GENERAL ROUTES TO 4-OXO-*4H*-PYRANO[2,3-*b*]PYRIDINE-3-CARBOXYLATES AND RELATED COMPOUNDS: SYNTHESIS OF THE OXYGEN AND SULFUR ISOSTERES OF NALIDIXIC ACID

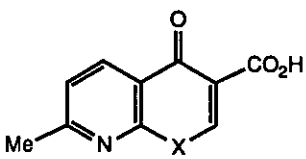
Stuart W. McCombie*, Sue-Ing Lin,and Jayaram R. Tagat

Chemical Research, Schering-Plough Research Institute, DDF
2015 Galloping Hill Road, Kenilworth, NJ 07033-0539, USA

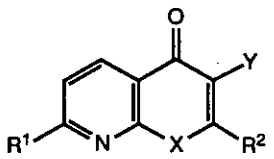
Abstract- Imidazolides of 2-hydroxy- and 2-mercaptonicotinic acids with $LiCH_2CO_2Bu$-t gave ketoesters which were cyclised with $MeOCH{=}NMe_2^+$ $MeOSO_3^-$ and i-Pr_2NEt or with $(RCO)_2O$-NEt_3-DMAP to the title 2-H or 2-R bicyclic esters; the corresponding 3-methylsulfonyl and 3-phosphonate analogs were similarly prepared. The 2-unsubstituted 4-oxopyranopyridine-3-carboxylates were unstable at physiological pH, whereas the thio analogs were stable.

Nalidixic acid (**1**) and related, bicyclic 3-carboxy-4-pyridinones are valuable antibacterial agents[1] whose mode of action involves the specific inhibition of bacterial DNA-gyrase. Although a vast number of analogs are known,[2] the oxygen and sulfur isosteres (**2**) and (**3**) have not been described. We became interested in these and related structures both in their own right and as synthetic intermediates for more complex systems. In this paper, we describe the synthesis and properties of **2** and **3**, and routes to compounds of general structure (**4**).

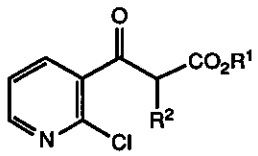
Dedicated to Professor Edward C. Taylor on the occasion of his 70th birthday



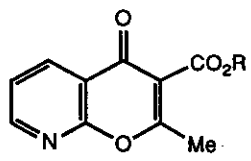
1 X = NEt
2 X = O
3 X = S



4 { X = O or S; Y = electron-with-drawing group

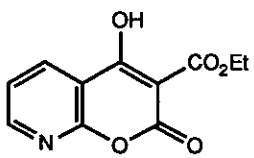


5 R^1 = Et, R^2 = COMe
9 R^1 = Et, R^2 = CO_2Et



6 R = Et
7 R = H
8 R = $CH_2CH{=}CH_2$

Our initial entry into the 4-oxopyranopyridine-3-carboxylate system involved reaction of sodio ethyl acetoacetate with 2-chloronicotinoyl chloride to give **5** (67%). Although decomposed by base[3] (NaH-DMSO), this substance cyclised in acid (catalytic MsOH, CH_2Cl_2, reflux) to the 2-methyl compound (**6**) [87%; mp: 63-64°C; ^{1}H nmr($CDCl_3$), δ=2.56(s,3; 2-C*H*$_3$)]#. Hydrolysis (aq. NaOH) to **7** was accompanied by extensive decomposition; Pd(0) cleavage[4] of the allyl ester (**8**), prepared (81%) in the same manner as **5** provided 92% of **7**. This cyclisation process was not useful for preparing the 2-H or 2-Ph analogs of **6**, although acylmalonate (**9**) was cyclised (MsOH, 1,2-$C_2H_4Cl_2$, reflux) in 44% yield to the 4-hydroxy compound (**10**).[5]



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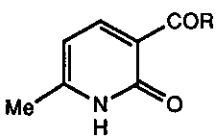
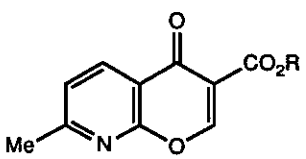


11 R = Imidazol-1-yl
12 R = $CH_2CO_2CH_2CH{=}CH_2$
14 R = CH_2CO_2Bu-t

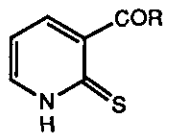


13 R = $CH_2CH{=}CH_2$
15 R = Bu-t

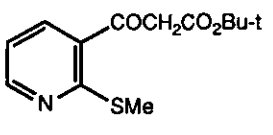
All new compounds were fully characterised and gave mass spectra and elemental analyses consistent with assigned structures.

Seeking a route to the 2-unsubstituted system, we treated the imidazolide (**11**)[6] with $LiCH_2CO_2CH_2CH{=}CH_2$ (4 eq., THF, -70° to 0°C) to afford keto ester (**12**) in 82% yield. Although reactions of **12** with $CH(OEt)_3$, $Me_2NCH(OMe)_2$ or $ClCH{=}NMe_2^+$ Cl^- under various conditions gave complex mixtures, clean conversion to the desired ester (**13**) was secured using i-Pr_2NEt and $MeOCH{=}NMe_2^+$ $MeOSO_3^-$ in CH_2Cl_2 at 25°C [**13**: 46%; mp: 79-82°C; ^1H nmr($CDCl_3$), δ=2.71(s,3; 7-C*H*$_3$) and 8.76(s,1; 2-*H*)].

