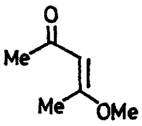
Reactions of β-Keto-enol Ethers with Bromine in Aqueous Solution

By **D. R. Marshall*** and **T. R. Roberts,** Department of Chemistry, University College of North Wales, Bangor, Caernarvonshire

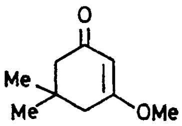
The β-keto-enol ethers acetylacetone enol methyl ether, dimedone enol methyl ether, and 2,3-dihydro-2,6-dimethyl-γ-pyrone undergo fast olefinic addition reactions with aqueous bromine. Rate measurements for the last two are correlated with published data for olefins and enols. The bromination products of the first two, but not those of the last one, undergo slow, acid-catalysed fission of the methoxy-group to give the bromo-enol.

β-Keto-enols react with bromine water to give the α-bromo-derivative by ' addition ' of bromine to the enol tautomer, essentially a modified substitution reaction. With β-keto-enol ethers, on the other hand, this cannot occur, and addition of bromine is likely to follow a normal olefinic course. The reaction rates should be lowered by the carbonyl substituent and raised by the methoxy-substituent, but in the β-keto-enol group these substituents are conjugated through the olefinic bond and this may further affect reactivity. Conjugation should be most effective in planar or near planar systems (as, for instance, in the chelated enol of acetylacetone), and might then cause significant resonance stabilisation lowering the reactivity. Noteworthy examples of similar interactions are found on the symmetrical mesomeric cations of 2,3-dihydro-1,4-diazepines[1] (diaza-analogues of the β-keto-enol system) and in the symmetrical, mesomeric transition-metal chelates of the β-keto-enols,[2] the interactions being so strong in these two classes of compound that bromine reacts, not by addition, but by substitution. Though the β-keto-enol ethers are not symmetrical, and should be less strongly mesomeric than symmetrical systems, it is of interest to examine their reactions in order to see what kind and degree of reactivity is shown, and whether the kind of reactivity is affected by varying the rigidity and coplanarity of the conjugated system.

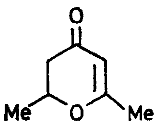
Three β-keto-enol ethers were examined, acetylacetone enol methyl ether (I), dimedone enol methyl ether (II), and 2,3-dihydro-2,6-dimethyl-γ-pyrone (III). Of these molecules, the ether (I) is the least rigid, as rotation of both the methoxy and acetyl groups is restricted only by relatively small rotational barriers, and coplanarity will be inhibited by interaction between the two *C*-methyl groups. In the ether (II) only the methoxy-group is free to rotate, the two double bonds being held nearly coplanar in a favourable position for conjugation. In the pyrone (III) the enol ether link is cyclic, and no part of the conjugated system can rotate.



(I)



(II)



(III)

All three compounds reacted rapidly with bromine. Spectrophotometry of aqueous solutions showed that the intense u.v. absorption of the β-keto-enol chromophore ($\varepsilon_{max.}$ *ca.* 10^3 m^2 mol^{-1} in the region 260—270 nm) was removed by bromination, and that exactly one molar proportion of bromine was consumed in this reaction. In kinetic experiments it was found that for all three compounds this reaction was of the first order with respect to bromine, and bimolecular rate constants in

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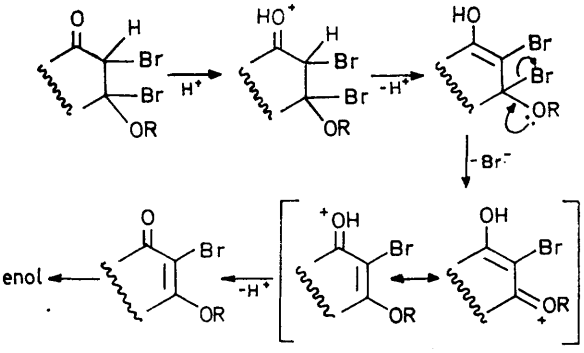
[1] Anita M. Gorringe, D. Lloyd, and D. R. Marshall, *J. Chem. Soc.* (*C*), 1970, 617.

