[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

3-Haloquinolines with Substituents in the 6- and 8-Positions[1,2]

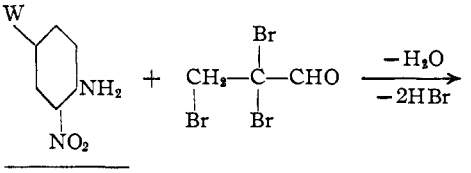
BY ROBERT H. BAKER, SAMUEL W. TINSLEY, JR., DOROTHY BUTLER AND BYRON RIEGEL*

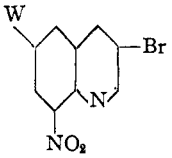
A variety of reagents useful for the preparation of simple 3-haloquinolines have been applied in this Laboratory without success in the production of 3-halo-6-methoxy-8-nitroquinoline. Direct halogenating agents have either failed altogether or have produced di- or trihalo products. Replacement of the carboxyl group by bromine in the corresponding 4-quinolinol could be accomplished but then removal of the hydroxyl was not practicable.

Having found that α-alkylacroleins would condense with 2-nitro-4-methoxyaniline in the presence of phosphoric acid to give the corresponding 3-alkylquinoline,[3] we then turned to α-bromoacrolein. The product of this reaction proved to be 6-methoxy-8-nitroquinoline, 68% yield, when no oxidizing agent was used and the yield was not improved by inclusion of arsenic pentoxide.

In a private communication Dr. Yale revealed that he had encountered a similar dehydrohalogenation in the use of α-chloroacrolein. Whereas Yale[4] was able to produce the 3-chloro compound in 20% yield by the use of hydrochloric acid, our use of 65% hydrobromic acid and α-bromoacrolein in a sealed tube at 120° with arsenic pentoxide produced the 3-bromo-6-methoxy-8-nitroquinoline in only minute quantities.

The pronounced tendency toward dehydrobromination, noted above, was avoided in a convenient and highly effective way by condensing 2,2,3-tribromopropanal with the appropriate amine in acetic acid on the steam-bath to give 3-bromo-6-methoxy-8-nitroquinoline in good yield. Although this remarkable ring closure is being investigated further, it may be tentatively formulated in the following way with a Schiff base as intermediate.

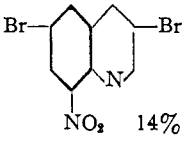


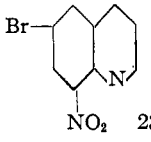


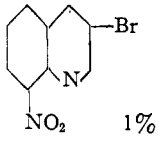
W = CH_3O, Cl, Br

The proof of structure of the products involved oxidative degradation to 5-bromonicotinic acid and conversion to the methyl ester.

An interesting variation of this reaction was noted when an amine having the para position unsubstituted (*i. e.*, *o*-nitroaniline) was employed. The following compounds were isolated (% yield based on starting amine).







The balance of the material was an acid-insoluble tar. It cannot be said at present whether the brominating agent was the tribromoaldehyde, a decomposition product thereof, or the intermediate "anil." Nor can it be said whether bromination occurred before or after ring closure.

Preliminary experiments indicate that the reaction of the tribromoaldehyde with aniline is of no use as a means of preparing 3-bromoquinoline, even more extensive bromination being encountered.

The nitroquinolines were reduced to the corresponding amines in the usual way with stannous chloride and hydrochloric acid. Two of the amines, 3-bromo-6-methoxy-8-aminoquinoline and 3-bromo-6-chloro-8-aminoquinoline, were selected to serve as nuclei for the preparation of drugs. These amines were coupled with 1-bromo-5-isopropylaminopentane hydrobromide and the products sent in for biological testing.

Experimental[5]

3-Bromo-6-methoxy-8-nitro-4-quinolinol.—The silver salt of 3-carboxy-6-methoxy-8-nitro-4-quinolinol[6] was suspended in dry carbon tetrachloride and the mixture brought to reflux. A 2:1 molar excess of bromine in dry carbon tetrachloride was added and refluxing continued for one hour after which the mixture was cooled and filtered. The residue was extracted with hot ethanol. Evaporation of the solvent produced an orange-colored product which was purified by two vacuum sublimations; m. p. 210°. The yield from 3.0 g. of silver salt was 0.5 g., 35%. Subsequent runs in *o*-dichlorobenzene and acetic acid showed that the latter was apparently the best solvent, affording a yield of 50%.

