

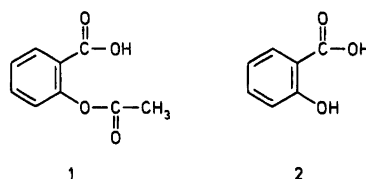
Chemical Feasibility Studies Concerning Potential Prodrugs of Acetylsalicylic Acid

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A rationale is developed for aspirin prodrugs based on non-acidic latentiated derivatives. Knowledge of the gastro-intestinal liabilities and pharmacological profile is required for this approach whereby aspirin is built into a common ortho ester function of the type 2-substituted 2-methyl-4*H*-1,3-benzodioxin-4-one with latentiated carboxyl and acetoxy groups. Twelve compounds of this type, ten substituted with various alkoxy and aryloxy groups and two with arylthio groups, have been isolated and characterized. A new synthetic route, comprising the reaction of 2-acetoxybenzoyl chloride with TMS derivatives of the corresponding alcohols and phenols, has been devised for the preparation of some of the compounds while others were prepared according to known methods. Subsequently, the prodrug candidates have been subjected to non-enzymatic hydrolysis for a first rapid screening *in vitro*. Only 2-*tert*-butoxy-2-methyl-4*H*-1,3-benzodioxin-4-one is observed to act as a true proaspirin, releasing aspirin, under these conditions, but analogous compounds with *tertiary* substituents may display the same behavior, and this chemical approach to aspirin modification may offer a viable rationale for aspirin prodrugs with reduced gastric irritancy or for making "superaspirins".

Aspirin (*O*-acetylsalicylic acid) *1* is widely used for its analgesic, antiinflammatory and antipyretic properties, while its clinical value in the prevention of platelet aggregation is less well-established. Among its disadvantages are the relatively narrow therapeutic margin, *1*'s irritancy towards the gastric mucosa (especially in the



crystalline state), and occasionally hypersensitivity towards *1*.

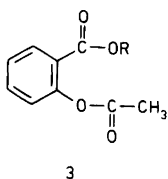
The mode of action of *1* is reasonably well understood though important unresolved problems remain. Administered orally, *1* has a short plasma half-life of 15–20 min., primarily due to its enzymatic hydrolysis (first-pass effect) to salicylic acid *2* whose plasma half-life is longer by about an order of magnitude. The pharmacological profile of *1* is thus determined by the two half-lives mentioned, as well as by the similar, though not identical, pharmacological properties possessed by *1* and *2*. Often in pharmacological discussions the distinction between *1* and *2* (and their anions) is dropped altogether and the all-encompassing term "salicylates" is used. Among clinical practitioners there is a strong consensus that the oral administration of *1* is a valid therapy and could not be substituted by the administration of *2* or precursors of *2* without loss of efficacy.¹⁻³

We felt that it might well be worthwhile to develop non-acidic prodrugs of *1* which probably could eliminate the gastro-intestinal liabilities of *1* while at the same time a substantially improved therapeutic index could be hoped for.⁴ A useful prodrug of *1* could thus either constitute a "superaspirin" or at least reduce the long-term xenobiotic burden of chronic *1* users. Probably a

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well-designed prodrug of *1* would be most beneficial in inflammation therapy while a different series of experimental candidate prodrugs might lead to another prodrug of *1* most useful as an analgesic. Ironically, *1* itself was developed as a prodrug of *2* half a century before the prodrug concept was explicitly presented in its rational, presently accepted context.⁵

It is interesting to note that most of the considerable number of "aspirin prodrugs" which so far have been described in the literature⁶⁻⁹ are basically salicylic acid prodrugs since they release *2* and not *1* upon hydrolysis. However, a few proaspirins of the type *3* have also been described¹⁰⁻¹² (*vide infra*).



Off-hand, one can envisage two levels of sophistication in the latention of the *1* molecule. If the acetoxy group is left intact and only the carboxyl group latented, the rate of hydrolysis of the acetoxy group will set the lowest

limit for the rate at which the prodrug can release *1* unless, of course, the less likely event occurs in which the latented carboxyl group anchimerically retards the hydrolysis of the acetoxy group relative to the rate of hydrolysis of *1*'s acetoxy group. This means that a prodrug of this type will have an even shorter half-life than *1* itself or constitute a prodrug of *2*. Thus, even methyl 2-acetoxybenzoate *3* (R = CH₃), the simplest latented *1* imaginable, is a prosalicylic acid and not a proaspirin.¹³ A number of compounds of type *3* with extremely labile R groups are indeed proaspirins, but only by virtue of a correspondingly short half-life^{10,11} (*vide supra*).

