

# Aspirin Prodrugs: Synthesis and Hydrolysis of 2-Benzyloxy-2-methyl-4*H*-1,3-benzodioxin-4-ones\*

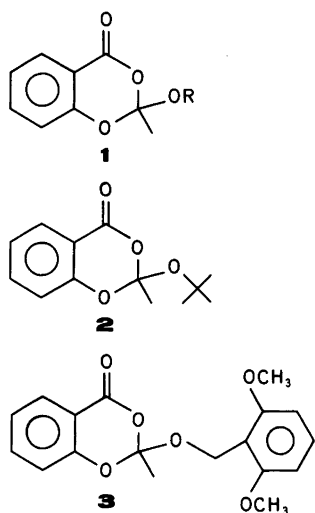
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Ankersen, M. and Senning, A., 1989. Aspirin Prodrugs: Synthesis and Hydrolysis of 2-Benzyloxy-2-methyl-4*H*-1,3-benzodioxin-4-ones. – Acta Chem. Scand. 43: 793–798.

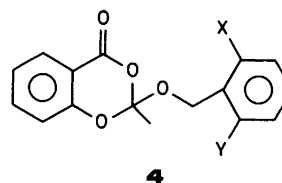
Aspirin is widely used for its analgesic, antiinflammatory and antipyretic properties. Among its disadvantages are the relatively narrow therapeutic margin, its irritancy towards the gastric mucosa, and occasionally patient hypersensitivity towards aspirin. As part of our effort to develop prodrugs without these liabilities eleven new title compounds have been isolated and characterized. These 'superaspirin' candidates were subjected to non-enzymatic hydrolysis for a first rapid screening *in vitro*. Only 2-(2,6-dimethoxybenzyloxy)-2-methyl-4*H*-1,3-benzodioxin-4-one (**4c**) was observed to act as an exclusive aspirin prodrug, while 2-(2-methoxybenzyloxy)-2-methyl-4*H*-1,3-benzodioxin-4-one (**4b**) and 2-(2-ethoxybenzyloxy)-2-methyl-4*H*-1,3-benzodioxin-4-one (**4d**) were shown to release both aspirin **6** and salicylic acid **7**. Subsequently, these three candidates were further characterized by investigation of the pH profile of their hydrolysis rates.

This paper is based on previous efforts to develop prodrugs of aspirin as first described by Hansen and Senning,<sup>1</sup> i.e. the synthesis of compounds with (1) a latent aspirin function protected against transformation to salicylic acid before it reaches the peripheral blood circulation and which by hydrolysis (2) will regenerate aspirin **6**, which then can act with great efficiency before further hydrolysis takes place. Even though a considerable number of compounds of structure **1** have been prepared and examined, only **2** and **3** appear to be hydrolysed *in vitro* to aspirin **6**.<sup>1,2</sup>



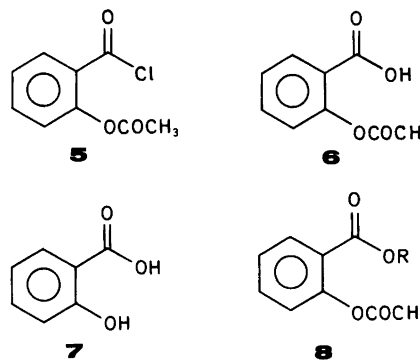
Since **3** is apparently hydrolysed to aspirin<sup>2</sup> we decided to vary the substitution pattern of the benzyl alcohol moiety in a series of **4** to optimize their rates of hydrolysis to aspirin and the corresponding benzyl alcohol.

\*An account of previous work is given in Ankersen, M., Nielsen, K. K. and Senning, A. Acta Chem. Scand. 43 (1989) 213.



Here the synthesis, the spectroscopic properties and the hydrolytic behaviour of **4** will be discussed. Led by previous work<sup>3,4</sup> Röchardt<sup>5</sup> devised a synthesis of ortho esters of acetylsalicylic acid **1** from acetylsalicylic acid chloride **5** and alcohols.

