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Prodrugs
Part 3 [1]. 2-Formylphenyl esters of indomethacin, ketoprofen and ibuprofen and 6-substituted 2-formyl and 2-acylphenyl esters of aspirin

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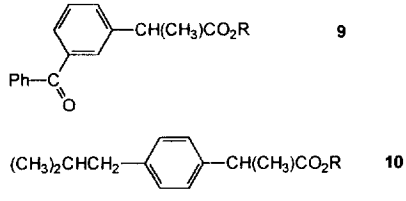
Abstract

The synthesis and study of a novel series of potential prodrugs of indomethacin, ketoprofen, ibuprofen and aspirin are reported. 2-Formylphenyl esters of the NSAIDs, together with two 6-substituted 2-formyl and two 2-acylphenyl aspirins and 4-formylphenyl indomethacin, have been prepared. A study of their alkaline and neutral hydrolysis shows that these compounds, with the exception of 2-acetylphenyl aspirin, act as true prodrugs of the NSAIDs, giving the NSAID and acylphenol. The rates of hydrolysis and activation parameters indicate that the 2-acylphenyl esters employ an intramolecular catalytic route. The 2-formylphenyl esters were more potent as anti-inflammatory agents than the parent compounds in the carragheenan-induced paw oedema test.

Keywords: Prodrugs; NSAID; Indomethacin; Ketoprofen; Ibuprofen; Aspirin

1. Introduction

A number of studies [2,3] have been made on prodrugs of non-steroidal anti-inflammatory drugs (NSAID). These have been concerned, in particular, with the problems associated with NSAIDs gastric irritation and bleeding, as well as transport characteristics [4,5]. Such prodrugs are commonly esters of carboxyl functions which can regenerate the drugs by hydrolysis either enzymatically or non-enzymatically [6]. However, a significant problem for certain of these esters is the lability of other groups in the prodrug Thus aspirin (2-acetoxybenzoic acid) ester prodrugs **1** can convert into aspirin **2** or the salicylic acid ester **3**, with both finally forming salicylic acid **4**, as shown in Scheme 1 [6]. Furthermore, indomethacin (1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid) ester prodrugs **5** can form either indomethacin **6** or the de-acylated indomethacin ester **7**, both finally forming 5-methoxy-2-methylindolyl-3-acetic acid **8**, as shown in Scheme 2 [7]. On the other hand, ketoprofen (2-(3-benzoylphenyl)propionic acid) and ibuprofen (2-(4-isobutylphenyl)propionic acid) ester prodrugs, **9** and **10**, respectively, can only hydrolyse to form the corresponding drugs.



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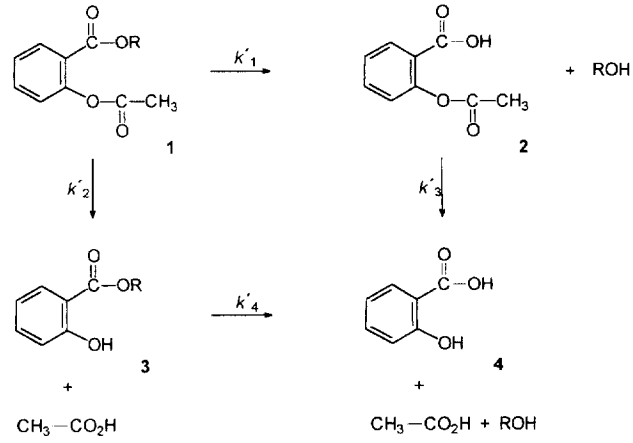
In our earlier study [8] of a series of 4-substituted 2-formylphenyl aspirins it was shown that, from an investigation of their alkaline hydrolysis, these esters act as true



Scheme 1.

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[1] For Part 2 see Ref. [1].

