# Stabilisation of the Thromboxane Ring System by Electron-withdrawing Substituents. Mechanism and Reactivity in the Hydrolysis of Alkyl and Aryl Oxetane Acetals.

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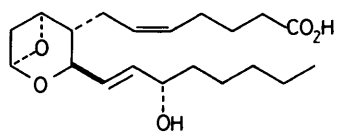
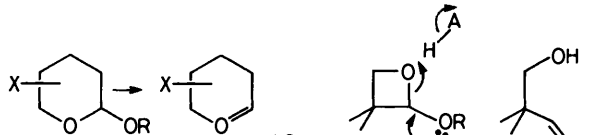
Rates of acid-catalysed hydrolysis are reported as a function of pH for eleven oxetane acetals (**6**) in 20% dioxane–water. The introduction of fluorine atoms into the 2-alkoxy group results in a $10^3$–$10^4$-fold kinetic stabilisation, and the system is also stabilised by 2-aryl substituents. The pH–rate profiles for the two most reactive compounds (**3b**) and (**12b**) show that at low pH the reaction involves rapid conversion into the intermediate hemiacetal, followed by its rate-determining decomposition. For these compounds at pH > 6, and for all other oxetane acetals studied, the ring-opening step is rate determining. No general acid catalysis is apparent.

The study of the potent platelet aggregating factor and vasoconstrictor thromboxane $A_2$ [$TxA_2$, (**1**)] is complicated by



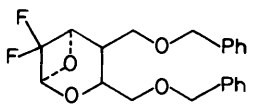
(**1**)

its short lifetime—of the order of 30 s under physiological conditions.[1] This is an intrinsic property of the oxetane acetal system,[2] and is a severe restriction on the design of potential antagonists. One response has been to make analogues with one or both of the acetal oxygen atoms replaced by carbon[3] or sulphur.[4] We are interested in stabilising the oxetane acetal ring system itself, by appropriate substitution. Electron-withdrawing substituents such as the OH groups of sugars have a large stabilising effect on tetrahydropyranyl acetals.[5] This is a result of inductive destabilisation of the developing oxocarbocation (**2**) generally involved in acetal cleavage. The oxetane acetal system (**3**) is different, in that hydrolysis involves cleavage of the endocyclic C–O bond, and—unusually for an alkyl acetal—is general acid catalysed,[2] at least for the simple compound (**3**; R = Me).[2] The build-up of positive charge in the transition state is thus likely to be greatest at the exocyclic oxygen.



(**2**) (**3**)

During the early stages of this work Fried and his co-workers[6] reported the synthesis of 7,7-difluoro-2,6-dioxa[3.1.1]-bicycloheptane (**4**), which is hydrolysed over $10^8$ times more slowly than $TxA_2$. Fried's work culminated in the recent synthesis of the corresponding difluoro derivitive of $TxA_2$ itself.[7] Still and his group also used the stabilising effect of a heteroatom in their successful synthesis of $TxA_2$ *via* (**5**).[8] These workers successfully used substitution in the oxetane ring to achieve the desired stabilisation. In this paper we report the substantial stabilising effects of electron-withdrawing substituents in the leaving group (R) of a series of oxetane acetals (**6**). We have also measured the effect of an aromatic substituent (R′ = substituted phenyl) as a probe of transition-state structure during hydrolysis.



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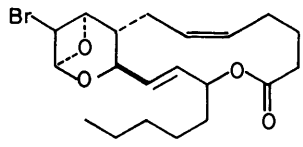

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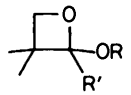
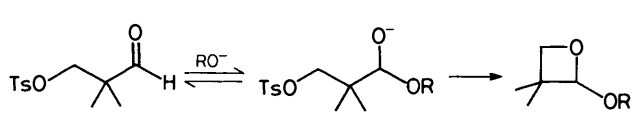


(**6**)

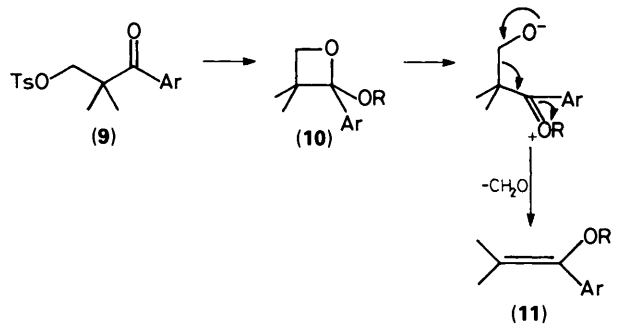
## Results

*Synthesis of Substrates.*—The most convenient route to oxetane acetals proved to be that developed by Nerdel and his co-workers,[9] who showed that the toluene-*p*-sulphonate (**7**) reacts with alkoxide ions to give the corresponding 2-alkoxyoxetanes (**8**). This reaction gives the unstable methoxy derivative (**8**; R = Me) in good yield, but we had very limited success in extending the synthesis to derivatives of more strongly acidic alcohols. Refluxing (**7**) in trifluoroethanol in the presence of KOH gave the 2,2,2-trifluoroethyl acetal (**8**; R = $CF_3CH_2$), which was stable enough to be purified by column chromatography. But, like Nerdel, we were unable to make the phenyl acetal (**8**; R = Ph) under similar conditions. We tried a range of other conditions, but gave up when we found that the preferred reaction of free phenoxide ion in dimethyl sulphoxide is direct displacement at the neopentyl position, to give the



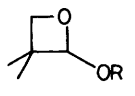
(**7**) (**8**)

phenyl ether corresponding to (7). Thiophenoxide, as might be expected, also gives direct displacement. The most convenient synthesis of simple oxetane acetals proved to be the similar reaction of the tosyl ketones [(9); Ar = 4-chlorophenyl in the original work[10]]. Addition–cyclisation with phenolic KOH gave an 8% yield of the acetal (10; R = Ph, Ar = 4-chlorophenyl), which could also be purified by column chromatography. The major product was the enol ether (11), no doubt derived from the oxetane acetal by fragmentation of the ring-opened form. This is a common by-product of these reactions, and the major product under the vigorous conditions necessary for the reaction of (9) with weaker nucleophiles. More basic alkoxides gave better yields of 2-alkoxyoxetanes, and with the 4-nitrophenyl ketone (9; R = 4-nitrophenyl) addition–cyclisation was possible with 3-fluorophenoxide. All the compounds used in this study, including ten prepared by this route, are listed in the Table.