This strongly suggests that a useful prodrug of *1* would need to be comprised of both a latented carboxyl and acetoxy group, the most obvious possibility being the incorporation of both latent groups into a common ortho ester function. A straightforward choice would be system *4* where the substituent R ideally should

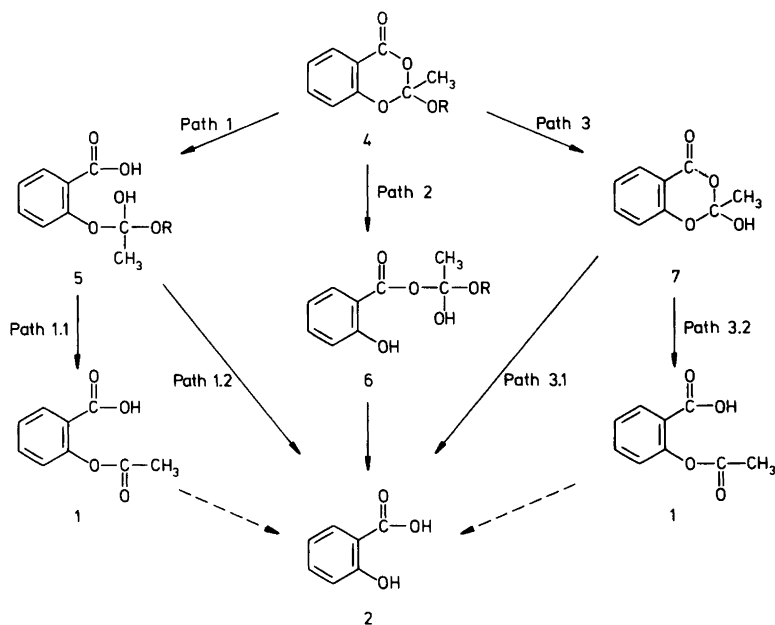
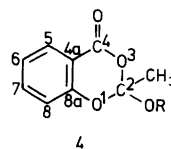
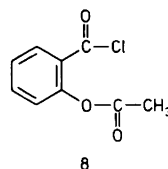


Fig. 1. Model pathways for hydrolytic breakdown of *4*(13) to *1* and *2* (ortho ester hydrolysis).

be chosen so as to ensure a proper balance of hydrophilic/lipophilic properties and an appropriate rate of hydrolysis of **4**. However, since the ortho ester carbon atom is linked to three non-equivalent oxygen atoms the hydrolysis of **4** can, in principle, involve the cleavage of any of these three carbon–oxygen bonds in its first step (Fig. 1).

Thus, only path 1 followed by path 1.1 and path 3 followed by path 3.2 are productive for the hydrolytic formation of **1** from **4** while the remaining pathways yield **2** only. Unless a serendipitous choice of R can be made, useful prodrug candidates **4** should be tailored with a built-in stereoelectronic control of the hydrolytic pathways¹⁴ in order to make them true **1** precursors. The theory of ortho ester hydrolysis is a well-developed subject,¹⁵ so that the desired stereoelectronic control ought to be achievable, but on the other hand it might be inherently difficult to optimize the choice of R with regard to three, probably unrelated, properties of **4**. In order to mimic the *in vivo* fate of **4**, separate hydrolysis experiments in gastric juice and in plasma would be required. Interestingly, the literature does not appear to contain any data concerning the hydrolysis of ortho esters in the presence of hydrolytic enzymes. For the sake of simplicity we chose to screen our candidate compounds in the first instance by *in vitro* non-enzymatic hydrolysis.

