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The Synthesis of 7-[1-Aza-2-(dimethylamino)vinyl]-4-methylhydroquinolin-2-ones and their Isomerism in Different Solvents

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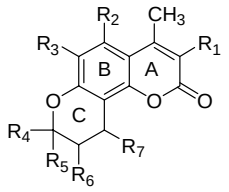
Abstract: The reaction of 7-amino-4-methyl-2(1*H*)-quinolone **1** and its 6-methyl derivative **2** with Vilsmeier reagent (DMF and $POCl_3$) afforded 7-[1-aza-2-(dimethylamino)vinyl]-4-methyl- hydroquinolin-2-one **3** and 7-[1-aza-2-(dimethylamino)vinyl]-4,6-dimethylhydroquinolin- 2-one **4**, respec-tively. ^{1}H-NMR analysis in different solvents indicated that isomerism occurred due to hindered rotation around the $(CH_3)_2N$–C:N σ-bond. The rotational energy barrier of **3** was calculated.

Keywords: 7-[1-Aza-2-(dimethylamino)vinyl]-hydroquinolin-2-ones, isomerism, ^{1}H-NMR.

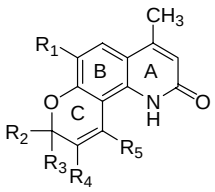
Interesting biological activities have been reported recently for 4-methylhydro-2*H*-pyrano [6,5-h]-chromen-2-ones and 4-methylhydro-2*H*-pyrano[6,5-h]quinolin-2-ones, including excellent anti-HIV activity with DCK derivatives[1] and significant cytotoxic activity with 4,8,8-trimethylhydro-2*H*-pyrano[6,5-h]quinolin-2-one[2]. These results prompted us to synthesize two series of corresponding diaza three-ring heterocyclic analogs, trihydro-pyridino[2,3-h]quinolin-2-ones and hydropyridino[2,3-h]quinolin-2-ones (**Scheme 1**).

We used 7-amino-4-methyl-2(1*H*)-quinolone 1 and its 6-methyl derivative 2 as starting materials and established the C-ring by intra- or inter-molecular electrophilic substitution with appropriate reagents and intermediates. However, many efforts failed because of the low nucleophilic reactivity of the B-ring. In order to find an electron-donating protective group for the 7-NH_2 of 1 and 2, we examined the reaction of these compounds with Vilsmeier reagent (DMF and $POCl_3$) and obtained 7-[1-aza-2-(di-methylamino)vinyl]-4-methyl-hydroquinolin-2-one 3 and 7-[1-aza-2-(dimethylamino) vinyl]-4,6-dimethyl-hydro- quinolin-2-one 4 respectively[3]. Their structures were identified from elemental analysis and ^{1}H-NMR ($CDCl_3$) spectral data (**Scheme 2** and **Table 1**).

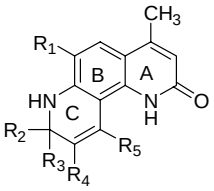
Scheme 1



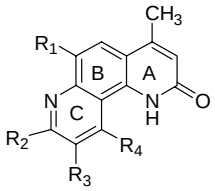
DCK derivatives



4-Methylhydropyrano[6,5-h]quinolin-2-one

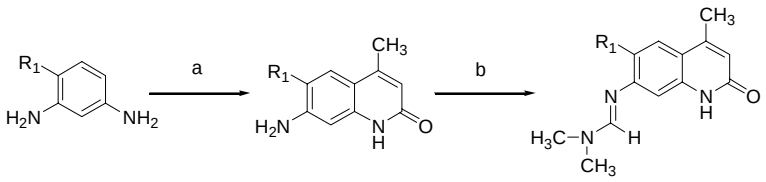


Trihydropyrido[2,3-h]quinolin-2-one



Hydropirido[2,3-h]quinolin-2-one

Scheme 2



R_1 =H
R_1 =CH_3

1 R_1 =H
2 R_1 =CH_3

3 R_1 =H
4 R_1 =CH_3

a. $CH_3COCH_2COOC_2H_5$ b: DMF / $POCl_3$

Table 1 Chemical shift (δ) of **3** and **4** in ^{1}H-NMR ($CDCl_3$)

Compd	N-H	N=C-H	5-H	6-H	8-H	3-H	N-Me_2	4-Me	6-Me
3	10.45	7.62	7.54	6.89	6.76	6.39	3.06	2.45	
4	11.41	7.66	7.37		6.90	6.36	3.11	2.43	2.35

Unexpectedly, when the ^{1}H-NMR spectra were measured in DMSO-d_6 at room temperature, both **3** and **4** gave different spectra from those in $CDCl_3$ (**Table 2**). The single signal for the two methyls of the dimethylamino group in the latter solvent separated into two signals. To illustrate the nature of this phenomenon, we selected **3** as an example and determined its ^{1}H-NMR (DMSO-d_6) spectra at different temperatures. As the temperature rose, the two signals at δ 3.04 and 2.94 broadened continuously from

25°C and finally coalesced to a sharp single signal at δ 2.99 at 45 °C. After cooling to 25°C, the original spectrum was recovered; that means the sample was unchanged during the temperature elevation (**Table 3**). This experimental result suggested that isomerism occurred due to hindered rotation around the $(CH_3)_2N$–C: N σ-bond in DMSO. Reasonably, this obstacle to δ-bond rotation may result from partial π-bonding due to partial conjugation between the unshared electron pairs on the nitrogen atoms of the dimethylamino and imine (C=N) groups in the aprotic solvent as shown in **Scheme 3**. According to the above experimental data, 66.5 KJ/mol of free energy ($\Delta G^{\neq}$) of activation was calculated for the bond rotation in **3** as follows[4]:

$$\Delta G^{\neq} = RTc[23+\ln(Tc/\Delta\nu)]$$
$$= 8.3\times10^{-3}\, Tc[23+2.3\log(Tc/\Delta\nu)]$$
$$= 66.5 \text{ KJ/mol}$$

Here Tc=273+45, Δν=29.24 Hz.

