The Synthesis of Quinoline- and Isoquinolinecarboxaldehydes (1)

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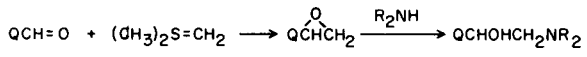
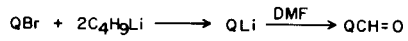
The recent elegant construction of the side-chain of various antimalarials by the following sequence (5,6)



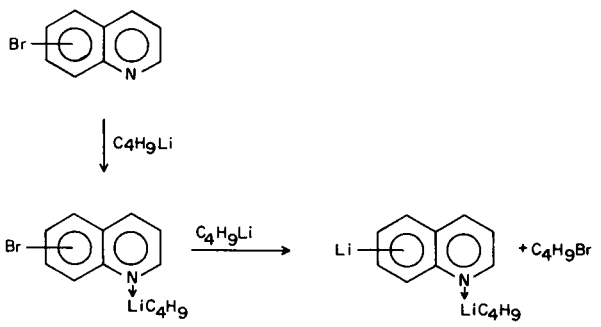
points out the importance of quinolinecarboxaldehydes as intermediates. Both 2- and 4-quinolinecarboxaldehydes are prepared readily by selenium dioxide oxidation of the corresponding methylquinolines, but any other isomers are acquired in very low yields by this reaction because of the required higher temperature conditions. On occasion, the Sommelet reaction (7) is useful in converting the methylquinoline to the corresponding aldehyde, but no other reaction has proved to be generally reliable.

A new method has now been developed involving two



steps. The generality of this reaction may be judged from the aldehydes prepared in Table I and its usefulness demonstrated by the fact that the final antimalarial product utilizing 6-phenyl-8-quinolinecarboxaldehyde (**5**) as an intermediate was prepared in 28.5% overall yield in 5 days starting from 4- aminobiphenyl.

Although this method of synthesis has been utilized at least once in making a pyrrocoline aldehyde (10), success in the preparation of quinolinecarboxaldehydes would not have been achieved were it not for the discovery that two equivalents of butyllithium and low temperatures (-70°) were vital requirements. The fact that no exchange with the bromoquinoline took place with one equivalent of butyllithium is interpreted below. In substantiation of this interpretation, 6-bromo-8-methyl-2-phenylquinoline, quite sterically hindered in the region of the nitrogen atom, was the only bromoquinoline which could be converted to the aldehyde with one equivalent of butyllithium. The low temperature was necessary to prevent addition of butyllithium to the azomethine grouping yielding a 2-butyl-1,2-dihydroquinoline. Oddly enough, a 6-bromoquinoline without a substituent in the 8- or 2-position always gave some azomethine addition even at temperatures as low as -100°, and this constituted a limitation to the generality of the reaction. On the other hand, the reaction was general enough to tolerate chlorine atoms substituted in the 6 or 8 positions or in the 2-phenyl groups and no butyllithium exchange with chlorine could be detected in these cases.



The combined aldehyde synthesis (this paper) and the aldehyde-epoxide synthesis (5) should serve to ease the often difficult route to various antimalarials and perhaps to other important compounds.

Of further interest (see Experimental) is the bromination with *N*-bromosuccinimide of some free anilines instead of the *N*-acetyl derivatives. The versatility of organolithium compounds is further illustrated in the azomethine addition of *p*-chlorophenyllithium to 6-bromoquinoline without interchange with the 6-bromo substituent.

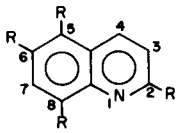
EXPERIMENTAL (11)

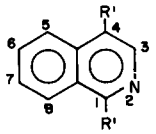
General procedure for the Synthesis of Quinolinecarboxaldehydes.