[2] J. P. Collman, ' The Chemistry of Quasi-aromatic Metal Chelates,' in ' Reactions of Organic Ligands,' American Chemical Society, 1963, p. 78.

excess of 10^5 l mol^{-1} s^{-1} were found (see below). No further spectral change took place in reaction mixtures containing the pyrone (III), but the bromination products of the ethers (I) and (II) underwent further reaction. In the otherwise transparent solutions new intense absorption at *ca.* 290 nm appeared slowly during ½—1 h, a process which was catalysed by additions of mineral acid. For reaction of the ether (II) the intensity of the new absorption was of similar intensity to that of the initial (II), while for reaction of (I) it was about a factor of 10 lower than that of the initial (I). This suggests that the final, optically absorbant, products were bromo-enols, together with the equilibrium amounts of the tautomeric bromo-diketones, since the ether (II) would yield bromodimedone, which contains 98% enol in water at 25 °C,[3] and (I) would yield bromoacetylacetone, which contains 8% enol in water at 20 °C.[4] Thereafter the solutions absorbed more bromine up to a total of two molar proportions, and separate kinetic experiments in which more than one molar proportion of bromine was added at one time to ethers (I) and to (II) showed that the reaction of the second molar proportion of bromine was slow, and was of zero order with respect to bromine. This reaction order is to be expected for brominations controlled by the slow production of reactive enols. In a larger scale experiment, the dimedone ether (II) was treated in ethereal solution (which probably contained some moisture) with an equimolar amount of bromine. The ethereal solution slowly deposited an oil which, after separation, crystallised and was identified as bromodimedone ($\lambda_{max.}$ 290 nm in water) showing that fission of the ether link had taken place.

The dibromination products of the ethers (I) and (II) took up further bromine very slowly. This is ascribed to slow reaction of the methyl groups of (I) and the methylene groups of the dimedone ether (II).

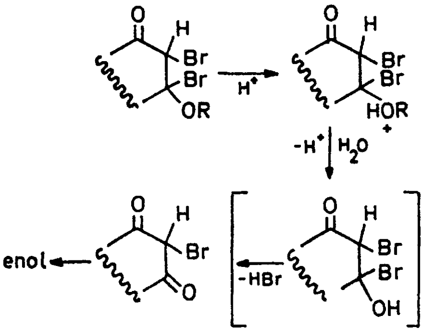
Fission of the dibromo-ethers from (I) and (II) giving optically absorbant products could take place in two main ways, corresponding to the two alternative protonation sites (at oxygen) for acid catalysis. In Scheme 1, initial enolisation is followed by intramolecular displacement of a bromide ion, facilitated by the stability of the intermediate product, a strongly mesomeric oxonium cation.



Scheme 1

Loss of the original catalyst proton gives the bromo-enol ether, which will react rapidly with bromine, and in the absence of bromine might readily undergo acid-catalysed ether fission to the enol. In this Scheme, to explain the absence of any large increase in optical absorbance after bromination of the acetylacetone ether (I) it is necessary to assume that the initial enolisation is rate-determining and that the ether fission is a much faster step. Since the bromo-enol ether would formally be a vinyl ether, this might be so.

In Scheme 2, protonation at the ether oxygen initiates ether fission, leading to generation of a second carbonyl group by loss of hydrogen bromide, and final enolisation of the bromo-diketone. The initial ether fission would probably be rate-determining, but the same kind of behaviour would be observed if the final enolisation were rate-determining.



Scheme 2

A tentative choice between these two Schemes may be made by considering the failure of the dihydropyrone dibromide to decompose in a similar way at any detectable rate. The only significant difference between the dibromide of the pyrone (III) and those of the ethers (I) and (II) appears to be that, in a scheme analogous to Scheme 1, the dibromide of the pyrone (III) could not give rise to an oxonium cation intermediate with an all-*trans*-structure, like those in Scheme 1, but only one with a *cis–trans*-structure. This factor, however, does not appear to be sufficient to prevent reaction. That the dibromide of the pyrone (III) does not decompose suggests, therefore, that the decompositions may proceed according to Scheme 2, which for the pyrone derivative would involve ring opening. Since there is no factor favouring formation of a stabilised carbonium ion by unimolecular loss of ROH from protonated ether, ether fission in Scheme 2 would be bimolecular. In the methyl ethers this would be likely to proceed by solvolytic attack on the methyl groups, rather than on the alternative carbon atom which is a highly hindered tertiary centre. In the pyrone derivative the only alternative to this tertiary centre is a secondary carbon atom, which will also be markedly hindered as a reaction site. Hydrolysis of the pyrone derivative might thus be slower

[3] R. P. Bell and G. G. Davis, *J. Chem. Soc.*, 1965, 353.

