Benzylic Halogenation of Methylquinolines

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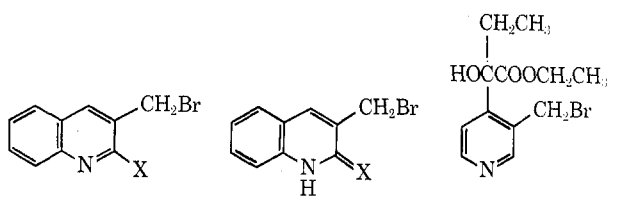
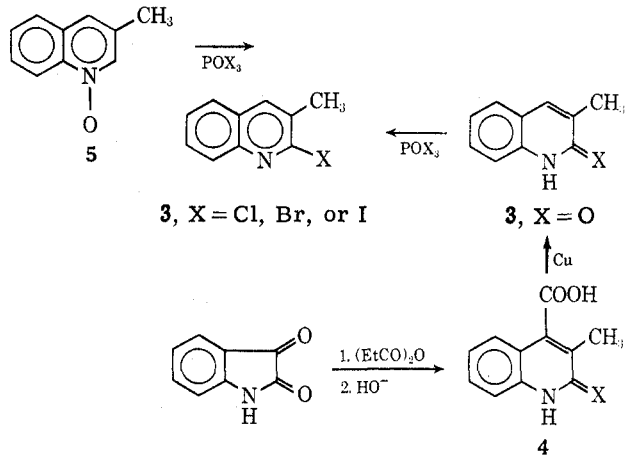
Benzylic halogenation by *N*-bromosuccinimide is a standard method of synthesis of bromomethyl aromatic compounds.[2] Thus, when a 2-substituted 3-bromomethylquinoline (**1**) and a 4-substituted 3-bromomethylpyridine (**2**) were needed for a synthetic approach[3a] to camptothecin,[3b] it was assumed that this reaction could be used with the corresponding methyl heterocycle. A literature survey described such halogenations of 2- and 4-methyl nitrogen heterocycles;[4] however, there was a disturbing lack of information about 3-methyl derivatives. Direct halogenation of 3-methylquinoline and β-picoline was reported to be unsuccessful.[5]



1, X = H, halogen **1**, X = O **2**

The halogenation of the 4-substituted β-picoline, β-picoline, and 3-methylquinoline gave no 3-bromomethyl derivative on treatment with a variety of bromination conditions. In each reaction it was evident that a salt was formed and apparently the salt failed to undergo benzylic halogenation. On this basis the preparation of **1** was attempted by benzylic halogenation of 2-halo-3-methylquinoline, since the 2-halo substituent should decrease the basicity of the nitrogen heterocycle and interfere with salt formation.[6]

The 2-halo-3-methylquinoline **3** was prepared by rearrangement of 3-methylquinoline 1-oxide[7] (**5**) or from the 3-methyl-2-quinoline prepared by the Pfitzinger reaction.[8-10] The 2-chloro and 2-bromo derivatives of **3** were prepared by using the appropriate phosphorus oxyhalide, and the 2-iodo derivative was prepared from the 2-chloro derivative by halogen exchange using sodium iodide in methyl ethyl ketone.



The halogenations of all the 2-substituted 3-methylquinolines (**3**, X = Cl, Br, I, or O) with *N*-bromosuccinimide were successful, giving good yields of 3-bromomethyl 2-substituted quinolines (**1**). These results strongly suggest that the decreased basicity of **3** (X = halogen or O) as compared with **3** (X = H) is necessary to allow successful benzylic bromination.

Experimental Section[11]

2-Hydroxy-3-methylcinchoninic Acid (**4**).—A mixture of 500 g (3.4 mol) of isatin and 885 g (6.8 mol) of propionic anhydride was stirred mechanically and heated under reflux for 2.5 hr. After this time the resulting orange solution was allowed to cool to room temperature and the solid was removed by filtration and washed well with ether. After drying, 556 g (81%) of 1-propionyl isatin, mp 140–141°, was obtained.

