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PREPARATION AND ANTIBACTERIAL ACTIVITY OF PYRIDOPYRIDONE ANALOGS: C-1 MODIFICATIONS

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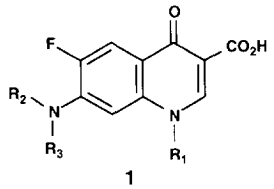
Abstract: Variation of the C-1 position of the pyridopyridone antibacterials shows a sensitivity to both size and electronic character of the substituent. © 1997 Elsevier Science Ltd.

The 4-quinolones (**1**) have proven to be an important class of antibacterial agents whose mode of action involves inhibition of DNA gyrase, an important bacterial topoisomerase enzyme.[1] These agents have undergone hundreds of modifications over the last decade resulting in some very potent derivatives in various stages of clinical study.[2] Recently, a related series of agents, the pyridopyridones (**2**) have been reported[3] and, while they exhibit the same mode of action as the 4-quinolones, this novel series has shown potent activity against resistant strains. Although optimization of the C-1 substituent of the 4-quinolones has led to the cyclopropyl derivative being one of the most active analogs, it was unknown whether this structural feature would also be optimal in the new series.[4] We report herein the synthesis and antibacterial activity of various C-1 analogs of the pyridone series along with a more expedient method for their preparation.



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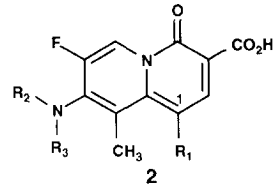

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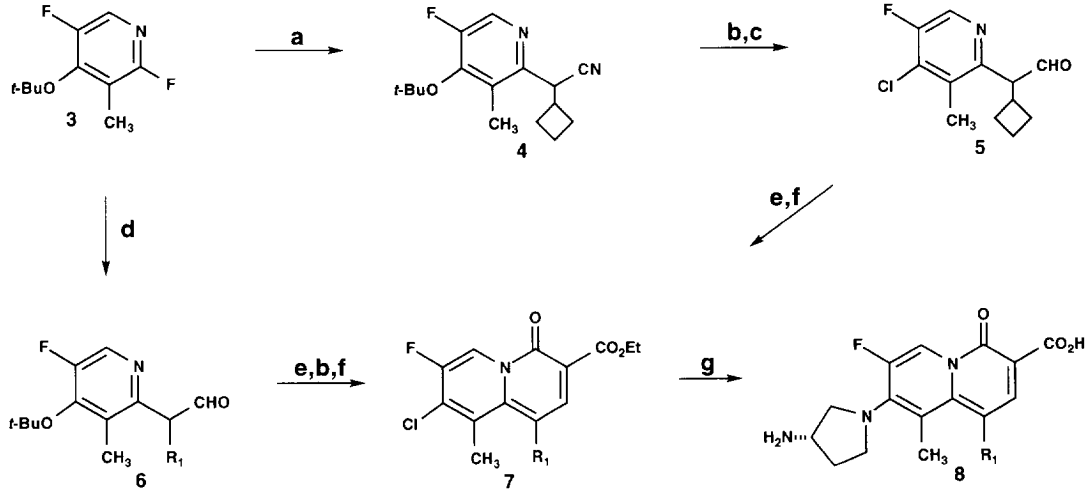
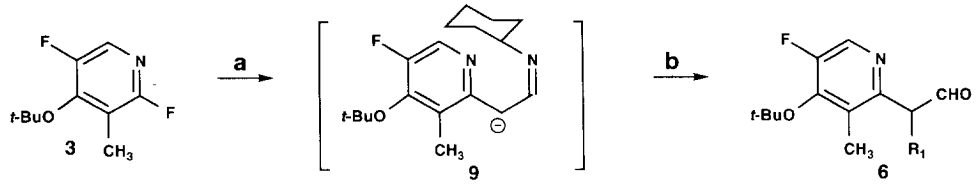
Chemistry. The initial approach toward C-1 analogs was to carry out the previously reported[3] synthesis of this ring system as depicted in Scheme 1 (**8**, R_1 = cyclobutyl). The key step involves the addition of a substituted acetonitrile anion to the fluoropyridine ring **3**. Direct reduction of the nitrile group to an aldehyde group with reagents such as diisobutylaluminum hydride (DiBAl) led to recovery of starting material due to possible coordination of the reagent with the cyano and pyridine nitrogens.[5] Therefore following hydrolysis/chlorination of the *t*-butyl ether in **4**, it was necessary to utilize a multi-step procedure for the formation of aldehyde **5** as shown in step **c** for the cyclobutyl analog. Unfortunately, the strongly acidic, reductive, and oxidative conditions required in these steps limited the type of functionality that could be present in the R_1 residue. Condensation of aldehyde **5** with diethyl malonate and thermal cyclization in DMSO produced key intermediate **7**. Addition of the Bocaminopyrrolidine to **7** followed by subsequent ester hydrolysis and acid removal of the Boc protecting group led to the final product **8** (R_1 = cyclobutyl).