Paris<sup>6</sup> prepared some ortho esters by allowing acetylsalicylic acid **6** and alcohols to react in the presence of a (substituted) acetic acid anhydride. Fried<sup>7</sup> obtained some ortho esters by treating salicylic acid **7** with ethynyl ethers, and Hansen and Senning<sup>1</sup> devised a further synthetic pathway by treating the acid chloride **5** with alkoxysilanes.



The acyclic isomer **8** is often formed together with **1** and the ratio **1:8** in the crude reaction product is notoriously unpredictable.

A large number of additional compounds **1** have been prepared by some of these methods.<sup>6-25</sup>

An attempt to use these compounds as true aspirin prodrugs was first described by Hansen and Senning.<sup>1</sup> In that work the prodrug candidates were subjected to non-enzymatic hydrolysis for a first rapid screening *in vitro* in a water-dioxane solution (6:1), followed by conventional UV spectrophotometry. This procedure is less suitable for a detailed mechanistic investigation. To obtain a more detailed mechanistic picture of the hydrolytic reaction sequence the hydrolyses of **4b**–**4d** were followed in depth with more careful product detection and identification (e.g. HPLC, pH-rate profile).

## Results and discussion

As mentioned already, this study deals only with compounds containing an *o*-substituted benzyl alcohol moiety. Table 1 shows the products which have been prepared.

We selected the substituents to include both electron donors (OCH<sub>3</sub>) and acceptors (NO<sub>2</sub>). Unfortunately, the strongest electron donor possible (O<sup>-</sup>), is incompatible with the chemistry of **4** formation. It was only necessary to use base to prepare **4b**, **4c** and **4d**. All other compounds **4** could be made without the use of bases. In the absence of a unifying rationale, the choice of the best synthetic method for a given compound **4** so far is based on trial and error.

Dialkoxycarbonium ions can react with nucleophiles in two ways depending on the reaction conditions:<sup>26</sup> either in a kinetically controlled reaction to form a saturated 1,1-dialkoxy compound or in a thermodynamically controlled reaction with alkylation of the nucleophile to give a carboxylic acid ester (Fig. 1).<sup>27</sup>

We examined the relation between the ratio **4/8** and the reaction time and reaction temperature. Fig. 2 shows the yield of **4** in relation to the reaction temperature after 3 h for **4b**, **4i** and **4k**. The reaction conditions for **4b** are described in 'General synthesis I' and **4i** and **4k** are described in 'General synthesis II' in the Experimental section. As

Table 1. Preparation of **4** and **8**.

	Substituents (X,Y)	Ratio <b>4/8</b> <sup>d</sup> Method <sup>a</sup>			Purity <sup>b</sup> of <b>4</b> (%)	Yield of <b>4</b> (%)
		I	II	III		
<b>a</b>	H,H	1:2	3:7	2:1	80	30
<b>b</b>	CH <sub>3</sub> O,H	1:1	<b>8b</b> <sup>c</sup>	1:4	100	15
<b>c</b>	CH <sub>3</sub> O,CH <sub>3</sub> O	1:1	<b>8c</b> <sup>c</sup>	1:4	100	50
<b>d</b>	CH <sub>3</sub> CH <sub>2</sub> O,H	1:1	<b>8d</b> <sup>c</sup>	–	95	20
<b>e</b>	CH <sub>3</sub> ,H	2:5	7:1	–	90	60
<b>f</b>	F,H	2:3	9:1	–	100	80
<b>g</b>	F,F	1:1	5:1	–	95	80
<b>h</b>	Cl,H	2:3	3:2	1:4	100	55
<b>i</b>	Cl,Cl	1:4	11:1	–	100	80
<b>j</b>	CF <sub>3</sub> ,H	1:4	5:1	–	90	70
<b>k</b>	NO <sub>2</sub> ,H	1:4	7:2	–	100	75