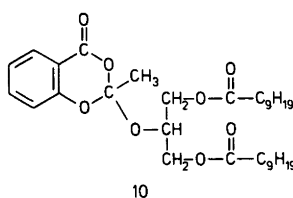
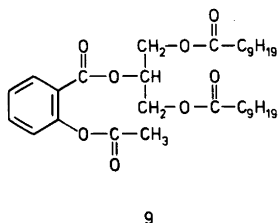
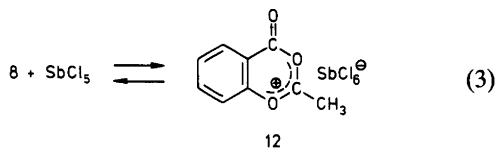
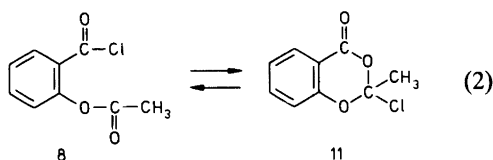
2-Alkoxy(aryloxy)-2-methyl-4H-1,3-benzodioxin-4-ones **4** have, in fact, been prepared by a number of authors for different purposes. R  chardt and Rochlitz¹⁶ prepared a number of **4** from 2-acetoxybenzoyl chloride **8** and alcohols or phenols, but did not investigate their hydrolysis. Paris *et al.* obtained, *inter alia*, the prodrug candidates **9**^{9b} and **10**¹⁷ and characterized them in whole animal studies as roughly equipotent (on a molar basis) with **1** while being essentially devoid of **1**'s ulcerogenic properties. However, Paris *et al.* did not characterize **9** and **10** as



proaspirins or prosalicylic acids by studying their hydrolysis. Similarly, an analogous compound (**4**, R = 2-methoxyphenyl) with claimed anti-inflammatory and antipyretic activity similar to that of **1**, but without gastric side-effects was patented recently.¹⁹

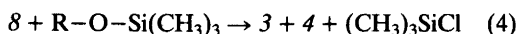
RESULTS AND DISCUSSION

Synthesis. The formation of **3** and/or **4** according to eqn. (1) depends in a complicated manner upon the presence or absence of base, the choice of solvent, and other reaction conditions.^{16–18} The known syntheses of **4** must be said to be based on trial and error, and our own experience has been similar. While there is no direct evidence of an equilibrium (2) in neat 2-acetoxybenzoyl chloride (according to a ¹³C NMR study²⁰ no **11** is present), R  chardt and Brinkmann²¹ found **8** to form **12** according to eqn. (3):

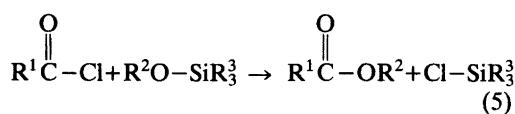


So far, however, *12* has not successfully been used as a starting material for the synthesis of *4*.²²

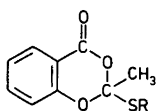
We did devise a new synthetic pathway leading to *4*, *i.e.* eqn. (4):



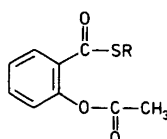
While the preparation of esters from acid chlorides and alkoxy silanes according to eqn. (5) is a known procedure,²³ we are not aware of any previous ortho ester syntheses *via* the TMS route. In spite of the mild conditions of this synthetic approach, it failed to bring about a dramatic improvement in selectivity or predictability with regard to the 4:3 ratio.



The ortho thioesters *13*, related to the thioesters *14* as *4* are to *3*, are also obvious candidates as potential proaspirins. Examples of *13* and *14*

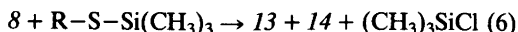


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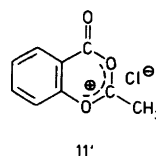
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are known from the literature¹⁶ and we prepared *13* according to standard procedures¹⁶ and also according to (6), patterned after (4).



The potential hydrolytic pathways that can be envisaged for *13* are parallel to what is shown for *4* in Fig. 1 and will not be elaborated further.

The formation of 2-alkoxy(aryloxy)-2-methyl-4*H*-1,3-benzodioxin-4-ones *4*, cyclic isomers of the alkyl (aryl) 2-acetoxybenzoates *3*, by reaction of *8* with alcohols and phenols, respectively, was first reported by Rüchardt and Rochlitz¹⁶ as well as by Fried²⁴ and shown to follow (1). The cyclic isomers *4* are assumed to form in a kinetically controlled reaction proceeding *via* the intermediate 2-methyl-4-oxo-4*H*-1,3-benzodioxin-2-ylum salt *11'*, *3* being the thermodynamically more stable group of products. Analogous ambident reactivity caused by anchimeric assistance of an



11'

acetoxy group has also been observed with α -acetoxy acid chlorides.²⁵

Table 1. Preparation of 4/3.

