Preparation of 2,4-Diarylquinolines and Substituted Dihydrobenz-[c]acridines by the Condensation of Certain C(α),O-Dilithiooximes with 2-Aminobenzophenones.

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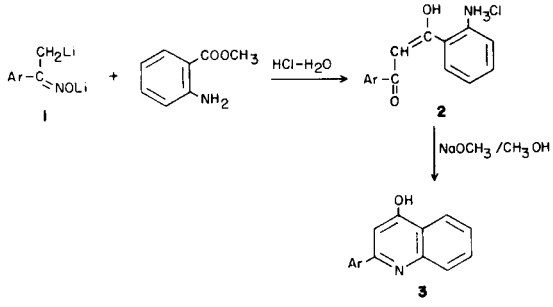
C(α),O-Dilithiooximes were prepared in an excess of lithium diisopropylamide and condensed with several 2-aminobenzophenones, followed by acid hydrolysis of the oximes to the ketones, which then underwent cyclodehydration and linear dehydration to give substituted quinolines or dihydrobenz[c]acridines.

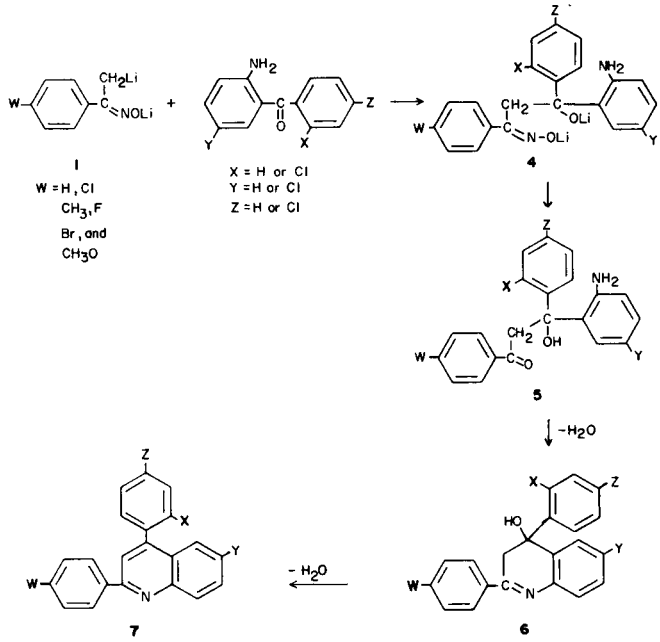
J. Heterocyclic Chem., **18**, 649 (1981).

In a preliminary study (2), we reported a Claisen-type condensation of C(α),O-dilithiooximes **1** with methyl anthranilate and isatoic anhydrides. The presumed intermediates were neutralized and hydrolyzed to give isolable keto-hydrochlorides **2**. Upon treatment of **2** with sodium methoxide in methanol, cyclization occurred to give the substituted 4-quinolinol **3**.



While the condensation of **1** with aldehydes and ketones has been reported (3), the condensation of **1** with ketones, such as 2-aminobenzophenone, has not been attempted. If this condensation was successful, and subsequent hydrolysis of the oxime to free the ketone was followed by cyclodehydration and linear dehydration, a substituted quinoline or related material would result. Interestingly, another preparation for similarly substituted quinoline derivatives (*e.g.*, 2,4-diaryl) involved the condensation of phenylacetylenes with *N*-phenylimidoyl chlorides followed by neutralization of resulting salts with ammonium hydroxide (4).

During the present investigation, several dilithiooximes **1** were prepared in an excess of lithium diisopropylamide (oxime:LDA - 1:3) and condensed with either 2-aminobenzophenone, 2-amino-5-chlorobenzophenone, 2-amino-4′-chlorobenzophenone or 2-amino-2′,5-dichlorobenzophenone. Each presumed intermediate **4** was neutralized with dilute hydrochloric acid and heated under reflux, which transformed the oxime to the ketone **5** (hydrolysis). This reaction was followed by cyclodehydration and linear dehydration to give the 2,4-diarylquinoline **7**.



