Imidazolinone Herbicides: Synthesis and Novel Chemistry*

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ABSTRACT

The imidazolinone herbicides were prepared from reaction of an α-methylvaline fragment with an α-dicarboxylic acid. Early syntheses were completed through an imide amide intermediate, such as I or XV, followed by further cyclization to 2,5-diones III or XXI. Reaction of these diones with nucleophiles led to imidazolinones IV and V. The significant and interesting activity of these compounds led to new and versatile methods of synthesis, including resolution of the α-methylvaline fragments, development of a metallation–carboxylation route, a one-step picoline to imidazolinone route, and several pyridine and fused-ring pyridine syntheses.

1 INTRODUCTION

The discovery and development of new herbicides is a long and trying endeavor. Retrospective discussions often fail to do justice to the hurdles overcome during this process. In this paper, some of the synthetic chemistry that was explored in the discovery of the commercialized imidazolinone herbicides will be discussed. Some aspects of imidazolinone chemistry have been reported previously in both the chemical and patent literature.1–5

The structure of the commercial herbicides are shown in Fig. 1. The structural prerequisites for high biological activity are an imidazolinone ring substituted with a methyl and an isopropyl group and a neighboring carboxylic acid group. Both the imidazolinone ring and the carboxylic acid group are attached to an aromatic

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nucleus. When the aromatic ring nucleus is a pyridine, the preferred regioisomer is the one depicted in the commercial product, i.e. the one with the imidazolinone ring adjacent to the ring nitrogen.

A brief history of the discovery of these compounds begins with phthalimide I (Fig. 2), originally synthesized as a potential anticonvulsant. This compound when first tested as a herbicide in 1971 had sufficient activity in the primary screen to warrant further investigation. The synthesis effort that ensued led to the discovery of chlorophthalimide AC 94,377, a plant growth stimulant which has been reported previously. One synthesis of this analog resulted in the isolation of a novel cyclized analog, II, also a plant growth stimulant. Exploration of analogs of II led to tricycle III, which was found to be a more active herbicide than I. Investigation of the chemistry of compound III led to the imidazolinylenzoate IV, which, although a good herbicide, was largely non-selective. The methyl-substituted benzoate ester imazamethabenz-methyl has been commercialized as a cereal selective herbicide. Replacement of the benzoic acid nucleus to give nicotinic acid V resulted in significant improvement in herbicidal activity and eventual commercial development of V and its analogs.

After it was discovered that some of the imidazolinone herbicides had commercial potential, mode-of-action work was initiated. It was found these imidazolinone

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**Fig. 1.** Commercial imidazolinone herbicides. ® Registered trademarks of American Cyanamid Company.
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Anticonvulsant; herbicide screen, active 1971

Nonselective pre- and postemergence herbicide AHAS inhibitor

![Chemical structures](image)

**Fig. 2.** Chronology of imidazolinone discovery and development.

Herbicides inhibit the enzyme acetohydroxyacid synthase (AHAS); additional details are given in an accompanying paper. Even some of the early analogs in this program, including I, showed inhibition of AHAS, albeit at high concentrations (Stidham, M. L. and Robson, P., 1985, pers. comm.). It has also been reported by Huppatz and Casida that phthaloylvaline analogs related to I are AHAS inhibitors.

2 METHODS

2.1 Synthesis and resolution of amino acid fragments

Many imidazolinones can be prepared from one of three amino acid fragments derived from 3-methyl-2-butanone (Fig. 3) and an o-dicarboxylic acid synthon. A Strecker synthesis gave amino nitrile VI which on hydrolysis yielded amino amide VII, while the Bucherer–Buchi reaction, followed by hydrolysis of the intermediate hydantoin VIII, afforded amino acid IX.

Since it was of interest to determine the biological activity of the individual (R)- and (S)-isomers containing these amino acid fragments, resolution of amino acid IX was carried out. The amino acid IX was acetylated (Fig. 3) under Schotten–Baumann conditions, yielding acid X. The (S)-isomer of X was selectively hydrolyzed with hog kidney acylase to (S)-IX, in analogy with similar selective hydrolyses of racemic N-acylated valines. The unhydrolyzed (R)-X was separated from (S)-IX by ion-exchange chromatography and converted to amino acid (R)-IX.
as depicted. Incorporation of the (R)- and (S)-enantiomers of IX into a number of imidazolinone analogs revealed the (R)-isomer as the more active enantiomer.