4/3	Substituent R	Synthetic method		Total yield/%		4:3 ratio	
		I ^a	II ^a	I ^b	II ^b	I ^c	II ^c
<i>a</i>	<i>tert</i> -butyl	+	—	72	—	6:1	—
<i>b</i>	<i>neo</i> -pentyl	—	+	—	90	—	9:1
<i>c</i>	4-chlorophenyl	+	+	78	95	4:1	5:1
<i>d</i>	2-nitrophenyl	+	—	<5	—	<i>n.d.</i>	—
<i>e</i>	phenyl	+	+	85	95	6:1	4:1
<i>f</i>	benzyl	—	+	—	90	—	8:1
<i>g</i>	2-methyloxycarbonylphenyl	+	—	<5	—	<i>n.d.</i>	—
<i>h</i>	2-[(3-pyridinylcarbonyl)amino]ethyl	+	—	78	—	9:1	—
<i>i</i>	(±)-1-phenylethyl	—	+	—	95	—	1:1
<i>j</i>	2-naphthyl	+	—	62	—	6:1	—
<i>k</i>	(-)-bornyl	—	+	—	90	—	3:1
<i>l</i>	(±)-menthyl	—	+	—	90	—	3:1

^a See Experimental for details. ^b Based on crude product. ^c Determined from ¹H NMR spectra of the crude product. *n.d.* not determined.

Table 2. Preparation of 13/14.

13/14	Substituent	Synthetic method		Total yield/%		13:14 ratio	
	R	I ^a	II ^a	I ^b	II ^b	I ^c	II ^c
<i>a</i>	<i>tert</i> -butyl	+	—	90	—	14 <i>a</i> only	
<i>b</i>	4-chlorophenyl	+	—	73	—	3:1	—
<i>c</i>	phenyl	—	+	—	95	—	14 <i>c</i> only
<i>d</i>	3-methylphenyl	+	—	54	—	1:1	—

^a See Experimental for details. ^b Based on crude product. ^c Determined from ¹H NMR spectra of the crude product.

Table 3. Physical properties of 2-alkoxy(aryloxy)-2-methyl-4*H*-1,3-benzodioxin-4-ones 4.

4	Formula	B.p./°C ^e (m.p./°C)	¹ H NMR ^a	¹³ C NMR ^a	IR	UV ^d	Analysis (Reference)
			δ _{CH₃} /ppm	δ _{C(2)} /ppm	ν _{C=O} /cm ⁻¹	λ(log ε)/nm	
<i>a</i>	C ₁₀ H ₁₆ O ₄	100–110	1.80	112.7	1750 ^b	301(3.40)	(16)
<i>b</i>	C ₁₁ H ₁₈ O ₄	80–90	1.85	113.4	1745 ^b	298(3.74)	C, H
<i>c</i>	C ₁₅ H ₁₁ ClO ₄	170–180	1.87	113.2	1755 ^b	300(3.58)	(16)
<i>e</i>	C ₁₅ H ₁₂ O ₄	150–160	1.86	113.3	1750 ^b	300(3.26)	(16)
<i>f</i>	C ₁₆ H ₁₄ O ₄	110–120 (49–50)	1.91	113.0	1735 ^c	300(3.43)	(16)
<i>h</i>	C ₁₇ H ₁₆ N ₂ O ₅	(98–99)	1.82	—	1745 ^c	300(3.38)	Found: C 60.23; H 5.01; N 8.45 Calc.: C 62.19; H 5.01; N 8.53
<i>j</i>	C ₁₉ H ₁₄ O ₄	(88.5–89.5)	1.97	113.6	1745 ^c	300(3.72)	(16)
<i>k</i>	C ₁₉ H ₂₄ O ₄	130–140	1.83	113.8	—	—	Found: C 70.28; H 7.81 Calc.: C 72.13; H 7.65
<i>l</i>	C ₁₉ H ₂₆ O ₄	130–140	1.80	112.7	1740 ^b	304(3.57)	Found: C 71.58; H 8.85 Calc.: C 71.67; H 8.23

^a In CDCl₃. ^b As film. ^c In KBr. ^d In 6:1 (v:v) aqueous phosphate buffer–dioxane solution at 37.0 °C and pH 7.40. ^e At 0.01 torr.

