Tautomerism In Quinaldyl Ketones

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The quinaldyl ketone, 4-phenyl-3-(quinolin-2-yl)-butan-2-one was prepared by two methods: (a) benzylation of 1-(1*H*-quinolin-2-ylidene)propan-2-one in the presence of sodium hydride in dimethylformamide and (b) by the benzylative demethoxycarbonylation of methyl 2-(1*H*-quinolin-2-ylidene)-3-oxobutanoate in the presence of lithium bromide in hexamethylphosphoramide at 135°. In the absence of acid, the compound exists exclusively in the tautomeric form, 4-phenyl-3-(1*H*-quinolin-2-ylidene)butan-2-one.

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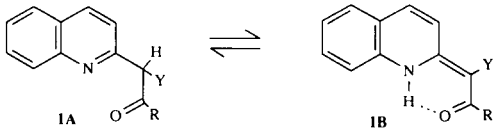
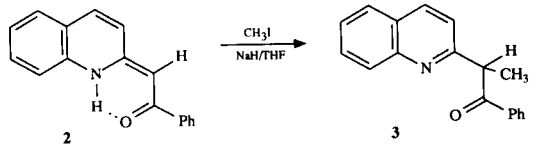
Tautomerism in quinaldyl ketones **1** has been studied in considerable detail over the past decade [1]. The position of the equilibrium between the azomethine form **A** and the intramolecularly hydrogen-bonded enamine form **B** is very sensitive to the structure of R and Y. When either R or Y is a strong electron-withdrawing group (*e.g.*, -COOEt or -CN), the corresponding compound exists exclusively in the enamine form **B** (*i.e.*, 99% or higher based upon ^{1}H nmr measurements [2-7]. When Y is hydrogen and R is alkyl or phenyl, a mixture of both tautomers is observed, although tautomer **B** always predominates [2,3,8-10].



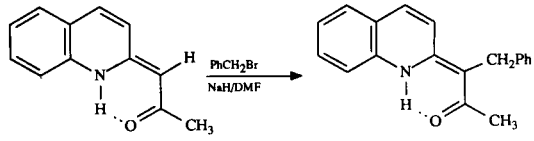
1A 1B

However, Greenhill and co-workers have reported [2] that the α-methylation of ketone **2**, which exists to the extent of 97% in form **B**, yields compounds **3**, which exists solely in form **A** (based upon ^{1}H nmr and infrared analysis).



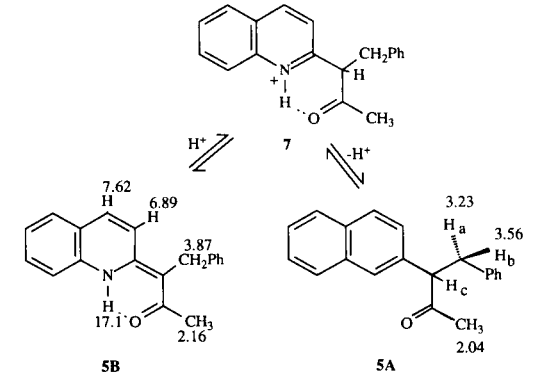
2 3

We wish to report some related work which also revealed some unexpected chemistry. In the course of studies involving 2-substituted quinolines, we had occasion to attempt the monobenzylation of 1-(quinolin-2-yl)-propan-2-one, which exists largely in the tautomeric form **A**, 1-(1*H*-quinolin-2-ylidene)propan-2-one (**4**) [5]. Under suitable conditions (sodium hydride in dimethylformamide at 0°), the expected product **5** was prepared in 68% yield, although a substantial amount (10-20%) of dibenzylated product 3-benzyl-3-(quinolin-2-yl)-4-phenylbutan-2-one (**6**), was always produced [11]. In view of the finding of Greenhill and co-workers that compound **3** exists solely in tautomeric form **A**, it came as a surprise to discover that the closely related compound **5** exists solely in tautomeric form **5B** (4-phenyl-3-(1*H*-quinolin-2-ylidene)butan-2-one) - if adventitious acid is carefully excluded when performing spectroscopic determinations.



4 5B

However, if a trace of acid is present in solution, tautomer **5B** comes into rapid equilibrium with tautomer **5A** to give a 60:40 mixture, probably *via* the cation **7**.