Whether the initial condensation of the lithiated oxime involves the neutral aminobenzophenone to give **4**, or a lithiated ketoanilide is uncertain (5). Our best results were obtained, however, when an excess of lithium diisopropylamide (LDA) was used. The initial studies (2) indicate that acid hydrolysis of the oxime to ketone **5** is the first step. While the aniline nitrogen in **5** can be protonated to give the hydrochloride under these conditions, there probably exists an equilibrium, which can be readily shifted in favor of the free amino function, due to the warm two phase system (water and THF). Amine **5** probably underwent cyclodehydration to the hydroxy-dihydroquinoline **6** before linear dehydration; final loss of the elements of water resulted in the aromatic heterocyclic products [**7a-i** and **9a-c** (Table)]. Although the nature of the *para*-substituent (*e.g.*, methoxy, chloro) on the parent oxime and the chloro (or dichloro) aminobenzophenone may influence the reaction, as noted by the variation in yield of products from 37-100% (see Table), the reaction sequence of hydrolysis of oxime, cyclodehydration, and linear dehydration does concur with our observations (6).

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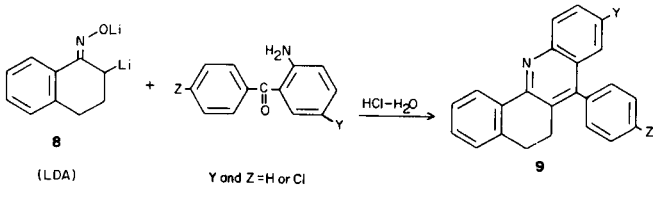
Table 1
Susbstituted Quinolines and Dihydrobenz[*c*]acridines

Compound Number	Name	Empirical Formula	Yield (%)	Melting Point (°C)	Elemental Analysis Calculated C	H	N	Found C	H	N	Spectral Data - NMR (d) δ ppm
7a	2-(4-chlorophenyl)-4-phenylquinoline	$C_{21}H_{14}ClN$ (a)	65	106 (c)	-	-	4.44	-	-	4.18	6.97-8.27 (ArH) ($CDCl_3$)
7b	2-(4-bromophenyl)-4-phenylquinoline	$C_{21}H_{14}BrN$ (a)	50	127	70.01	3.92	3.89	69.74	3.87	3.73	7.10-8.33 (ArH) ($CDCl_3$)
7c	6-chloro-2-(4-fluorophenyl)-4-phenylquinoline	$C_{21}H_{13}ClFN$ (a)	34	130-131	75.56	3.93	4.20	75.39	4.20	4.04	7.07-8.43 (ArH) ($CDCl_3$)
7d	2-(4-bromophenyl)-6-chloro 4-phenylquinoline	$C_{21}H_{13}BrClN$ (b)	72	174	63.90	3.32	3.55	63.64	3.16	3.53	7.20-8.23 (ArH) ($CDCl_3$)
7e	6-chloro-2-(4-methylphenyl)-4-phenylquinoline	$C_{22}H_{16}ClN$ (a)	100	132	80.11	4.89	4.25	80.17	4.81	4.20	2.37 ($ArCH_3$) and 7.10-8.33 (ArH) ($CDCl_3$)
7f	2-(4-bromophenyl)-6-chloro 4-(2-chlorophenyl)-quinoline	$C_{21}H_{12}BrCl_2N$ (b)	32	174-175	58.78	2.82	3.26	58.94	3.05	3.27	7.07-8.40 (ArH) (CF_3COOH and DMSO-d_6)
7g	6-chloro-2-(4-methoxy phenyl)-4-phenylquinoline	$C_{22}H_{16}ClNO$ (a)	75	117	76.41	4.66	4.05	76.44	4.79	3.96	3.80 ($ArOCH_3$) and 6.80-8.30 (ArH) ($CDCl_3$)
7h	2,4-di-(4-chlorophenyl)-quinoline	$C_{21}H_{13}Cl_2N$ (b)	91	143	72.01	3.74	4.00	71.96	3.83	3.90	7.27-8.43 (ArH) (CF_3COOH)
7i	2-(4-methylphenyl)-4-(4-chlorophenyl)-quinoline	$C_{22}H_{16}ClN$ (a)	76	102-103	80.11	4.89	4.25	80.15	5.02	4.35	2.37 ($ArCH_3$) and 7.03-8.20 (ArH) ($CDCl_3$)
9a	7-(4-chlorophenyl)-5,6-dihydrobenz[*c*]acridine	$C_{23}H_{16}ClN$ (b)	76	188-189	80.81	4.72	4.10	80.84	4.53	3.94	3.00 (-CH_2CH_2-) and 7.17-8.53 (ArH) (CF_3COOH and DMSO-d_6)
9b	7-phenyl-5,6-dihydro-benz[c]acridine	$C_{23}H_{17}N$ (a)	79	148-149	89.87	5.57	4.56	89.80	5.70	4.34	2.80 (-CH_2CH_2-) and 6.93-8.06 (ArH) ($CDCl_3$)
9c	9-chloro-7-phenyl-5,6-dihydrobenz[*c*]-acridine	$C_{23}H_{16}ClN$ (a)	68	145	80.81	4.72	4.10	80.55	4.88	4.07	2.77 (-CH_2CH_2-) and 7.03-8.63 (ArH) ($CDCl_3$)

