Synthesis of Bicyclo[2.2.2]octenones *via* Modified Wessely Oxidation of Phenols

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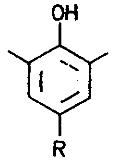
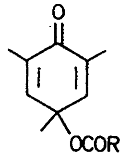
Summary The oxidation of *ortho*-substituted phenols with lead tetra-acetate in the presence of αβ-unsaturated acids followed by thermal intramolecular cycloaddition of the resulting cyclohexa-2,4-dienones provides a general method for the synthesis of bicyclo[2.2.2]octenones; such intramolecular reactions can lead to products that are regioisomers of related adducts formed by intermolecular Diels–Alder reactions.

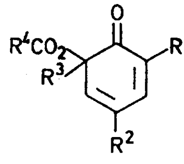
THE Wessely oxidation of *ortho*-substituted phenols with lead tetra-acetate provides a very useful method for the synthesis of cyclohexa-2,4-dienones.[1] Thus, mesitol (**1**) on treatment with lead tetra-acetate in acetic acid gives the 2,4-dienone (**5**) in 76% yield accompanied by 19% of the 2,5-dienone (**3**).[2] It has been shown that when the oxidation of (**1**) is carried out with lead tetra-acetate in propionic acid, a propionoxy group can be introduced to give (**6**).[3] Recently it has been found that a related 'modified' Wessely oxidation of (**1**) could be carried out with lead tetra-acetate in acrylic acid to give a mixture of (**7**) and (**4**).[4] These products were not separated, but when the mixture was heated in boiling benzene, (**7**) underwent an intramolecular Diels–Alder reaction to give the bicyclo[2.2.2]octenone (**9**), which was isolated in 41% yield. The synthesis of an analogue of (**9**) was also achieved *via* the reaction of 4-methylxanthen-3-ol with lead tetra-acetate and acrylic acid.[4] We report now the results of an investigation of the generality of this convenient synthesis of bicyclo[2.2.2]octenones with respect to variation of the unsaturated acid reactant and also record some types of transformation that these products undergo.



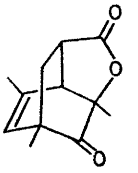
(**1**) R = Me
(**2**) R = H



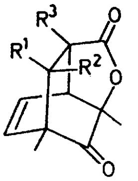
(**3**) R = Me
(**4**) R = CH=CH$_2$



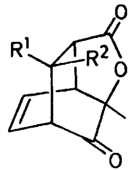
(**5**) R^1 = R^2 = R^3 = R^4 = Me
(**6**) R^1 = R^2 = R^3 = Me, R^4 = Et
(**7**) R^1 = R^2 = R^3 = Me, R^4 = CH=CH$_2$
(**8**) R^1 = R^3 = R^4 = Me, R^2 = H



(**9**)



(**10**)



(**11**)

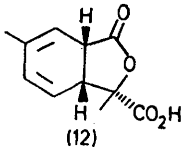
TABLE

Bicyclo[2.2.2]octenones from 2,6-dimethylphenol and *o*-cresol

αβ-Unsaturated acid		(**10**)
CH$_2$=CHCO$_2$H	(**a**)	R^1 = R^2 = R^3 = H
(*E*)-MeCH=C(Me)CO$_2$H	(**b**)	R^1 = R^3 = Me, R^2 = H
(*E*)-PhCH=CHCO$_2$H	(**c**)	R^1 = Ph, R^2 = R^3 = H
(*Z*)-MeO$_2$CCH=CHCO$_2$H	(**d**)	R^1 = R^3 = H, R^2 = CO$_2$Me
(*E*)-BrCH=CHCO$_2$H	(**e**)	R^1=Br, R^2 = R^3 = H
(*Z*)-BrCH=CHCO$_2$H	(**f**)	R^1 = R^3 = H, R^2 = Br
		(**11**)
(*Z*)-MeO$_2$CCH=CHCO$_2$H	(**a**)	R^1 = H, R$_2$ = CO$_2$Me
(*E*)-BrCH=CHCO$_2$H	(**b**)	R^1 = Br, R^2 = H

The generality of the reaction sequence has been established by the demonstration that 2,6-dimethylphenol (**2**) can be converted into the bicyclo[2.2.2]octenones (**10**) by treatment with lead tetra-acetate and a variety of αβ-unsaturated carboxylic acids in dichloromethane solution at room temperature followed by intramolecular cycloaddition in boiling benzene (Table).† In two cases it has been shown that the analogous compounds (**11**) can be obtained from *o*-cresol. The overall yields of bicyclo[2.2.2]octenones are dependent on the molar ratio of unsaturated acid and lead tetra-acetate; with a 4 : 1 molar ratio, *ca.* 40% yields of compounds (**10**) and *ca.* 20% yields of compounds (**11**) were obtained.‡ Although these yields are modest, this is compensated for by the simplicity of access that these reaction sequences provide to systems of type (**10**).

Compound (**10e**) has been found to undergo two noteworthy reactions under basic conditions. Treatment with aqueous sodium hydroxide leads to cleavage of the bicyclo[2.2.2]octenone system and formation of the lactonic acid (**12**). On the other hand, treatment with *NN*-dimethylhydrazine in methanol brings about opening of the lactone ring and elimination of hydrogen bromide to give the ester (**13**), whose structure was confirmed by its conversion on treatment with sodium borohydride in tetrahydrofuran into methyl *m*-toluate.§ The formation of (**13**) *via* the intramolecular Diels–Alder route may be contrasted with the formation of (**14**) by the intermolecular Diels–Alder reaction of (**8**), the conventional Wessely oxidation product from (**2**), with propiolic acid followed by esterification with diazomethane.¶ These observations reveal the potential general applicability of the modified Wessely oxidation, intramolecular Diels–Alder sequence to the synthesis of regioisomers of the bicyclo[2.2.2]octenones formed by intermolecular Diels–Alder reactions of conventional Wessely oxidation products. It may further be noted that although such intermolecular reactions are often sluggish [*e.g.*, the reaction of (**8**) with propiolic acid in boiling benzene requires 3 weeks], because of deactivation of the diene by the conjugated ketone group, the intramolecular reactions are very much more rapid (10 min—12 h in boiling benzene), owing to the compensating effect of favourable entropy factors.



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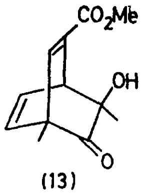

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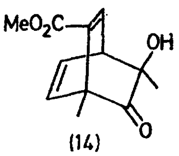

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† All new compounds have been characterized by elemental analysis and i.r., ^{1}H and ^{13}C n.m.r., and mass spectroscopy.

‡ The yields have not been optimized. Although the yields are increased by increasing the molar ratio of acid and lead tetra-acetate, the difficulty of work-up is also increased.

§ This transformation is considered to involve reduction of (**13**) to a diol that undergoes base-catalysed fragmentation to methyl *m*-toluate and hydroxyacetone.

¶ The isolation of the hydroxy rather than the acetoxy compound is attributable to ester exchange with the propiolic acid during the lengthy reaction period (*vide infra*).

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[3] G. W. K. Cavill, E. R. Cole, P. T. Gilham, and D. J. McHugh, *J. Chem. Soc.*, 1954, 2785.

[4] D. J. Bichan and P. Yates, *Canad. J. Chem.*, 1975, **53**, 2054.