*Properties of **13** indicated the sensitivity of this system to nucleophiles:* **13** decomposed slowly on silica gel (necessitating rapid chromatographic purification) and reacted rapidly with both sodium 2-ethylhexanoate and benzylamine. In contrast, **13** was stable to CF_3COOH, and this reagent served to quantitatively convert the corresponding t-butyl ester (**15**), prepared *via* keto ester (**14**) by the same cyclisation process, to the free acid (**2**), mp 140-150°C (decomp.). Although solutions of **2** in MeOH-H_2O at pH 4~5 were quite stable, addition of phosphate buffer, pH 7.5, led to rapid decomposition to unidentified, yellow materials; application of solutions of **2** to reversed-phase silica gel gave the same result. This sensitivity is presumably a consequence of C-2 attack, since the aforementioned 2-Me compounds were far less sensitive. Aspects of C=C *vs* C=O attack on the related 3-formylchromone have been discussed[7] and C=C reactivity of chromone 3-carboxylates towards cuprate addition[8] and in cycloadditions[9] have also been described recently.



16 R = Imidazol-1-yl
17 R = CH_2CO_2Bu-t



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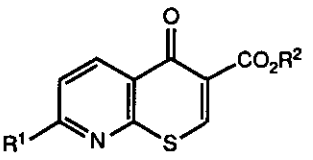
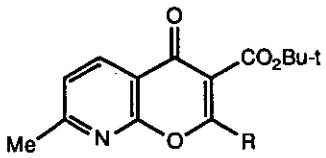


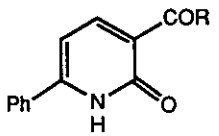
18 R^1 = H, R^2 = Bu-t
20 R^1 = R^2 = H
21 R^1 = Ph, R^2 = H

A similar reaction sequence gave the thia analogs. 2-Mercaptonicotinic acid was converted [(Imidazole)$_2$CO, then excess $LiCH_2CO_2Bu$-t] through **16** to **17**, and cyclisation with the DMF-

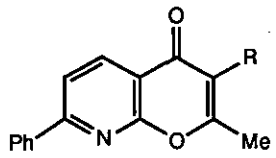
Me_2SO_4 adduct provided **18** in 40-50% yield, with significant amounts of the *S*-methyl compound (**19**). *Aqueous solutions of the sodium salt of the derived acid (**20**) were only slightly decomposed after 72 h at pH 7.5-8.5.* In a similar way, the 7-methyl-and 7-phenyl compounds(**3**)(42%) and(**21**) (45%) were obtained in three steps from 6-methyl- and 6-phenyl- 2-mercaptonicotinic acids,[10] respectively. None of these 4-oxo-*4H*-thiopyrano[2,3-*b*]pyridine-3-carboxylic acids showed any significant antibacterial activity.[11]



22 R = Me
23 R = Ph
24 R = Bu-i



25 R = CH_2SO_2Me
26 R = $CH_2PO(OEt)_2$



27 R = SO_2Me
28 R = $PO(OEt)_2$
29 R = $PO(OH)_2$

Finally, we report that keto esters such as **14** are convenient intermediates for a variety of 2-substituted compounds through reaction with $(RCO)_2O$-NEt_3 in the presence of 4-dimethylaminopyridine (DMAP).[12] Ac_2O in CH_2Cl_2 or MeCN at 25°C gave **22**, somewhat more vigorous conditions being required (MeCN or 1,2-$C_2H_4Cl_2$, reflux) for reactions with $(PhCO)_2O$ and $(i\text{-}BuCO)_2O$, which afforded **23** and **24**, respectively. Unoptimised yields for a variety of these bicyclic products were 50-80%.

Compounds with different electron-withdrawing groups at C-3 were prepared by the same cyclisation: reaction of the imidazolide or the ethyl ester of 6-phenyl-2-hydroxynicotinic acid[13] with $LiCH_2SO_2Me$ or $LiCH_2PO(OEt)_2$ gave **25** and **26**, readily converted (Ac_2O-NEt_3-DMAP, MeCN, 25°C) to **27** (30%) and **28** (27%). The latter phosphonate could be deprotected (99%) to the acid (**29**) using excess Me_3SiBr.

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REFERENCES AND NOTES

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2. R. Albrecht, *Prog. Drug Res.*, 1977, **21**, 9.
3. In contrast, intramolecular displacement of fluoride under basic conditions has been used to prepare chromone-3-carboxylates: G. M. Coppola and R. W. Dodsworth, *Synthesis*, **1981**, 523.
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5. The 2-oxo-4-hydroxy structure was consistent with a lack of the downfield shift for H-5 which is characteristic of authentic 4-oxo structures such as **6**.
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10. The 2-hydroxy acid (ref. 13) was converted (EtOH-H_2SO_4, then PCl_5-$POCl_3$) to the 2-chloro ester. Treatment with excess NaSH in EtOH followed by hydrolysis (NaOH, aq. EtOH) gave the mercaptoacid. Although 3-cyano-6-phenyl-2(*1H*)-pyridinethione could be prepared readily from $NCCH_2CSNH_2$ and Na^+ $^-OCH{=}CHCOPh$, hydrolysis of this material was inevitably accompanied by partial conversion of C=S to C=O.
11. A standard Disc assay on agar impregnated with a sensitive strain of *E. coli* was used, with Nalidixic acid as the positive control.
12. The inclusion of DMAP (or 4-(1-pyrrolidino)pyridine) was essential for efficient reaction, presumably by facilitating both *reversible O*-acylation and *irreversible C*-acylation/cyclisation sequences. 2-Methylchromone-3-carboxylates have been prepared in modest yield from hydroxy keto esters in refluxing NaOAc-Ac_2O: J. L. Charlton, G. Lykpa and V. Sayeed, *J. Heterocycl. Chem.*, 1980, **17**, 593.
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