<sup>a</sup>Method I is with triethylamine as the base. Method II is without the use of base. Method III is the reaction with trifluoroacetic acid anhydride. <sup>b</sup>The purity of **4** after recrystallization based on <sup>13</sup>C NMR and <sup>1</sup>H NMR spectroscopy; 100 % means that no other products are detectable. <sup>c</sup>No **4** was detectable. <sup>d</sup>The values are the ratio between **4** and **8** (**4/8**) based on <sup>1</sup>H NMR spectroscopy of the crude product.

can be seen it shows a weak, approximately linear dependence. This means that the higher the temperature, the higher the yield of **4**. This is not in agreement with the literature concerning simple ortho esters, in which increasing temperature and/or longer reaction time favour the thermodynamically controlled route 2 of Fig. 1 to give **8**.<sup>27</sup>

Fig. 3 shows the yield of the ortho esters of the same three compounds as a function of the reaction time at 50 °C under the same conditions as above. We see that the best reaction time is 3–5 h, but a longer reaction time does not lower the yield much. Also this does not agree with the standard hypothesis.<sup>27</sup>

Tables 2 and 3 show the physical data of our new compounds. The most characteristic difference between isomers **4** and **8** is that the normal ester has two carbonyl

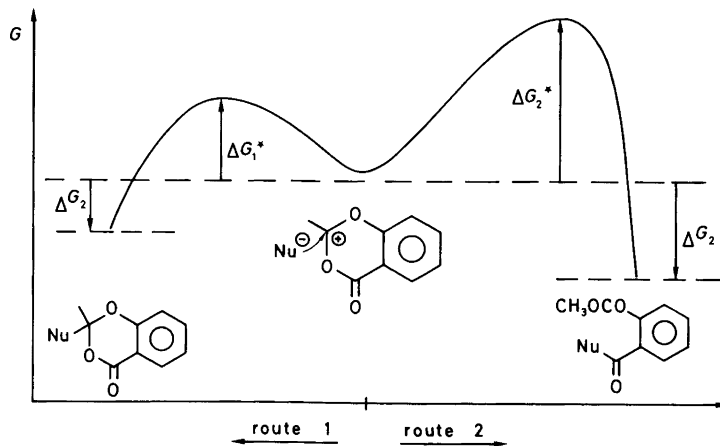


Fig. 1. Nucleophilic reaction with a dialkoxycarbonium ion.

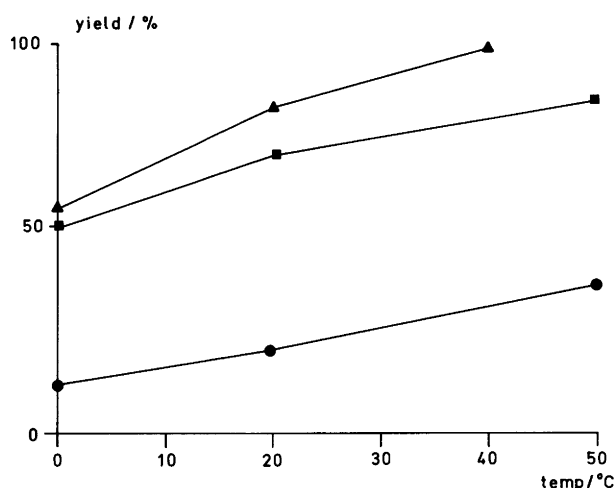


Fig. 2. Yield of ortho ester after 3 h as a function of the reaction temperature for 4b (●), 4i (■) and 4k (▲).

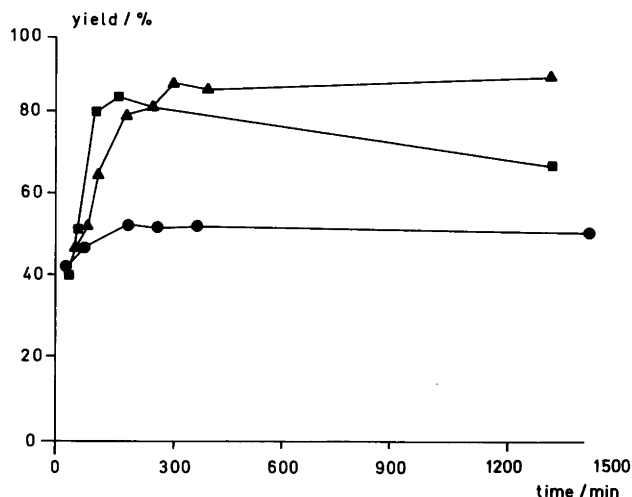


Fig. 3. Yield of ortho ester as a function of the reaction time at 50°C for 4b (●), 4i (■) and 4k (▲).

