ORGANIC REACTIONS AT HIGH PRESSURE. THE DIELS-ALDER REACTION OF $\underline{p}\text{-}\mathsf{BENZOQUINONE}$ WITH DIENIC ESTERS

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<u>Abstract</u>: The Diels-Alder reaction of <u>p</u>-benzoquinone with substituted dienoic esters affords good yields of 4a,5,8,8a-tetrahydro-1,4-naphthalenediones, free from the isomeric hydroquinone. The reactions were conducted at room temperature under 15 kbar (1.5 GPa) pressure in dichloromethane solutions.

In earlier studies in this laboratory,¹⁻³ the [4+2] cycloaddition between a wide variety of components of highly different electron density has been studied at very high pressure (10-20 kbar, 1-2 GPa). It has been found that in such a reaction which is known to possess a negative ΔV^{\dagger} , the rate enhancement found under very high pressure permits the utilization of many heat-sensitive and/or low reactive materials in the addition process.⁴ One particular area of interest has been the utilization of electron-poor dienes in this cycloaddition process. In the course of our initial study of the reaction of such dienes with electron-poor dienophiles, particular interest developed in the utilization of <u>p</u>-quinone as the dienophile in view of the potential utility of such a cycloaddition reaction in the synthesis of anthracycline antibiotics. Indeed, the recent synthesis of aklavinone by Li and Wu nicely illustrates the utility of the reaction.⁵ This present study describes the successful Diels-Alder reaction of p-quinone with electron-poor dienes at room temperature, under very high pressure.

In 1958, Woodward reported that methyl 2,4-pentadienoate could serve as a diene component in a Diels-Alder reaction with p-benzoquinone to produce the cycloadduct in 28% yield.



A serious drawback with this [4+2] cycloaddition reaction was the propensity of the initial cycloadduct to aromatize, under reaction conditions of refluxing benzene, to the hydroquinone. This problem was also evident in the synthesis of the cycloadduct from methyl-(\underline{E})-2-methyl-2,4-pentadienoate and <u>p</u>-benzoquinone where the major product was the hydroquinone, the desired product being formed only in very low yield and was not able to be isolated in pure form.⁵

The results of this present study are summarized in Table I and show that the employment of very high pressure at room temperature offers an efficient, high yield method for the production of 4a,5,8,8a-tetrahydro-1,4-naphthalenedione-5-carboxylic acid derivatives. No hydroquinones were observed. The reactions were performed in a sealed Teflon[®] tube which contained equimolar amounts of <u>p</u>-benzoquinone and diene in dichloromethane. The tubes were kept under 15 kbar (1.5 GPa) hydrostatic pressure at room temperature for the time indicated. The reaction was terminated by removal of the external pressure, the reaction mixture concentrated under reduced pressure, and the cycloadducts recrystallized from ether-pentane at -15°C.

The reaction of the parent diene methyl ester (entry 1) proceeded in good yield to give easily purified product. Terminal methyl substitution on the diene ester did not retard the reaction and ethyl 2,4-hexadienoate (entry 7) gave the cycloadduct in 92% yield. For comparison, this diene did not react with <u>p</u>-quinone when heated for 24 h in refluxing benzene, only starting materials were recovered. Of particular interest was the finding that the reaction of methyl (<u>E</u>)-3-ethyl-2,4-pentadienoate (entry 2)⁷ proceeded in 60% yield; starting material was recovered indicating incomplete reaction. Methyl (<u>Z</u>)-3-ethyl-2,4-pentadienoate (entry 3)⁷ failed to react; this diene probably exists in an <u>s</u>-trans conformation which minimizes the strain.

The Diels-Alder reaction is sensitive to the presence of the weak electron withdrawing group at the terminus of the diene chain. The electron withdrawing ability (inductive effect) of the substituents on the C-5 methyl group (entries 4-6) can be ordered as follows: dimethoxy > phthalimido > \underline{t} -butyldimethylsilyloxy. This order was determined by comparing the chemical shifts of the proton on the C-5 substituted methyl group. Only the silyloxy diene gave any cycloadduct, and this reaction required an extended reaction period. The electron withdrawing ability (resonance effect) of the pyrone carbonyl group (entry 9) also rendered the diene moiety unreactive. The reaction of \underline{p} -quinone with 2,4-hexadienal (entry 8) afforded

			+		$\begin{array}{c} 15 \text{ kbar} \\ \hline \text{CH}_2\text{CI}_2 \\ \text{R.T.} \\ \end{array} \xrightarrow[]{\text{H}} \end{array} \xrightarrow[]{\text{H}} $	COR1 H R2 R4	
	R ₁	R ₂	R ₃	R ₄	Yield % ^a	mp,°C	Time, hr.
1.	оснз	Н	н	н	64	94-95	18
2.	OCH3	с ₂ н ₅	Н	н	60 ^{b,C}	54-54.5	3
3.	OCH3	C ₂ H ₅	Н	Н	no reaction ^{d,e}		18
4.	ос ₂ н ₅	Н	Н	CH(OCH ₃) ₂	no reaction ^e	—	18
5.	oc ₂ H5	н	н	CH ₂ N	no reaction ^e	_	48
6.	0C2H5	н	Н	сн ₂ 051 +	84	102-103	65
7.	0C2H5	н	н	сн ₃	92	92-93	18
8.	н	н	н	CH3	90		18
9.	CO2CH3				no reaction ^e		18
10.	(-)-menthyl	н	н	Н	51 ^f	139-144	18

Table I. Diels-Alder Reactions of p-Benzoquinone with Dienoic Esters

^aSatisfactory spectral data and elemental analysis were obtained. The yields are isolated unless indicated otherwise. ^bNo attempt was made to optimize the yield. $c(\underline{E})$ -isomer. $d(\underline{Z})$ -isomer. ^eStarting material was recovered. ^fMixture of diastereomers.

a cycloadduct which could not be completely readily purified from minor contaminants. A bulky ester such as (-)-menthyl reacted equally well under the pressure conditions.

These studies show that the utilization of very high pressure is a valuable technique in the synthesis of a series of highly functionalized 4a,5,8,8a-tetrahydro-1,4-naphthalene-

diones. These heat sensitive cycloadducts would be difficult or impossible to synthesize by conventional methods.

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References and Notes

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