxidation reaction, was prepared in low isotopic purity (total deuterium content 90.8%, C_7D_8 55.9%) by Doering and Gaspar[1] by base-catalyzed hydrogen exchange between tropilidene and a deuterated solvent under drastic conditions. For our purposes a considerably higher deuterium content was desirable. As repeated equilibration turned out to be impractical (only about 50% tropilidene could be recovered after treating 5.0 g of tropilidene with 5.0 g of potassium dissolved in 75 g of triethylcarbinol under exchange conditions), a direct synthetic approach was sought.

Of the several methods of tropilidene syntheses available in the literature either the photochemically[2,3] or metal-catalyzed[4] reaction of benzene with diazomethane seemed most promising. The disadvantage of the photochemical method is the formation of toluene as a by-product. This drawback is removed in the catalytic process[4-7] which was explored in considerable detail by Müller and Fricke,[4] who were able to obtain yields up to 85% based on diazomethane. In their modification diazomethane was used in a benzene solution and a large excess of benzene over diazomethane (40:1) was required.

For the synthesis of perdeuteriotropilidene from ben-

---

[1] W. von E. Doering and P. P. Gaspar, *J. Amer. Chem. Soc.*, **85**, 3043 (1963).

[2] W. von E. Doering and L. H. Knox, *ibid.*, **72**, 2305 (1950).

[3] H. Meerwein, H. Disselnkötter, F. Rappen, H. v. Rintelen, and H. van de Vloed, *Ann.*, **604**, 151 (1957).

[4] E. Müller and H. Fricke, *ibid.*, **661**, 38 (1963).

[5] G. Wittig and K. Schwarzenbach, *ibid.*, **650**, 18 (1961).

[6] P. P. Gaspar, Doctoral Dissertation, Yale University, 1961.

[7] W. von E. Doering and W. R. Roth, *Tetrahedron*, **19**, 715 (1963).

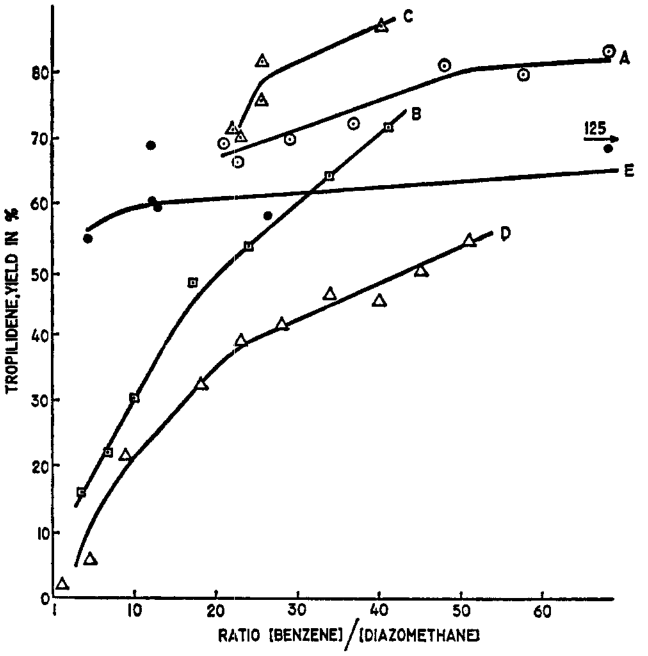


Figure 1.—Dependence of yield of tropilidene on the benzene-diazomethane ratio: (A) CH_2N_2 in benzene, CuCl catalysis, 78°; (B) CH_2N_2 in ether, CuCl catalysis, room temperature; (C) CH_2N_2 in benzene, CuCl catalysis, data from Müller and Fricke;[4] (D) CH_2N_2 in ether, photochemical reaction (yields include about 10% of toluene); (E) CH_2N_2 in ether, CuCl catalysis, 78°, in reactor column.

zene-d_6 and diazomethane-d_2 the use of benzene as solvent for the extraction of diazomethane as well as the use of a large excess of benzene in the reaction as recommended by Müller and Fricke would seem rather extravagant. The effect of the benzene-diazomethane ratio on the yields of tropilidene for benzene and ether solutions of diazomethane was therefore investigated. The results are given in Figure 1. The yields for ether solutions are consistently somewhat lower, but the general trend is the same for both solvents. Our results for benzene solutions are in general agreement with those of Müller and Fricke[4] (curve C), though slightly lower. The difference is probably due to the dependence of the reaction on the nature of the catalyst.

