113–115 °C (lit.[13] mp 112–115 °C).

(3-Hydroxy-4-methoxyphenyl)acetic Acid (1). Into a stainless steel bomb was placed 5.05 g (20.6 mmol) of **3b**. A degassed[19] solution of 45 g (1.1 mol) of NaOH in 450 mL of H_2O containing a catalytic amount of $CuSO_4$ (1 g) was then added. The bomb was sealed, heated to 150 °C for 1.5 days, and cooled. The solution was acidified and extracted manually with ether and then continuously extracted overnight with ether.[20] The combined ethereal solutions were evaporated to dryness to afford 3.72 g (99%) of 1, mp 127–129 °C (lit.[3d] mp 128.5–130.5 °C). Further purification was effected by recrystallization of the crude product with 20% 2-propanol/$CHCl_3$:[3d] mp 128–130 °C; ^1H NMR ($CDCl_3$) δ 6.87 (2 H, br s), 6.79 (1 H, br s), 3.87 (3 H, s), 3.55 (2 H, s).

***N*-[2-(3-Methoxyphenyl)ethyl](3-hydroxy-4-methoxyphenyl)acetamide (5).** Bromide **3b** (25 g, 102 mmol) was converted into crude 1 (16.42 g, 97%) by the method above. The melting point of the crude acid was 123–127 °C. A round-bottom flask containing 0.394 g (2.16 mmol) of this acid was reacted with *m*-methoxyphenethylamine by thoroughly mixing the components at 80 °C and then heating at 200 °C for 2 h. The resultant glass was dissolved in benzene and precipitated with hexane, and the crude product was recrystallized from toluene, mp 100–101 °C (lit.[6b] mp 101 °C). The yield of **5** was 0.576 g (84%).

(3,5-Dibromo-4-methoxyphenyl)acetic Acid (3c). To a solution of 20.09 g (120 mmol) of **3a** in 220 mL of anhydrous $CHCl_3$ (P_2O_5) was added 4.28 g (14.4 mmol) of $FeBr_2$. A solution of 18.5 mL (360 mmol) of Br_2 in 30 mL of $CHCl_3$ was added dropwise to the reaction vessel. After the mixture was stirred for 42 h at room temperature, an additional 10 mL of Br_2 (190 mmol) and 1.04 g (4.8 mmol) of $FeBr_2$ were added. The solution was stirred for 18 h, then poured carefully into an excess of 5% aqueous $NaHSO_3$, and extracted with ether. The combined ethereal extracts were washed with H_2O and brine and then dried (Na_2SO_4). Removal of the solvent afforded 37.76 g (96%) of dibromo **3c**, in greater than 98% purity, as determined by ^1H NMR. The crude solid was routinely used directly. Recrystallization from toluene/hexane gave **3c** with the following: mp 132–134 °C; MS, *m/z* (relative intensity) 322 (M^+, 48), 324 (91), 326 (44), 281, 279 (100), 277; IR (KBr) 3200–2600, 1710 cm^{-1}; ^1H NMR (acetone-d_6) δ 8.85 (COOH, br s), 7.47 (2 H, s), 3.77 (3 H, s), 3.58 (2 H, s); ^{13}C NMR (acetone-d_6) δ 171, 152, 133, 116, 59, 38.

Anal. Calcd for $C_9H_8Br_2O_3$: C, 33.37; H, 2.49. Found: C, 33.24; H, 2.47.

