

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

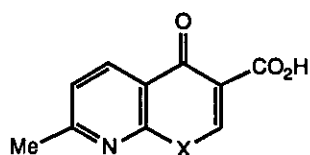
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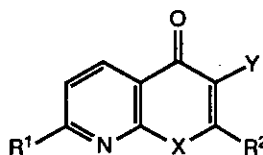
Abstract—Imidazolides of 2-hydroxy- and 2-mercaptonicotinic acids with $\text{LiCH}_2\text{CO}_2\text{Bu-t}$ gave ketoesters which were cyclised with $\text{MeOCH=NMe}_2^+ \text{MeOSO}_3^-$ and $i\text{-Pr}_2\text{NEt}$ or with $(\text{RCO})_2\text{O-NEt}_3\text{-DMAP}$ to the title 2-H or 2-R bicyclic 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 agents¹ 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**).

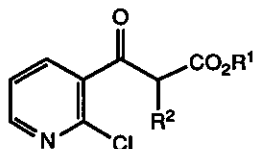
Dedicated to Professor Edward C. Taylor on the occasion of his 70th birthday



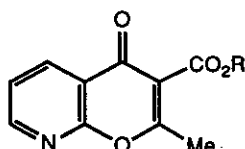
- 1 X = NEt
2 X = O
3 X = S



- 4 { X = O or S
Y = electron-withdrawing group

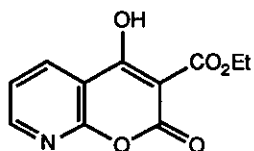


- 5 R¹ = Et, R² = COMe
9 R¹ = Et, R² = CO₂Et

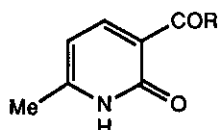


- 6 R = Et
7 R = H
8 R = CH₂CH=CH₂

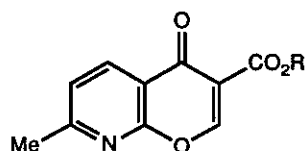
Our initial entry into the 4-oxopyranopyridine-3-carboxylate system involved reaction of sodio ethyl acetoacetate with 2-chloronicotinoyl chloride to give **5** (67%). Although decomposed by base³ (NaH-DMSO), this substance cyclised in acid (catalytic MsOH, CH₂Cl₂, reflux) to the 2-methyl compound (**6**) [87%; mp: 63-64°C; ¹H nmr(CDCl₃), δ=2.56(s,3; 2-CH₃)][#]. Hydrolysis (aq. NaOH) to **7** was accompanied by extensive decomposition; Pd(0) cleavage⁴ 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-C₂H₄Cl₂, reflux) in 44% yield to the 4-hydroxy compound (**10**).⁵



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- 11 R = Imidazol-1-yl
12 R = CH₂CO₂CH₂CH=CH₂
14 R = CH₂CO₂Bu-t