groups while the ortho ester has only one. The acetyl group of **8** has, typically, a stretching frequency of 1765–1755  $\text{cm}^{-1}$  while the aromatic carboxylic ester group shows an absorption at 1725–1715  $\text{cm}^{-1}$ .<sup>29</sup> In the cyclic ester **4** there is only one carbonyl group, absorbing typically at 1800–1745  $\text{cm}^{-1}$ .<sup>28,29</sup> In the UV spectra there is a weak absorption at 275–280 nm for the simple esters **8**, while there is an absorption at 295–305 nm for the ortho esters **4**.<sup>28–30</sup> In the  $^1\text{H}$  NMR spectra the acetyl methyl signal will move from 2.05–2.20 ppm in the normal esters to 1.85–2.00 ppm in the ortho esters due to deshielding.<sup>6,29,30</sup> These ranges are based on 43 compounds of type **1**.<sup>6–25</sup> Likewise the methylene group signal of the benzyl moiety moves to higher field from typically 5.10–5.20 ppm to 4.70–5.00 ppm, except for **4k**, where the methylene signal is at 5.45 ppm for the ester and 5.20 ppm for the ortho ester; moreover in the ortho esters the methylene signal splits into a doublet of doublets (AB system)<sup>29</sup> with a coupling constant of 10–15 Hz (Table 4),

because the protons now are diastereotopic. Table 4 shows the chemical shifts and the coupling constants for the diastereotopic protons of the methylene group.

In the ring closure the carbonyl C atom of the acetyl group is rehybridized from  $\text{sp}^2$  to  $\text{sp}^3$ , which means that the corresponding  $^{13}\text{C}$  signal moves from typically 165–170 ppm in **8** to 113–114 ppm in the ortho esters **4** (the latter range based on nine known compounds).<sup>1,7,8</sup> Also the C-methyl signal moves from 20–21 ppm in the normal esters **8** to 22–23 ppm in the ortho esters **4**.

It was not possible to distinguish between the two isomers by MS spectroscopy. An explanation for this could be either that the cyclic compounds rearrange in the mass spectrometer to the normal esters, or that the first step is loss of the alkoxy group, which renders the two fragmentation patterns identical. All new compounds gave satisfactory elemental analyses.

Table 2. Physical properties of 2-benzyloxy-2-methyl-4*H*-1,3-benzodioxin-4-ones **4**.

