Novel Synthesis of 1,6-Naphthyridin-2(6*H*)-ones, Quinolin-2(1*H*)-ones, and Quino[7,8-*f*]quinoline-2,9(1*H*,10*H*)-dione from Common Precursors

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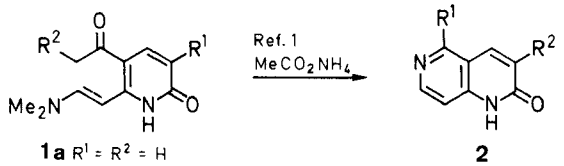
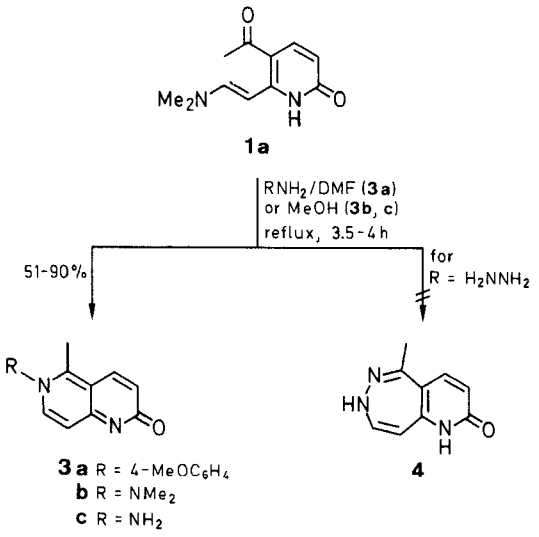
1,6-Naphthyridin-2(6*H*)-ones **3**, quinolin-2(1*H*)-ones **5**, and quino[7,8-*f*]quinoline-2,9(1*H*,10*H*)-dione **10** have been synthesized from 5-acyl-6-[2-(dimethylamino)ethenyl]pyridin-2(1*H*)-ones **1**.

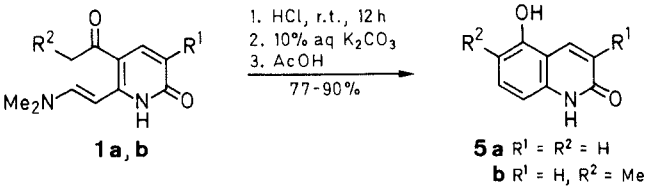
In a recent paper,[1] we described the synthesis of 1,6-naphthyridin-2(1*H*)-ones **2** by the condensation of ammonium acetate with 5-acyl-6-[2-(dimethylamino)-ethenyl]pyridin-2(1*H*)-ones **1**. We now wish to report on an extension of the use of **1** in the synthesis of other heterocyclic systems: namely, 1,6-naphthyridin-2(6*H*)-ones, quinolin-2(1*H*)-ones, and quino[7,8-*f*]quinoline-2,9(1*H*,10*H*)-diones.



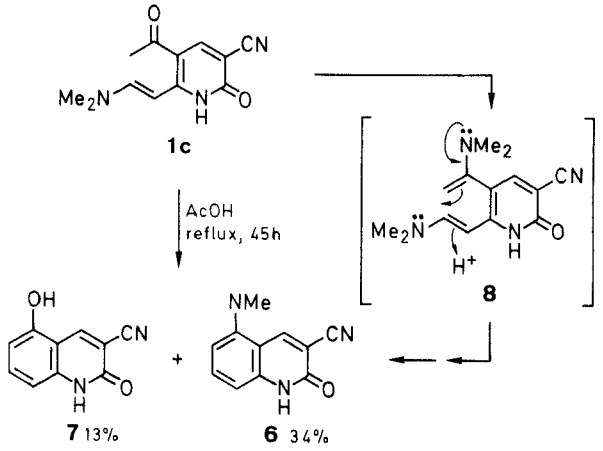
The condensation of 4-methoxybenzenamine with **1a** in refluxing dimethylformamide led to the formation of 1,6-naphthyridin-2(6*H*)-one **(3a)** in 51% yield. Similar reaction of **1a** with dimethylhydrazine and hydrazine in refluxing methanol gave **3b** and **3c** in 90% and 73% yield, respectively. The alternative structure **4** for the product resulting from the reaction between **1a** and hydrazine was ruled out by the spectral evidence. The pattern in the ^{1}H NMR spectrum of **3c** for 7-H and 8-H is similar to those of **3a** and **3b** whereas that of **4** would be different. The NMR spectrum of **3c** in (DMSO-d_6) showed a singlet at $\delta = 6.80$ for the NH_2 group. Furthermore, the mass spectrum of **3c** gave a strong peak at $m/z = 160$ ($MH^+ - NH_2$). This type of fragmentation due to the loss of NH_2 supports structure **3c**.