We strove to modify this route in order to allow for more efficient variation of the R_1 residue and to avoid the harsh reaction conditions. We found that by using imine anions[6] as aldehyde α-anion equivalents both goals could be accomplished. When the cyclohexylimine of propionaldehyde was deprotonated as above and added to pyridine **3**, a good yield of aldehyde **6** ($R_1 = CH_3$, 56%) was obtained following hydrolysis. Compound **6** was then reacted with diethyl malonate, chlorinated, and cyclized as before to give intermediate **7** ($R_1 = CH_3$). The cyclopropyl aldehyde **6** ($R_1 = C_3H_5$, 75%) was also produced in this manner from the corresponding imine of cyclopropylacetaldehyde. This shorter and milder route allows for the compatibility of other functionalities such as ethers or olefins to be incorporated as C-1 substituents.



Scheme 1. (a) i. LDA, *c*-$C_4H_7CH_2CN$, -78 °C, 2 h, 80%; (b) $POCl_3$, DMF, CH_2Cl_2, 25 °C, 16 h, 94%; (c) i. HCl_g, EtOH, 78 °C, 4 h, 80%; ii. $LiAlH_4$, THF, 0 °C, 2 h, 89%; iii. $(ClCO)_2$, DMSO, TEA, -78 °C, 91%; (d) LDA, $R_1CH_2CH{=}N\text{-}cC_6H_{11}$, 0-25 °C, see Table 2; (e) 2 equiv. Diethyl malonate, piperidine, HOAc, EtOH, reflux, 7 h, 81%; (f) DMSO, reflux, 7 h, 65%; (g) i. 2 equiv. (*S*)-Boc-aminopyrrolidine, CH_3CN, $NaHCO_3$, reflux 4 h, 64%; ii. LiOH, 30% aq. THF, reflux, 5 h, 90%; iii. 1M HCl/HOAc, CH_2Cl_2, 25 °C, 82%.

Further versatility was attained when the imine anion of acetaldehyde was used. Prior to hydrolytic workup, the incipient anion **9** was quenched with various electrophiles to give the new aldehydes **6** in one step after hydrolytic workup (Scheme 2). The yields produced in this in situ alkylation approach, even with poor electrophiles (Table 1, entry **d-f**) reflect the excellent nucleophilicity of the pyridylimine anion; however, the cyclopropyl analog (entry **g**) was best prepared via the preformed imine as described above. All new compounds (**8a-f, h-l**) were characterized by HPLC and high resolution mass spectral means (vinyl analog **j** forms directly under these conditions.[7]