	Formula	M.p./°C	$n_D^{20}$	$^1\text{H}$ NMR <sup>a,e</sup> $\delta_{\text{CH}_3}$ /ppm	$^{13}\text{C}$ NMR <sup>a</sup> $\delta_{\text{C}(7)}$ /ppm	$^{13}\text{C}$ NMR <sup>a</sup> $\delta_{\text{C}(8)}$ /ppm	IR $\nu_{\text{C=O}}$ / $\text{cm}^{-1}$	UV <sup>d</sup> $\lambda_{\text{max}}$ /nm
<b>a</b>	$\text{C}_{16}\text{H}_{14}\text{O}_4$	49–50		1.89	22.40	113.0	1745 <sup>c</sup>	300
<b>b</b>	$\text{C}_{17}\text{H}_{16}\text{O}_5$	65–66		1.94	22.54	113.6	1760 <sup>c</sup>	298
<b>c</b>	$\text{C}_{18}\text{H}_{18}\text{O}_6$	108–111		1.98	22.59	113.8	1750 <sup>c</sup>	303
<b>d</b>	$\text{C}_{18}\text{H}_{18}\text{O}_5$	104–105		1.93	22.63	113.3	1750 <sup>c</sup>	300
<b>e</b>	$\text{C}_{17}\text{H}_{16}\text{O}_4$	oil	1.5895	1.91	22.59	113.3	1750 <sup>b</sup>	300
<b>f</b>	$\text{C}_{16}\text{H}_{13}\text{FO}_4$	50–51		1.93	22.52	113.3	1760 <sup>c</sup>	298
<b>g</b>	$\text{C}_{16}\text{H}_{12}\text{F}_2\text{O}_4$	51–52		1.93	22.48	113.5	1760 <sup>c</sup>	298
<b>h</b>	$\text{C}_{16}\text{H}_{13}\text{ClO}_4$	125–126		1.92	22.49	113.3	1800 <sup>c</sup>	298
<b>i</b>	$\text{C}_{16}\text{H}_{12}\text{Cl}_2\text{O}_4$	107–108		1.97	22.33	113.6	1755 <sup>c</sup>	299
<b>j</b>	$\text{C}_{17}\text{H}_{13}\text{F}_3\text{O}_4$	oil	1.5080	1.90	22.42	113.3	1780 <sup>b</sup>	298
<b>k</b>	$\text{C}_{16}\text{H}_{13}\text{NO}_6$	67–68		1.96	22.75	113.2	1760 <sup>c</sup>	296

<sup>a</sup>In  $\text{CDCl}_3$ . <sup>b</sup>Film. <sup>c</sup>In KBr. <sup>d</sup>In MeOH. <sup>e</sup>See Table 3 for methylene signals.

Table 3. NMR spectroscopic data for **8**.

	Formula	<sup>1</sup> H NMR <sup>a</sup> δ <sub>CH<sub>3</sub></sub> /ppm	<sup>1</sup> H NMR <sup>a</sup> δ <sub>CH<sub>2</sub></sub> /ppm	<sup>13</sup> C NMR <sup>a</sup> δ <sub>C(7)</sub> /ppm	<sup>13</sup> C NMR <sup>a</sup> δ <sub>C(8)</sub> /ppm
<b>a</b>	C <sub>16</sub> H <sub>14</sub> O <sub>4</sub>	2.06	5.09	20.00	174.2
<b>b</b>	C <sub>17</sub> H <sub>16</sub> O <sub>5</sub>	2.11	5.35	20.26	169.7
<b>c</b>	C <sub>18</sub> H <sub>18</sub> O <sub>6</sub>	2.05	5.42	20.41	169.4
<b>d</b>	C <sub>18</sub> H <sub>18</sub> O <sub>5</sub>	2.12	5.38	20.22	169.6
<b>e</b>	C <sub>17</sub> H <sub>16</sub> O <sub>4</sub>	2.09	5.11		
<b>f</b>	C <sub>16</sub> H <sub>13</sub> FO <sub>4</sub>	2.18	5.38		
<b>g</b>	C <sub>16</sub> H <sub>12</sub> F <sub>2</sub> O <sub>4</sub>	2.06	5.20	20.17	169.5
<b>h</b>	C <sub>16</sub> H <sub>13</sub> ClO <sub>4</sub>	2.13	5.36		
<b>i</b>	C <sub>16</sub> H <sub>12</sub> Cl <sub>2</sub> O <sub>4</sub>	2.06	5.30		
<b>j</b>	C <sub>17</sub> H <sub>13</sub> F <sub>3</sub> O <sub>4</sub>	2.02	5.25		
<b>k</b>	C <sub>16</sub> H <sub>13</sub> NO <sub>6</sub>	2.15	5.40		

<sup>a</sup>In CDCl<sub>3</sub>.Table 4. NMR spectroscopic data for **4**.