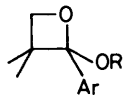



*Hydrolysis Reactions.*—The rates of hydrolysis of the oxetane acetals listed below, except that of (3a), already studied by Atkinson and Bruice[2] under similar conditions, were measured in dioxane–water (20% v/v) at 39 °C and with ionic strength maintained constant with KCl, by monitoring the appearance of the aldehyde or ketone chromophore in the UV spectrum. Details appear in the Experimental section below. All the reactions showed good first-order kinetics, with the exception of the 2-methoxyoxetane (12a) between pH 4.5–6, and our most reactive 2-trifluorethoxyoxetane (3b) below pH 4. Both these compounds showed induction periods, characteristic of consecutive first-order reactions.[2,11] The products of hydrolysis of compounds (12a) and (13b) under the conditions of the kinetic measurements were examined by $^1$H NMR spectroscopy. Only the expected 2-hydroxyalkyl ketones could be detected.

No spontaneous hydrolysis is observed with any of the compounds studied, so all the data refer to acid-catalysed reactions. General acid catalysis is also insignificant under our conditions, though it was observed for the hydrolysis of (3a) in 10% dioxane–water by Atkinson and Bruice.[2] We looked for




(3) a; R = $CH_3$
b; R = $CF_3CH_2$




(10) b; Ar = Ph, R = $CF_3CH_2$
(12) a; Ar = 4-$ClC_6H_4$, R = $CH_3$
b; Ar = 4-$ClC_6H_4$, R = $CF_3CH_2$
c; Ar = 4-$ClC_6H_4$, R = n-$C_4H_9$
d; Ar = 4-$ClC_6H_4$, R = Ph
e; Ar = 4-$ClC_6H_4$, R = 4-$MeC_6H_4$
(13) b; Ar = 4-$CH_3C_6H_4$, R = $CF_3CH_2$
(14) b; Ar = 4-$NO_2C_6H_4$, R = $CF_3CH_2$
e; Ar = 4-$NO_2C_6H_4$, R = 4-$CH_3C_6H_4$
f; A = 4-$NO_2C_6H_4$, R = 3-$FC_6H_4$

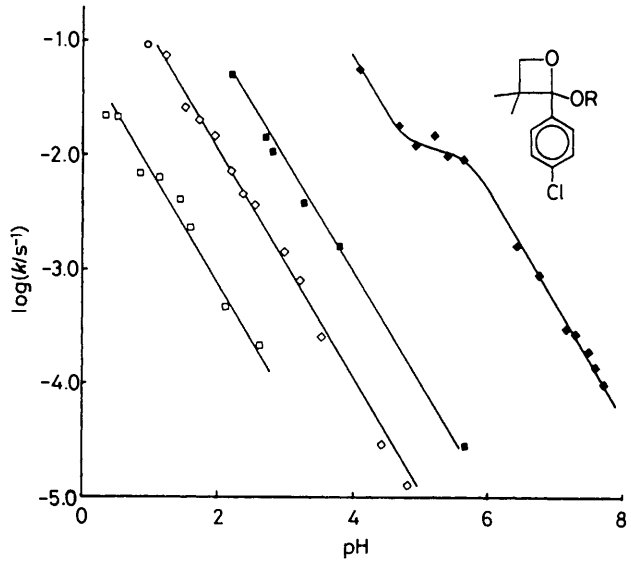



**Figure 1.** pH–rate profiles for the hydrolysis of 2-(4-chlorophenyl)-oxetane acetals: ◆, (12a; R = Me); ◇; (12b; R = $CH_2CF_3$); □, (12c; R = $CH_2C_3F_7$); ■, (12d; R = Ph), in 20% dioxane–water at 39 °C.

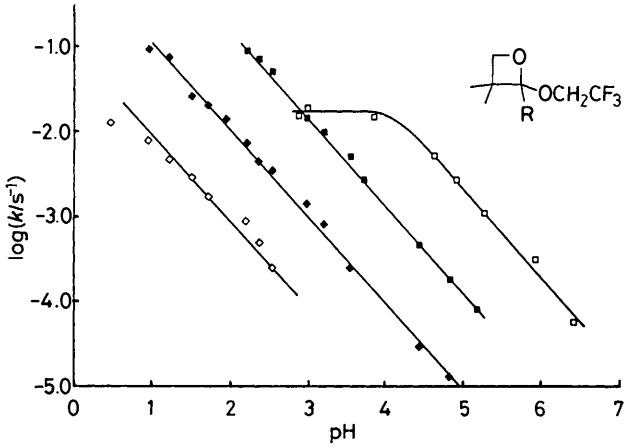



**Figure 2.** pH–rate profiles for the hydrolysis of 2-(2,2,2-trifloroethoxy)-oxetane acetals: □, (3b; R = H); (12b), (13b), and (14b) [R = 4-Cl (◆), 4-MeO (■), and 4-nitrophenyl (◇), respectively], in 20% dioxane–water at 39 °C.

buffer catalysis of the hydrolysis of the hydrolysis of three of our most reactive compounds. We could find no catalysis of the hydrolysis of the 2-methoxyoxetane (12a) by phosphate buffer at pH 6.75, and a slight *decrease* in its rate of hydrolysis at pH 6.4 in the presence of increasing concentrations of quinuclidinone buffer. Increasing acetic acid concentration had no significant effect on the rate of hydrolysis of the 2-trifluoroethoxyoxetane (13b) at pH 4.5; and we could detect no catalysis of the hydrolysis of the 2-trifluoroethoxyoxetane (12b) by chloracetic acid buffers at pH 2.95 or 3.75.

