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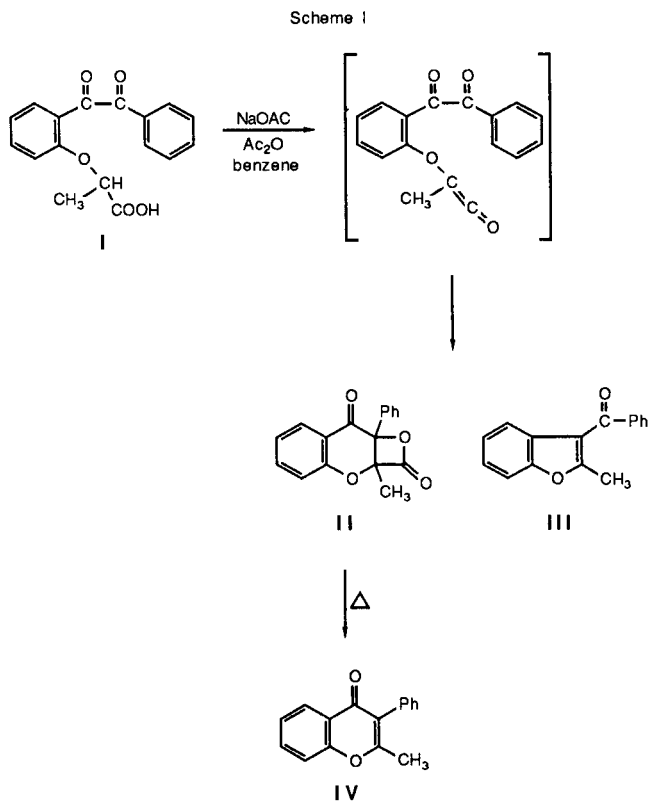
The intermediacy of ketenes in the intramolecular reaction of ketoacids with sodium acetate in acetic anhydride to form benzofurans is demonstrated. The Perkin reaction conditions are superior to the classical ketene generation method of triethylamine dehydrochlorination of the acid chloride.

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In our studies on synthetic applications of intramolecular ketene cycloaddition reactions, we have developed a new synthesis of benzofurans [1,2]. During the course of this investigation, we have treated ketoacids under Perkin reaction conditions, *i.e.*, acetic anhydride and sodium acetate, to obtain substituted benzofurans. This paper demonstrates the intermediacy of phenoxyketenes in these reactions rather than the classical Perkin reaction pathway involving a carbanion addition to the carbonyl. There are some recent reports in the literature on ketene intermediates in the intermolecular Perkin reaction but these are catalyzed by tertiary amines [3,4]. Spectroscopic evidence was provided for an intermediate  $\beta$ -lactone but the lactone could not be isolated.

In some recent studies on the synthesis of isoflavones and 3-arylbenzofurans, we discovered that Perkin reaction conditions on ketoacids such as **I** yielded the same

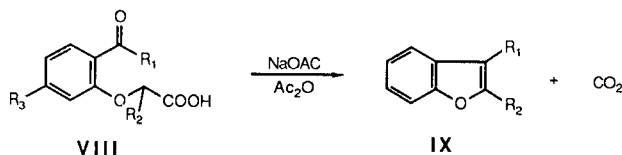
results as using the classical ketene generation method from the acid chloride [5]. The benzilphenoxyacid, **I**, yielded both the isoflavone  $\beta$ -lactone, **II**, and the 2-methyl-3-benzoylbenzofuran, **III**. After complete characterization of the isoflavone  $\beta$ -lactone, decarboxylation to the corresponding isoflavone, **IV**, was accomplished by heating at 150° for 5 hours. Also, (*o*-propenylphenoxy)phenylacetic acid, **V**, upon treatment with sodium acetate in acetic anhydride gave the cyclobutanone enol ester, **VI**,



which was easily hydrolyzed in basic methanol to the expected cyclobutanone, **VII**. These results prompted us to examine the use of Perkin reaction conditions on other ketoacids to determine the scope and general utility of this reaction.

