Bromo-6-methoxy-8-aminoquinolines: Preparation and ^{13}C-NMR Assignments

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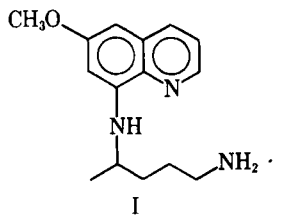
Abstract □ Preparation of all possible monobromo-6-methoxy-8-aminoquinolines is reported. These materials provided an opportunity to assess the effect of bromine substitution on ^{13}C-NMR chemical shift patterns. An explanation of the isomerization of 5-bromo-6-methoxy-8-acetamidoquinoline to 7-bromo-6-methoxy-8-aminoquinoline during hydrolysis is presented.

Keyphrases □ Bromine substitution—^{13}C-NMR chemical shifts, bromoaminoquinoline isomerization □ Bromoaminoquinolines—^{13}C-NMR chemical shifts, isomerization, bromine substitution

Various isomers of bromo-6-methoxy-8-aminoquinoline were required as intermediates in connection with syntheses of deuterated derivatives of the antimalarial drug primaquine (I) (1). Primaquine, 6-methoxy-8-(4-amino-1-methylbutyl)-aminoquinoline, is used for the radical cure of vivax malaria and, in combination with other antimalarial drugs such as chloroquine, for prophylaxis in endemic areas (2).

An obvious route of preparation of these bromoaminoquinolines should involve the reduction of the corresponding bromo nitro compounds. Examination of the literature showed that while 3-bromo-6-methoxy-8-aminoquinoline had indeed been prepared by this method (3), the 5-bromo derivative had been obtained by the bromination of 6-methoxy-8-acetaminoquinoline and the subsequent hydrolysis of the acetyl group (4). Reduction of 5-bromo-6-methoxy-8-nitroquinoline gave poor yields of the amino compound (4). The 7-bromo compound was prepared by a rather unusual transformation of the 5-bromo derivative in refluxing 10% hydrobromic acid (4). The 2- and 4-bromo derivatives have not been previously reported.

The present work describes the preparation of these two unknown compounds as well as a study of the ^{1}H- and ^{13}C-NMR spectra of all these monobromo and the 5,7-dibromo-6-methoxy-8-aminoquinolines. In addition we have reexamined the unusual transformation of the 5-bromo isomer into the 7-bromo material. The reduction of the various bromo-8-nitroquinolines was examined to develop an efficient nitro reduction without accompanying debromination.



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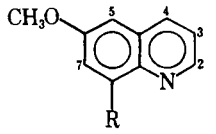
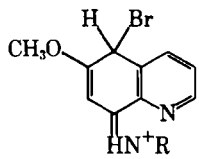


II: R = NO_2
III: R = NO_2, 2-Br
IV: R = NO_2, 3-Br
V: R = NO_2, 4-Br
VI: R = NH_2
VII: R = NH_2, 2-Br
VIII: R = NH_2, 3-Br
IX: R = NH_2, 4-Br
X: R = NH_2, 5-Br
XI: R = NH_2, 7-Br
XII: R = NH_2, 5-Br, 7-Br
XIII: R = $NHCOCH_3$, 2-Br



EXPERIMENTAL SECTION[1]

6-Methoxy-8-nitroquinoline (II)—Nitrobenzene (50 mL) was added slowly with stirring to fuming sulfuric acid (30% sulfur trioxide, reagent grade, 150 mL) at room temperature. The mixture was stirred at 60–65°C for ~8 h (until a drop of the mixture was found to be miscible when poured into water). The "sulfo mix" (5) was then added slowly with vigorous stirring to a paste of 2-nitro-4-methoxyaniline (85 g, 0.5 mol), glycerol (230 g, 2.5 mol), and water (230 mL). The resulting mixture was heated gradually in an oil bath to 130–135°C and kept at that temperature for 6 h. The color of the mixture changed from orange-red to dark brown. The mixture was allowed to cool, was poured into crushed ice, and then neutralized with 10% NaOH. The solid material was removed by filtration, washed with water, and dried. Recrystallization from chloroform gave 64.0 g (63% yield) of II as straw-colored crystals, mp 158–160°C [lit. (6) mp 158–160°C].