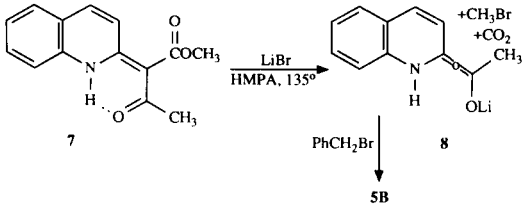


5B 5A

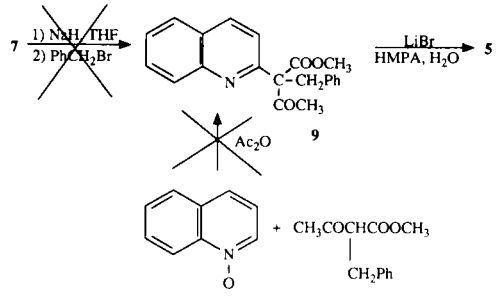
The ^{1}H nmr spectra of tautomers **5A** and **5B** deserve some comment. Tautomer **5B** showed singlets at δ 3.87 and 17.1 (relative intensities 2:1) and are assignable to the two benzylic protons and the intramolecularly hydrogen-bonded proton, respectively. Unexpectedly, the C_3 proton on the quinoline ring appeared at δ 6.88 as a doublet of doublets ($J_{3,4}$ = 10.1 Hz; $J_{1,3}$ = 1.4 Hz). Deuterium exchange and proton-proton decoupling experiments demonstrated that the small coupling constant arose from the proton on nitrogen [13]. The infrared spectrum of **5B** showed a strong band at 1618 cm^{-1}, typical for a carbonyl group conjugated with a carbon-carbon bond. The ^{1}H spectrum of **5A** (which could be observed only in the presence of **5B**) showed a typical ABX pattern arising from the diastereotopic benzylic protons adjacent to the methine

proton attached to a chiral carbon atom. The two benzylic protons (a and b) appeared at δ 3.23 and 3.56 as doublets of doublets ($J_{a,b}$ = 13.6 Hz; $J_{a,c} \cong J_{b,c}$ = 7.5 Hz) and the methine proton (c) appeared at δ 4.45 as a triplet [14]. The infrared spectrum of **5A** showed strong absorption at 1717 cm^{-1}, typical of an unconjugated carbonyl group.

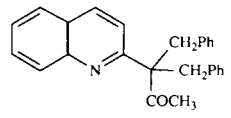
In an effort to improve the yield of compound **5** and also to avoid its troublesome separation from dibenzylated product **6**, an entirely different approach to its synthesis was studied, namely the alkylative demethoxycarbonylation of β-keto ester **7** which is readily prepared by the reaction of quinoline 1-oxide with methyl acetoacetate in the presence of acetic anhydride [15]. Dealkoxycarbonylation of acetoacetic and malonic esters under essentially neutral conditions has been long known [16]. More recently there have been several reports of alkylative dealkoxycarbonylation in which the intermediate anion (such as **8**) is trapped by a good electrophile [17]. The reaction of compound **7** with one equivalent of benzyl bromide proceeded smoothly in hexamethylphosphoramide at 135° in the presence of anhydrous lithium bromide to afford **5** in 57% yield; only tautomer **5B** was present. This suggests that benzyl bromide was very efficient in capturing postulated intermediate **8**, and that subsequent to its formation there was no favorable path for **5B** to equilibrate with **5A**.



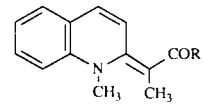
Two alternative approaches to the synthesis of compound **5** failed: (1) attempted benzylation of the anion of ketoester **7** to give **9** which should have been susceptible to demethoxycarbonylation to give **5**; and (2) attempted reaction of quinoline 1-oxide with methyl α-benzylacetoacetate to yield **9**.



A final comment regarding the structure of dibenzylated product **6** (3-benzyl-3-(quinolin-2-yl)-4-phenylbutan-2-one) is on order. We found it to be the *C,C*-dialkylated product as opposed to *C,N*-dialkylated product. It showed a singlet at δ 3.65 integrating for four protons consistent with two *equivalent* benzyl groups; its infrared spectrum showed an absorption at 1712 cm^{-1} typical of an unconjugated ketone. This finding is in contrast to a recent report of Greenhill and co-workers who found that dimethylation of two quinaldyl ketones closely related to compound **4** proceeds *via* *C,N*-dimethylation to afford compound **10** [2a]. However, our results are consistent with an earlier report by Hay and Wolfe who found that compound **4** undergoes *C,C*-dimethylation [18].



6



10 (R = Et, t-Bu)

EXPERIMENTAL

Melting points (uncorrected) were determined using a Mel-Temp device. Infrared spectra were recorded as potassium bromide pellets using a Nicolet 20 DXB FT spectrophotometer. The ^1H nmr spectra were obtained using a Varian XL-200 spectrometer and are reported as δ values relative to TMS as internal standard. The 300 MHz spectrum and the mass spectra were kindly provided by the Union Carbide Technical Center, South Charleston, WV, and were determined using a Varian XL-300 spectrometer and a Kratos MS-30 (70 eV) spectrometer, respectively. Radial chromatography was performed on a Harrison Research Chromatron Model 7924 T using Merck PF-254 silica gel (2 mm thickness).

All reactions were carried out under a nitrogen atmosphere.

4-Phenyl-3-(quinolin-2-yl)butan-2-one (**5**).

Method A.