(3,5-Dihydroxy-4-methoxyphenyl)acetic Acid (2a). Into a stainless steel bomb was placed 20.00 g (61.6 mmol) of **3c**. A degassed[19] solution of 47.0 g (1.18 mol) of NaOH in 470 mL of H_2O containing a catalytic amount of $CuSO_4$ (1.0 g) was added to the bomb. The bomb was sealed, heated to 110 °C for 9 days, cooled, and then worked up as for 1 to give 9.55 g (78%, based on conversion of **3c** to **2a**) of a 1.7/1 mixture of **2a** and 1. The continuous extraction afforded 1.50 g (12%) of a 3/1 mixture of **2a** and 1. Following the method of Cason,[15] the mixture of 1 and **2a** from the dehalohydroxylation reaction (10.89 g) was esterified with methanol and sulfuric acid to give 9.31 g of a 1.6/1 mixture of **6b** and **6a**. A portion of this product (1.58 g) was column chromatographed on silica gel, eluting with 20% acetone in $CHCl_3$. This returned 0.39 g (18.7% from **3c**) of **6a** as an oil[6f] and 0.90 g (40.0% from **3c**) of **6b** as a solid. Recrystallization from toluene gave **6b**, mp 116–117 °C. An analytical sample of **6b** was prepared by sublimation (0.1 torr, 100 °C): MS, *m/z* (relative intensity) 212 (M^+), 153 (100); IR (KBr) 3300, 1720, 1200, 1160, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45 (2 H, s), 6.32 (2 H, s), 3.84 (3 H, s), 3.56 (3 H, s), 3.40 (2 H, s).

Anal. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.61; H, 5.66.

To 0.106 g (0.50 mmol) of the methyl ester **6b** was added 1.1 mL of 10% aqueous NaOH. The solution was stirred for 30 min at room temperature and then acidified with 4 N HCl. The resulting aqueous solution was extracted with EtOAc. The combined organic extracts were washed with brine and then dried over Na_2SO_4. Evaporation afforded 0.10 g (100%) of **2a** as a solid, which was recrystallized from $CHCl_3$: mp 181–182 °C; MS, *m/z* (relative intensity) 198 (M^+), 197 (100), 153; IR (KBr) 3490, 3300–2700, 1705, 1600, 1505 cm^{-1}; ^1H NMR (acetone-d_6) δ 8.40 (CO_2H, OH, br s), 6.36 (2 H, s), 3.76 (3 H, s), 3.42 (2 H, s); ^{13}C NMR (acetone-d_6) δ 174, 157, 135, 131, 109, 60, 41.

Anal. Calcd for $C_9H_{10}O_5$: C, 54.55; H, 5.09. Found: C, 54.11; H, 4.94. Calcd M_r = 198.053. Found M_r = 198.053.

(3-Bromo-5-hydroxy-4-methoxyphenyl)acetic Acid (3e). Via the above methods, **3e** was obtained by interruption of the dehalohydroxylation of **3c** prior to completion. Subsequent esterification, chromatography, and saponification afforded **3e**, which was recrystallized from toluene: mp 159.5–160.5 °C; MS, *m/z* (relative intensity) 260 (M^+, 100), 262 (99), 247, 245, 217, 215; IR (KBr) 3500–2800, 1715, 1570, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.58 (1 H, d, J = 2 Hz), 7.21 (1 H, d, J = 2 Hz), 3.75 (3 H, s), 3.34 (2 H, s).

Anal. Calcd for $C_9H_9BrO_4$: C, 41.41; H, 3.48. Found: C, 41.43; H, 3.34.

Acknowledgment. We thank the NIH (DA-02708) for support of this research.

Registry No. 1, 1131-94-8; **2a**, 34021-73-3; **3a**, 104-01-8; **3b**, 774-81-2; **3c**, 89936-29-8; **3e**, 89936-30-1; **5**, 74007-21-9; **6a**, 15964-81-5; **6b**, 89936-31-2; *m*-$MeOC_6H_4CH_2CH_2NH_2$, 2039-67-0; $CuSO_4$, 7758-98-7.

(19) Degassing was performed by stirring the aqueous solution under aspirator vacuum for 2 h.

(20) Four hand extractions with ether, in the preparation of 1, generally recovered greater than 90% of the hydroxylated product. In the case of **2a**, these were much less efficient. In the latter case, ethyl acetate is a much superior extraction solvent.

Cyclodehydration of *o*-Vinyl Anilides. A General Synthesis of Substituted Quinolines

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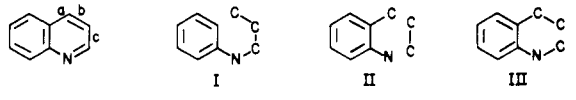
Received October 17, 1983

The quinoline ring system is usually synthesized from readily available aromatic amine derivatives.[2] The large number of reactions of this type can be classified according to the mode of final bond closure to form the heterocyclic ring. Important name reactions based on bond "a" formation include the Skraup and Doebner–von Miller synthesis of quinolines and the Combes, Conrad–Limpach, and Knorr synthesis of quinolones (see I). The Friedlander and Pfitzinger reactions are examples of final closure of bond "b" (see II). Most surprisingly, methods based on final closure of bond "c" are sparse[3] and usually highly specialized.[4,5] We now outline a general two-step preparation of substituted quinolines based on bond "c" formation via cyclization of in situ generated *o*-vinyl anilides (see III).