We investigated also the method employed by Doering and Roth[7] and Gaspar[6] in which diazomethane is introduced in a stream of nitrogen rather than in solution. However, only about a 10% yield of tropilidene was obtained when a benzene-diazomethane ratio of 10:1 was used.

The dependence of the yield of tropilidene on the benzene-diazomethane ratio is best explained by the assumption that tropilidene itself is not only capable of reacting with diazomethane[8] but is actually considerably more reactive than benzene. A large excess of benzene is therefore required to compete successfully with the already formed tropilidene for the newly introduced diazomethane. The relative reactivity of diazomethane toward tropilidene and benzene is about the same for the photochemically (curve D) and for the cuprous chloride catalyzed process (curves A, B, C).

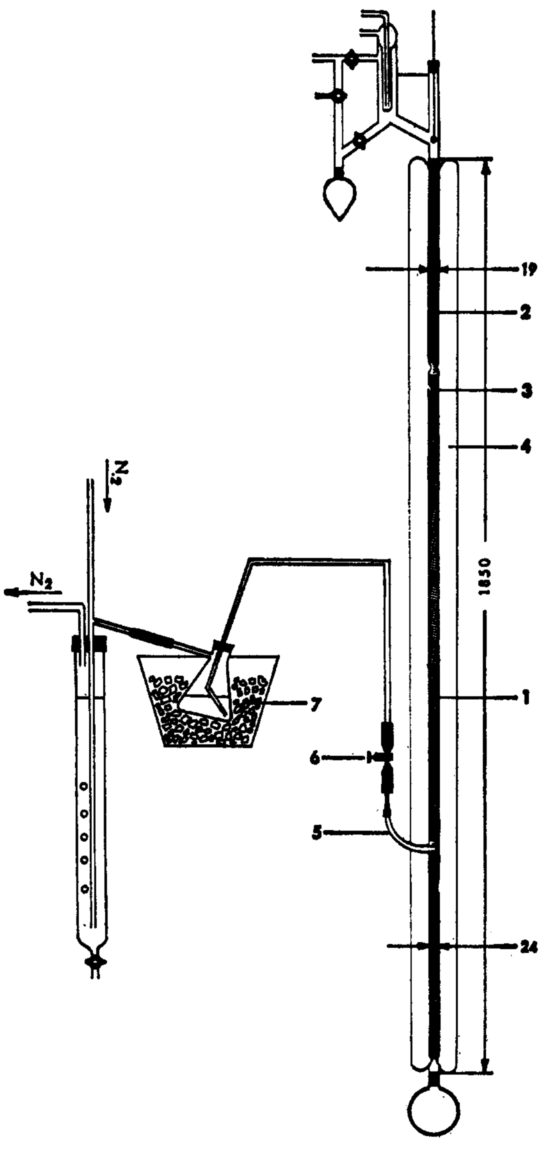


Figure 2.—Reactor column: 1, section with catalyst (CuCl on boiling chips); 2, section with "Heli-pak;" 3, thermocouple well; 4, thermal insulation (cotton wool and aluminum foil); 5, inlet of diazomethane solutions; 6, screw clamp; 7, Dry Ice bath.

The requirement of a high benzene-tropilidene ratio at the time of the reaction with diazomethane combined with a satisfactory over-all conversion of the benzene into tropilidene can be accomplished by the use of a distillation column using a packing material coated with the cuprous chloride catalyst (Figure 2). In this way a high local benzene-diazomethane concentration can be maintained in the reaction zone while the higher boiling tropilidene is concentrated in the pot protected from further reaction with diazomethane. An ether solution of diazomethane was introduced at the lower fourth of the column and the ether continuously removed from the top of the column. The reaction section of the column was kept at the boiling point of benzene to assure sufficient contact time for benzene and diazomethane. The separation of ether from diazomethane took place in the upper part of the column filled with "Heli-pak."[9] The temperature of the column head was not allowed to exceed the boiling point of ether in order to prevent losses of ben-

---

[8] The reaction of tropilidene with diazomethane in the presence of cuprous chloride was studied by Doering and Roth.[7] Bicyclo[5.1.0]octa-2,5-diene and bicyclo[5.1.0]octa-2,4-diene are the main products.