To a mechanically stirred mixture of 221 g (1.09 mol) of unpurified 1-propionylisatin in 3000 ml of water was added 90 g (2.25 mol) of sodium hydroxide pellets. The mixture was heated to boiling for 1 hr and subsequently charcoaled with 15 g of Norit A. After 10 min the mixture was filtered through Celite to afford a light yellow solution that was neutralized with 350 ml of 6 *N* HCl with mechanical stirring. The resultant yellow solid was removed by filtration, washed well with cold water, and then dried to constant weight at 100°. The bright yellow powder, **4**, mp 321–323° (lit.[8] mp 315–217°), weighed 103 g (46% conversion). From the filtrate was obtained 67 g of isatin, mp 204–205° (lit.[12] mp 197–200°). The yield of **4** based on consumed isatin was 81%.

3-Methyl-2-quinolone (**3**, **X = O**).—A mixture of 30 g (0.148 mol) of **4**, 6 g (0.094 mol) of copper powder, and 100 g of freshly distilled quinoline was stirred and heated for 5 hr at 235°. After this time 65 g of quinoline were removed by distillation, and on cooling crude **3** (X = O) precipitated. The solid was washed with petroleum ether (bp 30–60°), treated with Norit in isopropyl alcohol solution, and recrystallized from isopropyl alcohol to give 16 g (68%) of 3-methyl-2-quinolone (**3**, X = O), mp 238–240° (lit.[9] mp 234–235°).

2-Chloro-3-methylquinoline (**3**, **X = Cl**).—A mixture of 5.00 g (0.031 mol) of **3** (X = O) and 100 ml of phosphorus oxychloride ($POCl_3$) was stirred and heated under reflux for 2 hr. The hot reaction mixture was then slowly poured with stirring onto 400 g of crushed ice. The mixture was extracted with methylene chloride and this extract was dried over anhydrous K_2CO_3. After filtration and concentration, a red-brown oil was obtained which solidified upon cooling, and after recrystallization from hexane gave 4.9 g (88%) of **3** (X = Cl) as white crystals, mp 83–84° (lit.[9] mp 89–90°).

2-Chloro-3-methylquinoline (**3**, **X = Cl**).—To 200 ml of $POCl_3$ cooled in an ice bath was added 20.0 g (0.126 mol) of 3-methyl-

(1) NDEA Title IV Fellow, 1969–1971; UNH Dissertation Year Fellow, 1971–1972.

(2) W. Forest (Ed.), "New Methods of Preparative Organic Chemistry," Vol. III, Academic Press, New York, N. Y., 1964, p 151.

(3) (a) The general approach to the total synthesis of camptothecin was reported at the International Union of Pure and Applied Chemistry Meeting, Boston, Mass., Abstracts, XXII IUPAC, 1971, No. 163. (b) M. E. Wall, M. C. Wani, C. E. Cook, K. H. Palmer, A. T. McPhail, and G. H. Sim, *J. Amer. Chem. Soc.*, **88**, 3888 (1966).

(4) (a) B. R. Brown, D. L. Hammick, B. H. Thewlis, and P. J. Wolbridge, *J. Chem. Soc.*, 1369 (1953), and references cited therein; (b) M. Hasegawa, *Chem. Pharm. Bull.*, **1**, 47, 293 (1953); (c) B. Prijs, R. Gall, R. Hinderling, and H. Erlenmeyer, *Helv. Chim. Acta*, **37**, 90 (1954); (d) B. D. Mookherjee and E. M. Klaiber, *J. Org. Chem.*, **37**, 511 (1972).

(5) B. R. Brown, D. L. Hammick, and B. H. Thewlis, *J. Chem. Soc.*, 1145 (1951).

(6) P. T. Sullivan and S. J. Norton, *J. Med. Chem.*, **14**, 557 (1971).

(7) For example, see J. K. Lindquist, *J. Chem. Soc.*, 2816 (1953).

(8) H. Meyer, *Monatsh. Chem.*, **26**, 1322 (1905).

(9) G. Ornstein, *Chem. Ber.*, **40**, 1088 (1907).

(10) T. L. Jacobs, S. Winstein, G. B. Linden, J. H. Robson, E. F. Levy, and D. Seymour, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1956, p 456.

(11) All melting points were taken with a Mel-Temp apparatus and are uncorrected.