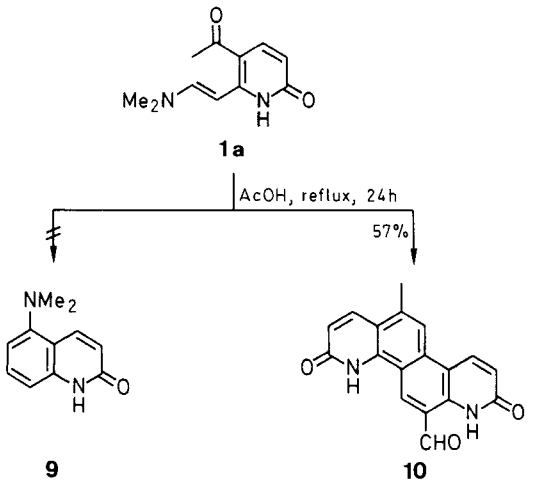
Treatment of **1a** with concentrated hydrochloric acid at room temperature gave 5-hydroxyquinolin-2(1*H*)-one **(5a)**[2], a key intermediate[3] in the synthesis of β-blockers, in 90% yield. Similar treatment of **1b** gave quinolone **5b** in 80% yield.



The reaction of **1c** was carried out in acetic acid due to the instability of the nitrile group in concentrated hydrochloric acid. Treatment of **1c** with refluxing acetic acid resulted in the formation of quinolines **6** and **7** in 34% and 13% yield, respectively. A possible mechanism for the formation of **6** requires enamine **8** which is formed by the reaction between **1c** and dimethylamine which in turn is produced by the initial reaction of acetic acid with **1c** or during the formation of **7**. The acid-catalyzed intramolecular cyclization of **8** leads to the formation of **6** and dimethylamine. The process is repeated until the starting material **1c** is consumed.



Treatment of **1a** with acetic acid under similar conditions, however, led to the formation of **10** (57%) instead of the expected product **9**. The structure of **10** is supported by the spectral data. The mass spectrum gave a MH^+ peak at 305; ^{13}C NMR spectrum indicated eight proton bearing carbon atoms, and ^{1}H NMR spectrum confirmed the presence of an aldehyde group, two pairs of ortho coupled protons, two uncoupled aromatic protons, and a methyl group. The initial step in the formation of **10** involves the acid-catalyzed dimerization of **1a**. The resulting intermediate undergoes further transformations to yield **10**.



6-(4-Methoxyphenyl)-5-methyl-1,6-naphthyridin-2(6*H*)-one (3a):
A mixture of **1a** (10.3 g, 0.05 mol), 4-methoxybenzenamine (7 g, 0.05 mol), and DMF (50 mL) was heated under reflux for 3.5 h and then concentrated under reduced pressure. The dark brown solid residue was recrystallized from 2-propanol after treating with charcoal; yield: 6.8 g (51%); mp 212–215°C dec.

$C_{16}H_{14}N_2O_2$	calc.	C 72.17	H 5.30	N 10.52
(266.30)	found	72.08	5.43	10.45

^{1}H NMR (DMSO-d_6/TMS): δ = 2.46 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 6.45 (d, $J_{3,4}$ = 9.6 Hz, 1H, H-3), 6.95 (d, $J_{7,8}$ = 7.3 Hz, 1H, H-8), 7.16, 7.58 (A_2B_2, J = 8.8 Hz, C_6H_4O), 7.84 (d, $J_{3,4}$ = 9.6 Hz, 1H, H-4), 7.90 (d, $J_{7,8}$ = 7.3 Hz, 1H, H-7).