[9] "Heli-pak," Nichrome, 0.050 in. × 0.100 in. × 0.100 in., Podbielniak, Franklin Park, Ill.

zene. The reactor column was tested in a set of experiments using 50 ml of benzene and variable amounts of diazomethane. The results are given in Figure 1 (curve E). They show that the reaction modified in this way gives indeed good yields of tropilidene even at benzene to diazomethane ratios as low as 4.25:1. Still lower ratios could probably be used and the yields could be further improved if the effectiveness of the column were improved either by a more efficient type of column packing or by increasing the length of the column in order to decrease further the concentration of tropilidene in the reaction zone.

The perdeuteriotropilidene prepared in the reactor column contained 87.7% C_7D_8, 11% C_7D_7H, and 1.3% $C_7D_6H_2$ (by low voltage mass spectrometry), corresponding to a total deuterium content of 98.31%. The heptadeuteriotropilidene contained 75% of the protons in the CH_2 group and 25% distributed equally over the three equivalent olefinic CH groups (by nmr). No appreciable amount of isomerization took place during the reaction.

Diazomethane-d_2 used in the synthesis was prepared from N-methyl-d_3-N-nitroso-*p*-toluenesulfonamide by a modified procedure of Dahn and coworkers.[10]

The method of tropilidene synthesis as developed here and tested on the preparation of tropilidene-d_8 would in general be applicable to any catalytic carbene synthesis in which a volatile substrate available in limited amounts yields a product capable of further reaction. Substrates of this kind are known in the literature. *E.g.*, Doering and Roth[7] applied their method of cyclopropanation to *cis*-hexatriene, cycloheptadiene, and tropilidene. Working with excess diazomethane they always found higher homologous compounds besides the starting material and the monocyclopropanated products in the reaction mixture. In the case of tropilidene they were able to isolate the monocyclopropanated compound in better yield after changing the tropilidene–diazomethane ratio.

Experimental Section

Analytical Methods.—Reaction products were identified and the yields determined on an analytical F & M Scientific 5750 research gas chromatograph using a 10-ft column with 10% Carbowax 20M, 80–100 WAW at 130°. Preparative gas chromatography was carried out on a F & M Prepmaster Jr. Model No. 776 with a 0.75-in. column of 80-in. length with 20% Carbowax 20M on Chromosorb PAW 10–30 at 90°. The deuterium content in nitromethane and in methylamine was determined on a mass spectrometer of Consolidated Engineering Co. Type 21-630. The final analysis of perdeuteriotropilidene was made on an Atlas mass spectrometer, Model CH4, at 10 eV and the distribution of deuterium determined by nmr spectroscopy on a Varian HR-100 spectrometer.

Preparation of Tropilidene. A. Batch Process.—Purified[11] cuprous chloride (Fisher Scientific Co., 50–100 mg) was weighed into a flask fitted with reflux condenser, dropping funnel, and drying tube, the flask with the catalyst flame dried under a stream of nitrogen, the desired amount of benzene (1–12 ml) introduced, and the solution of diazomethane[12] (10–30 ml) slowly added under stirring with a magnetic stirrer. The addition was carried out at room temperature if ether was used as a solvent, and under reflux when benzene solutions were employed. The time required for the addition varied from 10 to 15 min. After the reaction was completed, the tropilidene–benzene ratio was determined chromatographically.