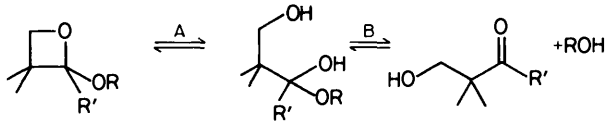
Nucleophilic catalysis is also not in evidence. Replacing the KCl used to maintain the ionic strength with an equal concentration of KI gave a substantial increase in the rate of hydrolysis of the 2-trifluoroethoxyoxetane (13b), at pH 4.39 (the rate more than doubling at 0.6 mol $dm^{-3}$ salt), and the effect was found to be linear in iodide concentration. However, an effect of similar magnitude was also observed when perchlorate anion was used, so it seems clear that our observations were of specific salt effects, rather than nucleophilic catalysis.[12]

pH–rate profiles for the hydrolysis of most of the oxetane acetals listed in above are shown in Figures 1 and 2. Figure 1 shows the effect of varying the leaving group (OR) on the rates of hydrolysis of four of our five 2-(4-chlorophenyl) acetals (**12**). Figure 2 illustrates the effect of varying the 2-substituent on the rates of hydrolysis of four of our five trifluoroethyl oxetane acetals. In all but two cases the plots are straight lines with slopes to within experimental error of −1, as expected for acid-catalysed reactions. Second-order rate constants for acid catalysis (Table) were calculated from the slopes of plots of observed first-order rate constant against $a_H$ calculated from the observed pH. (The intercepts of these plots passed through the origin in each case.) A Hammett plot of these second-order rate constants for the reactions of the four 2-aryl-2-trifluoroethoxyoxetanes [(**10b**), (**12b**), (**13b**) and (**14b**)] gave a ρ-value of −2.10 ± 0.12. The hydrolysis of the 2-trifluoroethoxyoxetane (**12b**) was 1.65 times faster in $D_2O$.

## Discussion

Before analysing the effects of substitution on the stability of our oxetane acetals we must identify the rate-determining step (RDS) of the hydrolysis reaction, and thus be sure that comparisons of reactivity involve rate constants that refer to a common RDS. The sigmoid shape of the pH–rate profile for the 2-methoxyoxetane (**12a**) (Figure 1), and the similar behaviour of our next most reactive compound (**3b**) (Figure 2), are consistent with a change of rate-determining step in each case. The pH–rate profiles for all our other compounds are linear, with slopes of −1, as expected for simple acid-catalysed reactions, without change of mechanism or rate-determining step. So we need to decide which limb of the sigmoid curve for the hydrolysis of (**12a**) the straight lines for the other compounds correspond to.

There is good evidence from the literature that hemiacetal hydrolysis becomes rate determining for the hydrolysis of strained (oxirane[13] or oxetane[2]) acetals at low pH (see the Scheme). Other possible pathways can be ruled out with some confidence on the basis of arguments presented by Atkinson and Bruice.[2]




(**6**) (**15**) (**16**)

**Scheme.**

This would mean that the pH–rate profile (Figure 1) for the hydrolysis of the 2-methoxyoxetane (**12a**), for example, represents rate-determining ring opening (Scheme, step A) at pH > 6, and rate-determining hemiacetal hydrolysis (Scheme, step B) at pH < 4.5. Some quantitative evidence to support this proposition follows.

If the reaction of the methoxyoxetane (**12a**) does involve rapid ring opening to give a significant concentration of the hemiacetal (**15**; R = Me, R′ = 4-chlorophenyl) at pH < 5 we can estimate a minimum value for $k_H$ in the region of 500 $dm^3$ $mol^{-1}$ $s^{-1}$ for its acid-catalysed decomposition. This compares well with values of 261 $dm^3$ $mol^{-1}$ $s^{-1}$, measured by Capon[17] for the hydrolysis of benzaldehyde methyl hemiacetal at 15 °C, and 352 l $dm^3$ $s^{-1}$ obtained for the reaction of the ethyl hemiacetal of 4-chlorobenzaldehyde at 30 °C by Fife.[14] The breakdown of the ketone hemiacetal (**15**; R = Me, R′ = 4-chlorophenyl) is expected to be faster than that of aldehyde derivatives.

We can also show that our reactions which show uncomplicated linear pH–rate profiles do not behave like hemiacetal hydrolyses. With the disappearance of ring strain the hemiacetal intermediates (**15**) are expected to behave normally. All reported studies of hemiacetal hydrolysis show evidence for significant acid, base and water-catalysed reactions. The acid-catalysed reaction is most relevant. Przystas and Fife[14] measured a ρ-value of −1.9 and a solvent deuterium isotope effect, $k_{D_2O}/k_{H_2O}$, of 1.7 for the acid-catalysed hydrolysis of substituted-benzaldehyde ethyl hemiacetals, very similar to the values we find for the reactions of our 2-aryl-2-(2,2,2-trifluoroethoxy)oxetanes. However, this isotope effect is also almost identical with that found for the ring-opening step of the hydrolysis of (**3a**),[2] so does not contradict all the other evidence, which suggests that we are looking at rate-determining ring opening (Scheme, step A). We find no significant general acid catalysis of our reactions: reasonable for less reactive oxetane acetals but surprising if the reaction we are following is hemiacetal hydrolysis. Atkinson and Fife[2] found general acid and general base catalysis of the hydrolysis of the hemiacetal intermediate involved in the hydrolysis of (**3a**).

Jencks and his co-workers[15] studied general species catalysis of the hydrolysis of a series of hemiacetals of formaldehyde. They found for the $H_3O^+$-catalysed reaction that hydrolysis, though slower for hemiacetals derived from more acidic alcohols, depends only weakly on the $pK_a$ of the leaving alcohol ($\beta_{LG}$ = 0.22). Our $H_3O^+$-catalysed reactions show a much larger dependence on the $pK_a$ of the 2-alkoxy substituent, with $'\beta_{LG}{}'$ = 1.18 for the series of three compounds (**12a–c**). Moreover this Brønsted plot gives an excellent straight line, $r$ = 0.9996, but only when the data at pH > 6 are used for (**12a**).

Finally, we can rationalise the observed differences in the shapes of the pH–rate profiles for the hydrolysis of oxetane acetals. The hydroxide catalysed reaction is known to be much faster for hemiacetals derived from more acidic alcohols: $\beta_{LG}$ = −1.1 for formaldehyde derivatives[15] and −1.3 for the hemiacetals of 4-chlorobenzaldehyde studied by McClelland and his group.[16] Thus the expectation is that the minimum in the V-shaped pH–rate profile[2] for the hydrolysis of hemiacetals (**15**; with R′ constant) will move to lower pH and to higher rates with better leaving groups (RO derived from more acidic alcohols), because of the dominant effect of the leaving group on the hydroxide-catalysed reaction. The ring-opening of the oxetane acetal (Scheme, step A), on the other hand, will be slowed substantially by the same structural change because it makes the RO-group oxygen a poorer donor. So as the R group becomes more electron-withdrawing (ROH a stronger acid) it becomes progressively more likely that ring-opening will remain rate determining over the whole pH range. (This is consistent with the general observation of Chiang and Kresge that the difference in the rates of acetal and hemiacetal hydrolysis decreases as $k_H$ for acetal hydrolysis increases.[18]) We conclude that the linear regions of the pH–rate profiles for the hydrolysis of the 2-methoxyoxetane (**12a**) and the trifluoroethoxy derivative (**3b**) at high pH, and the pH–rate profiles of all nine other oxetane acetals measured in this work, represent reactions of the oxetane acetal system (Scheme, step A), rather than cleavage of the derived hemiacetals.