With the exacting demands on the substituent R of a true proaspirin 4 or 13 in mind, our present synthetic study summarized in Tables 1–4 was devised as a somewhat crude pilot study and not as an optimization program. In order to obtain as much mechanistic information as possible, we did not restrict ourselves to latentiated entities releasing pharmaceutically acceptable alcohols, phenols or thiols. However, our series does include pharmaceutically acceptable examples such as 4*h*, 4*k* and 4*l*. Another important

consideration is the molecular weight of 4 or 13. If an ortho ester 4 or 13 contains so elaborate a group R that its maximum release of 1 amounts to only a small fraction of the molecular weight of 4 or 13, any therapeutic advantage achieved by the latentiation might be more than offset by the increase in equivalent weight (based on 1 released) of 4 or 13. For this reason we expressly restricted ourselves to low-to-moderate molecular-weight groups R.

When the cyclic aspirin derivatives 4 and 13

Table 4. Physical properties of 2-(4-chlorophenylthio)-2-methyl-4*H*-1,3-benzodioxin-4-one 13*b*.

13	Formula	M.p./°C	¹ H NMR ^a	¹³ C NMR ^a	IR ^b	UV ^c	Analysis
			δ_{CH_3} /ppm	$\delta_{\text{C}(2)}$ /ppm	$\nu_{\text{C}=\text{O}}$ /cm ⁻¹	$\lambda(\log \epsilon)$ /nm	
<i>b</i>	C ₁₅ H ₁₁ ClO ₃ S	60–61	2.00	112.4	1745	304(3.30)	C, H, Cl, S

^a In CDCl₃. ^b In KBr. ^c In 6:1 (v:v) aqueous phosphate buffer–dioxane solution at 37.0 °C and pH 7.40.

were first described,¹⁶ ¹H NMR and IR data were used to distinguish them from their acyclic isomers 3 and 14, respectively. In our experimental series we could confirm and extend these assignments with additional support from ¹³C NMR and UV data. For some of the ¹³C NMR signals an upfield shift similar to what has recently been reported for the analogous compounds 9 and 10¹⁷ is observed. The UV absorption of 4 and 13 resembles that of 2²⁶ and is found at 300–305 nm, while the esters 3 and 14 with a weak absorption at 275–280 nm resemble 1.²⁶ No UV data of the ortho esters 4 and 13 have previously been reported in the literature.

Unfortunately, the MS fragmentation patterns of 3(14) and 4(13) are too similar to allow safe structural conclusions to be drawn. In order to rule out the remote possibility that the compounds assigned the structures 4 and 13 are in fact 3 and 14, respectively, and *vice versa*, an X-ray structure investigation of 4*j* was initiated which confirmed the spectroscopic structure assignment.²⁷ Thus, an absolute degree of reliability has now been achieved for the spectroscopic identification of 3/14 and 4/13.

Hydrolysis. The hydrolytic breakdown of the isolated cyclic aspirin derivatives 4(13) in water–dioxane mixtures (37.0 °C, pH 7.40) was studied spectrophotometrically by monitoring the decrease in ultraviolet absorbance *versus* time. With 4*a* this was best done at 300 nm and with the other compounds at 240–250 nm, because the products, 1 or 2, respectively, (Fig. 1), absorb only weakly at these wavelengths²⁶ (Fig. 2).

Table 5 gives the obtained pseudo-first-order rate constants and in Fig. 2 typical spectra showing different stages of the breakdown to 1 (4*a*) and 2 (4*f*) can be seen. By comparing the product spectra following completion (10–12 half-lives) with reference spectra of 1 and 2 recorded under identical conditions, the salicylate formed was identified. In principle, the

hydrolytic breakdown of 4(13) may result in productive formation of either 1 or 2, or both (Fig. 1). With simultaneous formation of both salicylates the minor component may go undetected by this method due to overlapping spectra. However, the presence of 2 cannot arise from the hydrolysis of preformed 1 as the rate constant for this reaction is slower by more than an order of

