[Contribution from the Research Laboratories of Winthrop Chemical Company, Inc.]

Quinolines. IV. Some Bz-Iodo-3-methyl-4-(1′-methyl-4′-diethylaminobutylamino)-quinolines

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The investigations of quinoline derivatives as antimalarials have previously been concerned chiefly with compounds related to pamaquine. Recently, these laboratories have described researches dealing with certain 4-substituted quinoline types,[1-4] but there has been, as yet, no complete investigation of the influence of altering the position of various groups upon the activity of compounds with a constant side chain. Our studies upon 3-methyl-4-(1′-methyl-4′-diethylaminobutylamino)-quinolines[3] have been planned to include a thorough investigation of the relation of the position and nature of bz-substituents upon the antiplasmodial activity of these bases. Thus far, the parent compound (3-methyl-4-(1′-methyl-4′-diethylaminobutylamino)-quinoline) and all possible bz-monosubstituted chlorine and bromine compounds have been prepared, as well as the bases containing methyl, methoxy or ethoxy groups in the 6- or 8-position. Even as the influence of the halogen in position 6 of 2-methoxy-9-(1′-methyl-4′-diethylaminobutylamino)-acridines related to quinacrine has been investigated,[5-7] it was decided that the importance of each of the halogens in the benzenoid cycle of the quinoline derivatives should be determined. The topic will be completed by the present contribution on iodine derivatives and a forthcoming one on the corresponding fluorine compounds. 3-Methyl-4-(1′-methyl-4′-diethylaminobutylamino)-7-iodoquinoline, one of the compounds herein described, has been disclosed in the patent literature.[8] The results of the testing of these compounds for antimalarial activity will appear elsewhere (see footnote (*g*), Table I).

As in previous work,[3] recourse was made to the Conrad–Limpach[9] synthesis of 4-hydroxyquinolines for the preparation of the requisite compounds. The several iodoanilines were caused to react with ethyl ethoxalylpropionate to yield azomethines (I) which were cyclized to the iodoquinolines (II). Although no difficulty arose when mineral oil was employed as a diluent in the pyrolytic cyclization in previous cases,[3] this procedure was quite unsatisfactory with the present azomethines, which darkened appreciably even upon heating upon the steam-bath. The iodine atom was labile in all three cases, but particularly so when it was in the *p*-position. Cyclization of the azomethines was accomplished smoothly if diphenyl ether or Dowtherm A (a mixture of diphenyl and diphenyl ether) were employed as a diluent at *ca.* 240°. Since the completion of this work, Stephen, *et al*,[10] reported that boiling diphenyl gave better results than mineral oil when used in the synthesis of some quinoline types by the Conrad–Limpach procedure. The cyclizations of several other azomethines in Dowtherm A have been tried recently, and the quality of resulting quinoline esters has been found to be markedly better than when mineral oil was used.[3]

As expected,[3c] the azomethine from *m*-iodoaniline gave rise to a mixture of ethyl 5- and 7-iodo-3-methyl-4-hydroxyquinoline-2-carboxylates. The separation of the isomer mixture through the hydrochlorides was not nearly so effective as in the case of the chlorine and bromine series,[3c] hence fractional crystallization was necessary. There were some difficulties in obtaining pure samples of the 5-iodo compound, for it was not only formed in subordinate amounts, but also was contaminated with the 7-isomer through many crystallizations. While nearly equal amounts of the isomeric chlorine or bromine derivatives were formed by cyclization of the corresponding *m*-halogen azomethines, ethyl 5-iodo-3-methyl-4-hydroxyquinoline-2-carboxylate was formed in considerably smaller amounts (32% yield from the mixture) than the 7-iodo compound (60% yield). This is quite probably due to the grossness of the iodine atom, which could partly block the elimination of alcohol from the carbethoxy group and the hydrogen *ortho* to the iodine. The fact that the 7-iodo ester had a lower melting point (m.p. 231–231.5°) than the 5-isomer (m.p. 237–237.5°) was unexpected in the light of previous work.[3c] This matter is to be emphasized in view of the assumptions made by Surrey and Hammer[2] concerning the structure of the analogous ethyl 4-hydroxy-7-iodoquinoline-2-carboxylate. The proof of the structure of the 5- and 7-iodoquinoline derivatives was accomplished by the method previously described[3c] for the oxidation of the chlorine series to a chloroanthranilic acid. The compound which was here oxidized by alkaline permanganate was the acid derived from the lower-melting ester (m.p. 231–231.5°); isolation of a product which was identical with a known

(1) Huber, Bair and Laskowski, This Journal, **67**, 1619 (1945).