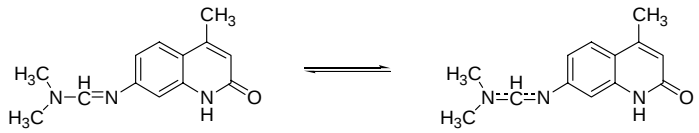
Table 2 Chemical shift (δ) of **3** and **4** in ^{1}H-NMR (DMSO-d_6) at 25 °C

Compd	N-H	N=C-H	5-H	6-H	8-H	3-H	N-Me_2	4-Me	6-Me
3	11.30	7.80	7.50	6.82	6.75	6.18	2.94 3.04	2.53	
4	11.20	7.59	7.39		6.58	6.14	2.99 3.01	2.35	2.21

Table 3 Chemical shift of N-methyls of **3** in ^{1}H-NMR(DMSO-d_6) at different temperature

Temperature (℃)	δ	
25	3.04	2.94
35	3.03	2.95
40	3.02	2.97
45	2.99	

Scheme 3



3

At room temperature, the two methyl signals in **4** were initially broader than those of **3**. Thus, because the melting point of DMSO is 18.4°C, the maximum signal separation and corresponding $\Delta G^{\neq}$ could not be determined for **4**.

Using **3** as the key intermediate, hydropyridino[2,3-h]quinolin-2-one derivatives were synthesized. The synthetic methodology will be published elsewhere.

Acknowledgment

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Reference and Notes

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2. Z. Y. Yang, Y. Xia, P. Xia, Y. Tachibana, K. F. Bastow, K. H. Lee, *Bioorg. Med. Chem. Lett.*,**1999**, *9*, 713.
3. Synthetic example: **7-[1-Aza-2-(dimethylamino)vinyl]-4-methylhydroquinolin-2-one (3):** $POCl_3$ (0.45 mL, 4.60 mmol) was added dropwise to a mixture of 0.80 g (4.59 mmol) of **1** and 8 mL DMF at –5- 0 ℃. After stirring for 30 min at 0 ℃, 20% Na_2CO_3 was added until pH=8. The precipitate was filtered and washed with ice water to give crude **3** in quantitative yield. Crystallization from chloroform gave colorless needle crystals. mp. 221-222℃; MS (*m/z*, %): 229 (M^+, 100), 214 (M^+-Me, 20.18), 44 (NMe_2^+, 16.49); ^{1}H-NMR ($CDCl_3$) δ : 10.45 (s, 1H, N-H), 7.62 (s, 1H, N=C-H), 7.54 (d, J=8.60 Hz, 1H, 5-H), 6.89 (dd, J=8.60 Hz, J=2.04 Hz, 1H, 6-H), 6.76 (d, J=2.04 Hz, 1H, 8-H), 6.39 (s, 1H, 3-H), 3.06 (s, 6H, NMe_2), 2.45 (s, 3H, 4-Me). ^{1}H-NMR (DMSO- d_6, 25℃) δ : 11.30 (s, 1H, N-H), 7.80 (s, 1H, N=C-H), 7.50 (d, J=8.67 Hz, 1H, 5-H), 6.82 (dd, J=8.67 Hz, J= 1.90 Hz, 1H, 6-H), 6.75 (d, J=1.90 Hz, 1H, 8-H), 6.18 (s, 1H, 3-H), 3.04 and 2.94 (2s, 6H, NMe_2), 2.53 (s, 3H, 4-Me). **7-[1-Aza-2-(dimethylamino)vinyl]-4,6-dimethylhydroquinolin-2-one (4):** colorless needle crystals.mp. 258- 260 ℃; MS (*m/z*, %): 243 (M^+, 100), 228 (M^+-Me, 13.98), 199 (M^+-NMe_2,53.44), 44 (NMe_2^+, 8.56). ^{1}H-NMR ($CDCl_3$) δ : 11.41(s, 1H, N-H), 7.66 (s, 1H, N=C-H), 7.37 (s, 1H, 5-H), 6.90 (s, 1H, 8-H), 6.36 (s, 1H, 3-H), 3.11 (s, 6H, NMe_2), 2.43 (s, 3H, 4-Me), 2.35 (s, 3H, 6-Me). ^{1}H-NMR (DMSO-d_6, 25℃) δ : 11.20 (s, 1H, N-H), 7.59 (s, 1H, N=C-H), 7.39 (s, 1H, 5-H), 6.58 (s, 1H, 8-H), 6.14 (s, 1H, 3-H), 3.01 and 2.99 (2s, 6H, NMe_2), 2.35(s, 3H, 4-Me), 2.21 (s, 3H, 6-Me).
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