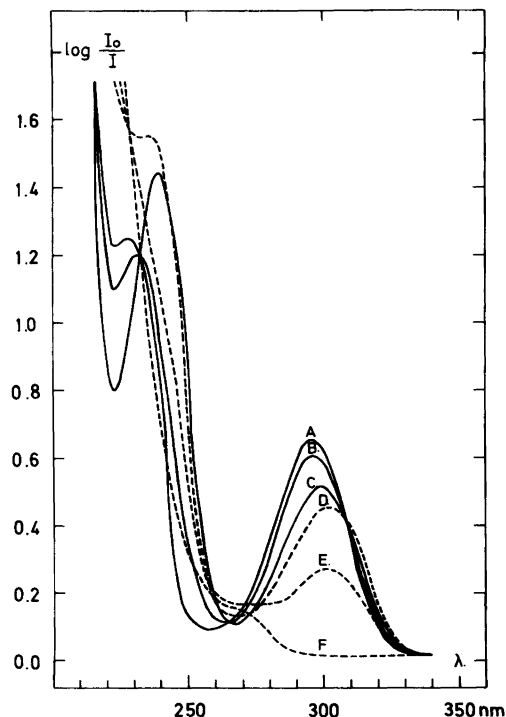


Fig. 2. Ultraviolet spectra of different stages of the hydrolysis of 4*a* in aqueous phosphate buffer–dioxane solution (1:1 (v:v)) and of 4*f* in 6:1 (v:v) solution at pH 7.40 ($\mu = 0.26$) and 37.0 °C. 4*a*: D, spectrum after 1 min; E, after 4 min; F, after 43 min (1). 4*f*: C, spectrum after 1 min; B, after 121 min; A, after 721 min (2).

Table 5. *In vitro* hydrolysis of 2-substituted 2-methyl-4H-1,3-benzodioxin-4-ones. Salicylate product, pseudo first-order rate constants and relative rates in dioxane-aqueous phosphate buffer (pH 7.40 and $\mu = 0.26$) at 37.0 °C.

Compound	Salicylate product	$k_{\text{obs}}/\text{min}^{-1}$ ^{a,d}	Relative rate
1	2	$1.1 \cdot 10^{-3}$ ^b	0.15
4a	1	$1.7(1) \cdot 10^{-1}$ ^c	22
4b	2	$3.4(2) \cdot 10^{-2}$	4.4
4c	2	$1.9(1) \cdot 10^{-2}$	2.4
4e	2	$5.0(3) \cdot 10^{-3}$	0.6
4f	2	$1.01(2) \cdot 10^{-2}$	1.3
4h	2	$7.8(1) \cdot 10^{-3}$	1.0
4j	2	$7.7 \cdot 10^{-3}$	1.0
4k	2	$1.4(1) \cdot 10^{-2}$	1.8
4l	2	$1.08(4) \cdot 10^{-2}$	1.4
13b	2(?)	$1.7(2) \cdot 10^{-3}$	0.2

^a Averages of three or more runs. ^b Cf. with values in Refs. 13 and 26b. ^c In 1:1 (v:v) dioxane-aqueous phosphate buffer solution. ^d In 1:6 (v:v) dioxane-aqueous phosphate buffer solution.

magnitude compared with the rate constants for formation of 2 from most 4. Only in the case of 13b does this remain speculative because the rate constant obtained here is of the same magnitude as for the hydrolysis of 1 (Table 5).

Similarly, to obtain a more detailed mechanistic picture of the hydrolytic breakdown of these compounds, the hydrolysis experiment would have to be complemented with more careful product detection and identification (e.g. HPLC, GLC-MS, etc.) and kinetics measurements (pH rate profiles and isotope effects). However, for a first rapid screening of the prodrug candidates for subsequent and more detailed enzymatic studies these experiments are considered sufficient.

Of the compounds studied, only 4a is observed to form 1 in detectable amounts (*vide supra*) upon hydrolysis while all the other compounds form 2. With 2 formation from different 4 the rate constants obtained are of the same magnitude while the rate constant for the hydrolysis of 4a is higher by more than an order of magnitude, even in a 1:1 (v:v) water-dioxane solution. In a 6:1 solution the reaction is too rapid to be followed by conventional ultraviolet spectrophotometry.