In order to capitalize on the superior activity of the (R)- versus (S)-isomers ((R)-imidazolinones are about eight times more active than their (S)-isomers), and to allow for more cost-effective use of the o-dicarboxylic acid fragment, a feasible method for resolution of aminonitrile VI was developed (Fig. 3). The desired (R)-(+)-VI could be isolated in high yield as its D-tartrate salt by effecting the resolution under conditions in which epimerization occurred via reversible addition of cyanide, yielding virtually a single isomer. The resolution—epimerization was best
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performed in methanol for high chemical and optical yields. Use of water as co-solvent led to reduced yields due to competition between water and cyanide for the intermediate imine. Since the aminonitrile \((R)\)-\(\text{VI}\) was found to autoracemize, it was hydrated to give the stable \((R)\)-amino amide, \((R)\)-\(\text{VII}\).
2.2 Imidazolinylbenzoic acid synthesis

The above amino acid synthons readily coupled with o-dicarboxylic acid anhydrides. Thus, reaction of aminonitrile VI with phthalic anhydride gave the phthalamic acid XI (Fig. 4), which was cyclized to imide XII in the presence of sodium acetate to isomerize any isomide formed, and hydrated to give amide I. Alternatively, reaction of amino acid IX with phthalic anhydride in toluene containing a catalytic amount of triethylamine (Fig. 4) yielded acid XIII, which was converted to amide I via the acid chloride as depicted.

Cyclization of imide amide I to imidazoisoindol-2,5-dione III could be effected with a variety of catalysts (Fig. 4). Sodium hydride in refluxing toluene gave the highest laboratory yields, while the use of a catalytic amount of solid sodium hydroxide was used for larger-scale preparations.

Since the tricycle III had significant non-selective herbicidal activity, both pre- and postemergence, the chemical and biological properties of a series of analogs were examined. The chemistry of 2,5-dione III was characterized by attack of nucleophiles (depicted in Fig. 4 for the case of alcohols) at C-9b (kinetic) to give adducts XIV or at C-5 (thermodynamic) to give ring-opened products IV. The interesting kinetic adducts will not be discussed further in this review, except to say that they are phytotoxic, presumably due to their metabolic transformation to an imidazolinylbenzoic acid.

Evidence in support of imidazolinone structure IV depicted in Fig. 4 was obtained via infrared spectral analysis of methyl ester IV (R = Me), which can be written as the conjugated IVa or nonconjugated isomer IVb. Schipper and Chinery studied a number of alklyated imidazolinones and found that the carbonyl and
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R = H, alkyl, alky1, benzyl, M+, HNR₃⁺
R¹, R² = Me, Et, i-Pr, i-Bu, cycloalkyl
X = Cl, OCH₃, CH₃, NO₂

Fig. 6. Imidazolinylbenzoic acid analogs.

Imino groups of the conjugated isomers absorbed at lower infrared frequencies than the nonconjugated isomers. On the basis of these models, solid-state and solution infrared spectra of IV supported the nonconjugated tautomeric structure IVb.

Mild hydrolysis of the 2,5-dione III did not give the expected imidazolinylbenzoic acid XVI by thermodynamic attack of water at C-5 (Fig. 5). Under mildly acidic conditions, kinetic addition to C-9b occurred, and the adduct XV was isolated. Under mildly basic conditions, reaction proceeded further via deprotonation and ring opening to give the imide amide I (which was isolated in one case when it precipitated) and subsequent imide opening to give the acid diamide XVII. The desired imidazolinylbenzoic acid XVI was obtained by treatment of tricycle III with strong acid (Fig. 5). Presumably the kinetic adduct XV is again formed, but in reversible fashion, allowing for competitive addition of water to C-5 and precipitation of this product from the reaction mixtures as its hydrochloride salt XVI-HCl. The salt, characterized by a shift of the carbonyl to 1785 cm⁻¹ in the infrared spectrum, was easily converted to acid XVI with one equivalent of base. Alternatively, the previously described (Fig. 4) methyl ester IV was readily saponified to the same product. The infrared spectra of acids such as XVI indicate that they are neutral, not zwitterionic compounds.