All solvents were dried carefully and operations were conducted under a nitrogen atmosphere. The bromoquinoline (0.01 mole) was added portionwise to a 100 ml. (50:50, THF and ether) solution of 0.02 mole of butyllithium at -70° and the dark orange-yellow mixture was stirred for about 30 minutes. A solution of 0.1 mole of dimethylformamide in 15 ml. of THF, cooled to -70°, was added rapidly to the quinolyllithium solution, causing the color to become pale yellow and the internal temperature to rise to near -65°. After stirring for 15 minutes, 10

TABLE I

Quinoline- and Isoquinolinecarboxaldehydes (a)





No.	2-R	5-R	6-R	8-R	% Yield	M.P.	δ (b)
1 (8)	H	CH=O	H	H	70	94.5-96°	10.1
2	H	H	F	CH=O	80	116-117°	11.3 (c)
3	H	H	CH=O	CH_3	76	98-98.5°	10.1
4	H	H	CH=O	C_6H_5	81.5	143.7-144.2°	10.2
5	H	H	C_6H_5	CH=O	68.5	133-134°	11.5
6	H	H	Cl	CH=O	83	158-159°	11.3
7	C_6H_5	H	CH_3	CH=O	72.5	135.5-137°	11.3
8	C_6H_5	H	CH=O	CH_3	71.5	108-109.5°	10.0
9	C_6H_5	H	CH=O	Cl	71	133.5-134°	10.1
10	*p*-ClC_6H_4	H	CH=O	H	78	154-155°	10.2
	1-R′	4-R′					
11 (9)	H	CH=O			76	101.5-103°	9.2
12	C_6H_5	CH=O			73	153-154°	10.35

(a) All synthesized by the reaction QBr + $2C_4H_9Li \rightarrow QLi \rightarrow QCH=O$ (see Experimental (b) δ is chemical shift (ppm) of aldehydic proton relative to TMS (c) All aldehydic proton signals were singlets except that for 2, a doublet, J = 3 cps.

ml. of cold ethanol was added followed by the addition of a saturated solution of ammonium chloride and warming to 25°. The organic layer, combined with the ether extraction layers, was dried, evaporated, and the residue was pumped under reduced pressure to remove valeraldehyde. An almost quantitative yield of crude aldehyde remained which was recrystallized from ethanol. Yields and characteristics of the aldehydes are recorded in Table I.

Preparation of Bromoquinolines and Bromoisoquinolines.

The intermediates leading to the aldehydes numbered in Table I were obtained as described below. If a Skraup reaction was used, the modification of Richter and Smith (12) was followed.

5-Bromoquinoline.

This compound, leading to **1**, was made by the method of Gordon and Pearson (13).

8-Bromo-6-fluoroquinoline.

This compound (new), b.p. 117-121° at 0.25 mm, m.p. 76-77°, leading to **2**, was made in 65% yield by the Skraup reaction. 2-Bromo-4-fluoroaniline, b.p. 46-47° at 0.05 mm., m.p. 22-23°, *N*-acetyl m.p. 114-116°, (literature (14) m.p. 41°, *N*-acetyl m.p. 114°) for the Skraup reaction was made by the bromination of *p*-fluoroaniline with *N*-bromosuccinimide as described for the preparation of 8-bromo-6-phenylquinoline.

6-Bromo-8-methylquinoline.

This compound, b.p. 113-115° at 0.15 mm., picrate m.p. 225-226°, (literature (15) picrate m.p. 224°), leading to **3**, was made in 60% yield by the Skraup reaction.

6-Bromo-8-phenylquinoline.

This compound (new), m.p. 71-72°, picrate m.p. 185-186°, leading to **4**, was made in 40% yield by the Skraup reaction with 2-amino-5-bromobiphenyl. The crude quinoline was eluted from an alumina column with benzene.

8-Bromo-6-phenylquinoline.

This compound (new), m.p. 67-68°, leading to **5**, was prepared in 58% yield by the Skraup reaction with 4-amino-3-bromobiphenyl. The latter compound was prepared by a unique and useful procedure: 4-aminobiphenyl (0.1 mole) in 100 ml. of methylene chloride, was cooled to 0° and treated with a slurry of 0.1 mole of *N*-bromosuccinimide in 100 ml. of methylene chloride and the mixture was stirred at 25° for 10 minutes. The solution was washed well with water, dried, and evaporated giving a quantitative yield of nearly pure 4-amino-3-bromobiphenyl, m.p. 62-65°, *N*-acetyl, m.p. 158-159° (literature (16) m.p. 66°, *N*-acetyl m.p. 161°).

8-Bromo-6-chloroquinoline.