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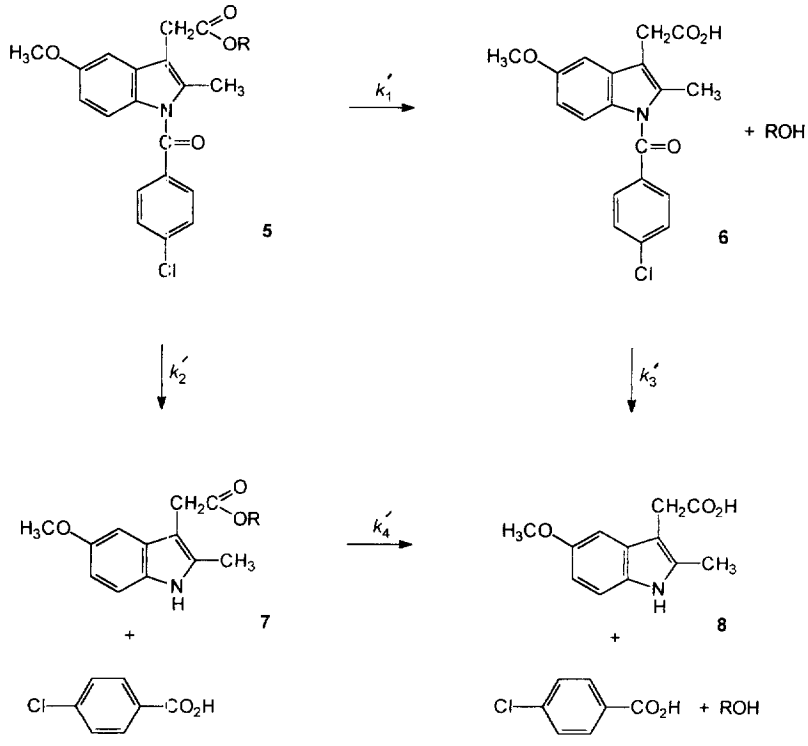


Scheme 2.

prodrugs of aspirin by an intramolecular catalytic route. The present report details an extension of this approach to prodrugs of indomethacin, ketoprofen and ibuprofen, as well as a study of two 6-substituted 2-formyl and two 2-acylphenyl esters of aspirin.

2. Chemistry

2.1. Design

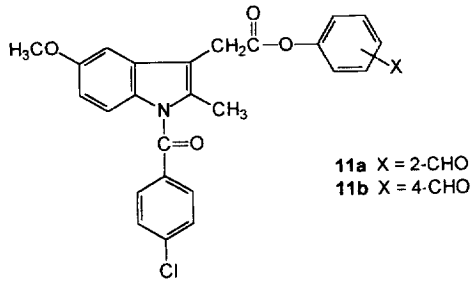
The ester prodrugs have been designed to suffer alkaline hydrolysis relatively rapidly, such that the acetoxy (aspirin) and amido (indomethacin) groups remain intact, i.e. k'_1 in Schemes 1 and 2 operating, and that the rates can be tuned by further substitution [8]. The ester prodrugs studied are shown in Fig. 1. The first series of esters are the 2-formylphenyl esters of indomethacin, ketoprofen and ibuprofen, **11a**, **12a** and **12b**, respectively, and the 4-formylphenyl ester of indomethacin, **11b**. The second series of esters are modifications either of 2-formylphenyl aspirin, **13a**, in which a further 2-formyl group has been added, **13c**, or a lipophilic substituent has been introduced, **13b**, or of 2-phenyl aspirin having varied 2-acyl substitutents, **13d** and **13e**. All the esters, except **11b**, are expected to hydrolyse employing an intramolecular route [9,10]; whereas ester **11b** would hydrolyse by a direct or normal $B_{AC}2$ pathway (according to Ingold's notation) [11]. The log P (octanol/water) values of indomethacin, ketoprofen, ibuprofen and aspirin have been measured or estimated to be 4.27, 3.12, 3.50 and 1.19, respectively [12,13]. The formation of the esters gives more lipophilic compounds, with lipophilicity increases over the parent drug estimated from π values [13] as shown in Table 1.

2.2. Synthesis

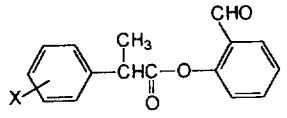
Two synthetic methods were employed in these studies. The first was a coupling process between the carboxylic acid and the appropriate phenol using dicyclohexylcarbodiimide (DCC) catalysed by *p*-toluenesulfonic acid [14]. This was successfully employed for the synthesis of **11a** and **11b**. The second was by conversion of the carboxylic acid into the acid chloride using thionyl chloride, followed by reaction of the acid chloride with the phenol in the presence of triethylamine [8,15]. This was successfully employed for **12a**, **12b** and **13a** to **13e**. The physical properties and methods of preparation of the esters are shown in Table 1.