The direction of C–O bond cleavage of oxetane acetals is expected to be reversed when the exocyclic OR group becomes sufficently electron-withdrawing to balance the effect of ring strain, thus defining a notional point of maximum stability for the system. We do not consider that this point has been reached with the present series of compounds. Although our 2-aryloxyoxetanes are hydrolysed more rapidly than the corresponding 2-trifluoroethoxy derivatives (Table), electron-withdrawing substituents on the aromatic ring still slow down the reaction. We can calculate the effect of substitution in the (O)R group in terms of the ρ* parameter, using standard σ* values of 0.0.6 and 0.92 for the methyl, phenyl, and trifluoroethyl

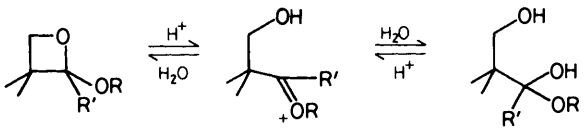
**Table.** Second-order rate constants for the hydrolysis of oxetane acetals in 20% dioxane–water at 39 °C.

| Compound | R,R′ | $k_H$/dm$^3$ mol$^{-1}$ s$^{-1}$ |
|---|---|---|
| **(3a)**[a] | H, Me | $2.24 \times 10^5$ |
| **(3b)** | H, $CH_2CF_3$ | $2.28 \pm 0.21 \times 10^2$ |
| **(10b)** | Ph, $CH_2CF_3$ | $4.51 \pm 0.89$ |
| **(12a)** | 4-$ClC_6H_4$, $CH_3$ | $4.85 \pm 0.48 \times 10^3$ |
| **(12b)** | 4-$ClC_6H_4$,$CH_2CF_3$ | $0.91 \pm 0.15$ |
| **(12c)** | 4-$ClC_6H_4$,$CH_2C_3F_7$ | $7.4 \pm 2.1 \times 10^{-2}$ |
| **(12d)** | 4-$ClC_6H_4$,$C_6H_5$ | $7.51 \pm 1.09$ |
| **(12e)** | 4-$ClC_6H_4$,4-Me-$C_6H_4$ | $10.37 \pm 2.17$ |
| **(13b)** | 4-$MeOC_6H_4$,$CH_2CF_3$ | $14.5 \pm 1.9$ |
| **(14b)** | 4-$NO_2C_6H_4$,$CH_2CF_3$ | $9.5 \pm 2.2 \times 10^{-2}$ |
| **(14e)** | 4-$NO_2C_6H_4$,4-Me-$C_6H_4$ | $1.34 \pm 0.32$ |
| **(14f)** | 4-$NO_2C_6H_4$,3-F-$C_6H_4$ | $0.15 \pm 0.02$ |

[a] Data from Atkinson and Bruice,[2] at 30 °C in 10% dioxane.

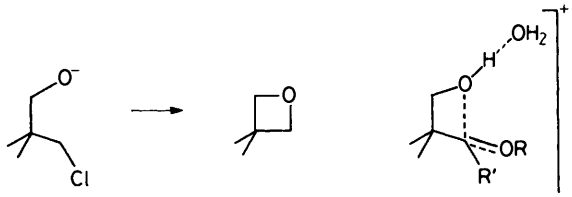
groups, respectively,[19] and obtain the large value of $\rho^* = -4.2$, consistent with substantial build-up of charge on the exocyclic oxygen in the transition state.

There remains one ambiguity in the identification of the RDS of the overall reaction. The formation of the hemiacetal is itself probably a two-step process, by way of the oxocarbocation (**17**), and either the formation or the hydration of (**17**) could be rate determining. The kinetic parameters are likely to be similar for




(**6**) (**17**) (**15**)

the two cases, involving addition to C=OR$^+$ of either the neighbouring OH group or of the OH group of water, so experiment is unlikely to give a clear answer. The advantage of intramolecularity is small when the reaction involves the formation of a strained four-membered ring: an effective molarity (EM)[20] of only 8 mol dm$^{-3}$ has been estimated for the cyclisation of (**18**). Solvent water—45 mol dm$^{-3}$ in 20% dioxane—might therefore react faster in any case. But there are also stereoelectronic problems associated with the alignment of the reacting orbitals in the 4-*exo-trig* cyclisation of (**17**): specifically, at its closest approach [see (**19**)] the nucleophilic OH oxygen is restricted to a trajectory 60° off line with respect to the C=O$^+$R bond. This is not a problem for the 4-*exo-tet* reaction of (**18**), where the C–Cl bond lies in the plane defined by the developing oxetane ring. It seems most likely therefore that the hydration of (**17**), which is subject to no geometrical restrictions, will be faster than recyclisation, so that the rate-determining step of the overall reaction is the opening of the oxetane ring.




(**18**) (**19**)

*Structure and Reactivity.*—The rate determing transition state for the acid-catalysed hydrolysis of oxetane acetals (**19**) has unit positive charge, most of it distributed unevenly over the three oxygen atoms, most probably in the order RO > HO > $H_2O$. Although we cannot detect buffer catalysis in any of our reactions, the data are not accurate enough to exclude general acid catalysis if the Brønsted exponent $\alpha > 0.8$; and even in the extreme case of classical specific acid catalysis the OH group will at least be hydrogen-bonded to solvent water. Most charge undoubtedly resides on the 'donor', RO, oxygen, as indicated by the large $\rho^*$ value of −4.2, quoted above, and a significant amount must remain on the ring oxygen, since a very late transition state is not likely for a reaction in which ring strain is relieved, nor consistent with the stabilising effects of electron-withdrawing substituents observed by other workers.[6–8]

Two unexpected observations probably result from steric crowding. The introduction of the 2-aryl substituent stabilises the oxetane acetal towards hydrolysis [(**10b**) is hydrolysed 50 times more slowly than (**3b**)] even though an aryl group at the pro-acyl centre usually promotes acetal hydrolysis. (Benzaldehyde diethyl acetal, for example, is hydrolysed $10^6$ times faster than the formaldehyde derivative at the same pH). Similar effects have been observed before, most notably on the hydrolysis of oxirane acetals[21] and on the hydrolysis of orthoesters,[22] and convincingly ascribed in the latter case to steric hindrance of resonance. A similar explanation accounts satisfactorily for our own observation. In the transition state (**19**) for ring-opening, stabilisation of the developing positive charge by π-overlap with the 2-aryl group requires the aromatic ring (R′) to be perpendicular to the breaking C–O bond. This conformation is unfavourable because it brings an *ortho* hydrogen atom into Van der Waals contact with one of the two 3-methyl groups of the oxetane ring. In the compromise conformation presumably adopted, the 2-aryl group must act primarily as a σ-acceptor rather than a π-donor, and thus slows the reaction. Consistent with this explanation, the effects of substitution in the 2-aryl ring are in the expected direction (Hammett $\rho = -2.1$), but smaller than typical values for the hydrolysis of acetals of aromatic ketones (compare $\rho = -4.0$ for the hydrolysis of the ethylene acetals of substituted acetophenones in 50% dioxane at 30 °C[22]).