I II III

(1) Recipient of a Camille and Henry Dreyfus Grant for Newly Appointed Young Faculty in Chemistry.

(2) (a) Jones, G. "The Quinolines"; Wiley-Interscience: London, 1977; pp 93–318. (b) "Comprehensive Organic Chemistry"; Barton, D., Ollis, G., Eds.; Pergamon Press: New York, 1979; Vol. 4.

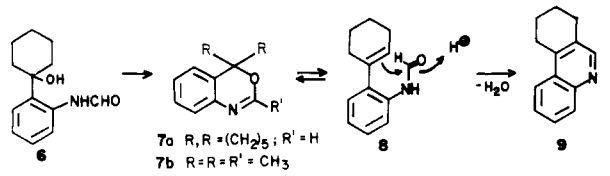
(3) For a related cyclization involving *o*-phenyl anilides, see: (a) Boyer, J. H.; Patel, J. R. *Synthesis* **1978**, 205. (b) *o*-Phenyl isocyanides. Boyer, J. H.; Patel, J. R. *J. Chem. Soc., Chem. Commun.* **1977**, 855.

(4) The Camps reaction forms quinolones via bond "c" closure. Mixtures of regioisomers are often possible. See: Camps, R. *Chem. Ber.* **1899**, *32*, 3228. Also see ref 2a, pp 191–197.

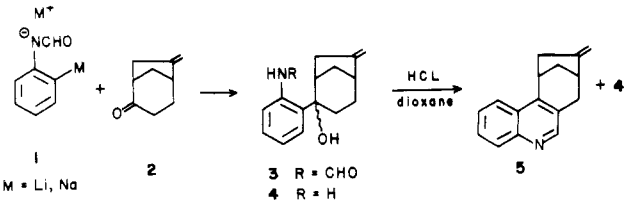
(5) For recent examples of bond c closure, see: DeMayo, P.; Sydnes, L. K.; Wenska, G. *J. Chem. Soc., Chem. Commun.* **1979**, 499. Hull, R. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2911. Künzle, F.; Schmutz, J. *Helv. Chim. Acta* **1970**, *53*, 798. Yanagisawa, H.; Nakao, H.; Ando, A. *Chem. Pharm. Bull.* **1973**, *21*, 1080.

0022-3263/84/1949-2063$01.50/0

Scheme I



The quinoline-forming reaction was encountered in the attempted hydrolysis of formanilide **3**. Compound **3** was prepared in the context of a synthetic project by addition of dianion **1** (generated by a modification of the Fleming procedure)[6] to ketone **2**. In an effort to hydrolyze the formanilide moiety, **3** was treated with 1 N HCl in dioxane (25 °C). In addition to the expected amine **4**, a second product was formed in variable yields (20–50%). The two products were readily separable by flash chromatography. Exact mass measurements indicated a molecular formula $C_{16}H_{13}N$ (i.e., loss of two molecules of water from **3**) for the unidentified product. ^{13}C and ^1H NMR readily confirmed the quinoline structure **5**.[7] Apparently the tertiary alcohol in **3** is dehydrated to give an *o*-vinylformanilide, which then undergoes cyclodehydration to give **5**. The facility with which the reaction occurs on this particular substrate is remarkable.



In order to determine the generality of this reaction, cyclohexanone adduct **6**[6] was prepared in a manner analogous to that described above. Not surprisingly, treatment of **6** with aqueous HCl/dioxane did not produce any tetrahydrophenanthridine (**9**) but gave mainly the hydrolyzed amine. However, treatment of **6** with a variety of standard dehydrating reagents (PPA, 130 °C; $POCl_3$, 110 °C; P_2O_5/CH_3SO_3H, 130 °C) resulted in smooth formation of **9** in 60–90% yields.