In the photochemical reaction benzene (0.5–8 ml) and diazomethane in ether (2–10 ml) were mixed in glass tubes of 8-mm o.d. and 50-cm length. The tubes were immersed in a water bath at 15° and irradiated for 3 hr at λ_{max} 3500 Å.[13]

B. Reactor Column (Figure 2).—Boiling chips coated with cuprous chloride[14] were used as packing material of the column in the reaction zone. The upper part of the column above the reaction zone was filled with "Heli-pak"[9] packing. Benzene (50 ml) was placed in the pot and heated. When the entire reaction zone was filled with benzene vapors (temperature at upper end >75°) the addition of a cooled (Dry Ice) solution of diazomethane in ether (about 0.5 *M*) was started. The rate of addition was regulated by the pressure of nitrogen and by a screw clamp; 4–6 hr was required for the addition of the diazomethane. Whenever the temperature in the reaction zone dropped the addition was interrupted. For a smaller column (16-mm diameter, 120-cm length), 30 ml of benzene was used. The yields in both columns were the same.

The product obtained by this method contained small amounts of ethanol from the preparation of diazomethane.[10] No toluene was formed, but small amounts of a higher boiling by-product could be observed when the benzene–diazomethane ratio was less than 10.

Nitromethane-d_3.—Nitromethane (30 g) was heated with deuterium oxide (38 g, Columbia Chemicals, 99.77% purity) in which 16 mg of sodium metal was dissolved (under nitrogen) in a 100-ml pressure bomb with a magnetic stirrer at 110° for 24 hr. The reaction mixture was transferred under pressure of nitrogen to a round-bottom flask and separated from polymer formed by distillation on a vacuum line and the nitromethane layer removed with a syringe. The remaining deuterium oxide was extracted with ether and the extract dried over calcium sulfate and evaporated; the combined yield was 85–90° for each step. The isotopic purity after five exchanges was 99%.

Methyl-d_3-amine Hydrochloride.—Nitromethane-d_3 (10.0 g) was added to 75 ml of dioxane (purified by distillation over sodium metal) containing 1.0 g of palladium catalyst (5%, on charcoal). The mixture was magnetically stirred under deuterium (CP grade, Matheson, 99.5%) for 4 days. After the flask was cooled with acetone and Dry Ice, 50 ml of concentrated hydrochloric acid was slowly added, the content of the flask let melt, and the solution filtered through a fritted funnel covered with Celite and evaporated to dryness. The crude deuteriomethylamine hydrochloride was used without purification for the next step. In an experiment with unlabeled nitromethane a 80% yield methylamine hydrochloride was obtained.

Diazomethane-d_2.—The crude amine was converted into the N-methyl-d_3-*p*-toluenesulfonamide (70%), N-nitroso-N-methyl-d_3-*p*-toluenesulfonylamide (85–87%), and dideuteriodiazomethane (50%) following Dahn's procedure.[10] Based on the determination of deuterium content and distribution in the product it could be estimated that the diazomethane had the following composition: 90.6% CD_2N_2, 8.3% $CDHN_2$, and 1.1% CH_2N_2. The diazomethane solution was dried over sodium metal before use.

Tropilidene-d_8.—Perdeuteriotropilidene was prepared from C_6D_6 (Merck Sharp and Dohme, Montreal, isotopic purity 99.5%) and CD_2N_2 in the reactor column. After all CD_2N_2 was introduced, the column was extracted with ether to recover the benzene and tropilidene retained by the column packing. The solution was then purified by bulb-to-bulb distillation, most of the benzene was removed on a spinning-band column (Nester–Faust), and the residue was purified in 1-ml fractions by preparative gas chromatography. The yield for the work-up procedure was 77%.

Registry No.—Perdeuteriotropilidene, 16675-63-1.

Acknowledgments.—Support of this work by the U. S. Army Research Office (Durham) is gratefully acknowledged. We also wish to express our appreciation to Professor K. L. Rinehart, Department of Chemistry,

---

[10] H. Dahn, A. Donzel, A. Merbach, and H. Gold, *Helv. Chim. Acta*, **46**, 994 (1964).

[11] R. N. Keller and H. D. Wycoff, *Inorg. Syn.*, **2**, 1 (1946).

[12] F. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1950, p 165.

[13] A Rayonet photochemical reactor of the Southern N.E. Ultraviolet Co. was used.

[14] Boiling chips (1 lb, Abrasive Grain Crystolon, Norton Co., Worcester, Mass.) were mixed with 3.0 g of cuprous chloride in hydrochloric acid, dried under vacuum with shaking, washed successively with acetic acid, water, and ethanol, and dried again under vacuum at 60°.

