flow rate was 1.2 liters/h. The IR spectra of suspensions of the compounds in hexachlorobutadiene and mineral oil were recorded with a UR-20 spectrometer. The PMR spectra of solutions in deuterochloroform were recorded with a Varian FT80A spectrometer (80 MHz) with hexamethyldisiloxane as the internal standard.

Typical Method for the Hydroxyethylamination of 1,5-Diketones I-III and VIII-X and Cyclic β-Ketols IV-VII. A 150-ml autoclave was charged with 0.05 mole of oxo compound I-X, 0.05 mole of ethanolamine, 80 ml of methanol, and the catalyst (10% of the mass of the starting oxo compound). The initial hydrogen pressure was 1.013 hPa, and the temperature was 100°C. When hydrogen absorption had ceased (0.1 mole for XI-XVI and 0.05 mole for XIX; H_2 absorption was not observed for XVII and XVIII) (after 7-10 h), the catalyst was removed by filtration. Bases XI and XVI-XVIII, which were obtained as crystalline precipitates when the hydrogenation products were evaporated, were recrystallized from methanol. Compounds XII-XV and XIX were obtained by vacuum distillation of the corresponding hydrogenation products. Base XIX crystallized on standing. The characteristics of the synthesized compounds are presented in Table 2.

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AROMATIC CHLORINATION AND IODINATION OF 8-METHYLQUINOLINE. BENZYL BROMINATION OF 5-HALO-8-METHYLQUINOLINES

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5-Chloro- and 5-iodo-8-methylquinoline were obtained by chlorination or iodination of 8-methylquinoline with chlorine or iodine in concentrated sulfuric acid in the presence of silver sulfate. 5-Fluoro-8-methylquinoline was synthesized from 5-amino-8-methylquinoline. 5-Chloro-, 5-bromo-, and 5-fluoro-8-methylquinoline were converted to the corresponding 5-halo-8-(bromomethyl)quinolines by bromination with N-bromosuccinimide. Partial displacement of iodine by bromine to give a mixture of 5-bromo- and 5-iodo-8-(bromomethyl)quinoline occurs in the analogous bromination of 5-iodo-8-methylquinoline.

Numerous studies have been devoted to the halogenation of various quinoline derivatives [1]. However, insufficient study has been devoted to halo-substituted (in the benzene part of the molecule) 8-methylquinolines. Only the synthesis of 5-bromo-8-methylquinoline has been described [2], and this compound was obtained only recently by the direct bromination of 8-methylquinoline [3]. The study of compounds of this class is of definite interest, since they can be used for the preparation of some biologically active compounds, such as monoamine oxidase inhibitors.

In the present research we synthesized 5-chloro- and 5-iodo-8-methylquinolines (Ia, b), as well as 5-fluoro-8-methylquinoline (Ic), for the first time and studied the benzyl bromination of 5-halo-8-methylquinolines (Ia-d).

Aromatic halogenation under the influence of halonium ions [4], which has been successfully used for the halogenation of quinoline [5-7], was used for the chlorination and iodina-

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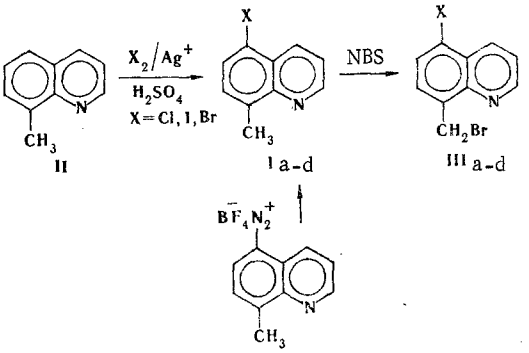

I, III a X=Cl, b X=I, c X=F, d X=Br

tion of 8-methylquinoline (II). Halogenation was carried out with chlorine and iodine in concentrated sulfuric acid in the presence of silver sulfate at room temperature, as in the bromination of 8-methylquinoline [3]. Derivatives Ia, b are formed in high yields under these conditions. Iodination proceeds considerably more slowly than chlorination and bromination, but the product is obtained in virtually quantitative yield. Substitution takes place chiefly in the 5 position under these conditions. The 8-methyl group facilitates substitution significantly; thus the iodination of quinoline in the 5 position requires considerably more severe conditions (150-200°C) [7].