A plausible mechanism for quinoline formation is outlined in Scheme I. Compound **6** is dehydrated to produce *o*-vinyl anilide **8**. Acid-catalyzed cyclodehydration of **8** then gives the quinoline ring as in **9**.[8] The possible intermediacy of **8** was confirmed by independent synthesis via dehydration of **6** ($TiCl_4$, CH_2Cl_2). Subjection of **8** to the standard PPA cyclization conditions produced **9** in 61% yield. The intermediacy of oxazines **7** is also likely. Although **7a** was never observed, treatment of **13d** with PPA at a lower temperature (110 °C) produced oxazine **7b**[9] in 98% yield. Resubjection of **7b** to PPA at 210 °C gave 2,4-dimethylquinoline (**14d**) in 81% yield.

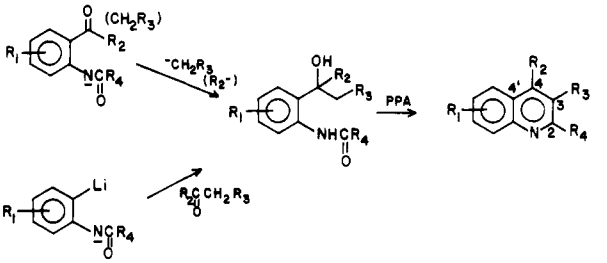
A second method for precursor formation involves addition of nucleophiles to *o*-acyl anilides. For example,

Table I

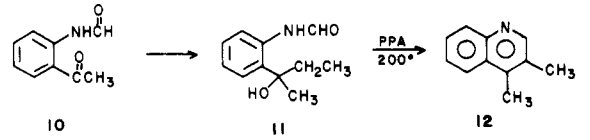
13a	R_1	R_2	prep[a]	temp, °C	% yield
13a	H	CH_3	A	160	75
13b	H	Ph	B	160	80
13c	CH_3	Ph	A	160	90
13d	CH_3	CH_3	A	210	95
13e	CH_3	H	C	210	82

[a] Preparation: A, addition of RMgBr to the acylanilide; B, addition of 1 to the ketone; C, $NaBH_4$ reduction of the acylanilide.

Scheme II



treatment of *o*-acetylformanilide (**10**) with 2 equiv of ethylmagnesium bromide resulted in smooth formation of **11** in 92% yield. This approach bypasses enolization problems encountered with **1**.[6] Most importantly, heating of crude **11** with PPA produced 3,4-dimethylquinoline (**12**) as the sole product (73%). No 4-ethylquinoline was detected. Thus, cyclization has occurred selectively from the most substituted olefin.



A series of quinolines were prepared as outlined in Table I, by employment of polyphosphoric acid as the dehydrating reagent. Although rather high temperatures are required, the yields of product are quite good. In two cases, (**13a, 13e**) the products were compared with authentic samples (300-MHz ^1H NMR, TLC) and shown to be identical.

The overall sequence is summarized in Scheme II. It is felt that this method will provide a useful complement to existing reactions for the synthesis of substituted quinolines. While advantages include brevity and simplicity, ready availability of precursors by two methods, good yields, and control of regiochemistry, limitations may be encountered due to higher temperatures required.

Experimental Section

Formamido Alcohol 3. Ketone **2**[11] (138 mg, 1 mmol) was added to the dianion generated from *o*-bromoformanilide (395 mg, 2 mmol) according to the general procedure described below. The product **3** could be isolated in yields ~45% by flash chromatography as a complex mixture of stereoisomers and formamide rotamers: IR ($CHCl_3$, cm^{-1}) 1680, 1600, 1585; ^1H NMR ($CDCl_3$)

(6) Fleming, I.; Loreto, M. A.; Michael, J. P.; Wallace, I. H. M. *Tetrahedron Lett.* **1982**, *23*, 2053. In order to avoid problems with metal–halogen exchange being competitive with deprotonation, *o*-bromoformanilide was sequentially treated with 1 equiv of NaH followed by 1 equiv of *n*-BuLi (see Experimental Section). In addition to 50% of the adduct, 50% recovered ketone was obtained, presumably resulting from enolization.

