The Preparation of Quinolines and Related Fused-Ring Heterocycles from the Dianions of Benzoylacetone, Certain Cyclic Ketone Oximes, or Certain Substituted Hydrazones

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C(α),*O*-Dilithiooximes, *C*(α),*N*-dilithiobenzoylhydrazones, or *C*(α),*N*-dilithiocarboalkoxyhydrazones were prepared in an excess of lithium diisopropylamide (LDA) and condensed with 2-aminobenzophenones, or isatoic anhydrides to give intermediates that were treated with aqueous acid, which caused their hydrolysis, cyclodehydration and/or linear dehydration to give products which were substituted quinolines or related fused-ring heterocycles (*e.g.*, cycloheptaquinolines). Dilithiobenzoylacetone was condensed with 2-aminobenzophenones, which was followed by acid cyclodehydration to substituted 2-phenacylquinolines.

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Introduction.

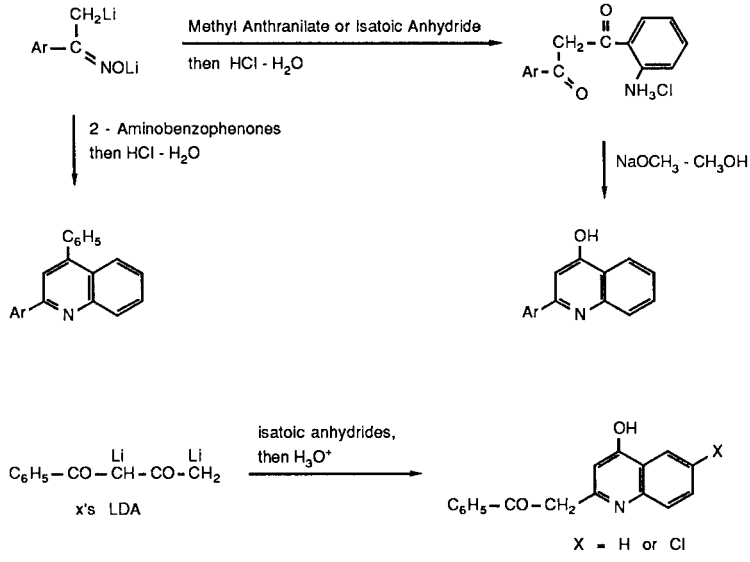
Several of our recent preliminary and follow-up studies have dealt with the following situations: the reactions of C(α)-dianions of oximes [3] or substituted hydrazones [4-8], such as their condensation-cyclizations with isatoic anhydrides, anthranilate esters, or 2-aminobenzophenones, to give a variety of substituted quinolines; and the condensation of dianions of benzoylacetone with isatoic anhydrides followed by cyclization of intermediates to give 2-phenacyl-4-quinolinols.

These studies did not include some of the following reaction-type/reactions, which have been the focus of this investigation: more aliphatic ketones could be utilized for the preparation of entry compounds (*e.g.*, benzoylhydrazones); benzoylhydrazone and carboalkoxyhydrazones (replacing oximes) could be metalated, condensed with electrophilic reagents, and resulting intermediates could be neutralized, hydrolyzed, and cyclodehydrated to give quinolines and related materials; and the condensation-cyclization of benzoylacetone dianions with 2-aminobenzophenones to give 2-phenacylquinolines.

During this and earlier studies, we observed [9] how much easier it was to hydrolyze (our) benzoylhydrazones and (our) carboalkoxyhydrazones [7,8] to ketone or aldehyde intermediates prior to their cyclodehydration to heterocyclic products. In addition, the similar experimental procedures for benzoylhydrazone [10] and carboalkoxyhydrazone preparations (starting materials) were more rapid than the traditional preparations of oximes [11].

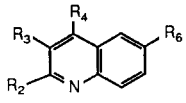
Results.