Compound	δ <sub>CH<sub>2</sub>(1)</sub> /ppm	δ <sub>CH<sub>2</sub>(2)</sub> /ppm	J <sub>12</sub> /Hz
<b>4a</b>	4.81	4.78	10.0
<b>4b</b>	4.89	4.72	11.8
<b>4c</b>	4.88	4.81	10.0
<b>4d</b>	4.86	4.74	12.1
<b>4e</b>	4.82	4.72	11.2
<b>4f</b>	4.87	4.81	11.7
<b>4g</b>	4.87	4.83	10.5
<b>4h</b>	4.93	4.81	12.8
<b>4i</b>	5.04	4.93	10.0
<b>4j</b>	5.02	4.90	13.0
<b>4k</b>	5.27	5.13	15.2

**Hydrolysis.** The pseudo-first-order rate constants of the various aspirin prodrug derivatives, which only hydrolyse to salicylic acid in aqueous phosphate buffer solution at 37°C (pH = 7.4 and μ = 0.5) are shown in Table 5. As can be seen the rate constant varies from 0.01 (**4i**) to 0.3 min<sup>-1</sup> (**4e**) independent of the electronic and steric nature of the substitution of the benzyl alcohol moiety. Compounds **4b–4d**, which by hydrolysis regenerate aspirin, were studied in aqueous solution at 37°C over a wide range of pH. The buffers used were acetate, phosphate and borate, respectively. The total buffer concentration was 0.01 M. The influence of the pH on the hydrolysis rate is shown in Fig. 4, where the logarithms of the observed pseudo-first-order rate constants (*k*<sub>obs</sub>) are plotted against pH. The pH–rate profiles for the derivatives **4b–4d** are U-shaped, indicating the occurrence of apparent specific acid and base catalysis as well as a spontaneous or water-catalysed reaction. All three compounds are most stable at neutral pH under the above-mentioned conditions. Table 6 shows the rate constants and percentage aspirin formed on the assumption that the only products formed by the ortho ester decomposition are aspirin **6** and salicylic acid **7**, which is in accordance with the HPLC results.

As can be seen **4c** is almost a true aspirin prodrug, since the 17.8% salicylic acid (82.2% aspirin) formed at pH = 10.0 can be ascribed to the rapid hydrolysis of aspirin to salicylic acid in an alkaline medium. Generally the amount of aspirin formed is slightly higher at low pH (3.0) than at high pH (10.0).

Buffer catalysis has been measured for aqueous phosphate buffer at pH = 7.40 and pH = 3.0, respectively, for molar concentrations of 0.005 M, 0.01 M and 0.02 M (μ = 0.50), respectively, but no significant change in the hydrolysis rate was observed.

**Conclusion.** The hydrolysis experiments performed here indicate that only **4c** acts as an exclusive aspirin prodrug, although **4b** and **4d** were observed to release aspirin *in vitro*. Hence, 2-alkoxy or 2,6-dialkoxy groups at the benzyl

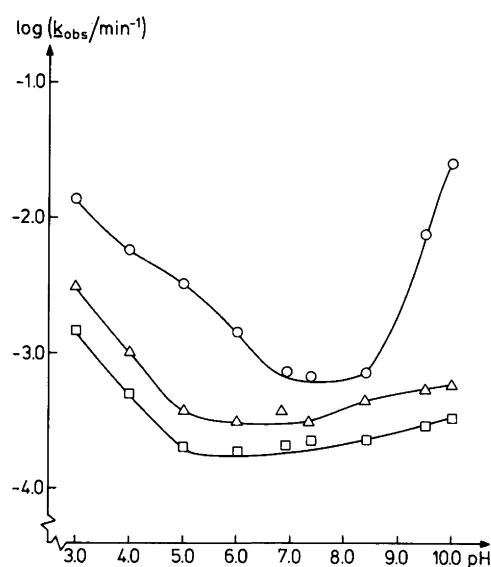


Fig. 4. log *k*<sub>obs</sub> as a function of pH for **4b** (●), **4c** (■) and **4d** (▲) in buffer solution at 37°C (μ = 0.5).

**Table 5.** *In vitro* hydrolysis of 2-substituted 2-methyl-4*H*-1,3-benzodioxin-4-ones to salicylic acid. Pseudo-first-order rate constants and half-lives in aqueous phosphate buffer (pH 7.40 and  $\mu = 0.50$ ) at 37 °C.