An alternative explanation of the low ρ value, in terms of an earlier transition state for the reaction of the oxetane, cannot offer more than a partial explanation because the inductive effect of the remaining substituent [$\rho^*$ for R in (**12a,b**, and **d**) = −4.2] is large and normal. In fact steric inhibition of resonance appears to affect this group also, since the rates of hydrolysis of this series of compounds (**12**) clearly do not follow the p$K_a$ values of the corresponding alcohols and phenols, ROH; the two phenol acetals (**12d,e**) being hydrolysed faster than the two fluoroalkyl derivatives (**12b,c**) even though the phenols are stronger acids. Within each series (alcohol and phenol acetals) rates do follow the p$K_a$ value. Once again the probable explanation is that the (O)Ar ring in the transition state for the hydrolysis of the phenol acetals (**12d,e**) cannot rotate into the plane defined by the developing C=O$^+$ system without severe serious interactions with either a 3-methyl group or the 2-aryl group, and the oxygen atom of a 2-aryloxy compound thus acts as a better π-donor than if it were fully conjugated with the aromatic ring.

## Conclusions

The introduction of electron-withdrawing substituents into the oxetane structure clearly has the expected stabilising effect. Substituting trifluoroethoxy for the methoxy group of the aldehyde acetal system (**3**) results in a kinetic stabilisation of $10^3$, uncorrected for the different conditions of the kinetic measurements. A more accurate estimate of the effect of the same substitution is available in the 2-(4-chlorophenyl) series

(**12**), where the trifluoroethoxy derivative is 5000 times less reactive. Our most stable oxetane acetal is the $OCH_2C_3F_7$ derivative (**12c**), which is hydrolysed $6.55 \times 10^4$ times more slowly than the corresponding OMe compound. A factor of this magnitude applied to $TxA_2$ itself would increase the half-life at pH 7.4 from 30 s to over three weeks.

Thus a $TxA_2$ analogue with two fluorines or a $CF_3$ group at C(13) is predicted to be stable in organic solvents and at high pH, and to be hydrolysed $10^3$–$10^4$ times more slowly than the parent compound in aqueous solution. This compares with the remarkably large $10^8$-fold stabilisation observed by Fried and his co-workers for the ring-difluorinated compound (**7**), which, though it may include a contribution from steric stabilisation (corresponding to the gem-dimethyl effect[19]), must be primarily electronic in origin.

## Experimental

*Synthetic Procedures.*—Infra-red spectra were recorded on a Perkin-Elmer 297, and UV spectra on a UVIKON 810P spectrophotometer. $^1$H NMR spectra were recorded on Varian EM-390 (90 MHz), Bruker WP-80 (80 MHz) and Bruker WM-250 (250 MHz) instruments. Data quoted are for 250 MHz spectra unless indicated otherwise. Mass spectra were recorded on an AEI MS30 spectrometer, and high resolution spectra on an AEI MS 902. Melting points were measured with a Reichert hot-stage apparatus and are uncorrected. Flash column chromatography was performed according to Still *et al.*[23] Analytical TLC used commercial plates coated with Merck Kieselgel 60 $F_{254}$.

3,3-*Dimethyl*-2-(2,2,2-*trifluoroethoxy*)*oxetane* (**3b**).—Trifluoroethanol (7 cm$^3$) was added to a flask fitted with a reflux condenser, containing the 2-tosyloxy aldehyde [(**7**)[9] 760 mg, 2.97 mmol] and KOH (300 mg, 5.4 mmol). The mixture was heated for 4 days at 80 °C, then the trifluoroethanol was removed under reduced pressure. The residue was taken up in $CH_2Cl_2$ (40 cm$^3$), washed with 10% NaOH solution (3 × 30 cm$^3$) and saturated brine (30 cm$^3$), then concentrated. The residue was columned on alumina [activity grade II; eluant light petroleum (b.p. 40–60 °C)–$CHCl_3$(9:1)], to give the title compound as an oil (100 mg, 17%), $R_f$ (1% THF–pentane) 0.42; $\nu_{max}$(film) 1 240 (CF) and 955 cm$^{-1}$ (ring C–O); $\delta_H$($CDCl_3$; 90 MHz) 5.12 (1 H, s, C*H*O$CH_2CF_3$), 4.25 and 4.13 (2 H, AB system, *J* 4.5 Hz, ring $CH_2$), 4.33–3.6 (2 H, m, O$CH_2CF_3$), 1.25 (3 H, s, C*Me*$_A$Me$_B$), and 1.13 (3 H, s, CMe$_A$*Me*$_B$); *m*/*z* 155 (80%, *M* − $CH_2O$), 85 (40, *M* − $CF_3CH_2O$), 55 (75, $C_4H_7$), and 41 (100, $C_3H_5$). The $^1$H NMR spectrum of the reaction mixture indicated a high yield of the title compound (**3b**), and the low isolated yield is attributed to its high volatility.