2.3. Alkaline and neutral hydrolysis

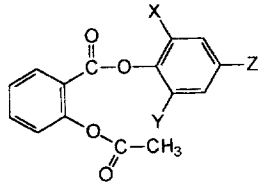
The alkaline and neutral hydrolysis of the esters resulted in the quantitative formation of indomethacin, ketoprofen, ibuprofen and aspirin, as well as the respective phenol, under the conditions of the study, with the sole exception of 2-acetylphenyl aspirin. Studies of hydrolysis down to pH 1.0 showed no significant acid-catalysed hydrolysis of the esters, compared to the neutral hydrolysis. The rate coefficients, k_2 and k_1, for the alkaline and neutral hydrolysis, respectively, of the esters in 30% (vol./vol.) dioxane–water at, normally,



11a X = 2-CHO
11b X = 4-CHO



12a X = 3-COPh
12b X = 4-$CH_2CH(CH_3)_2$



13a X = CHO; Y, Z = H
13b X = CHO; Y = $CH(CH_3)_2$, Z = H
13c X, Y = CHO; Z = CH_3
13d X = $COCH_3$; Y, Z = H
13e X = $COCF_3$; Y, Z = H

Fig. 1.

27.0, 37.0 and 47.0°C are shown in Table 2. The activation parameters are shown in Table 3.

3. Experimental

3.1. Chemistry

Melting points were determined using a Kofler melting point apparatus and are uncorrected. The structures of all the compounds were confirmed by IR and ^1H and ^{13}C NMR spectra. IR spectra were determined using a Zeiss Specord M-80 spectrophotometer. NMR spectra were recorded at ambient temperatures on $CDCl_3$ solution using a JEOL EX270 FT spectrometer with $(CH_3)_4Si$ as internal reference. All compounds were analysed for C, H, as well as N and halogen if suitable, and gave results within ±0.3% of the calculated values. Preparative column chromatography was performed using Still's method of flash chromatography [16]; the stationary phase normally was Sorbsil C60 silica gel with dichloromethane or hexane/ethyl acetate as the eluent. All organic solutions were dried over anhydrous magnesium sulfate. 2- and 4-Formylphenols and 2-acetylphenol were obtained commercially. 2,2,2-Trifluoro-1-(2-hydroxyphenyl)-1-ethanone was prepared by the Fries rearrangement of phenyl 2,2,2-trifluoroacetate [17] as described by Matsumoto et al. [18]. Oxidation in two stages of 4-methyl-2,6-bis(hydroxymethyl)phenol [19] gave 2,6-diformyl-4-methylphenol by the method of Ynefei and Hongwen [20]. 2-Formyl-6-isopropylphenol was prepared by the formylation of 2-isopropylphenol using paraformaldehyde and tin(IV) chloride [21].

3.2. General method A for the synthesis of formylphenyl esters of indomethacin **11** using DCC

Indomethacin (0.012 mol), formylphenol (0.010 mol) and *p*-toluenesulfonic acid (0.15 g) were dissolved in pyridine (50 ml). DCC (0.010 mol) was added and the solution was stirred at ambient temperature for 24 h. Acetic acid (4 ml) was added and the mixture was kept at 4°C for 24 h. The mixture was then filtered and the residue washed with cold pyridine (100 ml) and cold chloroform (100 ml). Ice (100 g) was added to the combined filtrate and the mixture was acidified to pH 3 by the addition of aqueous HCl. The organic layer was separated and washed with water (100 ml), 10% aqueous $NaHCO_3$ (100 ml) and water (100 ml). After drying (anhydrous $MgSO_4$) and filtering, the filtrate was evaporated under reduced pressure. The product was then purified by flash chromatography. It was then recrystallised to give the

Table 1
Preparation of phenyl esters of indomethacin (**11**), ketoprofen (**12a**), ibuprofen (**12b**) and aspirin (**13**)

		Method [b]	M.p. (°C)	Recryst. solvent	Yield (%)	Anal. [a]	log *P* [c]
11a	2-CHO	A	139–140	hexane/CH_2Cl_2	55	C,H,N,Cl	5.40
11b	4-CHO	A	119–120	hexane/CH_2Cl_2	80	C,H,N,Cl	5.40
12a	2-CHO	B	oil		74	C,H	4.25
12b	2-CHO	B	oil		85	C,H	4.63
13a	2-CHO	B	72–74 [d]	cyclohexane	50	C,H	2.32
13b	2-CHO,6-$CH(CH_3)_2$	B	96–97	hexane/$CHCl_3$	20	C,H	3.85
13c	2,6-$(CHO)_2$, 4-CH_3	B	100–102	cyclohexane	20	C,H	2.23
13d	2-$COCH_3$	B	91–93	hexane/$CHCl_3$	48	C,H	2.42
13e	2-$COCF_3$	B	88–89	hexane	26	C,H,F	2.99