Compound	$k_{\text{obs}}/\text{min}^{-1}$	$t_{1/2}/\text{min}$
<b>4a</b>	$1.0 \times 10^{-2}$	68.7
<b>4e</b>	$3.0 \times 10^{-1}$	2.3
<b>4f</b>	$9.1 \times 10^{-2}$	7.6
<b>4g</b>	$3.6 \times 10^{-2}$	19.2
<b>4h</b>	$4.1 \times 10^{-2}$	17.0
<b>4i</b>	$1.0 \times 10^{-2}$	68.7
<b>4j</b>	$4.6 \times 10^{-2}$	14.9
<b>4k</b>	$6.7 \times 10^{-2}$	10.3

alcohol moiety may, by virtue of steric or electronic effects, be responsible for the change in mechanism, and even though their relatively short half-lives (we find half-lives over 1 h desirable) probably make them of no practical value in prodrug formulations, **4c** and analogous cyclic aspirin derivatives **4** containing 2-alkoxy- or 2,6-dialkoxybenzyloxy as substituent should be considered seriously as potential aspirin prodrugs.

## Experimental

**HPLC equipment.** High-performance liquid chromatography (HPLC) was carried out with a Kontron apparatus consisting of an LC Pump T-414, a Uvikon 740LC UV detector operated at a fixed wavelength (215 nm), a Rheodyne 7125 injection valve with a 20  $\mu\text{l}$  loop and a Chrompack column (100 $\times$ 3 mm) packed with Chromspher C18 (5  $\mu\text{m}$  particles).

**Kinetics.** The hydrolytic breakdown of the cyclic aspirin derivatives **4** was studied in aqueous buffer solution at 37 °C and  $\mu = 0.5$ . The progress of the reaction was followed by

using reversed-phase HPLC procedures. The mobile phase system methanol–acetonitrile–water–phosphoric acid (30:10:60:1 v/v) was used for cases of acetylsalicylic acid–salicylic acid detection and acetonitrile–0.02 M acetate buffer (55:45 v/v) for ortho ester detection. The flow rate was 0.7 ml min<sup>-1</sup> and the column effluent was monitored at 215 nm. The reactions were initiated by adding 100  $\mu\text{l}$  of a stock solution of the compound to be examined in acetonitrile to 10 ml of preheated buffer solution in screw-capped test tubes, the final concentration of the compound to be tested being about 10<sup>-4</sup> M. The solutions were kept in a water bath at 37 °C and at appropriate intervals samples were taken and chromatographed immediately. For the compounds **4a** and **4e–4k**, which hydrolyse to salicylic acid, the pseudo-first-order rate constants were determined spectrophotometrically by monitoring the decrease in ultraviolet absorbance at 215 nm vs. time. The buffers used were phosphate at pH = 3.0 and in the pH range 6.0–7.4, acetate for pH = 4.0 and pH = 5.0, *N*-ethylmorpholine for pH = 8.4 and borate for pH = 9.5 and pH = 10.0. The compounds **4b–4d** were quantified by measuring the peak height in relation to those of standards chromatographed under the same conditions.

**Synthesis.** The identification of the cyclic products was carried out by IR (Nicolet MX-S), UV (Kontron Uvikon 860), and <sup>1</sup>H NMR and <sup>13</sup>C NMR spectroscopy (Varian XL-300 and Gemini 200), and MS (Micromass 7070F). Microanalyses were carried out by *Løvens Kemiske Fabrik*, DK-2750 Ballerup (Microanalytical Laboratory).