* Harvard University, National Research Council Fellow, 1936–1937.

(1) This work was supported by a grant from the National Institute of Health, U. S. Public Health Service.

(2) This is the second paper on 3-substituted quinolines from this Laboratory. For the first see R. H. Baker, J. G. Van Oot, S. W. Tinsley, Jr., Dorothy Butler and Byron Riegel, THIS JOURNAL, **71**, 3060 (1949).

(3) Our work on this reaction had been in progress for some months when the article of H. L. Yale and J. Bernstein, *ibid.*, **70**, 254 (1948), appeared. Our optimum conditions were essentially the same as reported by them.

(4) H. L. Yale, *ibid.*, **70**, 1982 (1948).

(5) Microanalyses by Margaret Hines and Virginia Hobbs. All melting points were taken on a Fisher–Johns block.

(6) R. H. Baker, G. R. Lappin, C. J. Albisetti, Jr., and B. Riegel, THIS JOURNAL, **68**, 1267 (1946).

Anal. Calcd. for $C_{10}H_7BrN_2O_4$: N, 9.37. Found: N, 9.02.

Modified Skraup Reaction with α-Bromoacrolein.—The method of Berlande[7] for the preparation of α-bromoacrolein was modified as follows. To a cold solution of one mole of acrolein in 500 ml. of water, one mole of bromine was added dropwise over a period of three hours. Steam distillation of the mixture followed by fractionation of the lower layer yielded 60 g. (45%) of α-bromoacrolein (b. p. 46–48° (28 mm.)). The phosphoric acid modification of the Skraup synthesis[8] was employed with 10 g. of α-bromoacrolein and 8.4 g. of 2-nitro-4-methoxyaniline. The product was dusty red, 6.8 g., m. p. 132–138°. Crystallization from ethanol, after treatment with Norit "A," yielded colorless material, m. p. 153–155°, which was shown by mixed m. p. to be 6-methoxy-8-nitroquinoline. When the oxidizing agent (arsenic oxide) was omitted, the yield was increased to 68%.

Upon substitution of 65% hydrobromic acid for phosphoric acid in the above procedures in addition to large amounts of 6-methoxy-8-nitroquinoline, a small amount of material, m. p. 160–162°, subsequently identified as 3-bromo-6-methoxy-8-nitroquinoline, was obtained by repeated fractional crystallization. Three runs were then made using sealed tubes at 120° for three hours. From a total of 12.6 g. of 2-nitro-4-methoxyaniline there was obtained only *ca.* 1 g. of the 3-bromo derivative.

3-Bromo-6-substituted-8-nitroquinolines.—In the most convenient procedure the 2,2,3-tribromopropanal itself need not be isolated. Thus, 27 g. of α-bromoacrolein was dissolved in 600 ml. of glacial acetic acid and the solution, cooled in an ice-bath, was titrated to the appearance of a faint reddish color with bromine; *ca.* 35 g. was required. To this solution was added the theoretical amount, 33 g., of 2-nitro-4-methoxyaniline and the solution was heated on a steam-bath for three hours with occasional shaking. Usually a copious fluffy precipitate formed at first, which gradually changed to the granular hydrobromide on heating. After cooling, the precipitated 3-bromo-6-methoxy-8-nitroquinoline hydrobromide was filtered off, washed thoroughly with dilute alkali and crystallized from ethanol. The resultant **3-bromo-6-methoxy-8-nitroquinoline** consisted of silvery flakes, weighing 51 g., 73%, m. p. 160–162°. The analytical sample melted 165–166°.

Anal. Calcd. for $C_{10}H_7BrN_2O_3$: C, 42.4; H, 2.49; N, 9.90. Found: C, 42.7; H, 2.47; N, 9.76.

The use of 2-nitro-4-chloroaniline in the above reaction produced **3-bromo-6-chloro-8-nitroquinoline**; light yellow needles, m. p. 173–175°.