University of Illinois, Urbana, for final deuterium analysis of tropilidene, to Professor J. Jonas, Department of Chemistry, University of Illinois, Urbana, for the determination of the deuterium distribution, and to Professor E. T. Kaiser, Department of Chemistry, University of Chicago, for the use of the mass spectrometer.

The Reaction of 4-Chloro-8-methoxyquinoline with Hydrogen Peroxide[1a]

TAKESHI FUJITA[1b] AND J. M. PRICE[1c]

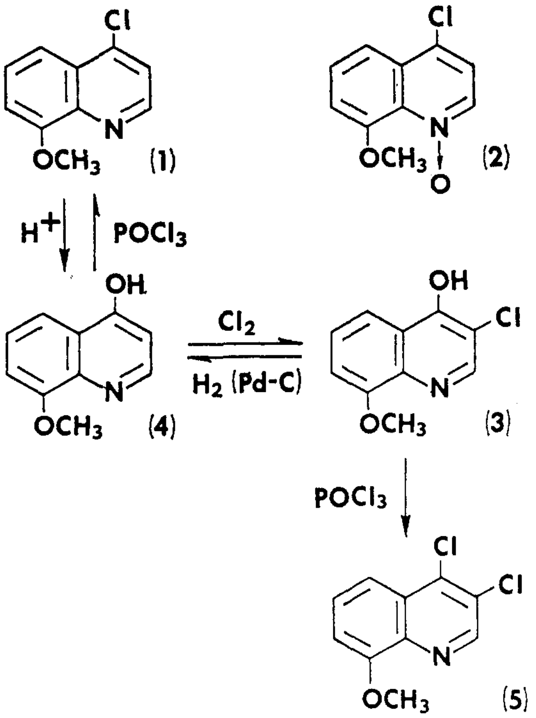
Division of Clinical Oncology,
University of Wisconsin Medical School,
Madison, Wisconsin 53706

Received January 9, 1967

In the course of an attempt to synthesize 4-chloro-8-methoxyquinoline 1-oxide by the treatment of 4-chloro-8-methoxyquinoline (1) with hydrogen peroxide, the resulting product failed to show the properties expected of the desired 1-oxide (2), but instead appeared to be 3-chloro-8-methoxy-4-quinolinol (3). The proposed structure (3) was considered as a possible product because it had an ultraviolet spectrum nearly identical with that of 8-methoxy-4-quinolinol (4), and because 3 was converted into 4 by reduction with palladium on charcoal in methanol containing hydrogen chloride (Scheme I). Furthermore, 3 was prepared from 4 and chlorine in acetic acid, and treatment of 3 with phosphorus oxychloride produced 3,4-dichloro-8-methoxyquinoline (5) in high yield. The nmr spectrum of 5 showed no doublet downfield expected of 2, but did show a singlet at τ 1.27, which was assigned to the proton at the C_2 position.

The bromination of 4-quinolinol[2] and 4-quinolinol 1-oxide[3] afforded the respective 3-bromo derivatives of these compounds. Brobański[4] reported that 4-chloroquinoline was converted into 4-quinolinol by acid hydrolysis. Robison and Robison[5] found that 4-chloroisocarbostyril was obtained in the reaction of 1-chloroisoquinoline with aqueous peracetic acid. Therefore, the hydrolysis of 1 in aqueous acetic acid followed by the halogenation of the resultant 4 by the chlorine produced from hydrogen chloride by hydrogen peroxide would explain the conversion of 1 into 3 instead of the desired 2. This mechanism was demonstrated by the experiments reported here.

SCHEME I



Experimental Section[6]

3-Chloro-8-methoxy-4-quinolinol (3).—8-Methoxy-2-carboxy-4-quinolinol was prepared according to the method of Furst and Olsen,[7] and decarboxylated[8] in refluxing Dowtherm A at 250° to yield 4 which was converted into 1 by refluxing for 1 hr in phosphorus oxychloride, mp 80–81° (lit.[8] mp 79–80°).