7-Chloro-8-methylquinoline (no more than 2% of the sum of the chlorination products) was detected in the reaction mixture after separation of the principal chlorination product by gas–liquid chromatography (GLC). Thus, in addition to substitution in the 5 position, a small degree of substitution in the 7 position is also observed in the chlorination of 8-methylquinoline, and this indicates a certain amount of activation of the 7 position in quinoline by the methyl group; this position is generally not inclined to undergo electrophilic substitution [8].

The positions of the halogen atom in chloro- and iodo-substituted Ia, b were confirmed by their conversion to 5-cyano-8-methylquinoline, the structure of which was established unambiguously in [3].

Upon the whole, the direct halogenation of 8-methylquinoline in the presence of the silver ion can serve as a preparative method in the synthesis of halo derivatives of quinoline.

5-Fluoro-8-methylquinoline (Ic) was obtained in 63% yield via the Balz–Schiemann reaction from 5-amino-8-methylquinoline [9] by a procedure similar to that used to obtain 5-fluoroquinoline [10, 11].

5-Halo-substituted Ia, c, d are converted smoothly to the corresponding 8-bromomethyl derivatives IIIa, c, d by bromination with N-bromosuccinimide (NBS). The bromination of 5-iodo-8-methylquinoline (Ib) is accompanied by the liberation of elementary iodine. Two sets of resonance signals, one of which belongs to 5-iodo-8-(bromomethyl)quinoline (IIIb), the other of which belongs to 5-bromo-8-(bromomethyl)quinoline (IIId), are observed in the PMR spectrum of the product of benzyl bromination of Ib with an equimolar amount of NBS. The ratio of the reaction products of the mixture was 1:1, which corresponds to the results of elementary analysis. Thus partial displacement of iodine by bromine to give dibromide IIId occurs in the bromination of 5-iodo-8-methylquinoline; the reaction cannot be stopped at the step involving the formation of iodo derivative IIIb. The reaction mixture obtained could not be separated by crystallization, sublimation, column chromatography, thin-layer chromatography (TLC), and gas-liquid chromatography (GLC) under the conditions that we used (see the experimental section). Complete replacement of iodine by bromine occurs when two equivalents of NBS are used: Only IIId, which was also isolated preparatively, was detected in the reaction mixture by PMR spectroscopy. Instances of such displacement of an aromatically bonded iodine atom in the benzyl bromination of aromatic compounds with NBS are evidently extremely rare: In particular, only 2-iodo-3-(bromomethyl)quinoline was obtained in the bromination of 2-iodo-3-methylquinoline [12]. Products of iodine exchange also were not detected in the benzyl bromination of p-iodotoluene with NBS [13]. However, displacement of iodine by bromine or chlorine, as well as displacement of bromine by chlorine, was noted in the halogenation of halothiophenes with N-bromo- and N-chlorosuccinimide [14].

EXPERIMENTAL

The PMR spectra of solutions of the compounds in $CDCl_3$ were obtained with a Tesla BS-567 spectrometer, with tetramethylsilane as the internal standard. Chromatographic analysis of the products of chlorination of 8-methylquinoline was accomplished with an LKhM-8-MD chromatograph with a 1000 × 2 cm column packed with PEG-4000 on Celite; the temperature was 150-200°C, and the carrier gas was helium. The following systems were used for TLC on Silufol UV-254: benzene–ethyl acetate–acetic acid (100:50:1) (A), chloroform–methanol (50:1) (B), acetonitrile–25% NH_4OH (9:1) (C), and acetonitrile–25% NH_4OH (6:1) (D).