2-(4-*Chlorophenyl*)-2-*methoxy*-3,3-*dimethyloxetane* (**12a**).—(Adapted from the method of Temnikova and Venediktova.[24]) Methanol (4 cm$^3$) was added to a flask fitted with a reflux–condenser, containing the 3-tosyloxy ketone (**9**; Ar = 4-chlorophenyl) (450 mg, 1.23 mmol) and KOH (200 mg, 3.6 mmol) under argon. The mixture was heated to 75 °C for 3 h then concentrated under reduced pressure. The residue was taken up in $CH_2Cl_2$ (25 cm$^3$) and washed with 10% KOH solution (3 × 15 cm$^3$) and saturated brine (20 cm$^3$). The organic layer was passed through phase-separating filter paper and concentrated to give a solid. $^1$H NMR spectroscopy showed this to be almost pure title compound. Attempted purification by column chromatography on alumina [activity grade II; eluant light petroleum (b.p. 40–60 °C)–$CHCl_3$ (9:1)] resulted in complete decomposition of the oxetane to the enol ether (**11**; R = 4-chlorophenyl), which was obtained as an oil, $\delta_H$($CDCl_3$; 90 MHz) 7.42–7.20 (4 H, m, ArH), 3.30 (3 H, s, $CH_3O$), 1.81 (3 H, s, C*Me*$_A$Me$_B$), and 1.63 (3 H, s, CMe$_A$*Me*$_B$). The crude title compound was crystallised from pentane to give needles, m.p. 48–49 °C, $R_f$ (EtOAc–pentane 1:8) 0.42, $\nu_{max}$(Nujol mull) 970 cm$^{-1}$ (ring C–O); $\delta_H$($CDCl_3$) 7.33 (4 H, m, ArH), 4.36 and 4.03 (2 H, AB system, *J* 4.9 Hz, ring $CH_2$), 3.03 (3 H, s, $OCH_3$), 1.28 (3 H, s, C*Me*$_A$Me$_B$), and 0.77 (3 H, s, CMe$_A$*Me*$_B$) (Found *M*$^+$ − $CH_3O$, 195.0587. $C_{12}H_{15}ClO_5$ requires *M* − $CH_3O$, 195.0577); *m*/*z* 196 (6%, *M* − $CH_2O$), 195 (4, *M* − $CH_3O$), 185 (48, *M* − $C_3H_5$), and 139 (100, $ClC_6H_4CO$); $\lambda_{max}$(20% dioxane in $H_2O$) 212 nm (ε 4500 dm$^3$ mol$^{-1}$ cm$^{-1}$).

Nine other 2-aryloxetane acetals were made by the same route, from the corresponding 3-tosyloxy ketones and alcohols or phenols in the presence of KOH. Variations in conditions, and details of purification and characterisation are given below.

2-(4-*Chlorophenyl*)-3,3-*dimethyl*-2-(2,2,2-*trifluoroethoxy*)-*oxetane* (**12b**).—Reaction heated at 82 °C for 5 days (2.64 mmol scale). Crude product purified by flash column chromatography on silical gel (eluant EtOAc–hexane 1:4), to give the title compound as an oil (540 mg, 70%), $R_f$(1% THF–pentane) 0.31, $\nu_{max}$(film) 1 604, 1 500 (aromatic), 1 195 (C–F) and 975 cm$^{-1}$ (ring C–O); $\delta_H$($CDCl_3$) 7.36 (4 H, m, ArH), 4.45 and 4.07 (2 H, AB system, *J* 5.0 Hz, ring $CH_2$), 3.81 (1 H, dq, $J_{AB}$ 11.5, $J_{HF}$ 8.9 Hz, C*H*$_A$H$_B$CF$_3$), 3.31 (1 H, dq, $J_{AB}$ 11.5, $J_{HF}$ 8.6 Hz, CH$_A$*H*$_B$CF$_3$), 1.31 (3 H, s, C*Me*$_A$Me$_B$), and 0.83 (3 H, s, CMe$_A$*Me*$_B$) (Found *M*$^+$ − $CH_2O$, 264.0514. $C_{13}H_{14}ClF_3O_2$ requires *M* − $CH_2O$, 264.0529); *m*/*z* 264 (15%, *M* − $CH_2O$), 239 (10, *M* − $C_4H_7$), 195 (4, *M* − $CF_3CH_2O$), 139 (35, $ClC_4H_6CO$), and 56 (100, $C_4H_8$); $\lambda_{max}$(20% dioxane in $H_2O$) 222 nm (ε 320 dm$^3$ mol$^{-1}$ cm$^{-1}$).

2-(4-*Chlorophenyl*)-2-(2,2,3,3,4,4-*heptafluorobutoxy*)-3,3-*dimethyloxetane* (**12c**).—Reaction heated at 95 °C for 30 h (2.49 mmol scale). Crude product purified by flash column chromatography on silica gel (eluant EtOAc–hexane, 1:4), to give the title compound as an oil (630 mg, 65%), $R_f$(EtOAc–hexane 1:10) 0.51, $\nu_{max}$(film) 1 190 (C–F) and 970 cm$^{-1}$ (ring C–O). $\delta_H$($CDCl_3$) 7.36 (4 H, m, ArH), 4.45 and 4.07 (2 H, AB system, *J* 4.9 Hz, ring $CH_2$), 3.94 (1 H, dt, $J_{AB}$ 11.9, $J_{HF}$ 11.0 Hz, C*H*$_A$H$_B$CF$_2$), 3.37 (1 H, q, $J_{AB}$ 11.9, $J_{HF}$ 11.9 Hz, CH$_A$*H*$_B$CF$_3$), 1.29 (3 H, s, C*Me*$_A$Me$_B$), and 0.83 (3 H, s, CMe$_A$*Me*$_B$) (Found: *M*$^+$ − $CH_2O$, 364.0430. $C_{15}H_{14}ClF_7O_2$ requires *M* − $CH_2O$, 364.0460); *m*/*z* 364 (2%, *M* − $CH_2O$), 339 (3, *M* − $C_4H_7$), 195 (5 *M* − $C_3F_7CH_2O$), 139 (20, $ClC_6H_4CO$), and 86 (100); $\lambda_{max}$(20% dioxane in $H_2O$) 228 nm (ε 310 dm$^2$ mol$^{-1}$ cm$^{-1}$).

2-(4-*Chlorophenyl*)-3,3-*dimethyl*-2-*phenoxyoxetane* (**12d**).—This compound had m.p. 76–78 °C (lit.,[10] 78 °C).