We have treated (*o*-carbonylphenoxy)acetic acids, **VIII**, with acetic anhydride and sodium acetate and found this procedure to be superior to the classical ketene generation methods for intramolecular [2 + 2] ketene cycloaddition reactions to form the substituted benzofurans, **IX**. The acids were prepared as previously described [1,2]. In the preparation of some benzofurans, **IXd,e,f**, benzene was used as a solvent instead of acetic anhydride in which case 1.5 equivalents of the anhydride were employed. The higher reaction temperature of refluxing acetic anhydride provided better yields of the benzofurans from the alde-

Table 1  
Benzofurans [a]



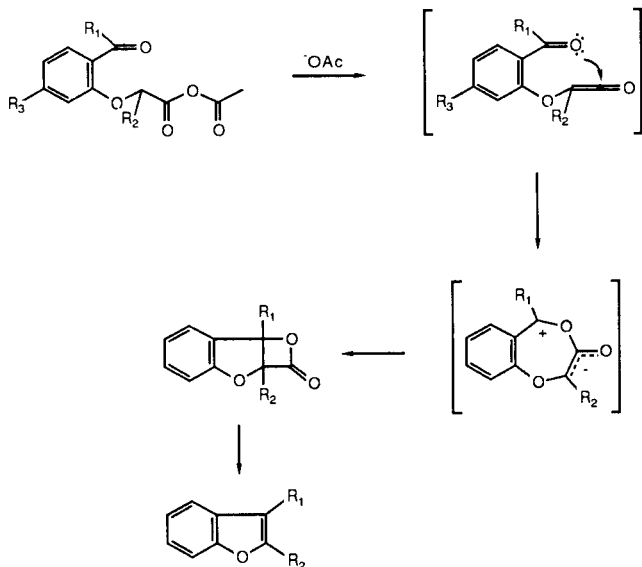
Compound	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Yield (%)	Reference
IXa	H	H	H	30	6
IXb	H	Me	H	52	7
IXc	H	Ph	H	66	8
IXd	Me	H	H	74	9
IXe	-CH <sub>2</sub> -CH <sub>2</sub> -Ph	Ph	H	87	2
IXf	Ph	Ph	OMe	75	2

[a] All of the benzofurans in this Table have been previously reported and the reference for each is given. We verified the structure of each of the benzofurans prepared by comparison of ir, <sup>1</sup>H-nmr and gc/ms spectra with authentic samples.

aldehydes, VIIIa,b,c, whereas the ketones, VIII d,e,f gave better yields of the corresponding benzofurans using benzene as the solvent.

The yields of the substituted benzofurans were 52-87% with the exception of IXa which was 30%. It is interesting to note that in the preparation of the benzofurans IXa-f, the ketones consistently give better yields (74-87%) than the aldehydes (30-66%) which is very inconsistent with the classical Perkin reaction. However, we believe this is quite consistent with the intermediacy of a phenoxyketene followed by a two step intramolecular [2 + 2] cycloaddition *via* a dipolar intermediate which undergoes ring closure to

Scheme III

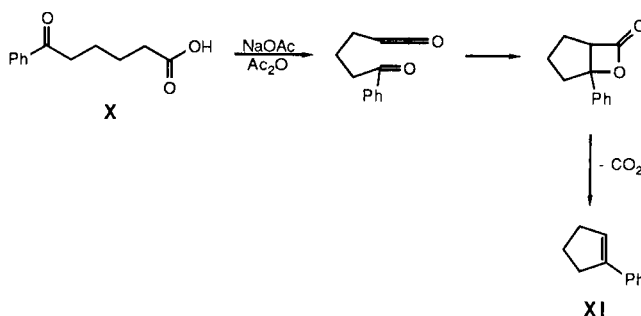


the  $\beta$ -lactone. Subsequent decarboxylation in the refluxing acetic anhydride or benzene yields the substituted benzofurans. When R<sub>1</sub> = H in the dipolar intermediate, VI is an aldehyde, the carbocation portion of the intermediate is not as stabilized as when R<sub>1</sub>  $\neq$  H, when VI is a ketone. The phenoxyphenylacetic acids, R<sub>2</sub> = Ph, give significantly higher yields than the other phenoxyacetic acids as demonstrated by compounds IXc,e,f. Furthermore, IXe could be formed at room temperature in 60% yield without refluxing in acetic anhydride or benzene. This is very consistent with the dipolar intermediate proposed because when R<sub>2</sub> = Ph, there is a greater degree of stabilization or delocalization of the negative charge in the dipolar intermediate.