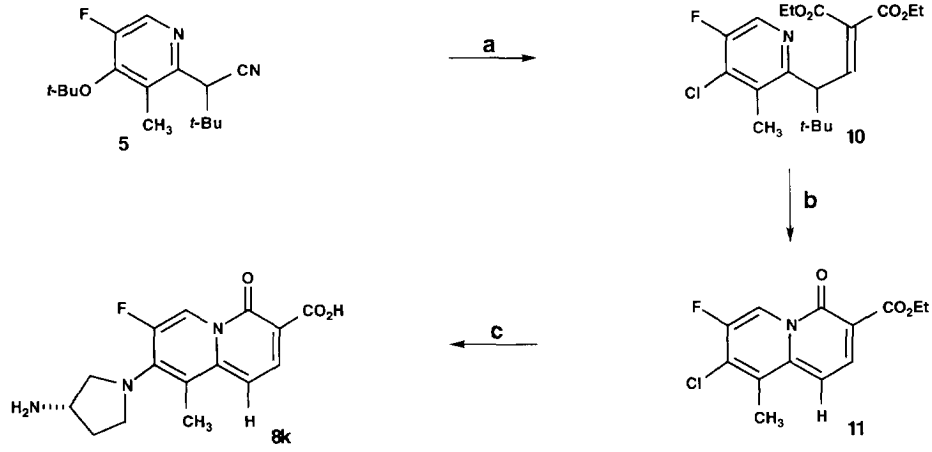


Scheme 2. (a) 3.5 equiv. LDA, $CH_3CH{=}N\text{-}cC_6H_{11}$, 0-25 °C, 1 h; (b) 3.5 equiv. R_1X, 25 °C, 0.3 h.

Table 1. In Situ imine anion alkylation

entry	R_1X	Yield (%)	entry	R_1X	Yield (%)	entry	R_1X	Yield (%)
a	methyl iodide	54	**d**	2-iodopropane	98	**h**	cyclopropylmethyl bromide	73
b	allyl bromide	85	**e**	2-iodobutane	88	**i**	2,2-dimethylpropyl iodide	91
c	1-bromoethyl methyl ether	75	**f**	cyclopentyl bromide	100	**j**	1-bromo-1-chloro-ethane	55
			g	cyclopropyl iodide	5		(**6**, R_1 = vinyl)	

Another C-1 substituent which has been shown to impart good activity to the quinolone nucleus is the *t*-butyl group, and so the corresponding acetonitrile[8] anion was added to pyridine **3**. The fact that DiBAl successfully afforded the aldehyde only in this case lends further evidence for a conformationally based coordination. Interaction of the *t*-butyl group and the *ortho*-positioned methyl group should disfavor this coordinative conformation. Following condensation with diethyl malonate to give **10**, the thermolytic cyclization yielded only the C-1 unsubstituted analog **11**, arising from an elimination of the *t*-butyl group. This dealkylation gives further evidence for the steric encumbrance encountered by the C-1 substituents.



Scheme 3. (a) i. $POCl_3$, DMF, CH_2Cl_2, 25 °C, 16 h, 98%; ii. 3 eq. DiBAl, hexane, -40 °C, 4 h, 30%; iii. Diethyl malonate, EtOH, reflux, 16 h, 70%; (b) Dowtherm, reflux, 7 h, 82%; (c) i. (*S*)-Boc-aminopyrrolidine, CH_3CN, $NaHCO_3$, reflux, 7 h, 81%; ii. LiOH, 30% aq, THF, reflux, 3 h; iii. 1 M HCl/HOAc, CH_2Cl_2, 25 °C, 1 h, 85%(two steps).