[a] Anal. results are within ±0.03% of calculated values.
[b] A,B = see Section 3.
[c] Estimated log *P* (octanol/water) [12,13].
[d] Lit. [8] m.p. 72–74°C.

Table 2
Rate coefficients (k_2) for the alkaline hydrolysis of the esters in 30% (vol./vol.) dioxane–water (at constant ionic strength of 1.0 mol dm^{-3}) [a]

		k_2 (dm^3 mol^{-1} s^{-1}) [c]			$t_{1/2}$ [d]	λ (nm) [b]
		at 27.0°C	at 37.0°C	at 47.0°C		
11a	2-CHO	334 (7.37)	406 (11.6)	514 (19.3)	6.9 min	320
11b	4-CHO		5.30		40.6 h	320
12a	2-CHO	345 (5.08)	410 (10.1)	497 (18.5)	7.6 min	324
12b	2-CHO	314 (3.91)	339 (7.51)	352 (14.0)	9.8 min	324
13a	2-CHO [e]	440 (0.785)	498 (1.30)	554 (2.20)	15 min	389,326
13b	2-CHO,6-$CH(CH_3)_2$	98.0 (1.93)	112 (3.32)	142 (5.69)	25 min	334
13c	2,6-$(CHO)_2$, 4-CH_3	3320 (47.5)	3260 (82.0)	3430 [f] (31.7) [f]	56 s	438
13d	2-$COCH_3$		0.624			300
13e	2-$COCF_3$	4.34 (0.163)	5.99 (0.314)	7.84 (0.607)	5.0 h	232

[a] Observed rate coefficients were reproducible to within ±3%, with k_1 and k_2 considered accurate to ±5%.
[b] Wavelength used to monitor hydrolysis.
[c] Values in parentheses are 10^4 k_1 (s^{-1}) for neutral hydrolysis.
[d] At pH 7.52 at 37°C in 30% aqueous dioxane.
[e] Lit. [8] values for k_2.
[f] At 21.5°C.

Table 3
Activation parameters for the alkaline hydrolysis of the esters in 30% (vol./vol.) dioxane–water at 20.0°C [a,b]

	$\Delta H^{\neq}$ (kcal mol^{-1}) [c]	$\Delta S^{\neq}$ (cal mol^{-1} K^{-1}) [c]
11a	3.5 (8.6)	−35 (−44)
12a	2.9 (11.7)	−37 (−34)
12b	0.5 (11.5)	−45 (−36)
13a [d]	1.6 (9.2)	−41 (−47)
13b	2.9 (10.3)	−40 (−43)
13c	−0.3 (11.0)	−43 (−35)
13e	5.1 (12.0)	−39 (−41)

[a] The uncertainties are ±500 cal mol^{-1} for $\Delta H^{\neq}$ and ±2 cal mol^{-1} K^{-1} for $\Delta S^{\neq}$.
[b] Values in parentheses are for k_1 for neutral hydrolysis.
[c] 1 cal = 4.184 J.
[d] Lit. [8] values for k_2.

product described in Table 1. The yields are given in Table 1. The ^{1}H NMR spectra of **11** both indicated a formyl group at 10.0 ppm (1*H*, s) and ^{13}C NMR spectra indicated three carbonyl groups at 188 (formyl), 167 (acetate) and 171 (benzamide) ppm. Other detailed spectra were in accordance with stated structures.