2-Bromo-6-methoxy-8-nitroquinoline (III)—1-Methyl-6-methoxy-8-nitroquinoline-2-one (7) (7.0 g, 0.03 mol) and phosphorus oxybromide (17.3 g, 0.113 mol) were heated at 120–125°C for 6 h. The mixture was cooled, poured into crushed ice, and neutralized with excess ammonium hydroxide. The pale-yellow solid was removed by filtration, washed, and dried. Recrystallization from ethanol gave 6.7 g (80% yield) of III as pale-yellow needles, mp 228–230°C.

Anal.—Calc. for $C_{10}H_7BrN_2O_3$: C, 42.23; H, 2.49; N, 9.89. Found: C, 42.08; H, 2.60; N, 9.90.

4-Bromo-6-methoxy-8-nitroquinoline (V)—In a similar manner, 4-hydroxy-6-methoxy-8-nitroquinoline (3.3 g, 0.015 mol) (8) was treated with phosphorus oxybromide (5.8 g, 0.02 mol) in quinoline to give V as yellow crystals (chloroform), 3.1 g (64% yield), mp 191–193°C.

Anal.—Calc. for $C_{10}H_7BrN_2O_3$: C, 42.23; H, 2.49; N, 9.89. Found: C, 42.52; H, 2.70; N, 10.20.

General Procedure for Nitro Group Reduction—The nitro compound (~10 mmol) was dissolved in concentrated hydrochloric acid (~30 mL), and the solution was cooled in an ice-salt bath. The ice-cold solution was added slowly with vigorous stirring to an ice-cold solution of stannous chloride (anhydrous, 98%, ~10 g) in 30 mL of concentrated hydrochloric acid. The resulting mixture was stirred at 0–5°C for 1 h and then poured into crushed ice. The mixture was made alkaline with concentrated ammonium hydroxide and extracted with ethyl acetate (5 × 50 mL). The combined organic layers were washed

[1] The ^{1}H-NMR spectra (90 MHz) were recorded on a Varian EM 390 spectrometer using Me_2SO-d_6 as solvent and tetramethylsilane as an internal standard. The ^{13}C-NMR spectra (15.03 MHz) were recorded on a JEOL-FX60 FT spectrometer using Me_2SO-d_6 as solvent and tetramethylsilane as internal standard. NMR data are reported as δ values (ppm). Mass spectra were obtained using a Finnigan 3200 GC–MS coupled to an INCOS data system. HPLC was accomplished on a μ-Bondapak C_{18} reverse-phase column and a mobile phase of 2.2 g of potassium dihydrogen phosphate, 3.3 g of potassium hydrogen phosphate, 1.2 L of distilled water, and 2.8 L of HPLC-quality methanol. TLC was accomplished on silica G (254) precoated plates; GC was done on base-deactivated 3% OV-17 packed on a 183 m × 0.6 cm o.d. glass column with flame-ionization detection on a Beckman GC-65, with a flow rate of 30 mL/min of nitrogen. All compounds gave satisfactory elemental analyses. Starting compounds were prepared by literature procedures or purchased from Aldrich unless otherwise noted.

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twice with water and once with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Recrystallization was from ethanol.

2-Bromo-6-methoxy-8-aminoquinoline (VII)—The aforementioned 2-bromo-6-methoxy-8-nitroquinoline (4.2 g, 0.015 mol) dissolved in concentrated hydrochloric acid (25 mL) was added to stannous chloride (15 g, 0.066 mol) dissolved in concentrated hydrochloric acid (25 mL). This afforded 3.44 g (90% yield) of colorless crystals, mp 88–90°C. ^{1}H-NMR: δ 8.00 (1, d, J = 8 Hz, H-4), 7.50 (1, d, J = 8 Hz, H-3), 6.51 (2, br s, H-5 and H-7), and 3.83 ppm (3, s, OCH_3); ^{13}C-NMR: 159.2 (s, C-6), 145.5 (s, C-8), 138.1 (d, C-4), 134.9 and 134.7 (s, C-2 and C-8), 128.8 (s, C-4a), 125.8 (d, C-3), 101.0 (d, C-7), 93.8 (d, C-5), and 55.1 ppm (q, OCH_3).