6-(Dimethylamino)-5-methyl-1,6-naphthyridin-2(6*H*)-one (3b):
A mixture of **1a** (10.3 g, 0.05 mol), *N,N*-dimethylhydrazine (6 g, 0.1 mol), and MeOH (200 mL) was heated under reflux for 4 h and then concentrated to dryness. The residue was crystallized from 2-propanol to afford **3b**; yield: 9.1 g (90%); mp 228–230°C dec.

$C_{11}H_{13}N_3O$	calc.	C 65.01	H 6.45	N 20.67
(283.24)	found	64.82	6.68	20.56

^{1}H NMR (CF_3CO_2D/TMS): δ = 3.11 [s, 6H, $N(CH_3)_2$], 3.35 (s, 3H, CH_3), 7.25 (d, $J_{3,4}$ = 9.7 Hz, 1H, H-3), 7.95 (d, $J_{7,8}$ = 7.3 Hz, 1H, H-8), 8.48 (d, $J_{3,4}$ = 9.7 Hz, 1H, H-4), 8.86 (d, $J_{7,8}$ = 7.3 Hz, 1H, H-7).

6-Amino-5-methyl-1,6-naphthyridin-2(6*H*)-one (3c):
Following the procedure for the preparation of **3b**, **3c** was prepared in 77% yield; mp 262–264°C dec.

$C_9H_9N_3O$	calc.	C 61.70	H 5.18	H 23.99
(175.19)	found	61.82	5.31	23.97

MS (CI/CH_4): m/z = 176 (MH^+), 175 (M^+), 160 ($MH^+ - NH_2$).

^{1}H NMR (DMSO-d_6/TMS): δ = 2.76 (s, 3H, CH_3), 6.38 (d, $J_{3,4}$ = 9.7 Hz, 1H, H-3), 6.80 (br s, 2H, NH_2), 6.91 (d, $J_{7,8}$ = 7.3 Hz, 1H, H-8), 7.83 (d, $J_{3,4}$ = 9.7 Hz, 1H, H-4), 7.97 (d, $J_{7,8}$ = 7.3 Hz, 1H, H-7).

5-Hydroxyquinolin-2(1*H*)-one (5a):
To a solution of conc. HCl (100 mL) cooled in an ice bath was added **1a** (10.3 g, 0.05 mol). The resulting solution was taken out of the ice bath, left at r.t. overnight, and concentrated to dryness under vacuum. The residue was treated first with a slight excess of 10% aq K_2CO_3 and then reacidified with AcOH. The resulting precipitate was collected and recrystallized from MeOH to afford **5a**: yield: 7.25 g (90%); mp > 300°C (Lit.[4] mp 336–341°C).

^{1}H NMR (DMSO-d_6/TMS): δ = 6.35 (d, $J_{3,4}$ = 9.7 Hz, 1H, H-3), 6.55 (d, J = 9.7 Hz, 1H), 6.73 (d, J = 8.2 Hz, 1H), 7.23 (*t*, J = 8.1 Hz, 1H, H-7), 8.05 (d, $J_{3,4}$ = 9.7 Hz, H-4), 10.3 (br s, 1H), 11.55 (br s, 1H).

5-Hydroxy-6-methylquinolin-2(1*H*)-one (5b):
Following the procedure for the preparation of **5a**, **5b** was prepared in 77% yield: mp 297–300°C.

$C_{10}H_9NO_2$	calc.	C 68.56	H 5.18	N 8.00
(175.19)	found	68.68	5.26	8.12

^{1}H NMR (CF_3CO_2D/TMS): δ = 2.49 (s, 3H, CH_3), 7.28 (d, $J_{3,4}$ = 9.6 Hz), 1H, H-3), 7.40 (d, $J_{7,8}$ = 8.3 Hz, 1H), 7.79 (d, $J_{7,8}$ = 8.3 Hz, 1H), 9.08 (d, $J_{3,4}$ = 9.6 Hz, 1H, H-4).

