Summary

1. The suitability of sodium amide for effecting the Claisen acylation of esters has been studied. Various self and mixed-ester condensations have been effected satisfactorily using this reagent. The results are compared with analogous cases using sodium alkoxides.

2. The β-keto esters from the mixed-ester condensations have been cleaved to the corresponding ketones.

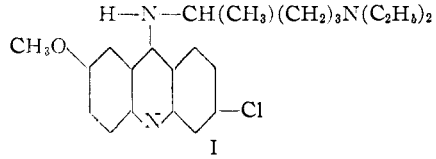
DURHAM, N. C. RECEIVED JULY 29, 1946

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

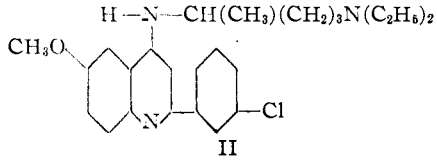
Some 7-Chloroquinolines Patterned as "Open Models" of Atebrin

BY HENRY GILMAN AND ROBERT A. BENKESER

In earlier papers[1] the syntheses of several "open models" of atebrin (I) were described.



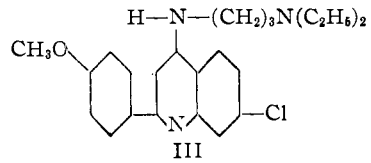
I



II

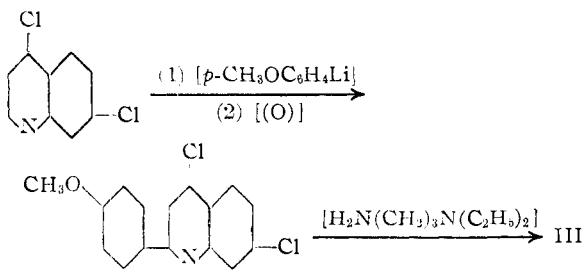
One[1a] of these (II) has a chlorophenyl group in place of the fused chlorobenzo group in atebrin.

It appeared particularly appropriate, in extension of these studies, to open the opposite benzo group of (I) to obtain a homolog like 2-*p*-methoxyphenyl - 7 - chloro - 4 - (3 - diethylaminopropylamino)-quinoline (III).



III

The synthesis of this compound was accomplished by the following sequence of reactions



The intermediate dihydro compound was oxidized by picric acid, and the picrate was incidentally helpful in isolating the product. It is interesting to note in connection with the RLi reaction that the 4-chlorine in the quinoline which is sufficiently reactive to undergo condensation with 3-diethylaminopropylamine, but relatively unreactive toward the RLi compound, does not show any deactivating effect on the anil linkage.[2]

Because a nuclear methyl group or a chlorine is effective in some types[1a] examined for experimental avian malaria, a related series of reactions was used for the preparation of 2-*p*-tolyl-7-chloro-4-(3-diethylaminopropylamino)-quinoline and of 2-*p*-chlorophenyl-7-chloro-4-(3-diethylaminopropylamino)-quinoline. The *p*-chlorophenyllithium was prepared by a halogen-metal interconversion reaction[3] between *p*-chlorobromobenzene and *n*-butyllithium.

In extension of studies of some compounds with sulfur-containing side-chains,[4] 2-phenyl-7-chloro-4-quinolyl 2-diethylaminoethyl sulfide was synthesized from 2-phenyl-4,7-dichloroquinoline and sodium 2-diethylaminoethyl mercaptide. The simple, unsubstituted 2-phenyl compound was used because such types are known to be effective occasionally.[1a]

Experimental

2-Aryl-4,7-dichloroquinolines.—In a typical experiment, there was added with stirring to 32 cc. of a solution containing 0.034 mole of phenyllithium cooled to 0°, 5 g. (0.026 mole) of 4,7-dichloroquinoline in 60 cc. of ether cooled in an ice-bath. The addition was complete in three and one-half minutes; the solution was stirred an additional two and one-half minutes; and hydrolysis was effected by the addition of 30 cc. of water. The ether layer was separated, dried, the solvent was removed under reduced pressure; the red, oily residue was dissolved in a small volume of 95% ethanol, and this solution was added to a hot solution of 7 g. of picric acid in 40 cc. of 95% ethanol. The solid, red picrate which precipitated immediately was filtered, dried, and decomposed by refluxing fifteen minutes with 1:1 ammonium hydroxide. The dark red solution was filtered while still hot, and after washing the dark brown precipitate several times with warm water it was crystallized from 95% ethanol (with the use of Norit) to yield 2.5 g. (35%) of 2-phenyl-4,7-dichloroquinoline melting at 99–100°.

Table I contains the 2-aryl-4,7-dichloroquinolines prepared by this general procedure.

(1) (a) Gilman and Spatz, THIS JOURNAL, **66**, 621 (1944); (b) Gilman, Christian and Spatz, *ibid.*, **68**, 979 (1946); Gilman, Towle and Spatz, *ibid.*, **68**, 2017 (1946).

(2) Gilman and Spatz, *ibid.*, **62**, 446 (1940); **63**, 1553 (1941).

(3) Gilman, Langham, and Moore, *ibid.*, **62**, 2327 (1940); Langham, Brewster, and Gilman, *ibid.*, **63**, 545 (1941); Gilman, Langham, and Jacoby, *ibid.*, **61**, 106 (1939); Gilman and Jacoby, *J. Org. Chem.*, **3**, 108 (1938).

(4) Gilman and Woods, THIS JOURNAL, **67**, 1843 (1945); Gilman and Tolman, *ibid.*, **67**, 1847 (1945).