Anal. Calcd. for $C_9H_4BrClO_2N_2$: N, 9.74. Found: N, 9.63.

From diagnostic runs using the above procedure, it was evident that the reaction of 2,2,3-tribromopropanal with *o*-nitroaniline yielded a mixture of products. Therefore, the tribromoaldehyde was prepared in pure form according to the method of Berlande[7] for the following run. To a solution of 89.7 g. of 2,2,3-tribromopropanal (b. p. 104–105° (30 mm.)) in 800 ml. of glacial acetic acid was added 42.0 g. of *o*-nitroaniline and the solution was heated on a steam-bath overnight. After cooling and filtering, the precipitate was washed with a little fresh acetic acid and dried in air. The cake was pulverized, washed with 250 ml. of ethanol, and from this washing, upon evaporation of the solvent, light tan crystals, 7.3 g., m. p. 158–176°, were obtained. Repeated crystallization from ethanol yielded colorless plates, m. p. 179–180°. Two more ethanol washings produced an additional 7.0 g. of the same compound, m. p. 179–180°. This material was shown to be 3,6-dibromo-8-nitroquinoline by mixed m. p. with an authentic sample prepared from 2-nitro-4-bromoaniline and 2,2,3-tribromopropanal by the method described before.

Anal. Calcd. for $C_9H_4Br_2N_2O_2$: C, 32.6; H, 1.21; N, 8.44. Found: C, 32.6; H, 1.21; N, 8.29.

The light yellowish-gray residue from the alcohol washings, m. p. 218–223° with much sublimation, was washed with 10% sodium hydroxide and taken up in hot ethanol. Cooling produced colorless fluffy needles, 11.4 g., m. p. 165–170°. Crystallization from ethanol raised the m. p. to 172–173°. The reported m. p. for 6-bromo-8-nitroquinoline is 170°.[8]

Anal. Calcd. for $C_9H_5BrN_2O_2$: C, 42.7; H, 1.99. Found: C, 42.7, 42.7; H, 2.07, 2.05.

Identification was confirmed by reduction to 6-bromo-8-aminoquinoline, m. p. 75–76° (lit. 76–77°).[8]

Anal. Calcd. for $C_9H_7BrN_2$: C, 48.5; H, 3.16. Found: C, 48.1; H, 3.30.

The original filtrate, *i. e.*, the acetic acid solution, was heated overnight on a steam-bath in a jet of air and thereby evaporated to 150 ml. Cooling produced a dark granular precipitate, 1.4 g., which was found to be crude 6-bromo-8-nitroquinoline hydrobromide. The filtrate was diluted with water, yielding a tar which was extracted with ether–benzene (after these extractions the tar contained no material which could be extracted with 30% hydrochloric acid). The dried ether–benzene extracts were combined and the solvents evaporated, producing a dark red mat, m. p. 143–165°. This material was dissolved in hot ethanol and, upon cooling, an additional 4.1 g. of crude 6-bromo-8-nitroquinoline, m. p. 160–165°, was obtained.

The mother liquors from the crystallization of 6-bromo-8-nitroquinoline were combined and evaporated. The red sticky solid thus obtained was dissolved in dry benzene (60 ml.) and chromatographed over activated alumina (25 × 2 cm. column). Six 30-ml. fractions were taken arbitrarily and the solvents evaporated from each. Fractions 1, 5 and 6 (total weight 1.2 g.) proved to contain 6-bromo-8-nitroquinoline. Fractions 2, 3 and 4 were orange colored, m. p. *ca.* 90–150°; total weight 7.3 g. These fractions were combined, covered with acetyl chloride and the excess was evaporated *in vacuo*. The residue was extracted with warm 30% hydrochloric acid and the acid extracts were made alkaline with 10% sodium hydroxide and filtered. The precipitate was crystallized from ethanol to give colorless crystals, m. p. 110–112°. This material was dissolved in dry benzene and passed through a column of activated alumina to yield 0.9 g. of a colorless compound, m. p. 121–123°. A mixed m. p. with an authentic sample of 3-bromo-8-nitroquinoline, m. p. 123–124°, prepared according to the method of Hauser and co-workers,[9] was 122–124°.