1,2-Dihydro-5-(dimethylamino)-2-oxoquinoline-3-carbonitrile (6) and 1,2-Dihydro-5-hydroxy-2-oxoquinoline-3-carbonitrile (7):
A stirred mixture of **1c** (81.5 g, 0.35 mol) and glacial AcOH (1 L) was heated under reflux for 45 h and then concentrated to dryness under reduced pressure. The reddish residue was treated with water (300 mL) and filtered off. Recrystallization from DMF (250 mL) gave **6**; yield: 25.4 g (34%); mp 295–298°C dec.

$C_{12}H_{11}N_3O$	calc.	C 67.59	H 5.20	N 19.71
(213.24)	found	67.44	5.31	15.50

IR (KBr): ν = 2230 (CN) cm^{-1}.

^{1}H NMR (DMSO-d_6/TMS): δ = 2.77 (s, 6H, $N(CH_3)_2$), 6.77 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 7.2 Hz, 1H), 7.48 (t, J = 8.1 Hz, H-7), 8.59 (s, 1H, H-4), 11.25 (s, 1H, NH).

The mother liquor from above was treated with charcoal, concentrated to ≈ 100 mL and then allowed to stand at r.t. whereupon the second, less polar, component **7** crystallized as orange needles; yield: 8.4 g (13%); mp > 300°C.

$C_{10}H_6N_2O_2$	calc.	C 64.52	H 3.25	N 15.05
(186.17)	found	64.34	3.42	15.09

IR (KBr): ν = 2235 (CN) cm^{-1}.

^{1}H NMR (DMSO-d_6/TMS): δ = 6.59 (d, J = 8.1 Hz, 1H), 6.71 (d, J = 8.1 Hz, 1H), 7.40 (t, J = 8.2 Hz, 1H, H-7), 8.59 (s, 1H, H-4), 10.91 (br s, 1H), 11.25 (br s, 1H).

1,2,9,10-Tetrahydro-5-methyl-2,9-dioxoquino[7,8-*f*]quinoline-11-carboxaldehyde (10):
A stirred mixture of **1a** (10.3 g, 0.05 mol) and glacial AcOH (100 mL) was heated under reflux for 24 h and then concentrated to dryness. The yellow solid residue was treated with water (100 mL). The product was collected and recrystallized from DMF to afford **10**; yield: 4.4 g (57%); mp > 300°C.

$C_{18}H_{12}N_2O_3 \cdot 0.25H_2O$	calc.	C 70.01	H 4.00	N 9.07
(308.81)	found	70.01	4.08	9.07

IR (KBr): ν = 1732 (CHO) cm^{-1}.

MS (CI/CH_4): m/z = 305 (MH^+).

^{1}H NMR (CF_3CO_2D/TMS): δ = 3.06 (s, 3H, CH_3), 7.46 (d, 1H, J = 10 Hz), 7.7 (d, 1H, J = 10 Hz), 8.63 (s, 1H), 8.83 (d, 1H, J = 10 Hz), 9.53 (d, J = 10 Hz, 1H), 9.90 (s, 1H), 10.46 (s, 1H, CHO).

^{13}C NMR (CF_3CO_2D/TMS): δ = 198.97, 183.64, 168.25, 166.30, 145.84, 145.54, 145.08, 141.06, 138.66, 137.59, 123.34, 123.11, 123.04, 121.75, 121.49, 120.50, 21.83.

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(1) Singh, B.; Lesher, G.Y. *J. Heterocycl. Chem.* **1990**, *27*, 2085.
(2) Shono, T.; Matsumura, Y.; Kashimura, S. *J. Org. Chem.* **1981**, *46*, 3719.
(3) Nakagawa, K.; Murakami, N.; Yoshizaki, S.; Tominaga, M.; Mori, H.; Yabuuchi, Y.; Shintani, S. *J. Med. Chem.* **1974**, *17*, 529.
(4) Fleming, W.C.; Pettit, G.R. *J. Org. Chem.* **1971**, *36*, 3490.