(12) C. S. Marvel and G. S. Hien, *Org. Syn.*, **5**, 71 (1925).

quinoline *N*-oxide[13] cautiously. The mixture was then heated under reflux for 15 min and poured slowly over crushed ice. The mixture was made strongly basic with a KOH solution. The aqueous layer was extracted with ether, and the ether extracts were dried (K_2CO_3) and concentrated to give a brown solid. This solid was dissolved in low-boiling petroleum ether and basic alumina was added. Stirring for 10 min followed by filtration gave a yellow filtrate which upon concentration gave 17.3 g (78%) of crude 2-chloro-3-methylquinoline (**3**, X = Cl). Recrystallization from hexane gave white needles, mp 82–84° (lit.[9] mp 89–90°).

2-Bromo-3-methylquinoline (3, X = Br).—A mixture of 5.00 g (0.031 mol) of **3** (X = O) and 12.70 g (0.045 mol) of phosphorus oxybromide was stirred at 140° for 3 hr. After this time the mixture was poured onto 200 g of crushed ice and subsequently extracted with both 600 ml of methylene chloride and water. When solution was complete, the layers were separated and the aqueous layer was extracted with 150 ml of methylene chloride. The combined organic layers were washed with 150 ml of water, dried ($MgSO_4$), filtered, and concentrated to yield **3** (X = Br) as a tan solid that weighed, after drying, 5.78 g (83%). The solid was recrystallized once from hexane to afford an analytical sample that melted at 96–97°: pmr (CF_3COOH) δ 8.42 (s, 1 H, 4-quin), 7.87–8.33 (m, 4 H, ArH), and 2.52 ppm (s, 3 H, CH_3).

Anal. Calcd for $C_{10}H_8BrN$: C, 54.07; H, 3.64; N, 6.31. Found: C, 54.41; H, 3.58; N, 6.36.

2-Chloro-3-methylquinoline Hydrochloride (3, X = Cl·HCl).—2-Chloro-3-methylquinoline (**3**, X = Cl) was taken up in ether and anhydrous HCl was bubbled into the solution until precipitation was complete. The solid was removed by filtration and dried to give **3** (X = Cl) hydrochloride: mp 215–218°; pmr ($CDCl_3$) δ 8.99 (s, 1 H, 4-quin), 9.63–7.61 (m, 4 H, ArH), and 2.74 ppm (s, 3 H, CH_3).

Anal. Calcd for $C_{10}H_9Cl_2N$: C, 56.11; H, 4.24; N, 6.54. Found: C, 56.34; H, 4.05; N, 6.61.

2-Iodo-3-methylquinoline (3, X = I).—To a stirred mixture of 24.0 g (0.112 mol) of **3** (X = Cl, HCl) in 600 ml of methyl ethyl ketone (MEK) was added 60 ml of a saturated aqueous solution of sodium iodide. The solution was heated under reflux for 24 hr. The solvent was removed by distillation, and excess water was added. The brown solid which precipitated was treated with saturated aqueous sodium bicarbonate and ether. The aqueous layer was extracted with chloroform and the combined organic phases were washed with aqueous sodium bisulfite, dried ($MgSO_4$), filtered, and concentrated to yield a light red oil that solidified upon the addition of hexane. Recrystallization of the solid from hexane gave 19.4 g (60%) of **3** (X = I) as long needles, mp 87–89°, pmr (CH_2Cl_2) δ 7.88–7.25 (m, 5 H, ArH) and 2.52 ppm (s, 3 H, CH_3).

Anal. Calcd for $C_{10}H_8IN$: C, 44.64; H, 3.00; N, 5.21. Found: C, 44.56; H, 2.82; N, 5.13.

2-Chloro-3-bromomethylquinoline (1, X = Cl).—To a solution of 14.7 g (0.082 mol) of **3** (X = Cl) in 300 ml of dry CCl_4 was added 14.8 g (0.082 mol) of *N*-bromosuccinimide (NBS) along with 0.1 g of dibenzoyl peroxide. The mixture was heated with a 100-W lamp and reflux was continued for 11 hr. After this time the mixture was filtered, and the solvent was evaporated to afford 20.0 g (95%) of a white solid, which on recrystallization from hexane gave 1 (X = Cl) as white needles, mp 121–125°, pmr ($CDCl_3$) δ 8.21–7.54 (m, 5 H, quin) and 4.69 ppm (s, 2 H, CH_2).