3-Bromo-6-substituted-8-aminoquinolines.—To 5 g. of the nitroquinoline dissolved in 60 ml. of concentrated hydrochloric acid was added 20 g. of pulverized stannous chloride (either dry or dissolved in concentrated hydrochloric acid). The solution was heated on a steam-bath for one to three hours, cooled, and poured into 100 ml. of 60% sodium hydroxide with stirring. The amine was filtered off, washed with water and crystallized from methanol–water, forming colorless or slightly yellowish crystals. The yields were 80–90%.

3-Bromo-6-methoxy-8-aminoquinoline, m. p. 95–96°. *Anal.* Calcd. for $C_{10}H_9BrON_2$: N, 11.1. Found: N, 11.0. 3-Bromo-6-chloro-8-aminoquinoline, m. p. 117–118°. *Anal.* Calcd. for $C_9H_6BrClN_2$: N, 10.8. Found: N, 10.8. 3,6-Dibromo-8-aminoquinoline, m. p. 119–120°. *Anal.* Calcd. for $C_9H_6Br_2N_2$: C, 35.8; H, 2.00. Found: C, 35.0; H, 2.13.

Proof of Structure of 3-Bromo-6-substituted-8-aminoquinolines.—Authentic reference samples were prepared as follows: 3-bromoquinoline (picrate m. p. 190°) was oxidized by refluxing in 150 ml. of concentrated nitric acid for thirty hours. The solution was evaporated to dryness on a steam-bath in a current of air and the residue crystallized from water. The 5-bromonicotinic acid thus prepared consisted of colorless plates (from hot water) or needles (from cold water), m. p. 178–180°. Four crystallizations from water raised the m. p. to 182.5–183° (lit. 183° for 5-bromonicotinic acid dihydrate). The struc-

(7) A. Berlande, *Bull. soc. chim.*, **37**, 1385 (1925).

(8) A. Claus and K. Reinhard, *J. prakt. Chem.*, **157**, 525 (1894).

(9) C. R. Hauser, M. S. Bloom, D. S. Breslow, J. T. Adams, S. T. Amore and M. J. Weiss, THIS JOURNAL, **68**, 1544 (1946).

ture of this compound seems well substantiated, since its preparation has been reported in the literature by three different routes (from x,y,z-tribromoquinoline by nitric acid oxidation,[10] from 5-bromoquinolinic acid by decarboxylation,[11] and from 5-aminonicotinic acid[12]). The yield of 5-bromonicotinic acid was 45%.

Anal. Calcd. for $C_6H_4BrNO_2$: C, 35.7; H, 2.00. Found: C, 35.9; H, 2.04.

The acid was then converted to the methyl ester by the usual method employing thionyl chloride and methanol. The ester was crystallized from methanol–water and consisted of colorless crystals, m. p. 93–95°. Chromatographing a small sample in benzene over activated alumina raised the m. p. to 99–100° (lit. 98–99[8]).

A small sample (1 g.) of each of the amines was then oxidized by refluxing in 40 ml. of concentrated nitric acid for twelve hours and the mixture worked up as before. The product in each case was identified as 5-bromonicotinic acid by mixed m. p. of the acid with the authentic sample and mixed m. p. of the methyl ester with the authentic sample.

3-Bromo-6-methoxy-8-(5-isopropylaminopentylamino)-quinoline Hydrobromide.—The coupling was accomplished using equimolecular (0.03 mole) quantities of 3-bromo-6-methoxy-8-aminoquinoline and 5-isopropylamino-1-bromopentane hydrobromide, and a one-mole excess of sodium acetate. This mixture was heated at steam-bath temperature for three days. At the end of this time 25 to 50 ml. of a methanol–water mixture was added, and the mixture was refluxed a day longer. When the mixture was removed from the steam-bath, a black oil settled to the bottom of the flask. Without allowing the flask to cool, the supernatant liquid was poured into a beaker. The black oil in the flask was taken up in benzene, decolorized with charcoal and cooled to yield the monohydrobromide of the drug. As the supernatant liquid cooled, crystals settled out, which generally consisted of a mixture of hydrobromide and the aminoquinoline. If the supernatant liquid was not separated from the black oil, it was not possible to separate the coupling product from starting amine. The hydrobromide as it was obtained from the first crystallization was quite pure and each crystallization (methanol–benzene solution) decreased the yield immensely. The best yield that could be obtained was 55% based on the amine used in the reaction. Usually, half the quantity of amine used in the reaction is recovered.