*3.3. General method B for the synthesis of phenyl esters of ketoprofen, ibuprofen and aspirin **12** and **13** using the carboxylic acid chloride in the presence of triethylamine*

The carboxylic acid chloride was prepared by refluxing the carboxylic acid (0.04 mol) and excess $SOCl_2$ in toluene for 5 h [22]. After evaporating under reduced pressure, the product in anhydrous ether (100 ml) was stirred and triethylamine (4.04 g, 0.04 mol) was added. After stirring at ambient temperature for 10 min, the appropriate phenol (0.04 mol) was added. The mixture was stirred at ambient temperature for 2 h and then refluxed under a gentle stream of nitrogen for 3 h. The solution was filtered after cooling and the filtrate was washed with water (100 ml), 10% aqueous $NaHCO_3$ (100 ml) and water (100 ml). After drying and filtering, the solution was evaporated under reduced pressure. The product was usually obtained as an oil and was purified by flash chromatography. The solid or oil was then normally recrystallised to give the product described in Table 1. The yields are given in Table 1. The ^{1}H NMR spectra of **12** both indicated a formyl group at 9.8 to 9.9 ppm (1*H*, s) and ^{13}C NMR spectra indicated two or three carbonyl groups at 188 (formyl), 172–173 (acetate) and 196 (benzoyl) ppm. The ^{1}H NMR spectra of **13a** to **13c** all indicated a formyl group(s) at 10.0 to 10.2 ppm (1 or 2*H*, s) and ^{13}C NMR spectra indicated three carbonyl groups at 188–189 (formyl), 162–163 (benzoate) and 169–170 (acetate) ppm. The ^{1}H NMR spectra of **13d** indicated an acetyl group at 2.5 ppm (3*H*, s) and ^{13}C NMR spectra indicated three carbonyl groups at 197 (acetyl), 163 (benzoate) and 169 (acetate) ppm. The ^{13}C NMR spectra of **13e** indicated three carbonyl groups at 179 (trifluoroacetyl), 162 (benzoate) and 169 (acetate) ppm. Other detailed spectra were in accordance with stated structures.

3.3.1. Alkaline and neutral hydrolysis of esters

The products of the alkaline and neutral hydrolysis of the esters were found to be the NSAID and the phenol in quantitative yield with the exception of 2-acetylphenyl aspirin **13d**. The results of the HPLC study (see below) were further confirmed spectrophotometrically by comparison of the spectrum of NSAID and the respective phenol in buffer with that of the reaction product. Rate coefficients for the hydrolysis of the esters were determined spectrophotometrically by use of a Perkin-Elmer lambda 5 or 16 UV-VIS spectrometer. A Haake thermostatted water circulating water bath was used to control the temperature of the cell to ±0.05°C. The procedure was that described previously [23]. The aqueous dioxane solution was pipetted into two 1 cm cells and the

cells were placed in a cell holder to enable equilibration. ~5 μl of a solution of the substrate in dioxane were added from a microsyringe such that the final substrate concentration was $\sim 5 \times 10^{-5}$ mol dm^{-3}. The complete UV spectrum was recorded continuously. The rate measurements were made by monitoring at a selected fixed wavelength, normally the maximum change in absorption between substrate and product. The final optical density was assumed to be that measured after ten 'half-lives' had elapsed. The reactions were followed at the wavelengths shown in Table 2. A constant ionic strength of 1.0 mol dm^{-3} was maintained and buffers used were composed of acetate, phosphate, borate, carbonate and glycine. The pH range employed was 4.93 to 10.24. Rates were extrapolated to zero buffer concentrations from up to 0.1 mol dm^{-3}. Plots of k_{obs} versus $[OH^-]$ were linear (correlation coefficients > 0.98). The slopes gave k_2 and, for the 2-formylphenyl and trifluoroacetyl esters, the intercept gave k_1. The methods used for the calculations and in the extrapolations are as described by Espenson [24]. The activation parameters were obtained from a least mean squares treatment of log k ν $1/T$ [24]. Solvents and buffer components were purified as required by literature methods [25].

An HPLC method was used for the analysis of hydrolysis products. These were performed using a Gilson 302 pump, holochromo UV-detector (operating at 230 nm), a Rheodine injection valve with a 20 μl loop and a Biorad RSL column (250×4.6 mm) with ODS (5 μm particle size). A flow rate of 1 mm min^{-1} was used and the reversed phase column eluted with a mobile phase consisting of acetonitrile/methanol/water/phosphoric acid (40:50:10:1 (vol./vol.)) used for all studies. The reactions were initiated by injecting 100 μl of a solution of the ester in dioxane into 10 ml of a buffer solution at 37°C such that the final ester concentration was $\sim 6 \times 10^{-4}$ mol dm^{-3}. A plot of peak heights versus the concentrations of each derivative was linear in the concentrations range studied (correlation coefficients > 0.97). The retention times of the esters and hydrolysis products were between 4 and 18 min. The products of the hydrolysis of the esters were the NSAID and the phenol alone, except for 2-acetylphenyl aspirin **13d**. For the latter ester, both aspirin (and 2-acetylphenol) and 2-acetylphenyl salicylate were produced in the proportion of ~2:1.