5-Chloro-8-methylquinoline (Ia). A stream of chlorine was passed through a solution of 11 g (0.035 mole) of silver sulfate and 9.4 g (0.066 mole) of 8-methylquinoline in 50 ml of concentrated sulfuric acid at ∿20°C until the starting 8-methylquinoline vanished (8 h), after which another 1 g of silver sulfate was added, and the mixture was maintained at room temperature for 20 h. It was then poured into 800 ml of water, and the silver chloride [11.2 g (100%)] was separated. The filtrate was made alkaline with 45% potassium hydroxide and allowed to stand overnight. The precipitate was removed by filtration and extracted with ether to give 10.6 g (90%) of quinoline Ia (initially as an oil, which crystallized on standing) with mp 31-32°C (from heptane–ether). The product was homogeneous in system A. Found: C 67.4; H 4.6; Cl 20.1; N 7.9%. $C_{10}H_8ClN$. Calculated: C 67.7; H 4.5; Cl 20.0; N 7.9%. The picrate had mp 182-185°C (from methanol). Found: Cl 8.8; N 13.9%. $C_{10}H_8ClN \cdot C_6H_3N_7O_9$. Calculated: Cl 8.7; N 13.8%. The 2,4,6-trinitrobenzenesulfonate had mp 264-265°C (from methanol). Found: Cl 7.5; N 12.0; S 6.8%. $C_{10}H_8ClN \cdot C_6H_3N_3O_9S$. Calculated: Cl 7.5; N 12.0; S 6.8%. In a similar experiment with 9.4 g of unpurified 5-chloro-8-methylquinoline we obtained an oily fraction (1.5 g), which, after sublimation at 0.1 mm, contained, according to GLC, 5.3% quinoline II, 81.8% chloride Ia, and 12.9% 7-chloro-8-methylquinoline. The latter was identical to the compound obtained by the method in [15] in 49% yield; after purification by sublimation at 0.5 mm, it had mp 43-44°C [from methanol–water (3:1)] (mp 45-48°C [15]).

5-Iodo-8-methylquinoline (Ib). A mixture of 5.2 g (0.017 mole) of silver sulfate, 4.7 g (0.033 mole) of 8-methylquinoline, and 8.4 g (0.033 mole) of ground iodine in 25 ml of concentrated sulfuric acid was stirred at ∿20°C until the reaction was complete (45 h) (an additional 2.6 g of silver sulfate and 3.2 g of iodine were added during the reaction), after which the mixture was heated at 90-95°C and worked up as described for Ia to give 8.1 g (91%) of quinoline Ib with mp 51.5-52°C (from alcohol). The product was homogeneous in system A. Found: I 47.7; N 4.9%. $C_{10}H_8IN$. Calculated: I 47.2; N 5.2%. The picrate had mp 189-192°C. Found: I 25.3; N 11.3%. $C_{10}H_8IN \cdot C_6H_3N_3O_7$. Calculated: I 25.3; N 11.2%. The 2,4,6-trinitrobenzene sulfonate had mp 282-284°C. Found: I 22.2; N 10.1; S 5.8%. $C_{10}H_8IN \cdot C_6H_3N_3O_9S$. Calculated: I 22.5; N 10.0; S 5.7%.

5-Fluoro-8-methylquinoline (Ic). An 8.2-g (0.051 mole) sample of 5-amino-8-methylquinoline (mp 141-143°C, purified by sublimation at 0.3-0.4 mm) was dissolved at 10-15°C in 70 ml of fluoboric acid (obtained from 31 g of boric acid and 100 ml of 40% hydrofluoric acid), and a solution of 3.7 g (0.053 mole) of sodium nitrite in 5 ml of water was added to the solution at 0-8°C. After 15 min, the precipitate was separated and washed successively with cold fluoboric acid, cold methanol, and ether to give 14.2 g (81%) of the corresponding diazonium tetrafluoroborate, which was heated at 80-90°C for 6 h in 50 ml of dry toluene until it gave a negative test for diazo coupling with 2-naphtholate. The cooled solution was extracted with 10% hydrochloric acid, the acidic filtrate was made alkaline to pH 9-10, and 5.1 g (63%) of 5-fluoro derivative Ic, with bp 120-122°C (20 mm) and mp 21-21.5°C, was extracted with ether. The product was homogeneous in system A. Found: F 12.0; N 8.7%. $C_{10}H_8FN$. Calculated: F 11.8; N 8.7%. The picrate had mp 182-184°C. Found: F 4.9; N 14.4%. The 2,4,6-trinitrobenzenesulfonate had mp 294-295°C. Found: F 4.3; N 12.4; S 7.2%. $C_{10}H_8FN \cdot C_6H_3N_3O_9S$. Calculated: F 4.2; N 12.3; S 7.1%.