Cyclopentanone and cyclohexanone oximes are commercially available, and these entry compounds were



Table

Substituted Quinolines and Related Fused-Ring Heterocycles



Compound No.	R_2	R_3	R_4	R_5	Empirical Formula	Yield (%)	Mp (°C)	Elemental Analysis Calcd./Found C	H	N	NMR (δ ppm) Solvent
1	$(CH_2)_3$		4-ClC_6H_4	H	$C_{18}H_{14}ClN$ [a]	71	134-135 [f]	77.28 76.99	5.04 5.13	5.01 4.98	(deuteriochloroform): 1.87-3.57 (m, $(CH_2)_3$) and 6.97-8.30 (m, ArH)
2	$(CH_2)_4$		C_6H_5	Cl	$C_{19}H_{16}ClN$ [a]	52	160-161 [f]	77.68 77.67	5.49 5.41	4.77 4.70	(deuteriochloroform/-DMSO-d_6/trifluoroacetic acid): 1.57-3.77 (m, $(CH_2)_4$) and 6.93-8.53 (m, ArH)
3	$(CH_2)_4$		4-ClC_6H_4	H	$C_{19}H_{16}ClN$ [a]	41	176-177 [f]	77.68 77.39	5.49 5.63	4.77 4.56	(deuteriochloroform): 1.43-3.57 (m, $(CH_2)_4$), and 6.87-8.27 (m, ArH)
4	$(CH_2)_5$		C_6H_5	H	$C_{20}H_{19}N$ [b]	67	109-110 [f]	87.87 87.53	7.01 6.81	5.12 5.17	(deuteriochloroform): 1.37-3.50 (m, $(CH_2)_5$) and 6.93-8.13 (m, ArH)
5	$(CH_2)_5$		4-ClC_6H_4	H	$C_{20}H_{18}ClN$ [b]	80	172-174 [f]	78.04 77.86	5.89 5.96	4.55 4.46	(deuteriochloroform): 1.30-3.57 (m, $(CH_2)_5$), and 6.87-8.20 (m, ArH)
6	$(CH_2)_5$		C_6H_5	Cl	$C_{20}H_{18}ClN$ [b]	92	194-196 [f]	78.04 78.33	5.89 6.12	4.55 4.46	(deuteriochloroform): 1.00-4.07 (m, $(CH_2)_5$), and 6.93-8.27 (m, ArH)
7	$(CH_2)_6$		C_6H_5	Cl	$C_{21}H_{20}ClN$ [b]	36	207-208 [f]	78.37 78.24	6.26 6.10	4.35 4.28	(deuteriochloroform): 1.07-3.47 (m, $(CH_2)_6$) and 6.87-8.17 (m, ArH)
8	$(CH_2)_6$		4-ClC_6H_4	H	$C_{21}H_{20}ClN$ [b]	55	211-212 [f]	78.37 78.55	6.26 6.36	4.35 4.29	(deuteriochloroform/trifluoroacetic acid): 1.03-3.70 (m, $(CH_2)_6$), and 7.00-8.33 (m, ArH)
9	$(CH_2)_{10}$		4-ClC_6H_4	H	$C_{25}H_{28}ClN$ [b]	65	144-146 [f]	79.45 79.73	7.47 7.63	3.71 3.68	(deuteriochloroform): 1.17-6.65 (m, $(CH_2)_{10}$), and 6.78-8.30 (m, ArH)
10	CH_2CH_2-$\underset{\displaystyle CH_3}{\underset{\vert}{C}}$H-$CH_2$		4-ClC_6H_4	H	$C_{20}H_{17}ClN$ [b]	93	140-142 [f]	78.29 78.27	5.58 5.86	4.57 4.60	(deuteriochloroform): 0.77-3.57 (m, CH_2CH_2-$\underset{\displaystyle CH_3}{\underset{\vert}{C}}$H-$CH_2$), and 6.87-8.13 (m, ArH)
11	2,3-dihydro-1,2-1H-indenyl		C_6H_5	Cl	$C_{22}H_{14}ClN$ [b]	21	180-181 [f]	80.61 80.37	4.30 4.02	4.27 4.12	(deuteriochloroform): 3.77 (s, CH_2) and 7.17-8.37 (m, ArH) and 7.00-8.33 (m, ArH)
12	2,3-dihydro-1,2-1H-indenyl		4-ClC_6H_4	H	$C_{22}H_{14}ClN$ [b]	57	173-175 [f]	80.61 79.34	4.30 4.54	4.27 4.33	(deuteriochloroform): 3.80 (s, CH_2) and 7.20-8.43 (m, ArH)
13	1,2,3,4-tetrahydro-1,2-naphthyl		CH_3	H	$C_{18}H_{13}N$ [b]	35	98-100 [k]	88.13 88.11	6.16 6.33	5.71 5.46	(deuteriochloroform): 2.40 (s, $ArCH_3$), 2.87 (s, $-CH_2CH_2-$) [o], and 7.00-8.83 (m, ArH)
14	4-ClC_6H_4	CH_3	C_6H_5	Cl	$C_{22}H_{15}Cl_2N$ [b]	30	150-151 [h]	72.54 72.54	4.15 4.23	3.84 3.84	(deuteriochloroform): 2.17 (s, $ArCH_3$), and 7.27-8.27 (m, ArH)