**General synthesis I (with base).** A solution of 2.15 g (0.011 mol) **5** in CHCl<sub>3</sub> was added to a solution of 0.010 mol *o*-substituted benzyl alcohol and 1.4 ml (0.010 mol) triethylamine in CHCl<sub>3</sub>. After 30 min the solution was refluxed for 3–5 h under a stream of nitrogen. The solution was then washed 3–4 times with 0.5 M sodium hydrogen carbonate and 1–2 times with a saturated solution of NaCl

**Table 6.** *In vitro* hydrolysis of **4b–4d**. Rate constants ( $k_{\text{obs}}$ ) and half-lives ( $t_{1/2}$ ) for the decomposition of **4b–4d**, percentage aspirin formed and rate constants ( $k_{\text{asp}}$ ) for the formation of aspirin over a wide range of pH at 37 °C ( $\mu = 0.5$ ).

pH	Hydrolysis data for <b>4b</b>				Hydrolysis data for <b>4c</b>				Hydrolysis data for <b>4d</b>			
	$k_{\text{obs}}/\text{min}^{-1}$	$t_{1/2}/\text{min}$	Aspirin formed/%	$k_{\text{asp}}/\text{min}^{-1}$	$k_{\text{obs}}/\text{min}^{-1}$	$t_{1/2}/\text{min}$	Aspirin formed/%	$k_{\text{asp}}/\text{min}^{-1}$	$k_{\text{obs}}/\text{min}^{-1}$	$t_{1/2}/\text{min}$	Aspirin formed/%	$k_{\text{asp}}/\text{min}^{-1}$
10.0	0.031	22.4	47.9	0.015	0.202	3.4	82.2	0.166	0.039	17.7	36.3	0.014
9.5	0.029	22.4			0.120	5.8			0.038	18.2		
8.4	0.026	26.7			0.042	16.5			0.035	19.8		
7.4	0.026	26.7	51.1	0.013	0.041	16.9	93.0	0.038	0.030	23.1	39.1	0.012
6.9	0.025	27.7			0.042	16.5			0.032	21.7		
6.0	0.024	28.9	55.3	0.013	0.060	11.6	95.9	0.058	0.030	23.1	47.7	0.014
5.0	0.025	27.7			0.083	8.4			0.032	21.7		
4.0	0.037	18.7			0.110	6.3			0.050	13.9		
3.0	0.059	11.7	63.9	0.038	0.155	4.5	96.1	0.149	0.081	8.6	59.6	0.048

before the solution was filtered 2–3 times through  $\text{Al}_2\text{O}_3$  to remove any remaining starting material. The compounds were crystallized with petroleum ether–ether (1:1). The solids so obtained were then recrystallized.

In the case of **4b** it was the acyclic compound which crystallized and thus it was necessary to remove the acyclic compound by repeated recrystallization until the cyclic compound was pure.

For **4c** and **4f** the cyclic compound was almost crystalline at once.

Compound **4h** was crystallized without solvent after 24 h. Compound **4d**, **4i** and **4k** were crystallized with petroleum ether–ether after 24 h.

For **4a** and **4g** it was necessary to let the cyclic compound crystallize from the oil without solvent before recrystallization.

Compound **4e** and **4j** did not crystallize, either with solvent or without.

*General synthesis II (without base).* This method is similar to I, but without triethylamine. Likewise it was not necessary to wash the crude product with sodium hydrogen carbonate and NaCl before filtration through  $\text{Al}_2\text{O}_3$ .

*General synthesis III (with  $(\text{CF}_3\text{CO})_2\text{O}$ ).* Trifluoroacetic acid anhydride (1.4 ml, 0.010 mol) was added to a stirred suspension of 1.63 g (0.010 mol) **6** in dry  $\text{CHCl}_3$ . If necessary, the reaction mixture was heated until a clear solution was obtained. After 30 min the alcohol was added dropwise and the preparation was continued as in synthesis I.

We attempted to separate the isomer pairs **4** and **8** by column chromatography [ $\text{SiO}_2$  (70–230 mesh ASTM), petroleum ether–ether], but no **4** could be isolated. This indicates that the cyclic compounds rearrange to the acyclic compounds, which can be explained by the catalytic effect of the slightly acidic column material on the ring opening of the cyclic compound.<sup>28,31</sup> To support this assumption, we dissolved **4k** in  $\text{CHCl}_3$  with suspended  $\text{SiO}_2$  for 24 h, whereafter 20% of **4k** had rearranged to **8k**.

Detailed descriptions of the methods of preparation for each individual compound are available on request.<sup>32</sup>

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