Using the methods discussed above, a number of imidazolinylbenzoic acid analogs and derivatives were prepared with the goal of finding a crop-selective herbicide (Fig. 6). A mixture of the methyl esters XVIII and XIX was found to control wild oats, black grass, and wild mustard in cereals, and, as mentioned previously, has been commercialized as the herbicide imazamethabenz-methyl.

2.3 Imidazolinylnicotinic acids

In order to assess the effect on biological activity of replacement of the benzene ring of imidazolinylbenzoic acids with a pyridine ring, commercially available 2,3-pyridinedicarboxylic acid anhydride XX was converted to ester diamide XXI via methods described in the previous section (Fig. 7(a)). Cyclization of XXI and methanolysis of the resulting tricycles XXII and XXIII afforded a mixture with
nicotinate ester XXIV as the major, more active product. It was accompanied by a smaller amount of the less active picolinate ester XXV; the two were readily separable by silica gel chromatography. It was thought that cyclization proceeded through amide XXVI (Fig. 7(b)) as esters XXIV and XXV did not cyclize to tricycles.
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XXII and XXIII under the reaction conditions. The structure of XXIV was supported by independent synthesis from XX as depicted. The structure of nicotinate ester XXIV is supported by the lower-field resonance of H₄ (relative to XXV) in the [¹H]NMR spectrum, due to the adjacent carboxyl group, and by the characteristic three-bond coupling of 4–5 Hz between the carboxyl group and H₄ in the [¹³C]NMR spectrum.

Since nicotinate ester XXIV possessed significantly better herbicidal activity than its benzoic acid analog IVb, although without crop selectivity, more efficient methods for its synthesis were investigated. Reaction of anhydride XX with nitrile VI, cyclization and hydration provided the amide XXVI (Fig. 7(b)), which could be converted to a mixture of esters XXIV and XXV via the tricycles XXII and XXIII in the same way as has been described for amide XXI (Fig. 7(a)). Attempts to improve the ratio of nicotinate ester XXIV to picolinate ester XXV by altering the ratio of XXII to XXIII in the initial cyclization step were not effective. The amount of nicotinate ester XXIV formed was dependent upon the amount of XXII formed. Reaction of the imide XXVI with methanol and a catalytic amount of sodium methoxide, however, resulted in exclusive formation of the nicotinate ester diamide XXVII. This diamide was cyclized with PCl₅ to the nicotinate ester XXIV regioselectively and hydrolyzed to the parent acid V.

The synthesis of the nicotinic acid V was further improved by allowing aminonitrile VI to react with 2,3-pyridinedicarboxylic anhydride XX, hydrating the resulting nitrile to a mixture of acid diamides XXVIII and XXIX, and cyclizing to a mixture of imidazolinones V and XXX (Fig. 7(c)).¹⁴ The equilibrium in this last step presumably greatly favors the cyclized form because deprotonation of the imidazolinone ring (pKₐ c. 11, Mangels, G., 1986, pers. comm.) prevents attack by alkali due to charge repulsion. The ratio of nicotinic acid V to picolinic acid XXX in the first step could be improved to c. 9:1 by running the reaction in the presence of a
catalytic amount of lutidine and acetic acid.\textsuperscript{15,16} Finally, isolation and purification of nicotinic acid V is facilitated by the water solubility of picolinic acid XXX. The infrared spectrum of isolated nicotinic acid V indicates that it is a neutral compound, while that of picolinic acid XXX shows the imidazolinone carbonyl shifted to 1775 cm\textsuperscript{-1}, indicating its zwitterionic nature and explaining its high water solubility.

Dehydration of acid V with N,N-dicyclohexylcarbodiimide (DCC) gave predominately a new tricycle XXXI having an infrared carbonyl absorption at 1770–1780 cm\textsuperscript{-1} and clearly different from 2,5-dione XXII (Fig. 8). The 3,5-dione XXXI reacted with sodium borohydride to give the hydroxymethyl compound XXXII while 2,5-dione XXII yielded dihydro compound XXXIII with the same reagent. Dehydration of acid V with acetic anhydride did in fact give the 2,5-dione XXII. Interestingly, the 3,5-dione XXXI could be isomerized to 2,5-dione XXII on refluxing with acetic acid.