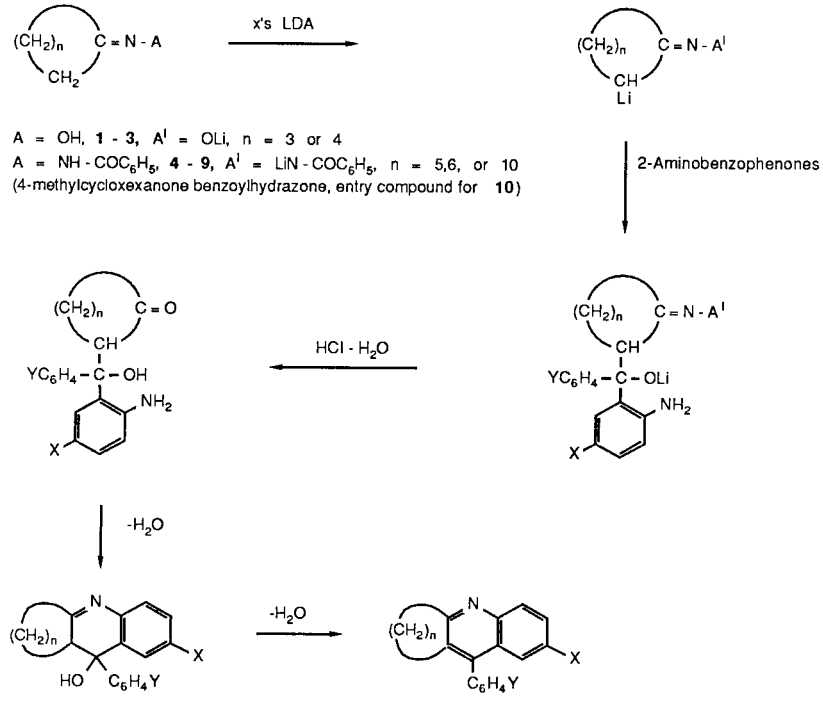
Table (continued)