[4] G. Schwarzenbach and E. Felder, *Helv. Chim. Acta*, 1944, 27, 1044.

than that of the other compounds by perhaps three powers of ten,[5] and would not then be observable.

When olefins react with bromine water, bromohydrins are often found as by-products. The initial attack is by bromine, and the bromohydrin formed from the dihydropyrone would, therefore, be 3-bromo-2-hydroxy-2,3,5,6-tetrahydro-γ-pyrone. This is a hemiacetal, and should be able to react readily in either of two ways, both yielding an optically absorbant, conjugated product. Protonation and elimination of the 2-hydroxy-group would restore a dihydropyrone structure, whilst protonation at position 1 would allow unimolecular ring-opening, assisted by the 2-hydroxy-group, which would become a carbonyl group in a new, enolisable β-diketone. Our failure to detect any increase of absorbance after bromination of the pyrone (III) suggests that little bromohydrin was formed. We did not attempt to analyse the bromination products for bromohydrins, however.

The rates of monobromination of the ethers (II) and (III) were measured by the potentiometric method of Atkinson and Bell[6] in dilute aqueous perchloric acid containing sodium bromide at 0 °C. Considerable experimental difficulties were encountered in handling the very dilute bromine solutions needed and in following the reactions, and the rates of fall of potential observed approached the upper limits measurable, about half of the reaction being followed in times of a few seconds. Rate values were not satisfactorily reproducible, and some experiments yielded rate plots which were curved even at the beginning. These were discarded. The Table gives average rate values obtained from sets of from 3 to 7 more satisfactory experiments, the standard errors of the means being of the order of 5%.

These values are consistent with reaction of each substrate with both bromine molecules and tribromide anions, the kinetic expression being (1) where k_1 refers

$$k_{\text{obs}}\,(1 + K[\text{Br}^-]) = k_1 + k_2K[\text{Br}^-] \qquad (1)$$

to reaction of bromine molecules, k_2 to tribromide anions, and K is the stability constant of the tribromide anion, taken to be 20 l mol^{-1} at 0 °C. (Kinetic analysis is not sensitive to the exact value of K.) Rate values in column 4 of the Table were calculated by use of the values $k_1 = 2{\cdot}8 \times 10^5$ and $k_2 = 8{\cdot}2 \times 10^4$ for dimedone enol ether, $k_1 = 7{\cdot}0 \times 10^5$ and $k_2 = 6{\cdot}1 \times 10^5$ for the dihydropyrone (all in l mol^{-1} s^{-1}). These values of k_1 and k_2 are less reliable than the precision to which they are here given, but they compare with the slightly greater value for the similar methylacetylacetone, reported by Bell and Davis,[3] of $5{\cdot}0 \times 10^6$ l mol^{-1} s^{-1} at 25 °C (corresponding to 2×10^6 l mol^{-1} s^{-1} when adjusted to 0 °C by assuming a normal frequency factor).

TABLE

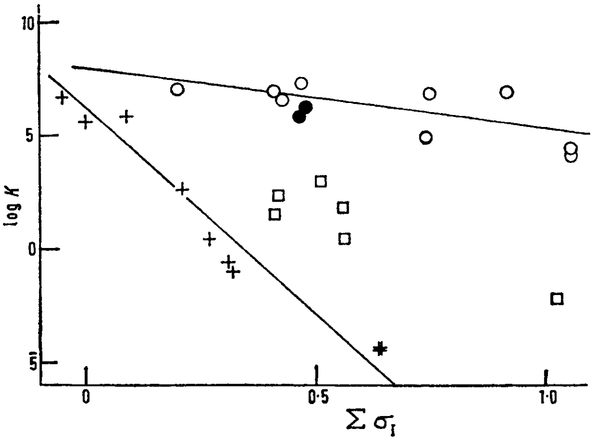
Bromination rates at 0 °C at ionic strength 0·51

(i) Dimedone enol methyl ether (II)