Anal.—Calc. for $C_{10}H_9BrN_2O$: C, 47.45; H, 3.58; N, 11.07. Found: C, 47.54; H, 3.68; N, 11.27.

3-Bromo-6-methoxy-8-aminoquinoline (VIII)—3-Bromo-6-methoxy-8-nitroquinoline (5.6 g, 0.02 mol) dissolved in concentrated hydrochloric acid (30 mL) was added to stannous chloride (20 g, 0.089 mol) dissolved in concentrated hydrochloric acid (30 mL). This afforded 4.57 g (90% yield) of colorless needles, mp 95–96°C [lit. (3) mp 95–96°C]. ^{1}H-NMR: δ 8.58 (1, d, J = 2 Hz, H-2), 8.31 (1, d, J = 2 Hz, H-4), 6.67 (1, d, J = 2 Hz, H-5 or H-7), 6.55 (1, d, J = 2 Hz, H-5 or H-7), and 3.91 ppm (3, s, OCH_3); ^{13}C-NMR: 159.8 (s, C-6), 146.3 (s, C-8), 144.6 (d, C-2), 135.7 (d, C-4), 132.8 (s, C-8a), 131.1 (s, C-4a), 117.5 (s, C-3), 100.4 (d, C-7), 93.0 (d, C-5), and 55.1 ppm (q, OCH_3).

4-Bromo-6-methoxy-8-aminoquinoline (IX)—The aforementioned 4-bromo-6-methoxy-8-nitroquinoline (4.2 g, 0.015 mol) dissolved in concentrated hydrochloric acid (25 mL) was added to stannous chloride (15 g, 0.066 mol) dissolved in concentrated hydrochloric acid (25 mL). The resulting mixture was stirred at 0–5°C for 1 h, poured into crushed ice, and neutralized to pH 8–9 with concentrated ammonium hydroxide. A solid (4-bromo-6-methoxy-8-aminoquinoline hydrochloride) separated and was removed by filtration and recrystallized from ethanol. This afforded 3.3 g (76% yield) of IX as pale-yellow needles, mp 98–100°C. ^{1}H-NMR: δ 8.35 (1, d, J = 5 Hz, H-2), 7.73 (1, d, J = 5 Hz, H-3), 6.63 (2, br s, H-5 and H-7), and 3.90 ppm (3, s, OCH_3); ^{13}C-NMR: 160.1 (s, C-6), 147.2 (s, C-8), 143.8 (d, C-2), 135.2 (s, C-8a), 131.3 (s, C-4), 129.0 (s, C-4a), 125.7 (d, C-3), 100.2 (d, C-7), 92.1 (d, C-5), and 55.1 ppm (q, OCH_3).

Anal.—Calc. for $C_{10}H_9BrN_2O$·HCl: C, 41.48; H, 3.48; N, 9.67. Found: C, 41.00; H, 3.00; N, 9.64.

5-Bromo-6-methoxy-8-aminoquinoline (X)—5-Bromo-6-methoxy-8-nitroquinoline (9) (1.5 g, 0.005 mol) dissolved in concentrated hydrochloric acid (10 mL) was added to stannous chloride (5 g, 0.022 mol) dissolved in concentrated hydrochloric acid (10 mL). This afforded 1.16 g (92% yield) of colorless needles, mp 152–153°C [lit. (4) mp 153–154°C]. ^{1}H-NMR: δ 8.73 (1, dd, $J_{2,3}$ = 5 Hz, $J_{2,4}$ = 2 Hz, H-2), 8.37 (1, dd, $J_{4,2}$ = 2 Hz, $J_{4,3}$ = 8 Hz, H-4), 7.63 (1, dd, $J_{3,2}$ = 5 Hz, $J_{3,4}$ = 8 Hz, H-3), 7.03 (1, s, H-7), and 3.91 ppm (3, s, OCH_3); ^{13}C-NMR: 155.0 (s, C-6), 146.7 (s, C-8), 144.8 (d, C-2), 134.0 (s, C-8a), 133.2 (d, C-4), 128.0 (s, C-4a), 123.1 (d, C-3), 96.3 (d, C-7), 89.9 (s, C-5), and 56.4 ppm (q, OCH_3).