5-Cyano-8-methylquinoline. A mixture of 0.007 mole of 5-halo-8-methylquinoline Ia or Ib and 0.69 g (0.007 mole) of cuprous cyanide in 12 ml of dry pyridine was heated at 205-215°C for 2.5 h, after which it was cooled, and the mixture, which began to solidify, was extracted with ether in a Soxhlet apparatus. The solvent was removed to give the 5-cyano derivative (75-80%), which was identical to the compound obtained by the method in [3]; after purification by sublimation at 0.5 mm, the product had mp 106°C (from methanol) (mp 106-107°C [3]).

5-Halo-8-(bromomethyl)quinoline (IIIa-d). A mixture of 5 mmole of 5-halo-8-methylquinoline Ia-d (bromide Ic was obtained by the method in [3]) and 0.95 g (5 mmole) of NBS in 40 ml of carbon tetrachloride was refluxed in the presence of benzoyl peroxide with irradiation with a 200-W lamp until the reaction was complete (2-6 h). The succinimide was separated, and the filtrate was evaporated to give the corresponding 5-halo-8-(bromomethyl)-quinolines. The products were homogeneous in system A.

5-Chloro-8-(bromomethyl)quinoline (IIIa). This compound, with mp 87-88°C (from alcohol), was obtained in 73% yield. Found: Br + Cl 45.2; N 5.6%. $C_{10}H_7BrClN$. Calculated: Br + Cl 45.0; N 5.4%.

5-Bromo-8-(bromomethyl)quinoline (IIId). This compound, with mp 111-112°C (from alcohol), was obtained in 63% yield. Found: C 40.1; H 2.3; N 4.7%. $C_{10}H_7Br_2N$. Calculated: C 39.9; H 2.3; N 4.7%. PMR spectrum: 9.05 (dd, 2-H), 7.56 (dd, 3-H), 8.57 (dd, 4-H), 7.82 (d, 6-H), 7.71 (d, 7-H), and 5.17 ppm (s, CH_2Br).

5-Fluoro-8-bromomethylquinoline (IIIc). This compound, with mp 94-95°C (from alcohol), was obtained in 43% yield. Found: Br 32.9; F 8.1; N 5.5%. $C_{10}H_7BrFN$. Calculated: Br 33.3; F 7.9; N 5.8%.

The benzyl bromination of iodo derivative Ib with an equimolar amount of NBS was a mixture of IIIb and IIId (800 mg) with mp 102-109°C (from alcohol). Found: N 4.3; Br 37.6; I 19.0%. $C_{10}H_7BrIN + C_{10}H_7Br_2N$. Calculated: N 4.3; Br 36.9; I 19.6%. The product gave one spot in systems C-D and was identical to IIId. Four fractions with mp 102-106, 107-109, 105-110, and 107-109°C were obtained by sublimation at 0.5 mm. A mixture of IIIb and IIId was obtained by column chromatography on silica gel (elution with chloroform with an increasing acetone gradient; the column was 35-cm long and had a diameter of 2 cm). Separation was not achieved by GLC on PEG-4000 on Celite, silicone oil, and Apiezon M (with a 1-m-long column with a diameter of 2 cm) at 150-200°C. PMR spectrum of the mixture of IIIb and IIId: IIIb: 8.99 (dd, 3-H), 7.51 (dd, 3-H), 8.42 (dd, 4-H), 8.12 (d, 6-H), 7.56 (d, 7-H), and 5.18 ppm (s, CH_2Br); IIId: 9.05 (dd, 2-H), 7.55 (dd, 3-H), 8.57 (dd, 4-H), 7.81 (d, 6-H), 7.73 (d, 7-H), and 5.18 ppm (s, CH_2Br).

The product (IIId) of benzyl bromination of iodo derivative Ib with two equivalents of NBS was obtained in 75% yield and had mp 110-112°C. With respect to its spectral characteristics it was identical to the compound obtained from monobromide Id. No melting-point depression was observed for a mixture of this product with a genuine sample of IIId.

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