In Fig. 5, the hydrolysis of imidazoisoindole-2,5-dione III with 6 M hydrochloric acid was described as yielding acid XVI \cdot HCl, rationalized as resulting from simple thermodynamic attack of water on the C-5 carbonyl group. When a similar hydrolysis was attempted on the pyridine-2,5-dione XXII, the product was unexpectedly the decarboxylated 3-imidazolinylpyridine XXXIV (Fig. 9(a)). The formation of this product can be rationalized as arising by kinetic attack of water at C-9b, ring expansion of hydroxy intermediate a to the diazocinetione b, cyclization to c, and dehydration to the isomeric 3,5-dione d. Attack of water on the carbonyl of d leads to the picolinic acid XXX which, under the reaction conditions, decarboxylates to give the observed product XXXIV shown. The different course observed in the reaction of the pyridine-derived 2,5-dione is presumably a

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**Fig. 8.** Synthesis of isomeric 3,5-dione XXXI.
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Fig. 9. Hydrolytic rearrangements of 2,5-diones.

Consequence of the greater electrophilicity of C-9b in this system. Subjecting the methyl-substituted 2,5-dione analog to the above hydrolysis conditions, XXXV (Fig. 9(b)) yielded predominantly the expected product XXXVI resulting from attack of water on the C-5 carbonyl, but also afforded XXXVII resulting from an analogous rearrangement sequence to that depicted in Fig. 9(a).

The (R)-isomer of nicotinic acid V was prepared via the (R)-(+-)-amino amide VII and was used to prepare the p-bromobenzyl ester derivative for X-ray crystal structure analysis (Fig. 10). The X-ray structure reveals several salient features. It confirmed the configuration of the most active isomer as (R) (inferred from the enzymatic resolution). The X-ray showed the crystal was dimeric with two molecules joined head to head at the imidazolinone group, reminiscent of the hydrogen-bonded carboxylic acid dimers frequently detected by infrared spectroscopy. This further supports the earlier infrared-based assignment of the nonconjugated structure to the imidazolinone ring. The imidazolinone ring is 19° out of the plane of the pyridine ring and the protic nitrogen, N-1, is syn to the pyridine nitrogen as shown. Finally, the carboxyl group is 75° out of the pyridine plane.
2.4 Synthesis of ortho-dicarboxylic acids

The o-dicarboxylic acid synthons depicted in Figs 4, 5 and 7 are all commercially available. The elaboration of sets of analogs via these methods required the synthesis of the requisite o-dicarboxylic acid fragments.

2.4.1 2,3-Pyridinedicarboxylic acids

The general route to 2,3-pyridinedicarboxylic acids involving oxidation of quinolines was used to convert commercially available 3-chloro- and 3-bromoquinoline XXXVIII (R₅ = Br or Cl, R₆ = H, X = H) to 5-bromo- and 5-chloro-2,3-pyridinedicarboxylic acid XXXIX (R₅ = Br or Cl, R₆ = H, Fig. 11(a)), while 5,8-dimethoxy-2-trifluoromethylquinoline XXXVIII (R₅ = H, R₆ = CF₃, X = 5,8-di-OCH₃) was oxidized to give 6-trifluoromethyl-2,3-pyridinedicarboxylic acid XXXIX (R₅ = H, R₆ = CF₃).

Several variations of de-novo pyridine ring synthesis with substrates allowing for direct incorporation of the dicarboxylic acid ester unit were investigated. Reaction of an ynone XL with aminofumarate XLI gave 6-alkyl and 6-arylpyridinedicarboxylate XXXIX (R₅ = H, R₆ = alkyl or aryl) in 50–65 % yield (Fig.
2,3-Pyridinedicarboxylic acid syntheses.

Attempts to utilize \( \beta \)-dimethylaminomethylene ketone XLII or its hydroxy or alkoxy analogs in this same reaction (Fig. 11(c)) afforded the desired pyridinedicarboxylate XXXIX, but in very low yield.