Anal. Calcd. for $C_{16}H_{26}BrN_3O\cdot HBr$: N, 9.11; C, 46.8; H, 5.86. Found: N, 8.62; C, 46.6; H, 5.67.

3-Bromo-6-chloro-8-(5-isopropylamino-1-pentylamino)-quinoline Hydrobromide.—This compound was prepared in a similar manner to its 6-methoxy analog.

Anal. Calcd. for $C_{17}H_{23}BrClN_3\cdot HBr$: N, 9.02. Found: N, 8.72.

(10) O. Srpek, *Monatsh.*, **10**, 710 (1889).
(11) A. Claus and F. Collischon, *Ber.*, **19**, 2763 (1886).
(12) R. Graf, *J. prakt. Chem.*, **138**, 244 (1933).

Summary

1. 2,2,3-Tribromopropanal has been found to react with *o*-nitro-*p*-substituted-anilines to produce the 3-bromoquinolines in good yields. Two of these nitroquinolines have been reduced to the amines and coupled with side chains to produce compounds of possible antimalarial activity.

2. *o*-Nitroaniline itself in this reaction produced little of the expected compound, 3-bromo-8-nitroquinoline, and large amounts of 6-bromo- and 3,6-dibromo-8-nitroquinoline.

3. A survey of numerous attempted direct halogenations of 6-methoxy-8-nitroquinoline is presented.

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[CONTRIBUTION FROM THE EXPERIMENTAL BIOLOGY AND MEDICINE INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

Derivatives of 4-Amino-4'-ethylaminodiphenyl Sulfone, 4-Nitro-4'-ethylaminodiphenyl Sulfone and N^1-Ethylsulfanilamide

BY ERNEST L. JACKSON*

4-Amino-4'-β-hydroxyethylaminodiphenyl sulfone[1] (I) possesses interesting pharmacologic and chemotherapeutic properties.[2] The first preparations of this compound by the reduction of 4-nitro-4'-β-hydroxyethylaminodiphenyl sulfone (II) regularly yielded crystals melting at 143.5–144.5°, but later a second crystalline form (Table I) melting at 130.5–131.5° usually was obtained. The dimorphic forms are distinguishable by the X-ray diffraction patterns (Fig. 1), which also demonstrate their homogeneity. The procedure[1] previously employed for the preparation of II by hydroxyethylation of 4-amino-4'-nitrodiphenyl sulfone has been improved by neutralization of the hydrobromic acid produced in the reaction and other modifications. Since compound I is only slightly soluble in water (74 mg. per 100 cc. of solution at 37°), it usually is administered orally in chemotherapeutic experiments. Phosphorylation affords its crystalline phosphoric ester (III), the sodium salt of which is readily soluble in water. This ester is prepared conveniently and in high yield by the reaction of a mixture of orthophosphoric acid and phosphorus pentoxide with I at 100°. It was obtained also by the reduction of compound IV, the phosphoric ester of II, with ammonium sulfide or ferrous sulfate. The preparation of IV by phosphorylation of II with a mixture of orthophosphoric acid and phosphorus pentoxide proved to be a superior method to preparation by way of the reaction of phosphoryl chloride with II at 100°, because in the latter reaction a considerable proportion of the material was converted into 4-nitro-4'-β-chloroethylaminodiphenyl sulfone (V). In dry pyridine solution at room temperature phosphoryl chloride showed no appreciable reaction with II. The reaction of hot 48% hydrobromic acid with I yields crystalline

* Harvard University Ph.D. 1924.

(1) Jackson, THIS JOURNAL, **70**, 680 (1948).
(2) Smith, Jackson, Junge and Bhattacharya, *Am. Rev. Tuberc.*, **60**, 62 (1949).