[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Some Substituted 2-Arylquinolines

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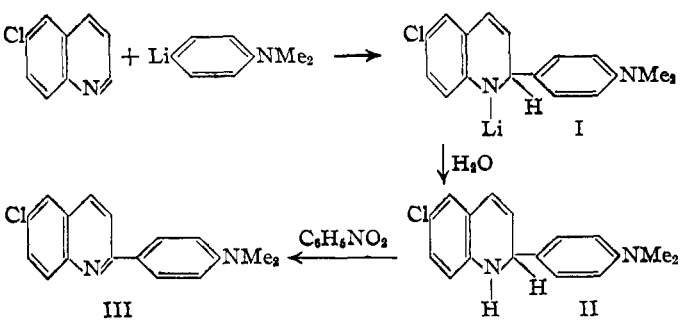
In connection with a study of the anti-malarial properties of certain substituted 2-arylquinolines,[1] the addition of aryllithium compounds to the azomethine linkage of quinoline and related types[2,3] proved to be a useful synthetic technique for the preparation of the needed intermediates. The present work has involved an examination of the applicability of this reaction to a variety of dialkylaminoaryllithium compounds in their reaction of addition with quinoline, substituted quinolines, benzo[*f*]quinoline, acridine and 2-arylpyridines.

The basic reaction involved is represented below using *p*-dimethylaminophenyllithium and 6-chloroquinoline. Addition of the aryllithium to 6-chloroquinoline followed by hydrolysis of the N-lithio compound (I) gives 1,2-dihydro-2-(4′-dimethylaminophenyl)-6-chloroquinoline (II) which on oxidation with nitrobenzene is converted to 2-(4-dimethylaminophenyl)-6-chloroquinoline (III). Isolation of the intermediate dihydro compound II was not effected in the majority of the types studied, and only the oxidized form III appeared in the product from the hydrolysis of the initial addition compound I. This may be due either to oxidation by contact with air of the dihydro compound II or to loss of lithium hydride from the addition compound I prior to hydrolysis.



2-(4′-Dimethylaminophenyl)-pyridine[4] reacted with *p*-dimethylaminophenyllithium to form 2,6-bis-(4′-dimethylaminophenyl)-pyridine by the addition of the organolithium compound to the azomethine linkage in the 1,6-position in the 2-arylpyridine. The possibility of addition of the organometallic to the 1,2-azomethine linkage of the 2-arylpyridine to give 2,2-bis-(4′-dimethylaminophenyl)-pyridine has not been excluded, but it appeared unlikely that the organometallic compound would add to the 2-substituted 1,2-position as long as the 6-position of the pyridine ring is open. It should be pointed out, however, that aryllithium compounds have been shown to add to the 1,2-position of 2-arylquinolines.[5]

p-Dimethylaminophenyllithium added to acridine in the 1,9-position corroborating the earlier work of Ziegler[6] and Bergmann[7] who showed that *n*-butyllithium and phenyllithium with acridine gave 9-*n*-butyl- and 9-phenylacridane. 9-(4′-Dimethylaminophenyl)-acridane was isolated in 61% yield and was converted to 9-(4′-dimethylaminophenyl)-acridine by nitrobenzene in quantitative yield.

Experimental

Compounds formed by the addition of various aryllithium compounds to quinoline and quinoline derivatives are summarized in Table I. In order to illustrate the general procedure used, the preparation of 2-(4′-dimethylaminophenyl)-6-chloroquinoline from 6-chloroquinoline and *p*-dimethylaminophenyllithium is described.

***p*-Dimethylaminophenyllithium** was prepared by addition of 55 g. (0.275 mole) of *p*-bromodimethylaniline to 6.0 g. (0.87 g. atom) of lithium metal in ether. The yield of organometallic compound (determined by the titration of an aliquot with standard acid)[8] was in the range 85–95% in various preparations. Other aryllithium compounds prepared in this work and the yield[9] obtained were *p*-diethylaminophenyl- (84%), *o*-dimethylaminophenyl- (92%)[9] and *m*-dimethylaminophenyl- (94%).[9]

1,2-Dihydro-2-(4′-dimethylaminophenyl)-6-chloroquinoline (II).—To a solution of 16.5 g. (0.10 mole) of 6-chloroquinoline in 100 ml. of ether was added a solution of 0.10 mole of *p*-dimethylaminophenyllithium in 175 ml. of ether. The addition required thirty minutes, and a yellow precipitate formed during this time. The reaction mixture was stirred for an additional thirty minutes and then hydrolyzed by the addition of 100 ml. of water. The ether layer was separated and extracted with three portions of dilute hydrochloric acid. The combined extracts were poured into excess dilute ammonium hydroxide which precipitated a yellow, oily solid. This solid was recrystallized twice from petroleum ether (b. p. 80–110°) and gave 12.5 g. (44%) of light yellow needles which melted at 95–96°.