Thie compound, m.p. 91-92° (literature (17) m.p. 94°) leading to **6**, was made in 56% yield by the Skraup reaction with 2-bromo-4-chloroaniline. The latter compound, m.p. 65-67°, *N*-acetyl, m.p. 134-135° (literature (18) m.p. 65°, *N*-acetyl m.p. 133°) was made in 98% yield by bromination of *p*-chloroaniline

with *N*-bromosuccinimide by the procedure described for 4-amino-3-bromobiphenyl.

8-Bromo-6-methyl-2-phenylquinoline.

This compound (new), m.p. 104-105°, leading to **7**, was prepared in 10% yield by a modified Doebner v. Miller reaction. 2-Bromo-4-methylaniline hydrochloride (0.4 mole) in 350 ml. of refluxing ethanol was treated dropwise with 0.65 mole of cinnamaldehyde in 200 ml. of ethanol over a 12-hour period. The ethanol was removed by means of a rotating evaporator and the black, tarry residue was extracted with several portions of concentrated hydrochloric acid. The acid extract was neutralized with ammonium hydroxide, and the precipitate was extracted with ether. The residue from the ether was recrystallized from ethanol.

6-Bromo-8-methyl-2-phenylquinoline.

This compound (new), m.p. 94.5-96°, leading to **8**, was made as above in 12.5% yield from 4-bromo-2-methylaniline hydrochloride and cinnamaldehyde.

6-Bromo-8-chloro-2-phenylquinoline.

This compound (new), m.p. 91-92°, leading to **9**, was made in 12% yield as above from 4-bromo-2-chloroaniline and cinnamaldehyde. Compound **9** was made by a different route (19) to corroborate its structure. 8-Chloro-6-methyl-2-phenylquinoline (new), m.p. 95-95.5°, which was made by the modified Doebner v. Miller reaction as above in 20% yield from 2-chloro-4-methylaniline hydrochloride and cinnamaldehyde, was oxidized by the Sommelet reaction (7) to the corresponding aldehyde in 57% yield, m.p. and mixed m.p. with **9**, 133-134°.

6-Bromo-2-(4-chlorophenyl)quinoline.

This compound, m.p. 172-173°, (literature (20) m.p. 177°) m.w. calcd. 318, found (m/e) 317 and 319, leading to **10**, was made by azomethine addition to 6-bromoquinoline. To a stirred solution 0.01 mole of *p*-bromochlorobenzene in 100 ml. of dry ether under nitrogen was added 0.01 mole of commercial butyllithium in hexane. After 10 minutes reflux, 0.01 mole of 6-bromoquinoline in 75 ml. of dry benzene was added and the mixture was refluxed for 15 minutes. Then, 20 ml. each of ethanol and nitrobenzene were added, the volatile solvents removed at water aspirator pressure, and the nitrobenzene residue was refluxed 10 minutes. On cooling and trituration with ether, the desired product precipitated and was removed by filtration and recrystallized from carbon tetrachloride giving white needles in 70% yield.

4-Bromoisoquinoline.

This compound, m.p. 40-43°, leading to **11**, was purchased from Columbia Organic Chemicals Co.

4-Bromo-1-phenylisoquinoline.

This compound (new), m.p. 123.5-124.5°, leading to **12**, was made in 60% yield by bromination of 1-phenylisoquinoline according to the method of Eisch (21). 1-Phenylisoquinoline, m.p. 93-94°, was made in 70% yield by azomethine addition to isoquinoline (22).

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(1) This research was supported by a contract with the U. S. Army Medical Research and Development Command (DA-49-193-MD-2752) and is Contribution No. 535 to the Army Research Program on Malaria.

(2) Post-doctoral student and principal contributor to this research.

(3) Pre-doctoral students.

(4) To whom correspondence should be sent.

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(11) Melting points were observed with a Thomas Hoover apparatus. Carbon, hydrogen, and nitrogen analyses on all new compounds were done by Galbraith Laboratory and were within 0.2% of the theoretical value except that on **12** which was 0.27% high in carbon. Nmr spectra of all compounds support the assigned structures. Analytical data and nmr spectra are on file. NSF Grant 1683 is acknowledged for the purchase of an nmr spectrometer and NSF-SDP, GU-2057 for the purchase of a mass spectrometer, instruments which greatly aided the research work.

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Received January 11, 1969

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