A much higher yielding sequence involved reaction of an enamine XLIII with enone XLIV followed by reaction with ammonia (Fig. 11(d)). In this example, the enamine XLIII is more reactive than the vinylogous amide XLI, and the enone XLII is very good Michael acceptor. The yields of these reactions ranged up to 75\%.\(^{19}\)

2.4.2 Quinolinedicarboxylic acids
Several methods for the preparation of 2,3-quinolinedicarboxylic acids are reported in the literature. For example, 2,3-quinolinedicarboxylic acid has been prepared by oxidation of acridine with potassium permanganate in 25\% yield\(^{20}\) or with ozone in 75\% yield.\(^{21}\) A substituted quinolinedicarboxylic acid and its esters could also be prepared from a 2-aminobenzaldehyde with oxalacetate\(^{22,23}\) or dimethyl acetylenedicarboxylate.\(^{24}\)

A Diels–Alder route to 2,3-quinolinedicarboxylic acid imide XLVIII from anthranil XLV and \( N \)-phenylmaleimide XLVI was reported by Taylor\(^{25}\) (Fig. 12(a)), who identified the major product of the Diels–Alder reaction as the aldehyde
anilide XLVII and showed that it could be converted into the quinoline XLVIII in good yield. The commercial availability and ease of handling of anthranil XLV made it attractive to investigate this route to 2,3-quinolinedicarboxylic acids.

Use of dienophile XLIX, obtained from reaction of the aminonitrile VI and maleic anhydride, in the above sequence gave an analogous series of reactions (Fig. 12(b)). The product distribution could be controlled by varying the temperature and changing the catalyst. At lower temperatures, the Diels–Alder adduct L could be isolated. At this temperature, the reaction was slow and unreacted starting
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Fig. 13. Alternative route to 2,3-quinolinedicarboxylic acid imides.

Materials remained. Raising the temperature increased the reaction rate and cracked the Diels–Alder adduct L to the aldehyde LI. This could be cyclized to imide LII in the presence of a catalytic amount of p-toluenesulfonic acid in refluxing xylene. If the reaction was carried out in refluxing o-dichlorobenzene, the imide LII could be formed directly from XLV and XLIX in 75% yield. The utility of the sequence was extended with the synthesis of analogs of LJI (Fig. 12(c)) from substituted anthranils. Anthranils with electron-withdrawing substituents worked best.

Since alkyl-substituted anthranils are not readily available, a modification of this route was necessary for alkyl-substituted quinoline diacids. Reaction of anilinoalcohol LIII with bromomaleimide LIV, obtained from bromination–dehydrobromination of maleimide XLIX, gave a maleimide alcohol LV (Fig. 13). The hydroxy group was oxidized with pyridinium chlorochromate to give an intermediate LI, similar to that obtained from the anthranil route, and cyclized with p-toluenesulfonic acid in toluene. This method was utilized to prepare analogs with electron-donating groups on the quinoline ring, thus nicely complementing the Diels–Alder route.

Meth-Cohn et al. reported that acetanilide reacts with phosphorous oxychloride to form an α-chloroenamine, which in turn reacts with two moles of Vilsmeier reagent to form 2-chloroquinoline-3-carboxaldehyde (Fig. 14(a)).26 Reaction of the anilinoacetaurate LVI, derived from an aniline with either dimethyl oxalacetate or dimethyl acetylenedicarboxylate, with a Vilsmeier reagent introduces the additional carbon and cyclizes to form the quinoline diester LVII (Fig. 14(b)).27,28 This reaction has been used to good advantage for the preparation of other quinoline derivatives including a thienopyridine LVIII (Fig. 14(c)).29

2.4.3 Other heterocyclic dicarboxylic acids
Pyridone diester LIX was used to prepare several fused-ring pyridinedicarboxylates (Fig. 15).28 The pyridone LIX, readily available from acetoacetamide and diethyl ethoxymethyleneoxalacetate, was brominated and reduced to give LX, which on
Fig. 14. Vilsmeier route to diesters.

Fig. 15. Other heterocyclic dicarboxylic acids.
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<table>
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</tr>
<tr>
<td>Ethylene oxide</td>
<td>52</td>
</tr>
<tr>
<td>Carbon dioxide</td>
<td>43</td>
</tr>
<tr>
<td>Ethyl iodide</td>
<td>16</td>
</tr>
<tr>
<td>4-Bromobutene</td>
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<td>Methyl bromoacetate</td>
<td>0</td>
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Fig. 16. Metallation of pyridylimidazolinone LXVI.

treatment with triethylamine cyclized to the hydroxydihydrofuran derivative LXI. Acetylation and subsequent elimination yielded the furanopyridine diester LXII. Pyridone LIX was also converted to the 5-hydroxy diester LXIII by Baeyer–Villiger oxidation followed by methanolysis (Fig. 15), and then alkylated with 1,2-dibromoethane and dibromomethane to give dioxane LXIV and dioxolane LXV respectively, albeit in low yield.