3.4. Pharmacology

The esters were screened for anti-flamrnatory activity in the carragheenan-induced paw oedema test and compared with the activity of aspirin or indomethacin as a standard. Male Wistar rats (180–200 g) were dosed orally with either aspirin or indomethacin (100–200 mg kg^{-1}; $n = 6$ per group) or vehicle (1 ml of 1% (wt./vol. in distilled water) carboxymethylcellulose). The animals were immediately gassed with 20–25% CO_2, followed by injection of carragheenan (0.1 ml of 1.3% (wt./vol. in sterile saline)) into the subplantar of the left paw. The right non-injected paws were used as control. The animals were allowed to recover and the treated paw circumference measured at hourly intervals for each rat. The effects of the esters prepared in this study were determined using the same procedure except that the animals were dosed orally with either aspirin (100 mg kg^{-1}), vehicle (1 ml of 1% (wt./vol. in distilled water) carboxymethylcellulose) or the ester (50–100 mg kg^{-1}). The results were analysed for significance using Student t-test indicating $P < 0.01$ or usually $P < 0.001$.

Selected potential prodrugs were screened for anti-inflammatory activity using the above method. These were selected on the basis of their $t_{1/2}$ values at pH 7.52 (see Table 2) and their lipophilicity (see Table 1) to give a selection of different types, i.e. relatively more lipophilic and short 'half-life', **11a**, relatively less lipophilic and short 'half-life', **13a**, relatively less lipophilic and long 'half-life', **13e**, and relatively more lipophilic and long 'half-life', **11b**. Aspirin, one of the reference compounds, was observed to suppress the oedema at 3–4 h post-induction. 2-Formylphenyl aspirin **13a** gave a time-dependent response similar to aspirin and suppressed the oedema at 3–4 h. Furthermore, **13a** was found to be approx. twice as potent as aspirin. Both the 2- and 4-formylphenyl indomethacin **11a** and **11b** showed a time-dependent response similar to indomethacin itself and suppressed the oedema at 3–4 h, being more potent than indomethacin. 2-Trifluoroacetylphenyl aspirin **13e** failed to elicit an anti-inflammatory response. The ester **13a** has an IC_{50} value of 1.4×10^{-5} mol dm^{-3} for cyclooxygenase and of $> 5.0 \times 10^{-4}$ mol dm^{-3} for lipooxygenase. The latter ester induced ulceration in rats at 30 mg kg^{-1} per os, producing haemorrhagic ulcers in the duodenum and gastrointestine with superficial mucosal lesions in the stomach. Indomethacin at the same dose level produced ulcers in the duodenum, stomach and gastrointestine.

The cyclooxygenase assay was determined in rat whole blood after addition of calcium ionophore A23/87 following the method of Foster et al. [26]. The ulcerogenic activity was assessed by macroscopic evaluation of stomach lesions in male rats carried out 14 h after administration of test compounds, with ten rats per group tested.