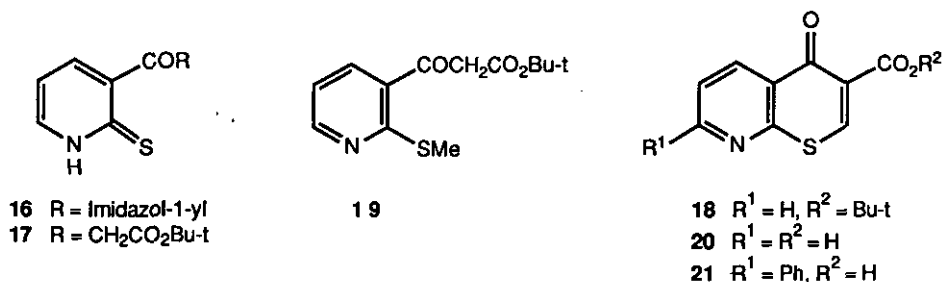


- 13 R = CH₂CH=CH₂
15 R = Bu-t

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

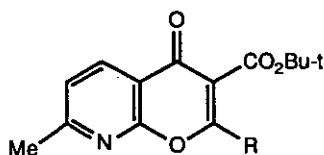
Seeking a route to the 2-unsubstituted system, we treated the imidazolidine (11)⁶ with $\text{LiCH}_2\text{CO}_2\text{CH}_2\text{CH}=\text{CH}_2$ (4 eq., THF, -70° to 0°C) to afford keto ester (12) in 82% yield. Although reactions of 12 with $\text{CH}(\text{OEt})_3$, $\text{Me}_2\text{NCH}(\text{OMe})_2$ or $\text{ClCH}=\text{NMe}_2^+ \text{Cl}^-$ under various conditions gave complex mixtures, clean conversion to the desired ester (13) was secured using $i\text{-Pr}_2\text{NEt}$ and $\text{MeOCH}=\text{NMe}_2^+ \text{MeOSO}_3^-$ in CH_2Cl_2 at 25°C [13: 46%; mp: $79\text{--}82^\circ\text{C}$; ^1H nmr(CDCl_3), $\delta=2.71(\text{s}, 3; 7\text{-CH}_3)$ and $8.76(\text{s}, 1; 2\text{-H})$].

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 $140\text{--}150^\circ\text{C}$ (decomp.). Although solutions of 2 in $\text{MeOH}\text{--}\text{H}_2\text{O}$ 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 $\text{C}=\text{C}$ vs $\text{C}=\text{O}$ attack on the related 3-formylchromone have been discussed⁷ and $\text{C}=\text{C}$ reactivity of chromone 3-carboxylates towards cuprate addition⁸ and in cycloadditions⁹ have also been described recently.

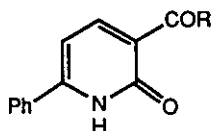


A similar reaction sequence gave the thia analogs. 2-Mercaptonicotinic acid was converted [(Imidazole)₂CO, then excess $\text{LiCH}_2\text{CO}_2\text{Bu-t}$] through 16 to 17, and cyclisation with the DMF-

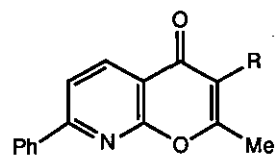
Me_2SO_4 adduct provided **18** in 40-50% yield, with significant amounts of the *S*-methyl compound (**19**). Aqueous solutions of the sodium salt of the derived acid (**20**) were only slightly decomposed after 72 h at pH 7.5-8.5. In a similar way, the 7-methyl- and 7-phenyl compounds (**3**) (42%) and (**21**) (45%) were obtained in three steps from 6-methyl- and 6-phenyl- 2-mercaptopyridine-3-carboxylic acids,¹⁰ respectively. None of these 4-oxo-4*H*-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 = $\text{CH}_2\text{SO}_2\text{Me}$
26 R = $\text{CH}_2\text{PO}(\text{OEt})_2$



- 27** R = SO_2Me
28 R = $\text{PO}(\text{OEt})_2$
29 R = $\text{PO}(\text{OH})_2$

Finally, we report that keto esters such as **14** are convenient intermediates for a variety of 2-substituted compounds through reaction with $(\text{RCO})_2\text{O}\cdot\text{NEt}_3$ 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- $\text{C}_2\text{H}_4\text{Cl}_2$, reflux) for reactions with $(\text{PhCO})_2\text{O}$ and $(i\text{-BuCO})_2\text{O}$, 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 acid¹³ with $\text{LiCH}_2\text{SO}_2\text{Me}$ or $\text{LiCH}_2\text{PO}(\text{OEt})_2$ gave **25** and **26**, readily converted ($\text{Ac}_2\text{O}\cdot\text{NEt}_3\cdot\text{DMAP}$, 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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10. The 2-hydroxy acid (ref. 13) was converted (EtOH-H₂SO₄, then PCl₅-POCl₃) 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(1*H*)-pyridinethione could be prepared readily from NCCH₂CSNH₂ 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-Ac₂O: J. L. Charlton, G. Lykpa and V. Sayeed, *J. Heterocycl. Chem.*, 1980, **17**, 593.
13. C. Barat, *J. Indian Chem. Soc.*, 1931, **8**, 801. Hydrolysis of the nitrile was accomplished quantitatively by refluxing in AcOH-H₂SO₄ containing a little H₂O.

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