$[\text{H}^+]$/M	$[\text{Br}^-]$/M	$10^{-5}k_{\text{obs}}$ / l mol^{-1} s^{-1}	$10^{-5}k_{\text{calc}}$ / l mol^{-1} s^{-1}
0·01	0·50	1·0	1·00
0·01	0·30	1·1	1·10
0·01	0·10	1·5	1·48
0·01	0·05	2·2	1·81
0·01	0·01	2·3	2·47
0·001	0·10	1·3	1·48

(ii) 2,3-Dihydro-2,6-dimethyl-γ-pyrone (III)

$[\text{H}^+]$/M	$[\text{Br}^-]$/M	$10^{-5}k_{\text{obs}}$ / l mol^{-1} s^{-1}	$10^{-5}k_{\text{calc}}$ / l mol^{-1} s^{-1}
0·01	0·50	5·9	6·18
0·01	0·20	6·2	6·28
0·01	0·10	6·5	6·40
0·01	0·01	7·1	6·85
0·10	0·01	6·9	6·85



Correlation of bromination rates in aqueous solution at 25 °C with $\Sigma\sigma_{\text{I}}$; +, olefins with no substituents able to supply electrons by conjugation; □, olefins containing conjugating chlorine or phenyl substituents; ○, enols; ●, present work

Since our results must represent *minimum* rates, it is clear that ethers (II) and (III) behave as highly reactive olefins. It has been observed[7] that the rates of aqueous bromination of olefins can be correlated satisfactorily with the sum of the σ* constants for the four substituents about the olefinic group. Equivalently, σ_{I} values may be used, and published bromination rates for enols[3,8] may be treated similarly, as in the Figure, which also contains the points for ethers (II) and (III), slightly adjusted to refer to 25 °C by assuming a normal frequency factor. The σ_{I} values used in the Figure are mainly published values.[9] Some are not available and were calculated from published values, by use of the attenuation factor[10] of 2·8 [equation (2)]. In a few

$$\sigma_{\text{I(X)}} = 2{\cdot}8\sigma_{\text{I(XCH}_2)} \qquad (2)$$

cases the σ_{I} value for a closely similar group is used instead, *e.g.*, CO_2Et for CO_2Me. The substituents chlorine and phenyl, able to supply electrons by conjugation, greatly increase olefinic reactivity, while the hydroxy-

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[5] A. Streitwieser, jun., *Chem. Rev.*, 1956, **56**, 571; 'Solvolytic Displacement Reactions,' McGraw-Hill, New York, 1962, p. 13.

[6] J. R. Atkinson and R. P. Bell, *J. Chem. Soc.*, 1963, 3260.

[7] R. P. Bell and M. Pring, *J. Chem. Soc.* (*B*), 1966, 1119; R. P. Bell and D. Dolman, *ibid.*, 1968, 500.

[8] R. P. Bell and D. J. Rawlinson, *J. Chem. Soc.*, 1961, 726; R. P. Bell and G. G. Davis, *ibid.*, 1964, 902.

[9] C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, 1964, **2**, 323.

[10] R. W. Taft in 'Steric Effects in Organic Chemistry,' ed. M. S. Newman, Wiley, New York, 1956, p. 556.

substituent in an enol has an ever larger effect. The points for ethers (II) and (III) fall close to the line representing the enols, showing that these ethers (II) and (III) are each activated by conjugation between the ether oxygen atom and the olefinic bond. There is no great diminution of reactivity by further conjugation to the carbonyl group, though the fact that the enol ethers (II) and (III) appear to be less reactive (at 25 °C) than methylacetylacetone enol by factors of 6 and 2·5 may indicate the operation of a small extra deactivating resonance effect of this kind. Resonance effects in similar enolic and other olefinic systems in bromination in methanolic solution have been evaluated by Dubois,[11] but to apply a similar treatment satisfactorily to the bromination in aqueous solution of the compounds used in the present work would require the use of a different experimental method.

The high olefinic reactivity of the pyrone (III) is in strong contrast to the low aromatic reactivity of the parent γ-pyrone system, often represented as a superficially similar *para*-quinonoid structure, and helps to emphasise further [12] the importance of the cyclic nature of the conjugation in γ-pyrones.

EXPERIMENTAL

Acetylacetone enol methyl ether (I) was prepared [13] by allowing acetylacetone (7·5 g) and diazomethane (5 g) in ether to react for several hours before working-up. The product was purified by fractional distillation (b.p. 66°/10 mm and 32°/1—2 mm) and then contained negligible impurity, as shown by g.l.c.