Anal. Calcd. for $C_{17}H_{17}N_2Cl$: N, 9.84. Found: N, 9.94.

2-(4′-Dimethylaminophenyl)-6-chloroquinoline.—A solution of 6.5 g. (0.023 mole) of 1,2-dihydro-2-(4′-dimethylaminophenyl)-6-chloroquinoline in 25 ml. of nitrobenzene was heated to boiling. Cooling the solution precipitated 5 g. of orange-yellow small crystals. These were recrystallized from benzene to give 4.5 g. (69%) of light yellow prisms melting at 200–201°.

(1) Gilman, Towle and Spatz, THIS JOURNAL, **68**, 2017 (1946).

(2) Gilman and Spatz, *ibid.*, **66**, 621 (1944).

(3) Gilman, Christian and Spatz, *ibid.*, **67**, 979 (1945).

(4) Prepared by addition of *p*-dimethylaminophenyllithium to pyridine; *cf.* "Organic Syntheses," Coll. Vol. II, 1943, p. 517.

(5) Gilman and Gainer, *ibid.*, **69**, 877 (1947).

(6) Ziegler and Zeiser, *Ann.*, **485**, 174 (1931).

(7) Bergmann, Blum-Bergmann and Christiani, *ibid.*, **483**, 80 (1930).

(8) Gilman, Wilkinson, Fishel and Meyers, *ibid.*, **45**, 150 (1923).

(9) Preparations of the *o*- and *m*-bromodimethylaniline, used for the formation of the corresponding aryllithium compounds, were made by the action of dimethyl sulfate and sodium carbonate on *o*- and *m*-bromoaniline in accordance with the procedure of Abbott, Doctoral Dissertation, Iowa State College, 1942, p. 163.

TABLE I

DERIVATIVES OF QUINOLINE

Derivative	M. p. or b. p. °C.	Mm.	Yield, %	Formula	Nitrogen, % Calcd.	Found	M. p., °C. picrate	Formula	Nitrogen, % Calcd.	Found
2-(4'-Diethylaminophenyl)-	99-99.5		27	$C_{19}H_{20}N_2$	10.13	10.17	210	$C_{25}H_{23}N_5O_7$	13.88	13.82
2-(4'-Diethylaminophenyl)-6-chloro-	123		30	$C_{19}H_{19}ClN_2$	9.03	9.25	224-226	$C_{25}H_{22}ClN_5O_7$	13.01	12.98
2-(4'-Diethylaminophenyl)-8-methyl-	110		26	$C_{20}H_{22}N_2$	9.65	9.84	187	$C_{26}H_{25}N_5O_7$	13.50	13.75
2-(4'-Diethylaminophenyl)-6-methoxy-	151.5-152		22	$C_{20}H_{22}N_2O$	9.15	9.40	226	$C_{26}H_{25}N_5O_8$	13.09	13.22
2-(2'-Dimethylaminophenyl)-	216-218	3	34	$C_{17}H_{16}N_2$	11.30	11.39	181	$C_{23}H_{19}N_5O_7$	14.69	14.90
2-(2'-Dimethylaminophenyl)-8-methyl-	153-159	0.1	35	$C_{18}H_{18}N_2$	10.69	10.98	171.5-172	$C_{24}H_{21}N_5O_7$	14.28	14.32
2-(3'-Dimethylaminophenyl)-	103-104		7	$C_{17}H_{16}N_2$	11.30	11.10	170-171	$C_{23}H_{19}N_5O_7$	14.69	14.51
2-(3'-Dimethylaminophenyl)-8-methyl-	168-171	0.1	26	$C_{18}H_{18}N_2$	10.69	10.96	189	$C_{24}H_{21}N_5O_7$	14.28	14.30
2-(2'-Dimethylamino-5'-methylphenyl)-	212-217	0.1	26	$C_{18}H_{18}N_2$	10.69	10.91	178	$C_{24}H_{21}N_5O_7$	14.28	14.41
2-(2'-Dimethylamino-5'-methylphenyl)-8-methyl-	200-202	0.1	28	$C_{19}H_{20}N_2$	10.14	10.36	176-177	$C_{25}H_{23}N_5O_7$	13.88	13.60
2-(4'-Dimethylaminophenyl)-6-chloro-	200-201		33	$C_{17}H_{15}ClN_2$	9.91	10.01	221	$C_{23}H_{18}ClN_5O_7$	13.70	13.58

Anal. Calcd. for $C_{17}H_{15}ClN_2$: N, 9.91. Found: N, 10.01.