Compound No.	R_2	R_3	R_4	R_5	Empirical Formula	Yield (%)	Mp (°C)	Elemental Analysis Calcd./Found C	H	N	NMR (δ ppm) Solvent
15	2-naphthyl	H	C_6H_5	Cl	$C_{25}H_{16}ClN$ [c]	44	142-143 [f] [l]	82.07 82.14	4.41 4.49	3.83 3.59	(deuteriochloroform/trifluoroacetic acid): 7.87-8.70 (m, ArH)
16	$C_6H_5COCH_2$-	H	C_6H_5	H	$C_{23}H_{17}NO$ [d]	72	91-92 [f]	85.42 85.63	5.30 5.53	4.33 4.21	(trifluoroacetic acid): 5.30 (s, $COCH_2$), 7.43-8.60 (m, ArH) [p]
17	$C_6H_5COCH_2$-	H	C_6H_4COOH-2	H	$C_{24}H_{17}NO_3$ [d]	50	255-257 [h]	78.46 78.67	4.66 4.58	3.81 3.57	(deuteriochloroform/trifluoroacetic acid): 5.20 (s, $COCH_2$), 7.42-8.67 (m, ArH)/(trifluoroacetic acid): 5.37 (s, CH_2CO), 6.80-8.77 (m, ArH)/IR (Nujol), 1705 (CO) and 2100-2800 cm^{-1} (OH)
18	$C_6H_5COCH_2$-	H	C_6H_5	Cl	$C_{23}H_{16}ClNO$ [d]	79	168-169 [f]	77.20 76.93	4.51 4.35	3.91 3.84	(trifluoroacetic acid): 5.37 (s, $COCH_2$), 6.80 (s, HO-C=CH- vinyl), 7.90-8.77 (m, ArH)/IR (Nujol), 1630 cm^{-1} (ArH-enol form) [p]
19	——— $(CH_2)_5$ ———		OH	Cl	$C_{14}H_{14}ClNO$ [c]	36	350-360 d[i] [m]	67.88 67.65	5.70 5.55	5.65 5.58	(deuteriochloroform/trifluoroacetic acid): 1.53-3.60 (m, $(CH_2)_5$), 8.01 and 8.53 (s [q], ArH)
20	——— $(CH_2)_6$ ———		OH	Cl	$C_{15}H_{16}ClNO$ [c]	42	360 d[i] [n]	68.83 68.62	6.16 6.03	5.35 5.35	(deuteriochloroform/trifluoroacetic acid): 1.00-3.53 (m, $(CH_2)_6$), 8.01 and 8.43 (s [q], ArH)
21	——— $(CH_2)_{10}$ ———		OH	Cl	$C_{19}H_{24}ClNO$ [c]	9	337-340 [j]	71.80 71.61	7.61 7.66	4.41 4.54	deuteriochloroform/trifluoroacetic acid): 1.12-2.12 (m, $(CH_2)_{10}$), 8.02 and 8.52 (s, [q], ArH)
22	4-$CH_3C_6H_4$	H	OH	Cl	$C_{16}H_{12}ClNO$ [e]	28	380 [i]	71.25 71.43	4.48 4.48	5.19 5.15	(deuteriochloroform/trifluoroacetic acid): 2.50 (s, CH_3), and 7.40-8.57 (m, ArH)
23	4-$CH_3OC_6H_4$	CH_3	OH	Cl	$C_{17}H_{14}ClNO_2$ [b]	70	290-291 [i]	68.12 68.12	4.71 5.00	4.67 4.65	(deuteriochloroform/trifluoroacetic acid): 2.53 (s, $ArCH_3$), 4.03 (s, OCH_3), and 7.21-8.60 (m, ArH)
24	4-ClC_6H_4	CH_3	OH	H	$C_{16}H_{14}ClNO_2$ [b] ($C_{16}H_{12}ClNO.H_2O$)	26	289-290 d[f]	66.79 66.54	4.90 5.13	4.87 4.80	(deuteriochloroform/trifluoroacetic acid): 2.43 (s, $ArCH_3$), and 7.47-8.75 (m, ArH)/IR (Nujol) 3350 cm^{-1} (OH)
25	4-$CH_3C_6H_4$	CH_3	OH	Cl	$C_{17}H_{16}ClNO_2$ [b] ($C_{17}H_{14}ClNO.H_2O$)	24	260-264 [i]	67.66 67.80	5.34 5.32	4.64 4.93	(DMSO-d_6/trifluoroacetic acid): 2.48 (s, $ArCH_3$), and 7.80-8.47 (m, ArH)/IR (Nujol) 3400 cm^{-1} (OH)