5-Bromo-6-methoxy-8-acetaminoquinoline (XIII)—6-Methoxy-8-acetaminoquinoline (3.2 g, 0.015 mol) was dissolved in glacial acetic acid (30 mL). Pyridinium hydrobromide perbromide (4.8 g, 0.015 mol) was added slowly, and the mixture was stirred at room temperature for 2 h. The solution was cooled in an ice bath and neutralized with excess concentrated ammonium hydroxide. The precipitate was removed by filtration and washed with ice-cold water; the dried material was recrystallized from ethyl alcohol to give 3.4 g (77% yield) of colorless needles, mp 167–169°C [lit. (4) mp 167–169°C].

7-Bromo-6-methoxy-8-aminoquinoline (XI)—The method of Lauer *et al.* (4) was used to give material with mp 110–112°C [lit. (4) mp 111.5–112.5°C]. ^{1}H-NMR: δ 8.63 (1, dd, $J_{2,3}$ = 5 Hz, $J_{2,4}$ = 2 Hz, H-2), 8.13 (1, dd, $J_{4,2}$ = 2 Hz, $J_{4,3}$ = 8 Hz, H-4), 7.47 (1, dd, $J_{3,2}$ = 5 Hz, $J_{3,4}$ = 8 Hz, H-3), 6.83 (s, H-5), and 4.00 ppm (3, s, OCH_3); ^{13}C-NMR: 154.2 (s, C-6), 145.5 (d, C-2), 143.8 (s, C-8), 134.9 (d, C-4), 134.1 (s, C-8a), 128.1 (s, C-4a), 122.3 (d, C-3), 95.6 (s, C-7), 93.5 (d, C-5), and 56.1 ppm (q, OCH_3).

5,7-Dibromo-6-methoxy-8-aminoquinoline (XII)—The method of Lauer *et al.* (4) was used to give off-white crystals from ethanol, mp 86–87°C [lit. (4) mp 87–88°C]. ^{1}H-NMR: δ 8.77 (1, dd, $J_{2,3}$ = 5 Hz, $J_{2,4}$ = 2 Hz, H-2), 8.33 (1, dd, $J_{4,2}$ = 2 Hz, $J_{4,3}$ = 8 Hz, H-4), 7.63 (1, dd, $J_{3,2}$ = 5 Hz, $J_{3,4}$ = 8 Hz, H-3), and 3.91 ppm (3, s, OCH_3); ^{13}C-NMR: 152.6 (s, C-6), 147.7 (d, C-2), 144.4 (s, C-8), 135.3 (s, C-8a), 134.6 (d, C-4), 126.7 (s, C-4a), 123.6 (d, C-3), 99.1 (s, C-7), 98.0 (s, C-5), and 60.5 ppm (q, OCH_3).

RESULTS AND DISCUSSION

2-Bromo-6-methoxy-8-nitroquinoline (III) was obtained by treatment of 1-methyl-6-methoxy-8-nitroquinoline-2-one with phosphorus oxybromide. The quinoline-2-one derivative was prepared in two steps from 6-methoxy-8-nitroquinoline (7). 6-Methoxy-8-nitroquinoline (II) may be prepared in good yield by the use of "sulfo mix" (5) in place of arsenic pentoxide (10), the duration of reaction being shorter and the workup of the reaction being comparatively easier. 4-Bromo-6-methoxy-8-aminoquinoline (V) was made from the corresponding 4-hydroxy compound (8).