2.4.4 Metallation-carboxylation route
The methods described in Sections 2.4.1 to 2.4.3 have focused on direct formation of an intact o-dicarboxylic acid synthon. A versatile alternative proved to be metallation-carboxylation of a pyridylimidazolinone such as LXVI (Fig. 6), analogous to Meyers and Gabel's ortho-metallation of oxazolines.

ortho-Metallation of the pyridylimidazolinone LXVI with methyllithium involved N-deprotonation, followed by formation of a dark red dianion with a second equivalent of methyllithium, and required less than one hour to complete (Fig. 16). The reaction was kept at \(-78^\circ C\) during the metallation to avoid methyllithium addition to the pyridine ring. The deep red color of the dianion made this species an extremely effective indicator for alkylithium reagents. The pre-formed dianion reacted with a variety of electrophiles with the highest yields of LXVII being obtained with methyl iodide, a result which was conveniently exploited to monitor the progress of the metallation reaction. The yields listed in Fig. 16 were not optimized and in some cases represent the result of a single experiment.

Having demonstrated the feasibility of the ortho-metallation–carboxylation method, its generality was then examined. The scope of the metallation method is dependent upon the availability of substituted picolinic acids, classically prepared from the more readily available 2-methylpyridines. For example, 5-ethyl-2-methylpyridine LXVIII, possibly the least expensive commercially available pyridine, was converted to its picolinic acid LXX (Fig. 17(a)) via ozonolysis of styrene LXIX and was isolated as its copper salt. Alternatively, the picoline LXVIII could be treated with sulfur and aniline in a Willgerodt reaction to give the
Fig. 17. Routes to metallation substrate LXXIII.

thioanilide LXXI which on hydrolysis with hydrochloric acid resulted in a higher overall yield of picolinic acid LXX. The picolinic acid LXX was converted to diamide LXXII via the mixed anhydride and subsequently cyclized with aqueous sodium hydroxide to the imidazolinone LXXIII (Fig. 17(a)).

Examination of the literature on reactions of picolines under Willgerodt–Kindler conditions revealed that the yields of thioanilides are reduced by the competing formation of amidines (in addition to other side products). Reasoning that an imidazolinone ring, itself a cyclic amidine, might be the product of reaction of a picoline with the amino amide VII and sulfur, the reaction was applied to 5-ethyl-2-methylpyridine LXVIII (Fig. 17(b)). After optimization, the desired product
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LXXVI was prepared in c. 65–75% yield along with the thiazoline LXXIV and thioamide LXXV.

A number of substituted picolines LXXVI were subjected to the Willgerodt-Kindler reaction (Fig. 18). While yields were optimized for the 5-methyl and 5-ethyl cases, with less available alkoxy and phenyl picolines LXXVI, stoichiometric excesses were not used and lower yields resulted. For 5-methoxypicoline, LXXVI (R = OCH₃), the methyl ether was cleaved to give the hydroxy compound (R = OH) in addition to the methoxy imidazolinone LXXVII (R = OCH₃).

Having prepared a number of substituted pyridylimidazolinones LXXVII, the metallation–carboxylation reaction was examined (Fig. 19). It consistently gave moderate to good yields for a variety of 5-alkyl and 5-alkoxy derivatives LXXVIII. Compounds failing to give the desired products were the 1-propenyl- (LXXVII, R = CH=CHCH₃) and 5-nitro-(LXXVII, R = NO₂) substrates. The propenyl side chain probably competes with ortho-metallation in dianion formation. The nitro analog might have failed due to addition of methylthiium to the pyridine ring and/or single electron transfer reactions.