(7) White, R. F. M.; Williams, H. In "Physical Methods in Heterocyclic Chemistry"; Katritzky, A. R., Ed.; Academic Press: New York, 1971; Vol. 4.

(8) The intermediacy of an isocyanide cannot be excluded. See ref 3b.

(9) Compound **7b**: IR ($CHCl_3$) 1625, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25–7.00 (4 H, m), 2.11 (3 H, s), 1.60 (6 H, s); MS, *m/e* 175 (M^+), 160 (calcd for $C_{11}H_{13}NO$, 175.0997; found, 175.0996).

(10) (a) Kenner, J.; Ritche, W. H.; Staham, F. S. *J. Chem. Soc.* **1937**, 1169. (b) Badger, G. M.; Cook, J. W.; Walker, T. *Ibid.* **1948**, 2011.

(11) Ketone **2** was prepared from nortricyclanone by the following sequence: (a) HOAc, $HClO_4$, (b) $Ph_3P{=}CH_2$, (c) NaOH, (d) CrO_3, (e) TMSCN, (f) LAH, (g) $NaNO_2$, HOAc. Kuo, S. C., unpublished results.

δ 9.85 (1 H, br s), 9.60 (1 H, br s), 8.64 (1 H, d), 8.40 (1 H, br s), 8.28 (1 H, br t), 7.4–7.0 (7 H, m), 4.95–4.80 (4 H, m), 2.90–1.10 (20 H, m); MS, *m/e* 257 (M^+), 239, 216, 211, 176, 158, 148, 120.

Quinoline 5. Crude alcohol **3** (323 mg, contains excess formanilide) was stirred for 18 h in dioxane (15 mL) and 1 N HCl (15 mL). After extraction with ether, the aqueous layer was basified with $NaHCO_3$ and extracted with ether. These ether extracts were washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. Purification of the crude product by medium-pressure liquid chromatography (10% EtOAc in hexane) gave the less polar quinoline **5** (37 mg, 17%) as a clear oil, followed by the amino alcohol. Higher reaction temperatures gave increased amounts of the quinoline. Kugelrohr distillation (120 °C, oven temperature, 0.5 mm) gave **5** as a white solid: mp 49–50 °C; MS calcd for $C_{16}H_{15}N$ 221.1204, found 221.1202; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.01 (1 H, d, H_8), 7.78 (1 H, s, H_2), 7.65 (1 H, d, H_5), 7.62 (1 H, t) and 7.42 (1 H, t) (H_6 and H_7), 5.11 (1 H, s) and 4.90 (1 H, s) (terminal olefin), 3.66 (1 H, t), 3.26 (1 H, dd), 3.10 (1 H, br s), 2.90 (1 H, d), 2.77 (1 H, m), 2.54 (1 H, d), 2.05 (1 H, m), 2.00 (1 H, d); ^{13}C NMR ($CDCl_3$, 67 MHz) δ 164.6 (s), 154.4 (s), 146.4 (s), 136.0 (d), 128.6 (d), 128.4 (s), 127.7 (s), 126.9 (d), 125.7 (d), (one aromatic doublet peak is assumed to account for two carbons) 107.4 (t), 44.5 (d), 42.2 (t), 41.0 (d), 38.8 (t), 35.4 (t). Anal. Calcd for $C_{16}H_{15}N$: C, 86.84; H, 6.83. Found: C, 87.09; H, 6.94.

General Procedure for Dianion Addition. *o*-Bromoformanilide (4.0 g, 20 mmol) in dry THF (20 mL) was added dropwise to a suspension of oil-free sodium hydride (1.0 g, 50% in oil, 20.8 mmol) in THF (15 mL). After cessation of hydrogen evolution (30 min, 25 °C) the reaction was cooled to −78 °C and *tert*-butyllithium (15.4 mL, 40.04 mmol, 2.6 M in pentane) was added dropwise over 30 min. Following this, HMPA (4 mL, 24.4 mmol) was added. After 30 min at −78 °C, cyclohexanone (2 mL, 19.3 mmol) in dry THF (2 mL) was added over 20 min. After 1 h at −78 °C, the mixture was quenched with saturated NH_4Cl, allowed to warm to room temperature, and extracted with ether. The combined ether extracts were washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Trituration of the crude product with 20% EtOAc in hexane followed by filtration gave 2.08 g (49%) **6**[6] as a white solid (mp 136–137 °C), which was used directly in the cyclization: ^1H NMR ($CDCl_3$) indicated a 1/1 mixture of formamide rotamers: δ 9.70 (1 H, br s), 9.50 (1 H, br s), 8.65 (1 H, d), 8.45 (1 H, s), 8.34 (1 H, d), 7.35–7.05 (7 H, m), 2.10–1.70 (20 H, m).