The unexpected result of isomerization of the 5-bromo isomer into the 7-bromo isomer, which was reported previously (4), was confirmed; the spectral data clearly distinguish the 5- and 7-bromo isomers. A clue to the explanation of this result is the observed rapid exchange of the hydrogen atoms at both C-5 and C-7. This suggests that protonation occurs at C-5 of the highly activated ring to form an iminium intermediate (XIV). Nucleophilic attack of this material by bromide ion would generate 6-methoxy-8-acetaminoquinoline and molecular bromine. Subsequent bromination of the 6-methoxy-8-acetaminoquinoline may proceed at C-5 to regenerate the starting bromo isomer, or alternatively, since C-7 is also activated, bromination may take place at C-7 to generate the isomeric product. Since protonation seems to be favored at C-5, this process should ultimately transform all of the 5-bromo derivative to the 7-bromo substance (4).

With all the bromo-8-nitroquinolines in hand, we turned our attention to the formation of the 8-aminoquinolines. The reduction of the nitro to an amino group caused several problems. It was found that use of either 10% palladium on charcoal or Raney Nickel-catalyzed reduction with hydrazine hydrate in refluxing ethanol resulted in considerable hydrogenolysis of the bromo group. Catalytic hydrogenation with Raney Nickel (50 psi, room temperature) also gave inconsistent results with the bromonitro compounds. Hence, a detailed study was undertaken to find the best method for the reduction of the nitro group without accompanying hydrogenolysis of the bromo substituent. The reduction was attempted under three different pH conditions (neutral, basic, and acidic), and the course of the reduction was monitored by GC; and bromoaminoquinolines were well separated from 6-methoxy-8-aminoquinoline and the starting nitro derivatives. It was found that reduction with stannous chloride in concentrated hydrochloric acid at low temperature for a period of 1 h gave the best results in all the cases examined. Longer reaction times resulted in extensive hydrogenolysis especially in the case of the 2- and 5-bromo derivatives. Hydrazine hydrate reduction catalyzed by Raney Nickel at room temperature gave satisfactory results only in the case of 3- and 4-bromo compounds. Raney Nickel-catalyzed reduction with hydrogen gas at 50 psi and room temperature for ≥6 h gave fair to poor yields of bromoamino compounds. Shorter duration of hydrogenation resulted in incomplete reduction and the recovery of the starting bromonitro compounds. Thus, the stannous chloride–hydrochloric acid method was found to be the best, and yields ranging from 85 to 95% could be achieved in all the cases. 5,7-Dibromo-6-methoxy-8-aminoquinoline (XII) was prepared as reported earlier (4).

The ^{1}H-NMR data of all these compounds are readily assigned by simple chemical-shift theory and coupling patterns. Since little data is available concerning the effects of bromine on carbon resonances, the complete assignments of the ^{13}C-NMR data were also examined.

The use of long-range coupling patterns of quinoline derivatives can be used to confirm assignments (11). The fully coupled ^{13}C-NMR spectra of 6-methoxy-8-aminoquinoline (III) readily confirms those assignments listed. The protons of the amino group also show long-range coupling to C-7 just like that observed for primaquine (12). This coupling can be removed by exchange using deuterium oxide, and the C-7 signal appears as the expected doublet of doublets (J = 158.2, 5.9 Hz). The carbon atom at the 5-position, on the other hand, remains unchanged after exchange [dt (J = 162.1, 4.9 Hz)]. The carbon atom at the 4a-position appears as a doublet (J = 6.8 Hz), C-6 as a quartet (J = 3.9 Hz), C-8 as a singlet, and C-8a as a complex multiplet. The coupling patterns for C-2, C-3, and C-4 appear just as for quinoline (11).