(2) Surrey and Hammer, *ibid.*, **68**, 113 (1946).

(3) Steck, Hallock and Holland, *ibid.*, (a) **68**, 129 (1946); (b) **68**, 132 (1946); (c) **68**, 380 (1946).

(4) Huber, Bair, Laskowski, Jackman and Clinton, *ibid.*, **68**, 322 (1946).

(5) Mietzsch and Mauss, German Patent 553,072 (*C. A.*, **26**, 4683[8] (1932)).

(6) Magidson, Grigorowski and Gal'perin, *J. Gen. Chem.* (USSR), **8**, 56 (1938).

(7) Magidson and Travin, *ibid.*, **11**, 243 (1941).

(8) Andersag, Breitner and Jung, U. S. Patent 2,233,970.

(9) Conrad and Limpach, *Ber.*, **20**, 944 (1887); Limpach, *ibid.*, **64**, 969 (1931).

(10) Stephen, Tonkin and Walker, *Nature*, **156**, 629 (1945).

TABLE I

Bz-IODO-3-METHYLQUINOLINE DERIVATIVES

Compound	Yield, %[a]	Appearance	Solvent[b]	M. p.,[c] °C.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Ethyl Bz-iodo-3-methyl-4-hydroxyquinoline-2-carboxylates										
5-I	32[d]	Pale yellow needles	E	237–237.5	43.71	3.37	3.92	43.88	3.41	4.08
6-I	82	Creamy white needles	aE	234–234.2	I = 35.53			43.82	3.40	3.95
7-I	60[d]	Creamy white plates	E	231–231.5				I = 35.55		3.89
8-I	89	Yellowish plates	E	179–180				43.93	3.64	3.92
Bz-Iodo-3-methyl-4-hydroxyquinoline-2-carboxylic Acids										
6-I	96	Yellowish platelets	P	269–270[d]	40.14	2.45	4.26	39.98	2.64	4.52
7-I	97	Pale yellow needles	P	250				40.22	2.32	4.48
8-I	96	Yellowish-white needles	P	238–238.5[d]				40.19	2.85	4.11
Bz-Iodo-3-methyl-4-hydroxyquinolines										
6-I	96	White platelets	aPy	290	42.13	2.83	4.91	41.98	3.02	5.02
7-I	95	White needles	E	290				42.32	3.00	4.85
8-I	97	White prismatic needles	E	235–235.5				42.11	3.06	4.78
Bz-Iodo-3-methyl-4-chloroquinolines										
6-I	93	White prismatic needles	S	137.8–138	39.56	2.32	4.61	39.72	2.27	4.78
7-I	90	White prisms	aE	109.5–110				39.41	2.30	4.75
8-I	91	Yell.-white prism. needles	S	136.5–137				40.00	2.34	4.84
Bz-Iodo-3-methyl-4-(1′-methyl-4′-diethylaminobutylamino)-quinolines										
				B. p., °C.						
6-I	82	Golden oil		[e]	53.65	6.63	9.98	53.95	6.92	10.60
7-I[g]	85	Golden brown oil		195–200 (0.5 mm.)				53.91	6.86	10.01
8-I	76	Golden oil		[f]				53.86	7.31	10.21