General Procedure for Grignard Addition. 1-Formamidoacetophenone (223 mg, 1.37 mmol) in dry THF (6 mL) was added dropwise to a solution of methylmagnesium bromide (1.1 mL, 2.85 M in THF, 3.14 mmol) at 0 °C. After stirring 16 h at 25 °C, the reaction was partitioned between ether and saturated NH_4Cl. The organic phase was washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give 178 mg (72%) crude **13a** as a clear oil: ^1H NMR ($CDCl_3$) ~1/1 mixture of formamide rotamers, δ 9.90 (2 H, br s), 8.63 (1 H, d), 8.40 (1 H, br s), 8.31 (1 H, d), 7.32–7.00 (7 H, m), 1.71 (6 H, s), 1.70 (6 H, s).

13b (1/1 mixture of formamide rotamers): mp 115–116 °C; ^1H NMR ($CDCl_3$) δ 9.00 (2 H, br s), 8.20 (2 H, m), 8.00 (1 H, s), 7.45–7.05 (17 H, m), 3.20 (1 H, br s), 2.80 (1 H, br s), 2.00 (3 H, s), 1.99 (3 H, s).

13c: mp 149–150 °C; ^1H NMR ($CDCl_3$) δ 8.65 (1 H, br s), 8.00 (1 H, d), 7.48 (1 H, d), 7.30–7.10 (7 H, m), 1.95 (3 H, s), 1.70 (3 H, s).

13d: mp 145–146 °C; ^1H NMR ($CDCl_3$) δ 9.90 (1 H, br s), 8.23 (1 H, d), 7.30–7.22 (2 H, m), 7.03 (1 H, t), 2.50 (1 H, s), 2.12 (3 H, s), 1.70 (6 H, s).

13e: oil; ^1H NMR ($CDCl_3$) δ 9.05 (1 H, br s), 8.05 (1 H, d), 7.27 (1 H, t), 7.18–7.00 (2 H, m), 4.95 (1 H, q), 2.18 (3 H, s), 1.60 (3 H, d).

11: oil (1/1 mixture of formamide rotamers); ^1H NMR ($CDCl_3$) δ 10.05 (1 H, br s), 9.87 (1 H, br s), 8.65 (1 H, d), 8.42 (1 H, s), 8.37 (1 H, d), 7.31–7.00 (7 H, m), 1.95 (4 H, m), 1.68 (3 H, s), 1.67 (3 H, s), 0.87 (6 H, m).

Olefin 8: Titanium tetrachloride (40 μL, 0.4 mmol) was added to a solution of alcohol **6** (30.5 mg, 0.14 mmol) in dry CH_2Cl_2 (5 mL) at −78 °C. After 1.5 h at −78 °C the mixture was diluted with ether, washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure to give crude **8** (27.7 mg, 99%) as an oil: IR ($CHCl_3$, cm^{-1}) 3490, 1690, 1600, 1580, 1510; ^1H NMR ($CDCl_3$, 1/1 mixture of formamide rotamers) δ 8.70 (1 H, d), 8.43 (1 H, d), 8.32 (1 H, d), 7.60 (2 H, br s), 7.30–7.05 (7 H, m), 5.75 (2 H, m), 2.20 (8 H, m), 1.78 (8 H, m); MS, *m/e* 201 (M^+), 183, 172. The crude olefin (27.7 mg) was directly cyclized following the standard procedure (PPA, 130 °C) to give **9** (25.0 mg, 61%), mp 61–62 °C (lit.[10a] mp 64 °C), identical with a sample of **9** obtained by direct PPA cyclization of **6**.

