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SYNTHESIS OF AN INDOLIZIDINEDIONE OXIME INHIBITOR OF ACETYL-COENZYME A CARBOXYLASE (ACCase)

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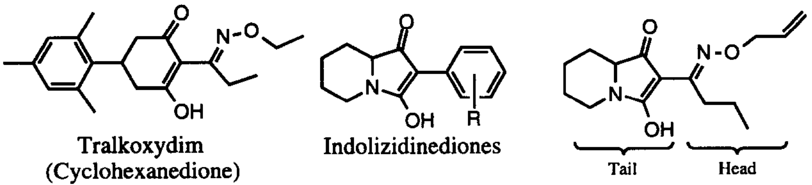
Abstract: The synthesis and enzyme inhibitory activity of a novel hybrid compound which incorporates substructures of two classes of inhibitors of ACCase are described.

There are several classes of herbicidal inhibitors of Acetyl-Coenzyme A Carboxylase (ACCase, E. C. 6.4.1.2), the enzyme responsible for the first committed step in fatty acid biosynthesis. The cyclohexanedione class, illustrated by tralkoxydim (**1**), has been known for some time.[1] The indolizidinediones **2** have emerged[2] as the newest class of compounds shown to inhibit the reaction (Figure 1). Due to their recent disclosure, we focused on the indolizidinediones and sought to combine structures **1** and **2**. Using this hybridization approach, we hoped for novel ACCase inhibitors which were more potent than any of the known classes of herbicides which inhibit ACCase. Our target thus was structure **3**, in which the indolizidinedione "tail" has been conceptually welded to the oxime "head" of a cyclohexanedione.



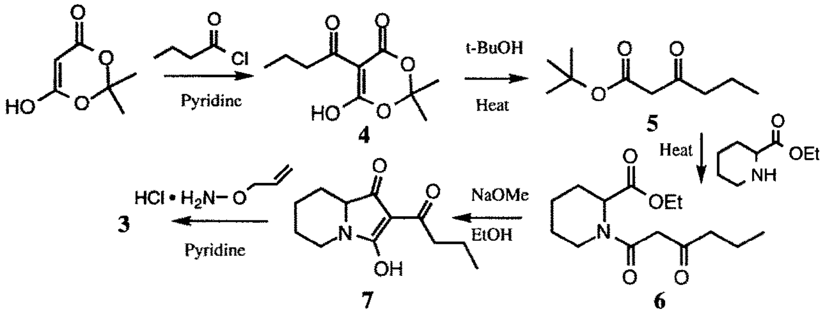
Tralkoxydim
(Cyclohexanedione)
1

Indolizidinediones
2

3

Figure 1

The synthesis of this material is outlined in Scheme 1, beginning with condensation of Meldrum's acid and butyryl chloride to give the trione **4**.[3] Pyrolysis of **4** to generate the acyl ketene in the presence of *tert*-butyl alcohol gave the β-keto ester **5** (49% over both steps).[4] A second pyrolysis, this time in the presence of ethyl pipecolinate, gave β-keto amide **6** (78%). Use of the *tert*-butyl ester **5** gave a much cleaner reaction than using trione **4** directly. Cyclization was accomplished by treatment of **6** with sodium methoxide in ethanol to give **7** (68%), which when treated with O-allylhydroxylamine hydrochloride and pyridine gave the desired target **3** (69%).[5]



Scheme 1

Compound **3** had an I_{50} of 80 μM when assayed for ACCase inhibition. By comparison, the indolizidinedione lead **2** (R=2,4-dichloro) showed an I_{50} value of 15 μM in the same assay and the I_{50} for tralkoxydim (**1**) is 1 μM. Although we succeeded in generating a novel structure which inhibits the reaction, combining the two areas of chemistry did not result in a more potent inhibitor. Thus, despite the similarity of the 1,3-dione moieties contained within the two classes of chemistry, the data suggest that they do not bind at the enzyme in the same manner.

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5. All new compounds gave satisfactory microanalyses, ^{1}H NMR, ^{13}C NMR, and IR spectra.

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