Biological Activity. The C-1 analogs were tested against both gram positive and gram negative bacterial strains, and the results are reported in Table 2 as the minimum concentrations of each compound to inhibit the growth of these various strains (MIC). All of the C-1 analogs exhibited whole cell antibacterial activity but none were as potent as the cyclopropyl analog **8g**. The methyl, isopropyl, and cyclobutyl analogs (entries **a**, **d** and **l**) had the best MIC's of the new compounds with the allyl and vinyl analog (**8b** and **8j**) showing moderate activity. Increasing the size of the C-1 substituent over that of cyclopropyl had great effect on the activity (compare **d**, **l**, and **f** with **g**); however, electronic effects were also important as the ether (entry **c**) was much less active than similar sized

substituents. Rather than a straightforward steric effect, the peculiar electronics of the cyclopropyl ring must play a role in this series as they do in the quinolone series since smaller substituents such as H and CH_3 or similar sized substituents with π-electronic character such as vinyl were less active.

Table 2. In Vitro Antibacterial Activity of Pyridone C-1 Modifications [MIC (μg/mL)][a]

8	R1	S.A.1	S.A.2	E.F.	S.P.	E.C.	P.A.
a	CH_3	0.1	12.5	0.39	0.39	0.05	3.1
b	allyl	0.78	>100	1.56	1.56	1.56	3.1
c	CH_2CH_2OMe	50	>100	>100	-	12.5	100
d	$CH(CH_3)_2$	0.1	6.2	0.2	0.2	0.39	1.56
e	(*R,S*)-*s*-butyl	6.2	>100	12.5	50	1.56	50
f		3.1	50	12.5	12.5	0.78	25
g		0.01	0.78	0.02	0.02	0.01	0.05
h		1.56	25	6.2	6.2	0.78	12.5
i	$(CH_3)_3C\text{-}CH_2$	1.56	50	6.2	3.1	-	12.5
j	$CH{=}CH_2$	0.78	>100	1.56	1.56	0.2	0.78
k	H	3.1	>100	25	12.5	0.39	6.2
l		0.1	12.5	0.39	0.39	0.05	3.1

[a] MIC's measured [b] SA1, *Staphylococcus aureus* NCTC 10649M; SA2, *Staphylococcus aureus* 1775; EF, *Enterococcus faecium* ATCC 8043; SP, *Streptococcus pyogenes* 930; EC, *Escherichia coli* juhl; PA, *Pseudomonas aeruginosa* K799/WT.

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7. HPLC: Purity% (retention time). HPLC data collected on Dynamax - 300A C18 column with gradient flow: 70% CH_3CN,30% H_2O (0.1%TFA). **8a**: HPLC: 100 (3.84); HRMS: $C_{16}H_{18}FN_3O_3$, calcd 330.1410; found 330.1411. **8b**: HPLC: 94 (5.19); HRMS: $C_{18}H_{20}FN_3O_3$, calcd 346.1567; found 346.1567. **8c**: HPLC: 100 (2.25); HRMS: $C_{18}H_{22}FN_3O_4$, calcd 364.1673; found 364.1669. **8d**: HPLC: 99.3 (6.06); HRMS: $C_{18}H_{22}FN_3O_3$, calcd 348.1723; found 348.1715. **8e**: HPLC: 98.3 (13.08); HRMS: $C_{19}H_{25}ClFN_3O_3$, calcd 362.188; found 362.188. **8f**: HPLC: 99.5 (12.85); HRMS: $C_{20}H_{24}FN_3O_3$, calcd 374.188; found 374.1837. **8h**: HPLC: 100 (9.03); HRMS: $C_{19}H_{22}FN_3O_3$, calcd 360.1723; found 360.1721. **8i**: HPLC: 81 (14.01); HRMS: $C_{20}H_{26}FN_3O_3$, calcd 376.2036; found 376.2037. **8j**: HPLC: 100 (5.8); HRMS: $C_{17}H_{18}FN_3O_3$, calcd 332.1410; found 332.1416. **8k**: HPLC: 99.4 (3.33); HRMS: $C_{15}H_{17}ClFN_3O_3$, calcd 306.1234; found 306.1259. **8l**: HPLC: 100 (10.47); HRMS: $C_{19}H_{23}FN_3O_3$, calcd 360.1723; found 3601727.
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