Anal. Calcd for $C_{10}H_7BrClN$: C, 46.83; H, 2.75; N, 5.46. Found: C, 46.82; H, 2.90; N, 5.42.

2-Bromo-3-bromomethylquinoline (1, X = Br).—Using the procedure above, 14.22 g (0.064 mol) of **3** (X = Br) and 11.39 g (0.064 mol) of NBS gave 18.65 g (93%) of 1 (X = Br), mp 136–138°, pmr ($CDCl_3$) δ 8.50–7.48 (m, 5 H, ArH) and 4.91 ppm (s, 2 H, CH_2).

Anal. Calcd for $C_{10}H_7Br_2N$: C, 39.90; H, 2.35; N, 4.65. Found: C, 40.20; H, 2.27; N, 4.83.

2-Iodo-3-bromomethylquinoline (1, X = I).—The method above was used to convert 19.4 g (0.072 mol) of **3** (X = I) and 13.3 g (0.072 mol) of NBS to 11.0 g (45%) of 1 (X = I), mp 125–128°, pmr ($CDCl_3$) δ 8.32–7.56 (m, 5 H, quin) and 4.72 ppm (s, 2 H, CH_2).

Anal. Calcd for $C_{10}H_7BrIN$: C, 34.52; H, 2.03; N, 4.02. Found: C, 34.82; H, 2.03; N, 3.89.

(13) O. Buchardt, J. Becker, and C. Lohse, *Acta Chem. Scand.*, **19**, 1120 (1965).

3-Bromomethyl-2-quinolone (1, X = O).—The method above converted 5.0 g (0.031 mol) of **3** (X = O) and 5.6 g (0.031 mol) of NBS to 5.4 g (72%) of 1 (X = O), mp 218–219°, pmr (CF_3COOH) δ 8.72–7.68 (m, 4 H, quin) and 4.74 ppm (s, 2 H, CH_2).

Anal. Calcd for $C_{10}H_8BrNO$: C, 50.45; H, 3.38; N, 5.88. Found: C, 50.17; H, 3.34; N, 5.85.

Registry No.—**1** (X = Cl), 35740-82-0; **1** (X = Br), 35740-83-1; **1** (X = I), 35740-84-2; **1** (X = O), 35740-85-3; **3** (X = Br), 35740-86-4; **3** (X = Cl) HCl, 35740-87-5; **3** (X = I), 35820-73-6; 1-propionylisatin, 17529-69-0.

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Tetraalkylammonium Trifluoromethanesulfonates as Supporting Electrolytes[1]

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The renewed interest in synthetic organic electrochemistry is derived in part from the increased use of nonaqueous and, in particular, aprotic solvents. The use of such solvents is limited, however, by the availability of supporting electrolytes which ionize to give solutions of sufficiently low resistance. This becomes particularly important in bulk electrolyses in which a high solution resistance results in the generation of considerable heat.

Among the most widely used supporting electrolytes in solvents such as acetonitrile, dimethylformamide, methylene dichloride, and tetrahydrofuran are the tetraalkylammonium salts. Their ready availability, ease of purification, and the potential range over which they can be used makes them ideally suited for a variety of electrochemical uses. While the cation determines the solubility, the choice of a specific tetraalkylammonium salt is governed principally by the chemistry of the anion. Unfortunately, the choice of anions is limited. The ease of oxidation of halides to the corresponding halogens, coupled with the high nucleophilicity of the halide ion, severely limits their use as supporting electrolytes. Acetates have been suggested as useful supporting electrolytes, since upon oxidation only ethane and carbon dioxide are generated (*via* the Kolbe reaction). However, it was not found possible to prepare tetraalkylammonium acetates free of acetic acid. House[3] has come to the conclusion that the tetraalkylammonium fluoroborates are the supporting electrolytes of choice, since they are readily prepared and purified, and exhibit the necessary electrochemical properties. Thus, the tetra-*n*-butylammonium salt shows a limiting reduction potential (at mercury) more cathodic than 2.7 V (all potentials are quoted against the sat-

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(2) NIH Predoctoral Fellow.

(3) H. O. House, E. Feng, and N. P. Peet, *J. Org. Chem.*, **36**, 2371 (1971).