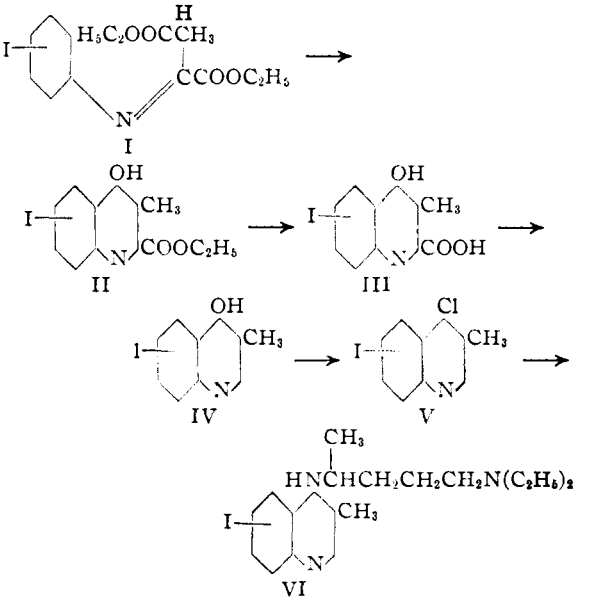
[a] Not purified, as used for next step. [b] E = ethanol; P = propylene glycol; Py = pyridine, S = Skellysolve B (ligroin, b. p. 50–60°), a = aqueous. [c] Uncorrected. d = decomposes. [d] Yields of the isomeric esters are those as obtained on isomer separation. [e] Could only be distilled under 3×10^{-4} mm., 180° bath temperature. [f] Could only be distilled under high vacuum (bath 180°, 2 μ pressure). [g] SN 9904, the Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey Numbers have been assigned will be tabulated in a forthcoming monograph.

specimen of 4-iodoanthranilic acid demonstrated conclusively that the structures of the compounds are those designated in Table I.

Hydrolysis of the several esters (II) was accomplished with boiling 5% caustic in the manner described earlier by us.[3] Although in all other cases the corresponding bz-iodo-3-methyl-4-hydroxyquinoline-2-carboxylic acids (III) resulted in excellent yields, the saponification of the 5-iodo compound led to the formation of a product which was free of halogen. The nature of this compound has not been clarified and will be considered subsequently.

The decarboxylation of the acids to bz-iodo-3-methyl-4-hydroxyquinolines (IV) could be effected quickly in mineral oil at 270–275°,[3] but it was expedient to employ Dowtherm A at lower temperatures (as low as 200°) and with considerably longer reaction times. The decarboxylation of 3-methyl-4-hydroxy-6-iodoquinoline-2-carboxylic acid proceeded outstandingly poorly when carried out in mineral oil; this compound not only failed to decarboxylate completely, but also lost *ca.* 20% of its iodine. Use of Dowtherm A as a medium for this and all other decarboxylations tried with it (including a number of quinoline-2-carboxylic acids prepared previously[3]) was found to be considerably better than mineral oil.

The 4-chloroquinolines (V) resulted in the usual good yields when the several bz-iodo-3-methyl-4-hydroxyquinolines (IV) were treated with boiling phosphorus oxychloride. Reaction of the dihalogen compounds (V) with 1-methyl-4-diethyl-



aminobutylamine in phenol at 165–170° was carried out in the presence of sodium iodide, and the resulting bases (VI), which were obtained in good yields, were distilled under high vacuum. The testing of the several bases, which has been accomplished under the direction of the National Research Council, will be reported elsewhere.

Experimental

Iodoanilines.—*o*-Iodoaniline and its *m*-isomer were produced from the corresponding nitroanilines by the method of von Baeyer[11,12] in over-all yields of 78–83%. The preparation of *p*-iodoaniline from aniline was accomplished in 80–85% yields by a modification of the Wheeler procedure.[13]

Ethyl Ethoxalylpropionate.—This β-keto ester was prepared by the Claisen condensation as described in our earlier work.[3]

1-Methyl-4-diethylaminobutylamine.—A commercial sample was redistilled before use; b. p. 71–72° (6 mm.), $n^{25}D$ 1.4415.

Ethyl Bz-Iodo-3-methyl-4-hydroxyquinoline-2-carboxylates.—The formation of the azomethines from the iodoanilines and ethyl ethoxalylpropionate was accomplished as before.[3] Yields of the individual orange to orange-brown oils (76–90%) were little influenced by the procedure involving no solvent, or methylene chloride, or glacial acetic acid, but the *p*-iodo compound was much darker when acetic acid was used. Cyclization of the azomethines by use of mineral oil as the diluent at 250°[3] was successful, but the resulting quinolines were always obtained purer, and in better yield, when Dowtherm A or diphenyl ether (3–4 cc. per gram of azomethine) was employed at 240–245°. The choice of diluent was of paramount importance in the case of the *p*-iodo series, in which the lability of the halogen was outstanding. It is of interest to note that the yield of the ethyl 5/7-iodo-3-methyl-4-hydroxyquinoline-2-carboxylates was best; as expected, this mixture had an unsharp melting point.