A solution of 0.5 g of 1 and 0.5 ml of hydrogen peroxide (30%) in 10 ml of glacial acetic acid was stirred for 3 hr at 65–70°. After another 0.5 ml of hydrogen peroxide was added to the solution, it was heated at 60–70° for 3 hr. Following evaporation of the acetic acid, the residue was dissolved in dilute aqueous sodium hydroxide and washed with ethyl ether, and the aqueous solution was neutralized with dilute hydrochloric acid. A yield of 0.21 g (39%) of colorless needles was obtained, mp 273–274°. In a second trial, 0.7 g (32%) of this product was obtained from 2.0 g of 1. The infrared spectrum of this product showed no strong absorption of the N–O stretching frequency expected of the 1-oxide near 1210 but had a hydroxyl band at 2900–3200 cm^{-1}; uv showed λ_{max} 232 mμ (ε 32,530), 303 (8130), 327 (12,310), 340 (10,610) (in ethanol). *Anal.* Calcd for $C_{10}H_8NO_2Cl$: C, 57.30; H, 3.85; N, 6.68; O, 15.26; Cl, 16.91. Found: C, 57.52; H, 3.92; N, 6.52; O, 15.63; Cl, 16.21.

Reduction of 3-Chloro-8-methoxy-4-quinolinol (3).—Compound 3 (0.5 g) in 30 ml of aqueous hydrochloric acid (10%) was hydrogenated over 0.5 g of palladium on charcoal (5%) under 20-psi pressure. After removal of the catalyst, the filtrate was evaporated *in vacuo*. The residue was dissolved in a small amount of water and was neutralized with dilute aqueous sodium hydroxide to yield 0.145 g (34.6%) of white needles. After recrystallization from water, the melting point was 183–184° (with 4, mmp 183–184°). The ultraviolet spectrum of this product was identical with that of 4 in 0.1 *N* hydrochloric acid, ethanol, and 0.1 *N* sodium hydroxide. The reduction product and 4 were also indistinguishable on paper chromatograms using the solvent system of Mason and Berg[9] containing 1% ammonia (R_f 0.90) or 1% acetic acid[10] (R_f 0.90) and 6% aqueous sodium acetate (R_f 0.50).

Chlorination of 8-Methoxy-4-quinolinol (4).—A mixture containing 2 g of 4, 70 ml of glacial acetic acid, and 0.7 g of chlorine was kept for 12 hr at room temperature. A white

---

[1] (a) This work was supported by Grant No. CA-07817 from the National Institutes of Health, U. S. Public Health Service. (b) Eisai Research Laboratories, Koishikawa 4, Bunkyo-ku, Tokyo, Japan. (c) American Cancer Society–Charles S. Hayden Foundation Professor of Surgery in Cancer Research. To whom all correspondence should be addressed at Abbott Laboratories, North Chicago, Ill. 60064.

[2] B. Riegel, G. R. Lappin, C. J. Albinsetti, Jr., B. H. Adelson, R. M. Dodson, L. G. Ginger, and R. H. Baker, *J. Amer. Chem. Soc.*, **68**, 1229 (1946).

[3] E. Hayashi, *J. Pharm. Soc. Jap.*, **71**, 213 (1951).

[4] B. Brobański, *Ber.*, **69**, 1113 (1936).

[5] M. M. Robison and B. L. Robison, *J. Org. Chem.*, **23**, 1071 (1958).

[6] Analyses were by Huffman Microanalytical Laboratories, Wheatridge, Colo., and Eisai Research Laboratories, Tokyo, Japan. Melting points are uncorrected. Ultraviolet spectra were determined using a Beckman Model DU spectrophotometer. Infrared spectra were determined in potassium bromide disks with a Hitachi spectrophotometer Model EPI-2. Nmr spectra were determined in carbon tetrachloride with a Varian A-60 magnetic resonance spectrophotometer. All chemical shifts are given as τ values (tetramethylsilane as internal standard).

[7] A. Furst and C. J. Olsen, *ibid.*, **16**, 412 (1951).

[8] W. M. Lauer, R. T. Arnold, B. Tiffany, and J. Tinker, *J. Amer. Chem. Soc.*, **68**, 1268 (1946).

[9] M. Mason and C. P. Berg, *J. Biol. Chem.*, **188**, 783 (1951).

[10] J. M. Price and L. W. Dodge, *ibid.*, **223**, 699 (1956).