2-(4-*Chlorophenyl*)-3,3-*dimethyl*-2-(4-*methylphenoxy*)*oxetane* (**12e**).— Reaction heated at 80 °C for 48 h (2.9 mmol scale). Crude product purified by flash column chromatography on alumina, activity grade II [eluant light petroleum (b.p. 40–60 °C) –$CHCl_3$ (9:1)], to give the enol ether (**11**; R = 4-methylphenyl, Ar = 4-chlorophenyl) as an oil, (240 mg, 30%) $\delta_H$($CDCl_3$) 7.30–6.70 (8 H, m, ArH), 2.37 (3 H, s, C*H*$_3$C$_6$H$_4$), 1.83 (3 H, s, C*Me*$_A$Me$_B$), and 1.77 (3 H, s, CMe$_A$*Me*$_B$) and the title compound (85 mg, 10%) as a solid. Recrystallisation from hexane gave needles, m.p. 66–69 °C; $R_f$ (1% THF–pentane) 0.31; $\nu_{max}$(Nujol mull) 970 cm$^{-1}$ (ring C–O); $\delta_H$($CDCl_3$) 7.37 and 7.26 (4 H, AB system, *J* 8.6 Hz, $ClC_6H_4$) 6.86 and 6.73 (4 H, AB system *J* 8.6 Hz, $CH_3C_6H_4$), 4.53 and 4.15 (2 H, AB system *J* 5.0 Hz, ring $CH_2$), 2.16 (3 H, s, C*H*$_3$C$_6$H$_4$), 1.47 (3 H, s, C*Me*$_A$Me$_B$), and 0.82 (3 H, s, CMe$_A$*Me*$_B$) (Found *M*$^+$, 302.1084. $C_{18}H_{19}ClO_2$ requires *M*, 302.1073); *m*/*z* 302 (4%, *M*$^+$), 272 (12, *M* − $CH_2O$), 195 (100, *M* − $CH_3C_6H_4O$), 139 (65, $ClC_6H_4CO$), and 111 (20, $ClC_6H_4$); $\lambda_{max}$(20% dioxane in $H_2O$) 230 nm (ε 1 050 dm$^{-3}$ mol$^{-1}$ cm$^{-1}$).

3,3-*Dimethyl*-2-*phenyl*-2-(2,2,2-*trifluoroethoxy*)*oxetane* (**10b**).—Reaction heated at 85–86 °C for 48 h (1.2 mmol scale). Crude product purified by flash column chromatography on silical gel (eluant EtOAc–hexane, 1 : 4), to give the title compound as an oil (196 mg, 63%). $R_f$ (1% THF–pentane) 0.42; $\nu_{max}$(film) 1 160 (C–F) and 965 $cm^{-1}$ (ring C–O); $\delta_H(CDCl_3)$ 7.38 (5 H, m, Ph), 4.46 and 4.08 (2 H, AB system *J* 4.9 Hz, ring $CH_2$), 3.81 (1 H, dq, $J_{AB}$ 11.9, $J_{HF}$ 8.9 Hz, $CH_AH_BCF_3$), 3.33 (1 H, dq, $J_{AB}$ 11.9, $J_{HF}$ 8.6 Hz, $CH_AH_BCF_3$), 1.32 (3 H, s, $CMe_AMe_B$), and 0.83 (3 H, s, $CMe_AMe_B$) (Found $M^+ - CH_2O$, 230.0910. $C_{13}H_{15}F_3O_2$ requires $M - CH_2O$, 230.0918); *m*/*z* 230 (65%, $M - CH_2O$), 215 (30), 205 (85, $M - C_4H_7$), 161 (30, $M - CF_3CH_2O$), 105 (90, PhCO), and 56 (100, $C_4H_8$); $\lambda_{max}$(20% dioxane in $H_2O$) 213 nm (ε 5 800 $dm^{-3}$ $mol^{-1}$ $cm^{-1}$).

2-(4-*Methoxyphenyl*)-3,3-*dimethyl*-2-(2,2,-*trifluoroethoxy*)-*oxetane* (**13b**).—Reaction heated at 90 °C for 20 h (1.22 mmol scale). Crude product purified by flash column chromatography on silical gel (eluant EtOAc–hexane, 1:4), to give the title compound as a solid (300 mg, 85%). Recrystallisation from pentane gave needles, m.p. 31–32 °C, $R_f$ (EtOAc–hexane 1:8) 0.27; $\nu_{max}$(Nujol mull) 1 600 (aromatic ring), 1 160 (C–F) and 970 $cm^{-1}$ (ring C–O); $\delta_H(CDCl_3)$ 7.31 and 6.90 (4 H, AB system, *J* 8.5 Hz, ArH), 4.44 and 4.05 (2 H, AB system *J* 4.9 Hz, ring $CH_2$), 3.82 (3 H, s, $CH_3$), 3.79 (1 H, dq, $J_{AB}$ 11.6, $J_{HF}$ 9.0 Hz, $CH_AMe_BCF_3$), 3.37 (1 H, dq, $J_{AB}$ 11.6, $J_{HF}$ 8.7 Hz, $CH_AH_BCF_3$), 1.30 (3 H, s, $CMe_AMe_B$), and 0.83 (3 H, s, $CMe_AMe_B$) (Found $M^+ - CH_2O$, 260.1040. $C_{14}H_{17}F_3O_3$ requires $M - CH_2O$, 260.1024); *m*/*z* 260 (22%, $M - CH_2O$), 234 (75, $M - C_4H_8$), 191 (5, $M - CF_3CH_2O$), and 135 (100, $CH_3OC_6H_4CO$); $\lambda_{max}$(20% dioxane in $H_2O$) 228 and 260 nm (ε 11 500 and 2 100 $dm^{-3}$ $mol^{-1}$ $cm^{-1}$).

3,3-*Dimethyl*-2-(4-*nitrophenyl*)-2-(2,2,2-*trifluoroethoxy*)-*oxetane* (**14b**).—Reaction heated at 85 °C for 20 h (0.27 mmol scale). Crude product purified by flash column chromatography on silica gel (eluant EtOAc–hexane, 1:4), to give the title compound as a solid (48 mg, 60%). Recrystallisation from pentane gave pale yellow prisms, m.p. 66–68 °C (Found: C, 50.7; H, 4.6; N, 4.6. $C_{13}H_{14}F_3NO_4$ requires, C, 51.1; H, 4.60; N, 4.6%); $R_f$ (EtOAc–hexane 1:8) 0.27; $\nu_{max}$(Nujol mull) 1 510 and 1 340 ($NO_2$), 1 180 (C–F) and 970 $cm^{-1}$ (ring C–O); $\delta_H(CDCl_3)$ 8.25 and 7.60 (4 H, AB system, *J* 9.0 Hz, ArH), 4.50 and 4.13 (2 H, AB system, *J* 5.0 Hz, ring $CH_2$), 3.87 (1 H, dq, $J_{AB}$ 11.3, $J_{HF}$ 8.7 Hz, $CH_AH_BCF_3$), 3.28 (1 H, dq, $J_{AB}$ 11.3, $J_{HF}$ 8.5 Hz, $CH_AH_BCF_3$), 1.35 (3 H, s, $CMe_AMe_B$), and 0.83 (3 H, s, $CMe_AMe_B$) (Found $M^+ - CH_2O$, 275.0770. $C_{13}H_{14}F_3NO_4$ requires *M* $CH_2O$, 275.0770); *m*/*z* 275 (10%, $M - CH_2O$), 206 (4, $M - CF_3CH_2O$), 150 (12, $NO_2C_6H_4CO$), and 56 (100, $C_4H_8$); $\lambda_{max}$(20% dioxane in $H_2O$) 270 nm (ε 10 600 $dm^{-3}$ $mol^{-1}$ $cm^{-1}$).