The picrate derivative consisted of orange-red minute crystals which melted at 221° with decomposition.

Anal. Calcd. for $C_{23}H_{18}ClN_5O_7$: N, 13.70. Found: N, 13.58.

In Table II are listed the products from the reaction of dialkylaminophenyllithiums with some compounds other than quinoline which contain the azomethine linkage.

TABLE II

MISCELLANEOUS PRODUCTS FROM ADDITION OF ARYLLITHIUMS TO AZOMETHINE LINKAGES

Product R' = 4'-dimethylamino-phenyl R = 4'-diethylaminophenyl	M. p., °C.	Yield, %	Nitrogen, % Calcd.	Found
2-(R)-pyridine[a]	79–80[g]	31	12.39	12.68
2,6-Bis-(R')-pyridine[b]	246–248	22	13.23	13.33
3-(R')-benzo(f)quinoline[c]	249–250[d]	56	...	...
9-(R')-acridine	285–286[e]	61	...	...
9-(R)-acridine	196–197[f]	6	...	...

[a] Formula, $C_{15}H_{18}N_2$. Picrate derivative, m. p. 188°, calcd. for $C_{21}H_{21}N_5O_7$: N, 15.40. Found: N, 15.30. [b] Formula, $C_{21}H_{13}N_3$. Prepared by reaction of *p*-dimethylaminophenyllithium and 2-(4'-dimethylaminophenyl)-pyridine. [c] Picrate derivative, m. p. 238–239°. Calcd. for $C_{21}H_{22}N_3$: N, 13.29. Found: N, 13.11. [d] Prepared by Sachs and Steinert, *Ber.*, **37**, 1743 (1904), by another method and reported to melt at 245°. [e] Prepared by Ullmann, Bader and Lobhardt, *Ber.*, **40**, 4796 (1907), by another method and reported to melt at 279°. [f] Ullmann and co-workers, *loc. cit.*, report 197° as the m. p. of this compound. [g] B. p. 205–210° (0.1 mm.).

Table III lists the intermediate dihydro compounds isolated in this work.

During the course of earlier work in this laboratory on 2-arylquinolines,[1] it was noted that 2-(4'-dimethylaminophenyl)-quinoline in dilute solution caused a severe dermatitis when brought into contact with the skin. While individuals differed markedly in their susceptibility, it appeared in a few orienting experiments that solutions as dilute as 0.01% of 2-(4'-dimethylaminophenyl)-quinoline in benzene caused erythema at the point of application in 50% of eight individuals tested. Tests were conducted by application of approximately two drops of a benzene solution of known concentration to the upper arm of the test subject. More concentrated solutions caused severe

TABLE III

DIHYDRO INTERMEDIATE COMPOUNDS FROM ADDITION OF ARYLLITHIUM COMPOUNDS TO AZOMETHINE LINKAGES

Compound R = -(4'-dimethylamino-phenyl)	M. p., °C.	Yield, %	Formula	Nitrogen, % Calcd.	Found
1,2-Dihydro-2-R-6-chloro-quinoline	95–96	44	$C_{17}H_{17}ClN_2$	9.84	9.94
3,4-Dihydro-3-R-benzo(f)-quinoline	138–139	62	$C_{21}H_{20}N_2$	9.35	9.44
9-R-acridane	196	61	$C_{21}H_{20}N_2$	9.33	9.24

reactions similar in most respects to the commonly known effects of poison ivy.

All of the compounds prepared in this research were tested for possible activity in causing dermatitis, and only the 2-(4'-diethylaminophenyl)-quinoline showed activity in this respect. This compound was, however, only approximately one tenth as active as 2-(4'-dimethylaminophenyl)-quinoline.

A number of other quinoline and pyridine types available from other research programs in this laboratory were evaluated for possible skin irritation activity. Of forty of these types tested, the following showed some activity: 2-(4'-aminophenyl)-quinoline,[5] 2-(4'-[2",5"-dimethyl-1"-pyrryl]-phenyl)-quinoline,[10] 1-(2'-pyridyl)-2-(3"-nitrophenyl)-ethylene,[11] and 2-(4'-dimethylaminophenyl)-8-methylquinoline.[1]

None of these compounds was as active as the 2-(4'-dimethylaminophenyl)-quinoline.

Summary

1. Several new 2-arylquinolines have been prepared by addition of aryllithium compounds to the azomethine linkage of quinoline and some of its derivatives followed by hydrolysis and oxidation of the intermediate dihydro compound.

2. Similar addition reactions have been carried out with pyridine, acridine, and benzoquinoline types.

3. Some observations have been made relating to the effect of skin irritation caused by certain 2-arylquinoline types.

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(10) Prepared by Dr. S. M. Spatz.

(11) Prepared by Mr. George Karmis.