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A Novel Catechol Compound, an Unusual Side Reaction Product of a β-Ketoester with Pyruvic Aldehyde and Its Inhibition by Sodium Dithionite

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ABSTRACT

The structure of an usual catechol byproduct in the aldol condensation of the salt of 3-oxo-6-heptenoate and pyruvic aldehyde, and the discovery of an additive to inhibit its formation are described.

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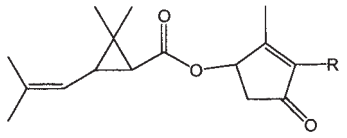
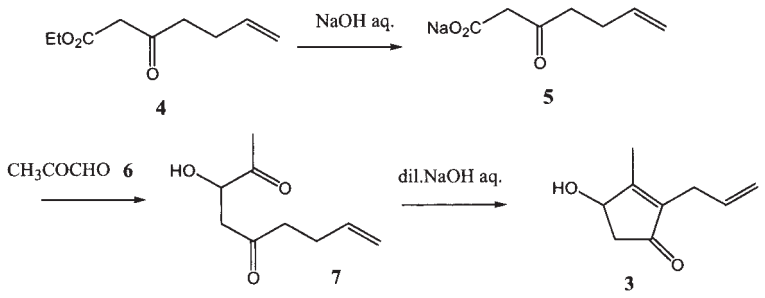
Commercial use of synthetic pyrethroids having structures based on natural pyrethrin as lead compounds is one of the most remarkable success stories in insecticide development. Allethrin (**1**) or 2-methyl-4-oxo-3-allylcyclopent-2-enyl 2,2-dimethyl-3-(2-methylpropenyl)cyclopropanecarboxylate, was first synthesized by Schechter et al. in 1949[1] and found to be equipotent to pyrethrin I (**2**) , the most active component of natural pyrethrins. This pioneering invention led to the development of various synthetic pyrethroids[2] for agricultural use and for the control of major household insect pests.



1 : R: -$CH_2CH{=}CH_2$
2 : R: -$CH_2CH{=}CHCH{=}CH_2$

The synthesis of allethrolone (**3**), the alcohol moiety of allethrin, has attracted considerable attention not only in its own right[3] but because of its structural relationship to certain prostaglandin and jasmonoids.[4] Despite extensive studies, only two industrial processes to allethrolone are known.[5] One such process was based on the original Schechter method starting from ethyl 3-oxo-6-heptenoate (**4**). The key step was the aldol reaction between the β-ketoacid salt (**5**) and pyruvic aldeyde (**6**) to give 3-hydroxy-8-nonene-2,5-dione (**7**), as in Sch. 1. However, the yield of this aldol was consistently unsatisfactory because of the formation of a significant amount of a higher-boiling byproduct.

In order to make this process viable, it was essential to establish the nature of this byproduct and to find a method to inhibit its formation.

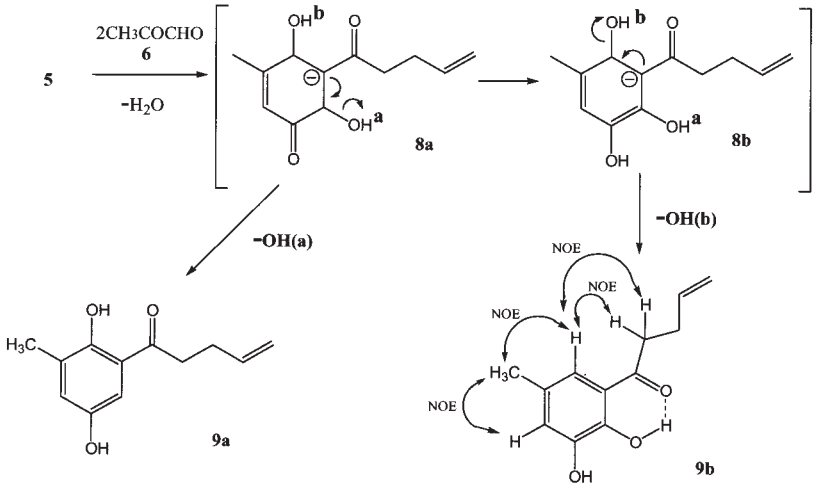


Scheme 1.

We now report the structure of the major byproduct of this aldol reaction, and the discovery of an additive which inhibits its formation.