General Cyclization Procedure. 4-Phenylquolinoline. Crude alcohol **13b** (1.28 g, 5.3 mmol) and polyphosphoric acid (80 g) were admixed and stirred under N_2 for 20 h at ~160 °C (bath temperature). The cooled reaction mixture was diluted with water and washed with ether. The aqueous layer was basified with solid $NaHCO_3$ and extracted with ether. This organic phase was washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure to give virtually pure (TLC, 300-MHz NMR[7]) 4-phenylquinoline as a tan solid. Recrystallization of a small sample ($CHCl_3$/hexane) gave white crystals, mp 61–62 °C (lit.[10b] mp 61 °C).

Acknowledgment. We thank Research Corporation for partial support of this worrk.

Registry No. **2**, 89936-95-8; *endo*-**3**, 89936-96-9; *exo*-**3**, 89936-97-0; **4**, 89936-98-1; **5**, 89936-99-2; **6**, 82757-20-8; **7b**, 41797-85-7; **8**, 89937-00-8; **9**, 62833-92-5; **10**, 5257-06-7; **11**, 89937-01-9; **12**, 2436-92-2; **13a**, 89937-02-0; **13b**, 89937-03-1; **13c**, 89937-04-2; **13d**, 41797-86-8; **13e**, 89937-05-3; **14a**, 491-35-0; **14b**, 605-03-8; **14c**, 1721-92-2; **14d**, 1198-37-4; **14e**, 91-63-4; *o*-BrC_6H_4NHCHO, 10113-38-9; *o*-AcC_6H_4NHAc, 5234-26-4; acetophenone, 98-86-2; cyclohexanone, 108-94-1.

Covalent Hydration and Ring Opening of Some 2,4-Disubstituted-Pyrimido[4,5-*d*]pyrimidines[1]

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Received August 16, 1983

The phenomenon of covalent hydration[3] in heterocyclic rings has recently been reviewed.[4] First observed in the pteridine system,[5] covalent hydration has subsequently been reported in a variety of heterocyclic ring systems, including the quinazolines,[6] the isomeric 1,3,*x*-triazanaphthalenes,[7] the pyrazinopyridines,[8] and the pyrimido[5,4-*e*]-*as*-triazines.[9]

Our interest was focused on the pyrimido[4,5-*d*]pyrimidines possessing amino and/or hydroxy substituents in only one of the rings. Taylor has indicated[10] that derivatives of 4-(methylthio)pyrimido[4,5-*d*]pyrimidine undergo

(1) This paper may be considered part 3 in a series entitled Fused Pyrimidines. For parts 1 and 2 see: Delia, T. J.; Sami, S. M. *J. Heterocycl. Chem.* **1981**, *18*, 929. Delia, T. J.; Kirt, D. D.; Sami, S. M. *Ibid.* **1983**, *20*, 145.

(2) This work was conducted while the author was on leave at A.N.U. Correspondence should be addressed to Macolm H. Filson Laboratories, Department of Chemistry, Central Michigan University, Mt. Pleasant, MI 48859.

(3) The hydrogen ion or, less commonly, hydroxyl ion catalyzed reversible addition of water across the C=N bond of a π-deficient heterocycle is a reasonable working definition of covalent hydration.

(4) For a recent review, see: Albert, A. *Adv. Heterocycl. Chem.* **1976**, *20*, 117.

(5) Albert, A.; Brown, D. J.; Cheeseman, G. *J. Chem. Soc.* **1952**, 1620.

(6) Albert, A.; Armarego, W. L. F.; Spinner, E. *J. Chem. soc.* **1961**, 5267.

(7) Armarego, W. L. F. *J. Chem. Soc.* **1962**, 4094.

(8) (a) Perrin, D. D.; Inoue, Y. *Proc. Chem. Soc.* **1960**, 342. (b) Inoue, Y.; Perrin, D. D. *J. Chem. Soc.* **1962**, 2600.

(9) (a) Clark, J.; Yates, F. S. *J. Chem. Soc. C.* **1971**, 2475. (b) Brown, D. J.; Sugimoto, T. *Ibid.* **1971**, 2616.

(10) Albert, A.; Armarego, W. L. F. *Adv. Heterocycl. Chem.* **1965**, *4*, 32.

0022-3263/84/1949-2065$01.50/0