[a] Entry compounds, oximes of cyclopentanone for **1** and cyclohexanone for **2** and **3**. [b] Entry compounds, benzoylhydrazones of cycloheptanone for **4-6**, cyclooctanone for **7** and **8**, cyclododecanone for **9**, 4-methylcyclohexanone for **10**, 1-indanone for **11** and **12**, 1-tetralone for **13**, 4-chloropropiophenone for **14**, and **24**, 4-methoxypropiophenone for **23**, and 4-methylpropiophenone for **25**. [c] Entry compound, carbomethoxyhydrazone of 2′-acetonaphthone for **15**, cycloheptanone for **19**, cyclooctanone for **20**, cyclododecanone for **21**. [d] Entry compound, benzoylacetone. [e] Entry compound, oxime or benzoylhydrazone for **22**, see ref [3]. [f] Recrystallized from ethanol/water. [g] Recrystallized from ethanol. [h] Recrystallized from ethanol/water/benzene. [i] Recrystallized from xylene/dimethylformamide. [j] Recrystallized from dimethylformamide. [k] Lit mp 100°, see ref [12]. [l] Lit mp 153-155°, see ref [15]. [m] Lit mp 380° dec for 2-chloro-7,8,9,10-tetrahydro-6*H*-cyclohepta[*b*]quinolin-11-one, see ref [16]. [n] Lit mp 320° for 2-chloro-6,7,8,9,11-hexahydrocycloocta[*b*]quinolin-12-one, see ref [17]. [o] Isochronous absorption. [p] Infrared (nujol), no carbonyl absorptions indicating enol form. [q] Displayed as singlet absorptions for 4-quinolinol.

metalated with an excess of lithium diisopropylamide (LDA), condensed with several 2-aminobenzophenones to give lithiated intermediates that were neutralized, hydrolyzed (oxime → ketone), and cyclodehydrated to give **1-3** in 41-71% yield. Cycloheptanone and cyclooctanone were readily transformed into benzoylhydrazones (1:1 condensation of ketone with benzoylhydrazine). These entry compounds were metalated (excess LDA), condensed with 2-aminobenzophenones, neutralized, hydrolyzed, and cyclodehydrated to give **4-8** in 36-92% yield. In a similar manner, cyclododecanone, 4-methylcyclohexanone and 1-indanone benzoylhydrazones were metalated (excess LDA), and condensed (2-aminobenzophenones)-hydrolysed-cyclodehydrated to give **9-12** in 21-93% yield. In the past, we have had difficulty with metalation-condensation of 1-indanone phenylhydrazone; however, 1-indanone benzoylhydrazone was a satisfactory entry compound for metalation-condensation during this study. Interestingly, 1-tetralone benzoylhydrazone was also easily metalated with excess LDA, and the resulting dianion was condensed with 2-aminoacetophenone, to give intermediates that were neutralized-hydrolyzed-cyclodehydrated to give **13** in 35% yield. 4-Chloropropiophenone benzoylhydrazone and 2′-acetonaphthone carbomethoxyhydrazone were metalated, condensed with 2-aminobenzophenone, followed by hydrolysis-cyclodehydration to give **14** (30%) and **15** (44%), respectively.