It is most significant that the same substituted benzofurans described in Table I are formed by treatment of the corresponding acid chloride with triethylamine, *i.e.*, the classical method of ketene generation.

Another interesting example of a different type of ketoacid reacting under Perkin reaction conditions is 5-benzoylpentanoic acid, X. Refluxing this acid with acetic anhydride containing sodium acetate resulted in a 56% yield of 1-phenylcyclopentene, XI. This product is apparently the

Scheme IV



result of a ketene intermediate which undergoes a [2 + 2] cycloaddition to give a  $\beta$ -lactone, which readily decarboxylates under the reaction conditions yielding 1-phenylcyclopentene. Refluxing this acid in benzene containing sodium acetate and acetic anhydride did not yield the 1-phenylcyclopentene. Apparently, the higher reaction temperature provided by refluxing in the anhydride is required for this cycloaddition.

We believe the above described experiments clearly demonstrate the intermediacy of ketenes in the intramolecular reaction of these ketoacids under Perkin reaction conditions. It is quite likely that other intramolecular as well as intermolecular Perkin reactions proceed *via* ketene intermediates which undergo a [2 + 2] cycloaddition reaction to the carbonyl group to yield a  $\beta$ -lactone followed by decarboxylation. Furthermore, the treatment of the ketoacids with acetic anhydride and sodium acetate in one pot

to yield the cycloaddition products is a much simpler procedure than going through the acid chloride with subsequent triethylamine dehydrochlorination to give the ketene.

### EXPERIMENTAL

Proton nmr and  $^{13}\text{C}$  nmr spectra were recorded on a VXR-300 Spectrometer, employing deuteriochloroform as the solvent with tetramethylsilane as the internal standard. The infrared spectra were obtained on a Perkin-Elmer 1330 spectrometer. The gc/ms spectra were recorded on a Hewlett-Packard 5790A Series gc/mass spectrometer. Rotary preparative chromatography was performed with silica gel 7GF from Baker Chemical Company precoated tlc plates 2.5 mm thick, 50 g silica gel on glass.

#### General Procedure for Intramolecular Cycloadditions.

##### Method A.

A 1.0 g portion of the (*o*-carbonylphenoxy)acetic acid was treated with 10 ml of acetic anhydride containing 2.0 g of sodium acetate and refluxed under a nitrogen atmosphere for 4-6 hours. The reaction mixture was cooled and diluted with 30 ml of benzene. This mixture was cooled in an ice bath and 10-20 ml of 10% aqueous sodium hydroxide solution was added with stirring. The benzene layer was separated and dried over anhydrous magnesium sulfate. Upon evaporation of the benzene under reduced pressure, the residue was chromatographed over silica gel using a rotary chromatograph employing hexane as an eluting solvent.

##### Method B.

A 1.0 g portion of the (*o*-carbonylphenoxy)acetic acid was dissolved in dry benzene containing 1.5 equivalents of acetic anhydride and 2.0 equivalents of sodium acetate. This mixture was refluxed for 18-24 hours under a nitrogen atmosphere. The reaction mixture was washed with 20

ml of 5% aqueous sodium hydroxide solution. The benzene solution was then washed with water and dried over anhydrous magnesium sulfate. The benzene was removed under reduced pressure and the residue chromatographed as described above.

1-Phenylcyclopentene [10].

Method A was used for 5-benzoylpentanoic acid and the reflux time was 10 hours. IR: 2965, 2860, 1595  $\text{cm}^{-1}$ ; gc/ms (70 eV), m/e (relative intensity) 144 (M+, 78), 143 (64), 129 (100), 116 (10), 115 (51), 91 (12), 77 (13);  $^1\text{H}$ -nmr (deuteriochloroform):  $\delta$ , 2.1 (m, 2 H), 2.6 (m, 2 H), 2.8 (m, 2H), 6.25 (t, 1H), 7.2-7.6 (m, 5 H);  $^{13}\text{C}$ -nmr (deuteriochloroform):  $\delta$ , 142.5, 136.9, 128.3, 126.8, 126.1, 125.6, 33.4, 33.2, 23.4.

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