Considering the three-stage mechanism now generally accepted for the hydrolysis of ortho esters¹⁵ and the possible hydrolytic pathways so derived for 4(13) (Fig. 1), the shift in mechanism

observed with 4a may simply be explained by the initial cleavage of a different C-O bond. According to recent studies on hydrolysis of ortho esters and related substrates, several possible routes for hydrolytic breakdown exist. Cyclic ortho esters have been observed to hydrolyze with initial cleavage of the exocyclic C-O bond under stereoelectronic control,^{15,28} whereas in acylals²⁹ and acyl ortho esters³⁰ the acyloxy group is split off in a first rate-determining step. Besides, the structurally related 3-methoxyphthalides are observed to hydrolyze as acetals at low pH values and as esters at higher (neutral-basic) values.³¹

The hydrolysis experiments performed here do not allow detailed mechanistic conclusions to be drawn. Interestingly, however, 4a is the only compound observed definitely to release 1 just as it is the only compound containing a tertiary alkoxy group as substituent. Hence, the *tert*-butyl group may by virtue of its steric or electronic effects be responsible for the shift in mechanism, and even though its relatively short half-life (4 min) probably makes it of no practical value in prodrug formulations, 4a and analogous cyclic aspirin derivatives 4(13) containing tertiary exocyclic substituents should be considered seriously as potential aspirin prodrugs.

EXPERIMENTAL

Kinetics. For measuring the kinetics of the hydrolytic breakdown of the cyclic aspirin derivatives 4 and 13b, a Varian Cary 219 UV-VIS double beam spectrophotometer was used. The apparatus was equipped with a jacketed multiple cell block through which water was circulated from a constant-temperature bath operating at 37.0 ± 0.1 °C and an automatic sample-changing and recording facility. In a typical run 3.0 ml aliquots of prethermostatted buffer solution were placed in 1-cm quartz cells. Reactions were initiated by adding a stock solution (0.5 ml) of the substrate in dioxane (spectral grade), shaking a few seconds, and replacing the cell in the cell block. The stock solutions of substrates were prepared so as to give a final concentration of $1-2 \times 10^{-4}$ M which resulted in maximum absorbances about 2. Reactions were followed to completion and pseudo first-order rate constants were calculated by least-squares analysis as gradients by $\ln|A - A_i| = k_{\text{obs}}t + b$. Experiments with correlation coefficients lower than 0.999 were rejected. For very slow reactions the modified Guggenheim expression

$$\ln|A'_i - A_i| + k_{\text{obs}}t = \text{constant}$$

was used.³²

The buffer solution was purchased from Struers A/S, Copenhagen, Denmark, and adjusted to pH 7.40 at 37.0 °C with $[\text{H}_2\text{PO}_4^-/\text{HPO}_4^{2-}] = 0.2857$ and ionic strength (μ) = 0.26.

Synthesis. Starting materials were all prepared by known methods as follows: 8,¹⁶ *N*-(2-hydroxyethyl)-nicotinamide,³³ *neo*-pentoxytrimethylsilane,³⁴ benzyloxytrimethylsilane,³⁵ (\pm)-1-phenylethoxytrimethylsilane,³⁶ (-)-boryloxytrimethylsilane,³⁷ (\pm)-menthyloxytrimethylsilane,³⁵ phenoxytrimethylsilane³⁸ and 4-chlorophenoxytrimethylsilane.³⁸ I was kindly placed at our disposal by Alfred Benzon A/S, Copenhagen, Denmark.

All solvents used were analytical grades. Elemental analyses were carried out by Elemental Micro-Analysis Ltd., 33 Cambridge Road, Kingston upon Thames, Surrey KT1 3NQ, England.

Method I. Reaction of 8 with alcohols, phenols, and thiols. General procedure. To a solution of 8 in an anhydrous solvent (tetrahydrofuran-acetonitrile) an equimolar solution of alcohol (phenol, thiol) was added over a period of 30 min. The mixture was then stirred under a stream of nitrogen until the evolution of hydrochloric acid had stopped and the starting materials could no longer be detected (TLC, silica gel, dichloro-

methane). The solvent was then evaporated and the crude product was dissolved in chloroform, washed successively with 0.5 N sodium hydroxide and brine and dried over sodium sulfate. After evaporation of solvent the product was purified by *kugelrohr* distillation in the case of oils or by recrystallization in the case of solids.

Method II. Reaction of 8 with trimethylsilylated alcohols, phenols, and thiols. General procedure. A solution of trimethylsilylated alcohol (phenol, thiol) in anhydrous tetrahydrofuran (acetonitrile) was added to an equimolar solution of 8 over a period of 30 min at ambient temperatures. A catalytic amount of triethylamine was added and the mixture refluxed under nitrogen allowing the trimethylchlorosilane to distill off as formed. When starting materials were no longer detectable (TLC) the reaction was stopped and the solvent evaporated. Products were purified by *kugelrohr* distillation.

Detailed descriptions of the methods of preparation for each individual compound are available on request.

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