Dimedone enol methyl ether (II) was prepared by treating dimedone (10 g) in ethyl acetate with diazomethane (4·7 g) in ether at 0 °C, and allowing the mixture to stand overnight before the bulk of the solvent was distilled off. The residue was washed with dilute aqueous potassium hydroxide, and the organic layer was separated, dried, and fractionated. The product (b.p. 136°/20 mm and 51—55°/0·1 mm) contained only a small amount of dimedone, as shown by t.l.c., and this was removed completely by partitioning the product between ether and aqueous sodium hydrogen carbonate solution.

2,3-Dihydro-2,6-dimethyl-γ-pyrone (III) was prepared by hydrogenating 2,6-dimethyl-γ-pyrone at 3—5 atm in alcohol,[14] with a palladium oxide catalyst.[15] 2,3,5,6-Tetrahydro-2,6-dimethyl-γ-pyrone (apparently, from g.l.c., an unequal mixture of *cis*- and *trans*-isomers) was also produced in quantity, with small amounts of other products. The products were isolated by preparative g.l.c. on a 20 ft column of 20% SE 30 on Celite, temperature programmed between 120 and 200 °C. The progress of the hydrogenation was followed by g.l.c., and when the amount of dihydropyrone no longer increased the mixture was worked up. The identity of the dihydropyrone was confirmed by analysis and from its n.m.r. spectrum, the τ values of which closely resembled those of 2,3-dihydro-2,2-dimethyl-γ-pyrone [16] (Found: C, 66·6; H, 8·0. Calc. for $C_7H_{10}O_2$: C, 66·7; H, 7·9%); n.m.r.: τ 8·60 (doublet, *J* 6 Hz; 2-methyl); 8·04 (singlet; 6-methyl); 7·63 (doublet, *J* 8 Hz; 3-methylene); 5·46 (multiplet; 2-H); 4·73 (singlet; 5-H), integral ratio 3 : 3 : 2 : 1 : 1.

In a preparative bromination of the ether (II), bromine (1·04 g) in ether (20 ml) was added to (II) (1 g) in ether (20 ml) with stirring. The ether was not specially dried, and the bromine was ordinary reagent grade. During several hours a colourless oil separated, which, when removed from the ether, crystallised to colourless 2-bromodimedone, m.p. 172—174° (from water), not depressed by admixture with authentic 2-bromodimedone.

U.v. spectra were recorded on Unicam SP 700 or SP 800 instruments. Compounds (I), (II), and (III) in water showed: (I), $\lambda_{max.}$ 263 nm (log ε/m^2 mol^{-1} = 3·07); (II), $\lambda_{max.}$ 258 nm (log ε/m^2 mol^{-1} = 3·15); (III), $\lambda_{max.}$ 269 nm (log ε/m^2 mol^{-1} = 3·06). Bromine solutions contained sodium bromide, and were standardised against thiosulphate after addition of potassium iodide.

Bromination rates were measured potentiometrically by the method described by Atkinson and Bell,[6] with a bright platinum electrode with a glass reference electrode. The potential changes were measured with an E.I.L. 23A pH meter connected through an output resistance of, typically, 50 or 100 ohms to a Control Instruments 'Hi-speed' 6-inch chart recorder with a span of 10 mV and a pen speed of 0·7 s for full-scale deflection. Typical initial concentrations were 10^{-6}M-substrate and 5×10^{-7}M-bromine. For working at these low bromine concentrations it was found necessary to purify distilled water by redistillation from alkaline permanganate, followed by treatment with bromine and redistillation. As second-order kinetics were observed, the bromine concentrations at various times were calculated from the fall of potential, and corresponding substrate concentrations were found from stoicheiometry.

In a reaction of zero order with respect to bromine, the bromine falls at a constant rate when a large excess of substrate is present. The potential–time curve is then described by equation (3), where the subscript zero denotes

$$kt = [\mathrm{Br_2}]_0\{\exp [nF(E_t - E_0)/RT] - 1\} \qquad (3)$$

an initial value and *t* denotes elapsed time. This plunging curve is characteristic of zero-order kinetics, and was observed in the slow, second bromination step undergone by the ethers (I) and (II)

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[15] *Org. Synth.*, Coll. Vol. II, 1943, 566.

[16] E. M. Kosower and T. S. Sorensen, *J. Org. Chem.*, 1963, **28**, 687.