Separation of Isomeric Ethyl 5/7-Iodo-3-methyl-4-hydroxyquinoline-2-carboxylates.—A preliminary separation of the isomers produced by the cyclization of the azomethine from *m*-iodoaniline could be effected by employing the differences of the solubility of the hydrochlorides in glacial acetic acid,[3c] but was not complete. It was necessary to repeat the procedure on both fractions[3c] and then fractionally crystallize the bases from alcohol or acetone. The considerable amount of extraneous material which was formed during the cyclization in mineral oil rendered the process tedious and led to the use of diphenyl ether as a diluent. In all cases it was rather difficult to isolate samples of the 5-iodoquinoline ester free from the 7-isomer, which was the less soluble of the two in alcohol or acetone; partial fractionation from these solvents, alternately, was fairly effective in accomplishing the separation. The iodine atom apparently hindered the cyclization, giving a lower yield of the 5-substituted quinoline than the corresponding fluorine,[14] chlorine or bromine[3c] types (a 60% yield of ethyl 3-methyl-4-hydroxy-7-iodoquinoline-2-carboxylate and a 32% yield of the 5-isomer were obtained from the isomer-mixture). It should be noted that the lower-melting quinoline (m. p. 231–231.5°) ester proved to be the 7-substituted compound (*cf.* refs. 2, 3c).

Proof of Structure of the 5/7-Iodo-3-methyl-quinoline Series.—Twenty grams (0.061 mole) of the iodo-3-methyl-4-hydroxyquinoline-2-carboxylic acid obtained by hydrolysis of the corresponding ester which melted 231–231.5° was oxidized by alkaline potassium permanganate as described for the corresponding chloro compound.[3c] After hydrolysis with 6 *N* hydrochloric acid, the product was crystallized twice from alcohol, giving 3.0 g. of light tan needles. This compound melted at 214° (cor.) and showed no depression in melting point upon being admixed with an authentic sample of 4-iodoanthranilic acid which was prepared by the method of Wheeler and Johns.[15] The melting point of the compound was previously given as 208°.

Bz-Iodo-3-methyl-4-(1′-methyl-4′-diethylaminobutylamino)-quinolines.—The procedure for the conversion of the several bz-iodo-3-methylquinoline esters into the desired 4-(1-methyl-4′-diethylaminobutylamino) derivatives was essentially as described for analogous compounds.[3] The only difference lay in the use of Dowtherm A or diphenyl ether for the decarboxylations, for mineral oil gave remarkably poor results in this series. There was no difficulty in accomplishing decarboxylation of any of the quinoline-2-carboxylic acids thus far prepared[3] when *ca.* 5 cc. of Dowtherm A or diphenyl ether was used at *ca.* 235–245°, but some lost carbon dioxide at even lower temperatures. Particular care was required in the distillation of the final products containing iodine.

Hydrolysis of ethyl 5-iodo-3-methyl-4-hydroxyquinoline-2-carboxylate with three equivalents of boiling 5% sodium hydroxide gave a yellow solid which crystallized from 2-methyl-2,4-pentanediol in the form of prisms, m. p. 251° dec. The compound did not give concordant analyses for carbon and hydrogen or nitrogen and was found to be free of halogen. This substance is under further study.

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Summary

A group of 3-methyl-4-(1′-methyl-4′-diethylaminobutylamino)-quinolines containing an iodine atom in the benzene moiety has been described. The synthesis of these compounds was accomplished by the method of Conrad and Limpach, and an improvement in manipulation has been reported. The anomalous behavior of ethyl 5-iodo-3-methyl-4-hydroxyquinoline-2-carboxylate upon hydrolysis with 5% sodium hydroxide has been observed.

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(11) von Baeyer, *Ber.*, **38**, 2761 (1905).

(12) We are indebted to Dr. John A. King, of these laboratories, for the preparation of a quantity of *m*-iodoaniline.

(13) Brewster, "Organic Syntheses," Coll. Vol. *II*, John Wiley and Sons, New York, N. Y., 1943, p. 347.

(14) Steck, Hallock and Holland, unpublished work, to appear subsequently.

(15) Wheeler and Johns, *Am. Chem. J.*, **14**, 449 (1910).