(a) Recrystallized from ethanol-water. (b) Recrystallized from ethanol-water-benzene. (c) Lit. m.p. 104°, See ref. (4). (d) Infrared spectra (Perkin Elmer 700 Infrared Spectrometer) did not contain carbonyl and amino absorptions and did contain numerous aromatic absorptions, *e.g.* 6.33 mμ.

Alpha-tetralone oxime was metalated to dilithiooxime **8** (excess LDA - 1:3), and **8** was condensed with aminobenzophenones, hydrolyzed, cyclized, and linearly dehydrated to give several 5,6-dihydrobenz[*c*]acridines **9a-c** in 68-79% yield.



Diarylquinoline **7a**, prepared by this procedure, had a melting point that corresponded well with the literature (4). Proton magnetic resonance spectra displayed pendant methyl and methoxy group absorption where applicable (Table); 5,6-dihydrobenz[*c*]acridines **9a-c**, displayed isochronous dimethylene absorptions from δ 2.77-3.0 ppm (Table).

The new synthon described requires the use of oximes which are one step away from readily available *C*(α)-ketones (7); the straight-forward experimental procedure is readily reproduced by someone not very familiar with strong-base synthetic techniques.

EXPERIMENTAL

Combustion analyses were performed by Dr. G. I. Robertson's Microanalytical Laboratory, 73 West End Ave., Florham Park, NJ 07932. Nmr spectra were obtained from a Varian Associates EM-300X Nuclear Magnetic Resonance Spectrometer, and chemical shifts are reported (Table) in δ ppm downfield from an internal tetramethylsilane (TMS) standard. Tetrahydrofuran (THF) was distilled from sodium (benzophenone) immediately before use. The *n*-butyllithium was purchased from the Lithium Corporation of America, Bessemer City, North Carolina. The oximes were prepared by a standard procedure (7) and stored in a vacuum desiccator until used. Melting points were taken in open capillary tubes in a Thomas-Hoover melting point apparatus and are uncorrected.

General Procedures for Preparation of Quinolines and Dihydrobenz[c]acridines.

A 0.066-mole sample of *n*-butyllithium was cooled to 0° under a dry nitrogen atmosphere, and 0.066 mole of diisopropylamine dissolved in 25-30 ml. of dry THF was added during 5 minutes. The resulting solution was stirred for 20-30 minutes. After 0.02 mole of oxime dissolved in 25-35 ml. of dry THF was added, the solution was stirred again at 0° for an additional 45 minutes (metalation time *ca.* 45 minutes). The resulting dilithiooxime was treated with 0.022 mole of the 2-aminobenzophenone (added during 5 minutes), dissolved in 25-30 ml. of THF, and stirred for 60 min. (condensation time *ca.* 1 hour). Condensation was terminated by addition of 100 ml. of 3*N* hydrochloric acid. The two-phase mixture was stirred and heated under reflux for at least 1 hour (reflux time *ca.* 1 hour), cooled to room temperature, poured into a large flask along with 100 ml. of ether and carefully neutralized with sodium bicarbonate. The layers were separated, and the aqueous layer was extracted with two 50-75 ml. portions of ether. The organic layers were combined, not dried, and concentrated (Rotovac). The resulting oil or residue was usually crystallized and recrystallized from ethanol and water. In the case of some dihalogenated products, a benzene-ethanol-water solution was used for recrystallization.

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REFERENCES AND NOTES

(1) To whom correspondence should be directed.

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(4) R. R. Schmidt, *Angew. Chem.*, **76**, 991 (1964).

(5) The electron-withdrawing *ortho*-substituted carbonyl group, may enhance the acidity of anilino hydrogens and cause some hydrogen abstraction by lithium diisopropylamide.

(6) See: C. F. Beam, R. M. Sandifer, R. S. Foote, and C. R. Hauser, *Chem. Ind.*, 487 (1976). We have not observed linear dehydration readily occurring under these reaction conditions, even though the resulting double bond would be in conjugation with the benzene ring.

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