TABLE I

2-ARYL-4,7-DICHLOROQUINOLINES

4,7-$Cl_2C_9H_5N$, mole	RLi	Product	Solvent	Yield, %	M. p., °C.	Anal., % Cl Calcd.	Found
0.026	*p*-$CH_3C_6H_4Li$ (0.034 mole)	$C_{16}H_{11}NCl_2$	95% ethanol	43	124–125	24.6	24.5
.052	*p*-ClC_6H_4Li	$C_{15}H_8NCl_3$	Methylcellosolve	57	167–168	34.5	33.6
.052	*p*-$CH_3OC_6H_4Li$[a]	$C_{16}H_{11}NOCl_2$	Dil. ethanol	58	121–121.5	23.3	23.0
.026	C_6H_5Li (0.034 mole)	$C_{15}H_9NCl_2$	95% ethanol	35	99–100	25.9	25.4

[a] The *p*-methoxyphenyllithium was prepared in essential accordance with some directions of John T. Edward. To 3.8 g. (0.46 g. atom) of finely cut lithium suspended in 160 cc. of ether was added, over a twelve-minute period, 37.4 g. (0.2 mole) of *p*-bromoanisole in 150 cc. of ether. Cooling by an ice-bath was necessary during the addition to control the reaction. When addition was completed, the dark solution was stirred for an additional eight minutes (spontaneous refluxing ceased at the end of this period). The flask was then immersed in ice for five minutes, the contents filtered in a nitrogen atmosphere; and to 200 cc. of this solution cooled to 0° was added the ether solution of 4,7-dichloroquinoline which had been cooled in ice.

TABLE II

2-ARYL-7-CHLORO-4-(3-DIETHYLAMINOPROPYLAMINO)-QUINOLINES

2-Aryl-4,7-dichloroquinoline Mole	$(C_2H_5)_2N(CH_2)_3NH_2$, mole	Product[a]	Yield, %	M. p., °C.	Anal., % Cl Calcd.	Found
2-*p*-ClC_6H_4- 0.039	0.078	$C_{22}H_{25}N_3Cl_2$	57	127 –128	17.6	17.2
2-*p*-$CH_3C_6H_4$- 0.014	0.032	$C_{23}H_{28}N_3Cl$	42	119.5–120.5	9.3	9.2
2-*p*-$CH_3OC_6H_4$- 0.029	0.062	$C_{23}H_{28}ON_3Cl$[b]	52	118 –119	8.9	8.5

[a] The solvent used for crystallization was dilute ethanol. [b] The dihydrochloride melts at 245–255°. *Anal.* Calcd. for $C_{23}H_{28}ON_3Cl{\cdot}2HCl$: Cl, 15.1. Found: Cl, 15.6.

2-Aryl-7-chloro-4-(3-diethylaminopropylamino)-quinolines.—A mixture of 4.2 g. (0.014 mole) of 2-*p*-tolyl-4,7-dichloroquinoline, 4.2 g. (0.032 mole) of 3-diethylaminopropylamine, 10 g. of phenol, and a trace of sodium iodide was heated with stirring at 160° for twenty-three hours. The resulting mixture was poured into 130 cc. of 35% sodium hydroxide solution, and after extracting three times with 100-cc. portions of ether the extracts were dried over sodium sulfate and the solvent was removed under reduced pressure, leaving a residue that was part crystalline and part oily. Crystallization from dilute ethanol gave 2.2 g. of 2-*p*-tolyl-7-chloro-4-(3-diethylaminopropylamino)-quinoline which melted at 119.5–120.5°.

Table II contains the 2-aryl-7-chloro-4-(3-diethylaminopropylamino)-quinolines prepared by this general procedure.

2-Phenyl-7-chloro-4-quinolyl 2-Diethylaminoethyl Sulfide Dihydrochloride.—To sodium ethoxide prepared from 40 cc. of absolute ethanol and 0.23 g. (0.01 g. atom) of sodium was added 1.33 g. (0.01 mole) of 2-diethylaminoethyl mercaptan[5] in 10 cc. of absolute ethanol. To the resulting mercaptide was added 2 g. (0.007 mole) of 2-phenyl-4,7-dichloroquinoline, and the mixture was refluxed for three hours. After cooling and filtering, the ethanol was removed under reduced pressure; the oily residue was dissolved in ether; the mixture filtered again; and on the addition of ethanolic hydrogen chloride an oil separated which solidified after cooling and scratching. Crystallization from an ethanol–ether mixture gave 2.5 g. (81%) of a yellowish-white product melting over the range of 165–175°.

Anal. Calcd. for $C_{21}H_{23}N_2ClS{\cdot}2HCl$: Cl, 24.0. Found: Cl, 23.5.

(5) Gilman and Woods, THIS JOURNAL, **67**, 1843 (1945); Albertson and Clinton, *ibid.*, **67**, 1222 (1945); Gilman, Plunkett, Tolman, Fullhart, and Broadbent, *ibid.*, **67**, 1845 (1945).

Summary

The following "open model" homologs of atebrin have been prepared by addition of appropriate RLi compounds to 4,7-dichloroquinoline followed by condensation with 3-diethylaminopropylamine: 2-*p*-methoxyphenyl - 7 - chloro - 4-(3 - diethylaminopropylamino)-quinoline, 2-*p*-chlorophenyl - 7 - chloro - 4 - (3 - diethylaminopropylamino)-quinoline, and 2-*p*-tolyl-7-chloro-4-(3-diethylaminopropylamino)-quinoline.

In addition, 2-phenyl-7-chloro-4-quinolyl 2-diethylaminoethyl sulfide dihydrochloride has been synthesized from 2-phenyl-4,7-dichloroquinoline and sodium 2-diethylaminoethyl mercaptide.

AMES, IOWA RECEIVED MAY 14, 1946