The assignments of the signals for the various bromo derivatives (VII–XI) were made using chemical-shift theory, single-frequency off-resonance decoupling, and long-range coupling patterns in the proton-coupled spectrum. Introduction of a bromine substituent in benzenes causes a shielding of the substituted carbon (5–6 ppm) and a deshielding of the *ortho* carbon (3–4 ppm) (13). The *meta* and *para* effects are much smaller. This general trend appears to hold for the substituted carbon and the protonated carbons of the bromoquinolines as well. The shift of the nonprotonated *ortho* carbon, on the other hand, is in the opposite direction (shielded) by several ppm. It is also interesting to compare the 5,7-dibromo derivative (XII) with VI, X, and XI. The C-7 signal in XII appears at nearly the same place as in VI, whereas C-5 is deshielded by ~5 ppm. Also, C-5 in X appears near 90 ppm, while in XII it appears at 98 ppm, showing that introduction of a bromine at C-7 (*meta* position) causes a deshielding effect of ~8 ppm. Comparison of C-7 in XII and XI shows a deshielding effect of only ~2 ppm. Clearly, we can conclude that one must be careful in drawing any generalizations with bromine substituents, particularly in highly substituted systems.

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Determination of the Structure of a Synthetic Impurity in Guaifenesin: Modification of a High-Performance Liquid Chromatographic Method for Phenylephrine Hydrochloride, Phenylpropanolamine Hydrochloride, Guaifenesin, and Sodium Benzoate in Dosage Forms

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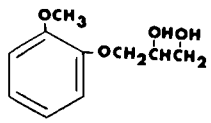
Received October 13, 1983, from the *Analytical Chemistry Division, Norwich Eaton Pharmaceuticals, Inc., Norwich, NY 13815.* Accepted for publication March 12, 1984.

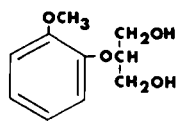
Abstract □ An impurity present in all commercial guaifenesin-containing dosage forms examined was isolated and identified as 2-(2-methoxyphenoxy)1,3-propanediol (VI). The eluant of a previously developed stability-indicating liquid chromatographic method for phenylephrine hydrochloride (I), phenylpropanolamine hydrochloride (II), and guaifenesin (III) was modified to yield a better separation between phenylpropanolamine and the impurity. The method was expanded to include sodium benzoate (IV), a preservative found in some liquid formulations.

Keyphrases □ Guaifenesin—synthetic impurity, HPLC with phenylephrine hydrochloride, phenylpropanolamine hydrochloride, and sodium benzoate

A stability-indicating reverse-phase high-performance liquid chromatographic (HPLC) method for phenylephrine hydrochloride (I), phenylpropanolamine hydrochloride (II), and guaifenesin (III), primarily in capsule formulations, was recently presented (1). However, on further examination of a wide variety of capsule, tablet, and liquid formulations from various manufacturers, it became evident that all chromatograms of products containing III (and even standard III solutions) yielded an impurity that eluted immediately following the II peak. In early method development work involving the capsule formulations, the peak area of this III impurity was only slightly more than 2% of the area of II (~0.2% of the III area) and barely discernable in the tail of the II peak (*cf.* Fig. 2 of Ref. 1). The separation was sufficient to yield good analytical data. However, impurity peak areas were later observed in other commercial formulations that were >20% of the area of the II peak. Because of the relatively large amount of the III impurity in some formulations, the ubiquitous nature of the impurity, and the danger of loss of resolution between II and the impurity for less efficient columns, both elucidation of the impurity structure and modification of the chromatographic eluant system to yield better resolution between II and the impurity were sought.



III



VI

EXPERIMENTAL SECTION

Reagents and Chemicals—All reagents and chemicals were ACS, USP or NF quality and were used without further purification. Compounds I, II, and III were used as received[1].

2-(2-Methoxyphenoxy)-1,3-propanediol (VI) was synthesized according to a literature procedure (2). Recrystallization from ethyl acetate–hexane, yielded a white powder, mp 62–64°C [lit. (2) mp 61–62°C]. IR (KBr): 3325 (O—H), 3041 (ArC—H), 3000–2850 (aliphatic C—H), 2837 (methoxy C—H), 1600–1450 (Ar deformations), 1240 and 1100–1000 (C—O), and 750 cm^{-1} (1,2-substituted Ar ring C—H, out of plane deformation); ^{1}H-NMR (acetone-d_6): δ 7.07 (ArH), 4.25 (—OCH), 3.87 (—OCH_3) and 3.85 ppm (—CH_2OH).

The *para* isomer of III, 3-(4-methoxyphenoxy)-1,2-propanediol, was pre-

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