The metallation–carboxylation reaction of 5-ethylpyridylimidazolinone LXXXIII was examined carefully as a route for the preparation of larger quantities of the 5-ethylnicotinic acid LXXIX (Fig. 20). Butyllithium was substituted for methyllithium, with some addition to the pyridine nucleus accompanying the deprotonation process (estimated at 5% after oxidation of the dihydropyridine dianion intermediate to pyridine LXXX), but this addition product did not react with carbon dioxide to contaminate the desired product LXXIX. The use of lithium diethylamide was also substituted for methyllithium, but it resulted in metallation of the ethyl side chain and carboxylation yielded LXXXI.

The only instance in which a competing directing effect was observed occurred on metallation of the 5-fluoro compound LXXXII. It gave a small amount of acid LXXXIV from metallation ortho to the fluorine atom in addition to the expected product LXXXIII (Fig. 21).
2.4.5 Recent procedures

Subsequent to development of the metallation–carboxylation procedure, two new methods which have proven to be of great value in the preparation of analogs have been reported. The first procedure involves the preparation of 2,3-pyridinedicarboxyate esters from ethyl chlorooxalacetate LXXXVI and an enal LXXXV in the presence of a buffered ammonia source (Fig. 22(a)). This has proven to be a versatile synthesis of 5-substituted diesters. The second reaction (Fig.

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<th>Yield (%)</th>
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<td>F</td>
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<td>OC₂H₅</td>
<td>36*</td>
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*Isolated as methyl ester.
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Fig. 21. Metallation of 5-fluoro analog LXXXII.

\[
\text{LXXXII} \xrightarrow{n-\text{BuLi} \text{ 2 eq.}} \text{[LXXXII]} \rightarrow \text{LXXXIII} 30\% \quad \text{LXXXIV} \sim 5\%
\]

\[
\begin{align*}
&\text{COOEt} \\
&\text{OOEt} \\
&\text{COOEt Ammonium sulfamate} \\
&\text{OOEt} \\
&\text{2h - 50-40\% yield}
\end{align*}
\]

Fig. 22. New methods.

\[
\begin{align*}
&\text{R}_5 \text{COOEt} \quad \text{Cl} \quad \text{COOEt} \\
&\text{H} \quad \text{O} \quad \text{COOEt} \\
&\text{LXXXV} \quad \text{LXXXVI} \quad \text{Ammonium sulfamate} \\
&\quad \text{EtOH/heat 2h} \quad \sim 50-80\% \text{ yield} \\
&\text{LXXXVII}
\end{align*}
\]

(a)

\[
\begin{align*}
&\text{VII} \quad \text{KOr-Bu} \\
&\text{PhCH}_3 \quad 70\% \text{, 2h} \\
&\text{LXXXVII} \quad \text{LXXXVIII}
\end{align*}
\]

(b)

22(b)) directly utilizes a diester in the reaction with \(z\)-methylvalinamide VII in the presence of potassium \(t\)-butoxide. This procedure gives good yields, saves several steps, and is regioselective for the desired nicotinic acid regioisomer LXXXVIII. \(^{35}\)

2.5 Imidazolinone ring stability

During the course of this work, a number of observations on the stability of the imidazolinone ring under conditions of diverse functional group transformations were made and are included in Table 1.
TABLE 1
Imidazolinone Stability

<table>
<thead>
<tr>
<th>Compatible with</th>
<th>Not compatible with</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong base (NaOH, 5 M)</td>
<td>Mild base (pH c. 8)</td>
</tr>
<tr>
<td>Strong acid (HCl)</td>
<td>Alkylation (CH₃N₂, DMF acetal, MeI)</td>
</tr>
<tr>
<td>LiAlH₄ reduction</td>
<td>Peracids (must acylate to protect)</td>
</tr>
<tr>
<td>NaBH₄ reduction</td>
<td>Na(CN)BH₃/pH 3 reduces to dihydro</td>
</tr>
<tr>
<td>Hydrogenation (H₂/Pd, 1 atm)</td>
<td>Refluxing POCl₃, slow degradation</td>
</tr>
<tr>
<td>Pyridinium chlorochromate oxidation</td>
<td>NBS (must acylate stop N-Br, slow C-bromination)</td>
</tr>
<tr>
<td>Grignard reaction</td>
<td>P₂S₅ (becomes thiono)</td>
</tr>
<tr>
<td>Wittig reaction</td>
<td></td>
</tr>
<tr>
<td>Alkoxide substitution (RO-)</td>
<td></td>
</tr>
</tbody>
</table>

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REFERENCES