A 100-ml 3-neck flask was charged with 0.39 g (16.3 mmoles) of sodium hydride (60% dispersion in mineral oil). After washing with hexane, the sodium hydride was covered with 10 ml of dry DMF. A solution of 3.00 g (16.2 mmoles) of 2-quinolinylacetone (**4**) in 30 ml of dry DMF was added with stirring at room temperature over a period of thirty minutes. After stirring for an additional hour, the mixture was cooled to 0° and 2.78 g (16.2 mmoles) of freshly distilled benzyl bromide was added rapidly *via* syringe. The reaction mixture was stirred at 0° for one hour and then allowed to warm to room temperature. One ml of acetic acid was slowly added followed by dilution with 150 ml of water. The resulting solution was extracted with ether (3 x 50 ml), and the combined ether extracts were in turn extracted with 1.5 *M* hydrochloric acid (3 x 50 ml). Aqueous sodium hydroxide (3 *M*) was added to the combined extracts to raise the *p*H to about 7 and then enough 10% aqueous potassium carbonate was added to raise the *p*H to about 10. The resulting basic solution was extracted with ether (3 x 50 ml), and after drying (magnesium sulfate), the combined ether extracts were passed through a short column of silica to remove dark colored impurities. After evaporation of the ether, the residue was recrystallized twice from methanol to yield 3.02 g (68%) of bright yellow flakes, mp 128-130°; ir (potassium bromide): ν 1618 cm^{-1} (CO/C=C); pmr (deuteriochloroform): δ 2.18 (s, 3H, CH_3), 3.81 (s, 2H, CH_2), 6.89

(dd, 1H, 3-H, $J_{3,4}$ = 10.1 Hz, $J_{1,3}$ = 1.5 Hz), 7-7.8 (m, 10H), 17.1 ppm (br s, 1H, N-H···O); ms: (m/z) 275 (M^+, 4), 260 (M^+ -CH_3, 15), 232 (M^+ -$COCH_3$, 100), 184 (M^+ -C_7H_7, 3), 128 ($C_9H_6N^+$, 27), 91 ($C_7H_7^+$, 14), 77 ($C_6H_5^+$, 16).

Anal. Calcd. for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.46; H, 6.18; N, 4.99.

Method B.

Methyl 2-(1*H*-quinolin-2-ylidene)-3-oxobutanoate (**7**) (2.97 g, 12.2 moles), anhydrous lithium bromide (1.06 g, 12.2 mmoles), benzyl bromide (2.09 g, 12.2 mmoles) and 25 ml of dry hexamethylphosphoramide (**CAUTION**: suspected carcinogen) were placed in a 100-ml flask equipped with a reflux condenser. The mixture was heated with stirring at 135° (oil bath) for two hours. The cooled material was poured into 200 ml of water and the resulting mixture was extracted with ether (3 x 50 ml). After washing the combined extracts with water (100-ml) and subsequent drying over magnesium sulfate, the ether was evaporated. The dark viscous residue was subjected to radial chromatography (1:1 dichloromethane:ethyl acetate) to afford 1.31 g (37%) of product, mp 126-129°.

3-Benzyl-3-(quinolin-2-yl)-4-phenylbutan-2-one (**6**).

A mixture of 1.85 g (10.0 mmoles) fo 2-quinolinylacetone (**4**), 3.08 g (18.0 mmoles) of benzyl bromide, 3.04 g (22 mmoles) of potassium carbonate, and 20 ml of dry acetonitrile was heated under reflux with stirring for two days. After removal of excess potassium carbonate by filtration from the cooled mixture, the solvent was evaporated to leave a dark oily residue. Flash chromatography of the residue through silica eluted with 1:1 dichloromethane:ethyl acetate gave material which after recrystallization from methanol yielded 1.42 (43%) of white flasks, mp 126-127°; ir (potassium bromde); ν 1712 cm^{-1} (CO); pmr (deuteriochloroform): δ 2.01 (s, 3H, CH_3), 3.65 (s, 4H, 2 x CH_2), 6.85-8.4 ppm (m, 16H); ms: (m/z) 365 (M^+, 8), 322 (M^+ -$COCH_3$, 100), 274 (M^+ -C_7H_7, 72), 128 ($C_9H_6N^+$, 18), 91 ($C_7H_7^+$, 50), 77 ($C_6H_5^+$, 5), 43 (CH_3CO^+, 28).

Anal. Calcd. for $C_{26}H_{23}NO$: C, 85.45; H, 6.34; N, 3.83. Found: C, 85.71; H, 6.46; N, 3.80.

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[11] Compounds **6** can be easily made in good yield simply by allowing 2-quinolinylacetone dissolved in acetonitrile to react with two equivalents of benzyl bromide in the presence of potassium carbonate; see Experimental.

[12] Before dissolving samples in deuteriochloroform for nmr analysis, the solvent was passed through a bed of anhydrous powdered potassium carbonate in order to remove any trace of hydrogen chloride.

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