The formation of an unidentified higher-boiling byproduct in the aldol condensation of the salt (**5**) with pyruvic aldehyde (**6**) had been reported in Schechter's original studies. We found that when the Schechter procedure was used, fractional distillation of the crude aldol product gave 3-hydroxy-8-nonen-2,5-dione (**7**) in 59% yield and, from the after-run, a byproduct which crystallized on cooling. Recrystallization of this byproduct gave pale yellow needles, m.p. 114–115°C, of a $C_{12}H_{14}O_3$ compound which found a diacetate with acetic anhydride and a semicarbazone on treatment with semicarbazide hydrochloride. The ^{1}H NMR of this compound showed, *inter alia*, an apparent methyl singlet at δ 2.29, and two aromatic protons meta-coupled to each other at δ 6.96 and δ 7.10.

Consideration of the above data pointed to a mechanism whereby the sodium salt (**5**) underwent two successive aldol condensations with pyruvic aldehyde, followed by an aldol cyclization and dehydration, as in the two alternative reaction sequences depicted in Sch. 2. There are two possibilities for the final dehydration step, namely loss of OH(**a**) or OH(**b**). Dehydration by loss of OH(**a**) would lead to the hydroquinone (**9a**), whereas loss of OH(**b**) would produce the catechol **9b**, both consistent with the data provided.



Scheme 2.

Differentiation between alternatives **9a** and **9b** was achieved by observing NOE enhancements of both aromatic protons upon irradiation of the methyl singlet at δ 2.29, indicating that this methyl group has two adjacent aromatic protons. Thus the byproduct formed under Schechter conditions must be the catechol **9b**. A possible origin of the regioselective elimination of OH(**b**) may be that this elimination can occur from the enediol tautomer of the α -ketol system in intemediate **8b**, leading directly by the driving force of aromatization to the observed **9b**. Since the catechol byproduct **9b** was very stable, lipophilic, and sufficiently volatile, attempts in our hands to efficiently remove **9b** from **7** on an industrial scale were unsuccessful. To obtain pure allethrolone in high yield, inhibition of the formation of **9b** was needed. Diverse additives were empirically screened as potential inhibitors. Such agents as zinc, sodium sulfite, sodium bisulfite, and sodium sulfide were ineffective.

Ultimately it was found that addition of sodium dithionite ($Na_2S_2O_4$) to the reaction led to an 84% yield of the desired allethrolone (**7**), and no higher-boiling byproduct was observed. The role of $Na_2S_2O_4$ in inhibiting the formation of **9b** is unclear, but this finding permits the Schechter process to be suitable for production of allethrolone on a commercial scale.

EXPERIMENTAL

General

Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. All bps and mps were uncorrected. ^{1}H NMR was performed at 300 MHz in $CDC1_3$. Chemical shifts are in ppm downfieid from internal tetramethylsilane.

1-(2,3-Dihydroxy-5-methylphenyl)-4-penten-l-one (9b). According to the reported procedure,[1] 3-hydroxy-8-nonen-2,5-dione(**7**) was synthesized. The crude product was subjected to fractional distillation to give **7** in 59% yield and from the after-run, on cooling, crystals was collected. Recrystallization from 50% ethanol–water gave pale yellow needles in 20% yield. M.p. 114–115°C. ^{1}H NMR δ: 2.29 (3H ,s), 2.50 (2H, m), 3.08 (2H, t, $J = 7.1$ Hz), 5.0–5.1 (2H, m), 5.66 (OH, s), 5.90 (1H, m), 6.96 (1H, br.d, $J = 1$ Hz), 7.10 (1H, br.d, $J = 1$ Hz), 12.31 (OH, s). Anal. Found: C, 69.92; H, 6.91%. Calcd. for $C_{12}H_{14}O_3$; 69.88; H, 6.84% $FeCl_3$ was deep green. Its semicarbazone, m.p.193°C. Its diacetate from acetic anhydride and sodium acetate; m.p. 70.5°C.

Synthesis of 3-hydroxy-8-nonene-2,5-dione(7)[8] in the presence of sodium dithionite. A mixture of ethyl 3-oxo-6-heptenoate (140 g,

0.8 mol) and 10% aqueous sodium hydroxide (395 g) was allowed to stand for 18 h, at 15°C. After neutralization of excess alkali with 10% hydrochloric acid on cooling, sodium dithionite (42 g, 30 w/w% of starting ester), sodium bicarbonate (21 g), and 42% aqueous pyruvic aldehyde (184 g, 1.07 mol) was added over 2 h under N_2. Then, the clear mixture was allowed to stand overnight at room temperature at pH 8.0–8.5. The reaction was slightly exothermic. The reaction mixture was saturated with sodium chloride and extracted with toluene twice. The organic layers were combined and evaporated, and the residual oil was distilled in vacuo. The yield of (**7**) was 114 g(84%). B.p. 76–78°C/ 0.03 mmHg any higher boiling fraction was not observed.

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