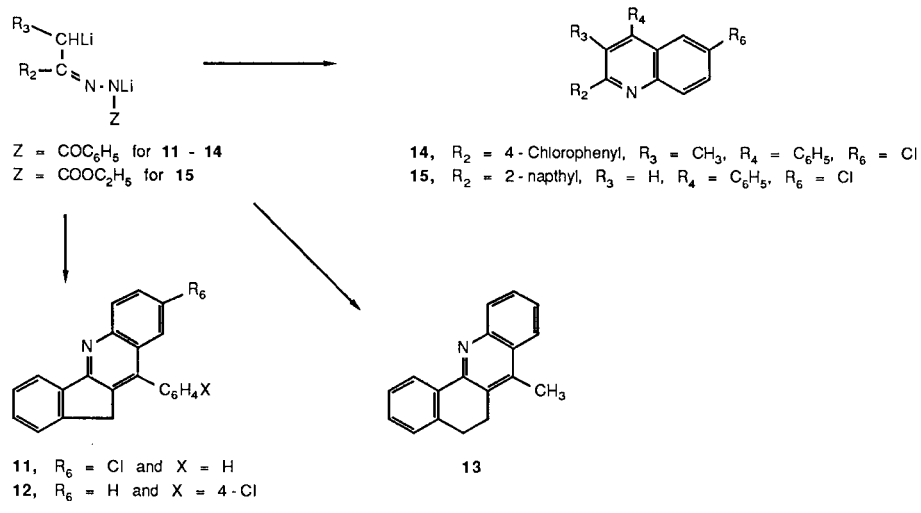
2-Phenacylquinolines, **16-18**, were prepared in 50-79% yield from the condensation of dilithiobenzoylacetone with 2-aminobenzophenones (followed by cyclodehydration of lithiated intermediates). The condensation of this



A = OH, **1 - 3**, A^1 = OLi, n = 3 or 4
A = NH - COC_6H_5, **4 - 9**, A^1 = LiN - COC_6H_5, n = 5,6, or 10
(4-methylcycloxexanone benzoylhydrazone, entry compound for **10**)

1 - 9

X(R_6) = Cl for **2, 6, 7**; X(R_6) = H for **1, 3, 4, 5, 8-10**, Y(R_4) = 4 - ClC_6H_4 for **1, 3, 5, 8-10**, Y = H(R_4, C_6H_5) for **2, 4, 6, 7**

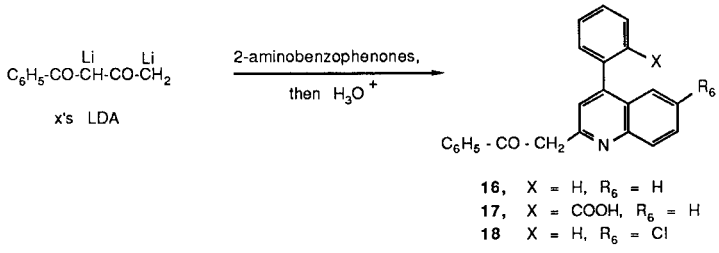


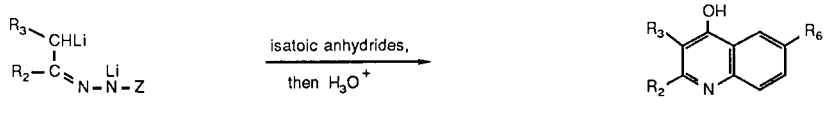
dianion with isatoic anhydrides for the preparation of 2-phenacyl-4-quinolinols was reported by us earlier [3].

4-Quinolinols **19-25** could be prepared in 9-70% yield by the condensation of carboalkoxyhydrazone (for **19-21**) or benzoylhydrazone (for **22-25**) dianions with isatoic anhydrides, followed by hydrolysis and cyclodehydration of condensation intermediates. 4-Quinolinol **22** could be prepared in a one-step or a two-step procedure. The condensation of dilithio-4-methylacetophenone oxime (two-step procedure) with 5-chloroisatoic anhydride followed by acid-hydrolysis of the oxime to the isolatable keto-hydrochloride (29%). This intermediate was suspended in hot methanol, treated with an equivalent amount of sodium methoxide to neutralize the hydrochloride, and the free anilo-nitrogen instantaneously cyclized to the 4-quinolinol (74% yield - second step). We preferred to make this compound with the benzoylhydrazone of 4-methylacetophenone (entry compound), which was a one-step process. This material was metalated (excess LDA), condensed with 5-chloroisatoic anhydride, and the resulting intermediates were neutralized, hydrolyzed, and cyclodehydrated to the 4-quinolinol **22** in 28%. This is compared to an overall yield of 21% for the two-step process.