2-(3-*Fluorophenoxy*)-3,3-*dimethyl*-2-(-4-*nitrophenyl*)*oxetane* (**14f**).—Reaction heated at 84 °C for 48 h (0.29 mmol scale). Crude product purified by flash column chromatography on alumina (activity grade II, eluant $CHCl_3$–hexane, 1:8), to give the title compound as a pale yellow crystalline solid (19 mg, 21%). Recrystallisation from ether–pentane gave pale yellow plates, m.p. 81–85 °C (decomp.), $R_f$ (EtOAc–hexane 1:8) 0.24; $\nu_{max}$ (Nujol mull) 1 520 and 1 350 ($NO_2$) and 970 $cm^{-1}$ (ring C–O); $\delta_H(CDCl_3)$ 8.18 and 7.62 (4 H, AB system, *J* 8.0 Hz, $NO_2C_6H_4$), 7.05–6.54 (4 H, m, $FC_6H_4$), 4.60 and 4.22 (2 H, AB system *J* 5.1 Hz, ring $CH_2$), 1.51 (3 H, s, $CMe_AMe_B$), and 0.84 (3 H, s, $CMe_AMe_B$) (Found $M^+ - CH_2O$, 287.0967. $C_{17}H_{16}FNO_4$ requires $M - CH_2O$, 287.0958); *m*/*z* 287 (8%, $M - CH_2O$), 206 (100, $M - FC_6H_4O$), and 150 (85, $NO_2C_6H_4CO$); $\lambda_{max}$(20% dioxane in $H_2O$) 271 nm (ε 10 300 $dm^{-3}$ $mol^{-1}$ $cm^{-1}$).

3,3-*Dimethyl*-2-(4-*methylphenoxy*)-2-(-4-*nitrophenyl*)*oxetane* (**14e**).—Reaction heated at 86 °C for 48 h (0.20 mmol scale). Crude product purified by flash column chromatography on alumina (activity grade II, eluant $CHCl_3$–hexane, 1:4), to give the title compound as a pale yellow solid (12 mg, 15%). Recrystallisation from hexane gave plates, m.p. 112 °C (decomp.); $R_f$ (EtOAc–hexane, 1:8) 0.28; $\nu_{max}$(Nujol mull) 1 520 and 1 350 ($NO_2$) and 970 $cm^{-1}$ (ring C–O); $\delta_H(CDCl_3)$ 8.15 and 7.62 (4 H, AB system, *J* 9.0 Hz, $NO_2C_6H_4$), 6.86 and 6.73 (4 H, AB system, *J* 8.5 Hz, $CH_3C_6H_4$), 4.58 and 4.19 (2 H, AB system, *J* 5.1 Hz, ring $CH_2$), 2.15 (3 H, s, $CH_3C_6H_4$), 1.51 (3 H, s, $CMe_AMe_B$), and 0.83 (3 H, s, $CMe_AMe_B$) (Found $M^+$ 313.1314. $C_{18}H_{19}NO_4$ requires *M* 313.1314); *m*/*z* 313 (3%, $M^+$), 283 (11, $M - CH_2O$), 257 (4, $M - C_4H_8$), 206 (94, $M - CH_3C_6H_4O$), and 150 (100, $NO_2C_6H_4CO$); $\lambda_{max}$ (20% dioxane in $H_2O$) 274 nm (ε 12 600 $dm^{-3}$ $mol^{-1}$ $cm^{-1}$).

*Kinetic Procedures.*—Dioxane used in making up solutions was stored over sodium and under argon. It was refluxed for at least an hour, then distilled immediately before use. The salts used to maintain the ionic strength (NaCl, KCl, KI, and $NaClO_4$) were all of AR grade: particular care was taken to ensure that $NaClO_4$ was anhydrous. Acetic acid was purified by partial crystallisation at 13 °C and decanting of the remaining liquid. Chloroacetic acid was recrystallised from chloroform, then dried in a desiccator over $P_2O_5$. Quinuclidinone hydrochloride was recrystallised from ethanol–water, then dried under high vacuum. HCl and KOH solutions were made up from concentrated solutions (CONVOL) supplied by BDH. Water was triply distilled from an all-glass apparatus.

Reactions were followed in solution in 20% (v/v) dioxane–water, maintained at constant ionic strength with KCl (except for experiments investigating specific salt effects), in the thermostatted cell compartment of a Zeiss PMQ 3 or Gilford 2600 spectrophotometer, at the wavelength of maximum change of absorbance. [252 nm for (**12a–e**), 240, 257, and 270 nm for (**10b**), (**14b**), and (**13b**), respectively, 288 nm for (**3b**) and 300 nm for (**14e,f**)]. pH values were measured at 39 °C using a Radiometer PHM 82 standard pH meter equipped with a Radiometer GK 2321C combination glass electrode standardised with commercial standard buffer solutions. Reactions were measured as a function of pH in HCl (pH 0.33–3.2), and in chloroacetic acid (pH 2.36–3.78), acetic acid (pH 4.42–5.73), quinuclidinone hydrochloride (pH 6.4 only) and phosphate (pH 6.75–7.7) buffers. Stock solutions [$10^{-2}$ mol $dm^{-3}$, except for (**3b**), 1.25 mol $dm^{-3}$] in dioxane were added to buffer solutions (dilution × 250) to start reactions. Final spectra matched the spectra of authentic samples of 2-hydroxyalkyl aryl ketones (**16**). These reaction products were isolated and characterised by $^1H$ NMR spectroscopy in two cases (**12a**) and (**13b**), by carrying out preparative-scale hydrolysis reactions of (35 mg in 10 $cm^{-3}$ of in 40% THF–water containing 0.2 mol $dm^{-3}$ HCl). No traces of retro-aldol products were detected.

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