Discussion.

The quinolines and related heterocyclic materials **1-25** prepared were characterized by absorption spectra with support from combustion analyses (for C, H, and N). Nmr spectra for **1-9** and **19-21** displayed multiplets for aliphatic methylene absorptions from δ 1.00-6.65 ppm. Pendant methyl ($ArCH_3$) groups in **13, 14** and **23-25** were





Z = $COOCH_3$, **19 - 21**;
Z = COC_6H_5, **22 - 25**

19, R_2-R_3, -$(CH_2)_5$-, R_6 = Cl
20, R_2-R_3, -$(CH_2)_6$-, R_6 = Cl
21, R_2-R_3, -$(CH_2)_{10}$-, R_6 = Cl
22, R_2 = 4-ClC_6H_4, R_3 = H, R_6 = Cl
23, R_2 = 4-$CH_3OC_6H_4$, R_3 = CH_3, R_6 = Cl
24, R_2 = 4-ClC_6H_4, R_3 = CH_3, R_6 = H
25, R_2 = 4-$CH_3C_6H_4$, R_3 = CH_3, R_6 = Cl

recorded as singlet absorptions from δ 2.17-2.53 ppm. Pendant methoxy ($ArOCH_3$) groups in **23** were displayed as a singlet at δ 4.03 ppm.

2-Phenacylquinolines **16-18** displayed methylene (CH_2) absorptions at δ 5.20-5.37 ppm (keto), and the vinyl absorption in **18** was clearly discernible at δ 6.80 ppm (enol). Infrared spectra were mainly utilized to distinguish entry compounds (containing a carbonyl or carboalkoxy functional group) from products (missing characteristic, CO, absorptions). Ir spectra (Nujol) of **16-18** indicated that these materials were in the enol form, and characteristic carboxylic acid absorption for **17** was displayed at 1705 cm^{-1} (CO) and 2100-2800 cm^{-1} (OH). 4-Quinolinols **19-25** displayed OH absorptions 3200-3400 cm^{-1}, which were not always clearly discernable from aromatic absorptions.

We utilized 2-aminoacetophenone (to prepare **13**) [12] and 2-aminobenzophenone-2'-carboxylic acid (as the carboxylate) (to prepare **17**) for electrophilic-nucleophilic reagents for condensations with C(α)-dianions during this investigation. The potential for these reagents for condensation with other multiple anion appears promising. 4-Quinolinols **24** and **25** are hydrated (H_2O) materials and not precyclization intermediates. Under the conditions of the reactions, benzoylhydrazone or carboalkoxyhydrazone intermediates undergo hydrolysis (to give free anilino nitrogen) then cyclodehydration (to give product). Formerly [3], when oxime anions and intermediates were involved, the slow hydrolysis of the oxime to ketone was accompanied by formation of the anilinium hydrochloride intermediate, which was isolated and separately cyclized to the quinolinol with sodium methoxide/methanol. If ketoaniline (free amine) were present under the reaction conditions, cyclodehydration to the fused-ring aromatic quinoline system would have been rapid, and isolation of this intermediate would not have occurred.

Many of the compounds prepared during this investigation are new. Materials already reported of similar structure types have been prepared by others [12-17] using different synthetic pathways and sometimes utilizing starting materials that are less readily available than C(α)-ketones and β-diketones. While this report emphasizes the use of benzoylhydrazones as entry compounds, carboalkoxyhydrazones gave similar results (for **15, 19-21**).

EXPERIMENTAL

Tetrahydrofuran (THF) was distilled from sodium (benzophenone) immediately before use. Benzoylhydrazones and carboalkoxyhydrazones were prepared by simple modification of standard procedure [10] which involved heating an alcohol solution of equimolar quantities of the C(α)-ketone and benzoyhydrazine or methyl (or ethyl) carbazate plus a small amount of glacial acetic acid. These materials could be readily recrystallized from methanol (or ethanol) air dried, and subsequently dried in a vacuum desiccator. Nuclear magnetic resonance spectra were obtained with a Varian Associates EM 360L NMR Spectrometer or Varian Associates EM 300X NMR Spectrometer, and absorptions were reported in δ ppm downfield from an internal tetramethylsilane (TMS) standard. Infrared spectra were obtained with a Perkin-Elmer 700, 710B, or 267 Spectrometer. Melting points were obtained in Mel-Temp or a Thomas-Hoover melting point apparatus in open capillary tubes and are uncorrected. Combustion analyses were performed by Robertson's Microanalytical Laboratory, 29 Samson Avenue, Madison, NJ 07940. *n*-Butyllithium was purchased from the Lithium Corporation of America, Bessemer City, NC 28106.

Quinolines and Related Fused-Ring Compounds.

A 0.033-mole (0.044-mole for preparation of **17**) sample of *n*-butyllithium (*ca* 1.6 *M*) was added to an oven-dried three-necked (500 ml) round-bottomed flask with a syringe. The contents of the flask were kept in a dry nitrogen atmosphere, and after cooling the flask in an ice bath, a 0.033-mole (0.044-mole for preparation of **17**) sample of diisopropylamine dissolved in 35-40 ml of dry tetrahydrofuran (THF) was added at a fast dropwise rate to the stirred *n*-butyllithium solution. The resulting lithium diisopropylamide (LDA) was stirred at 0° for an additional 20-30 minutes before adding, during 5-7 minutes, a 0.010 mole sample of *C*(α),*O*-oxime, or *C*(α),*N*-benzoylhydrazone, or *C*(α),*N*-carboalkoxyhydrazone, or benzoylacetone dissolved in 50 ml of THF.

If the benzoylhydrazone was less soluble in THF, it could be added as a slurry or powder followed by solvent. An extra 50 ml of THF could then be added, and the resulting dianion mixture was usually a solution. The metalation time was usually 60 minutes; but it could be extended another 15-20 minutes. A 0.011-mole sample of ketone (2-aminobenzophenones) or isatoic anhydride (or 5-chloroisatoic anhydride) dissolved in 30-40 ml of THF (or slurry) was then added during 5 minutes, and the condensation was allowed to proceed with stirring at 0° for an additional 1.5-2 hours. Neutralization was accomplished by directly adding 100 ml of 3*N* hydrochloric acid at room temperature, which was followed by heating the stirred two-phase mixture under reflux for 1.5 hours. If precipitation accompanied acidification, 50-100 ml of solvent grade THF was added to the mixture prior to heating. At the end of the reflux period, the mixture was cooled and poured into a large flask (1 or 2 liter) containing ice. The mixture was neutralized with excess solid sodium bicarbonate, and the aqueous and organic layers separated. The aqueous layer was extracted with three, 75-ml portions of ethyl ether, or 50 ml of solvent grade THF if there was any insoluble organic material present. The ether extracts and organic phase were combined, dried with anhydrous magnesium sulfate (drying omitted if solid material still present) and concentrated (rotoevaporator). The resulting oil or solid residue was crystallized and recrystallized from solvent or solvents noted in the footnote of the Table.

Amine-hydrochlorides were not obtained for preparation of **1-3** from lithiated oximes [4]. If lithiated 4-methylacetophenone oxime was used instead of lithiated 4-methylacetophenone benzoylhydrazone (for preparation of **22**), amine-hydrochloride was isolated, dried, suspended in 150 ml of methanol and treated with an equivalent amount of solid sodium methylate. The volume of methanol was reduced and the solid residue was recrystallized from xylenes/dimethylformamide. Infrared and nmr spectra of quinolinol **22** prepared by both methods were identical.

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REFERENCES AND NOTES

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