4. Results and discussion

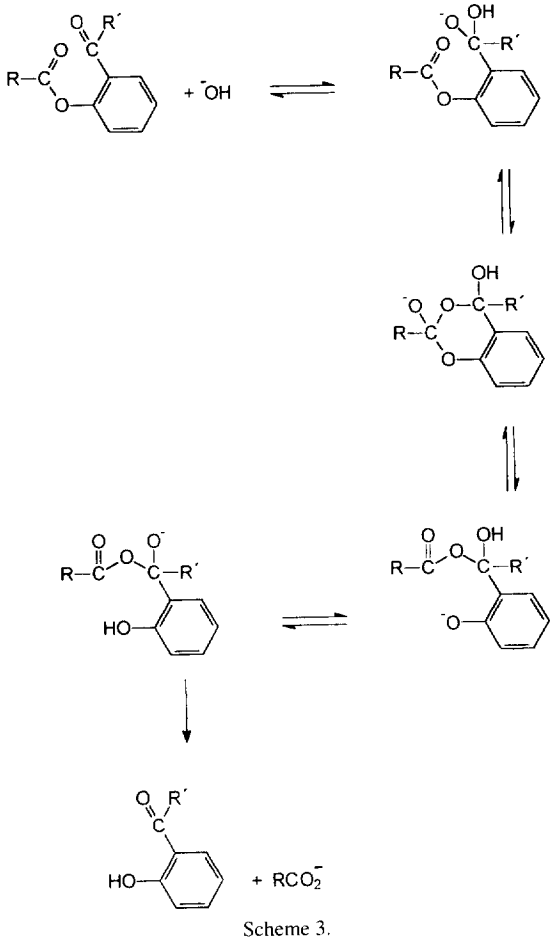
4.1. Alkaline and neutral hydrolysis

The hydrolysis of the esters were found to be a combination of an alkaline hydrolysis, i.e. first-order in both substrate and hydroxide, and a neutral hydrolysis, i.e. first-order in substrate, to give the NSAID and the phenol, with the exception of 2-acetylphenyl aspirin **13d**. The latter ester was the only ester studied here that was not acting on hydrolysis as a true prodrug for the NSAID. All the other esters conformed to the pathways shown in Scheme 1 and Scheme 2 as k'_1. The hydrolysis of the only 4-formylphenyl ester studied here, **11b**, showed only alkaline hydrolysis, but was a true prodrug for indomethacin.

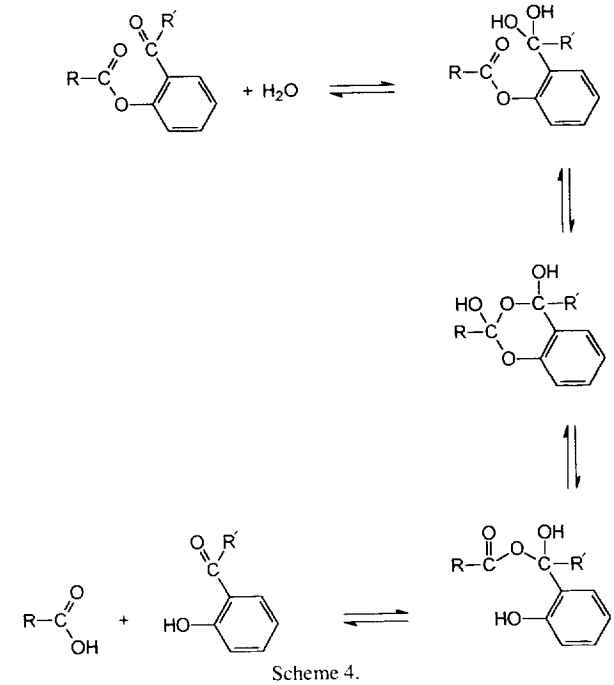
The comparison between the rates of alkaline hydrolysis of the esters **11a** and **11b** indicates that the 2-formylphenyl ester hydrolyses ~38 times faster than that expected for 'normal' unassisted hydrolysis [9]. This is closely comparable to the factor previously found for the 2-formylphenyl aspirin [8]. Furthermore, the activation parameters for the alkaline hydrolysis of **11a**, shown in Table 3, demonstrate the very small $\Delta H^{\neq}$ and large negative $\Delta S^{\neq}$ values associated with intramolecular catalysis of alkaline hydrolysis by formyl or certain acyl groups. A reaction pathway for the latter is shown in Scheme 3. The rates of alkaline hydrolysis and activation parameters for the 2-formylphenyl esters **12a** and **12b** are closely comparable to those of esters **11a** and **13a**, indicating the same reaction pathway. The activation parameters for the alkaline hydrolysis of the esters **13b**, **13c** and **13e** also show the same pattern. The rate of reaction of 2-formyl-6-isopropylphenyl ester **13b** shows a modest decrease, relative to that of **13a**, expected from an alkyl group which is effectively '*meta*' to the formyl substituent. Likewise, the 2,6-diformyl-4-methylphenyl ester **13c** has a very much faster rate than ester **13a** arising both from having two '*ortho*' formyl groups capable of participation and the '*meta*' activation of one formyl group on the other. The relative rate of hydrolysis of the 2-trifluoroacetylphenyl ester **13e** appears to be in accord with an intramolecular pathway. Thus, the σ_I and E_s values for CF_3 are 0.40 and −2.4, respectively, relative to those for H of 0.0 [13]. The favourable electron-withdrawing effect is overpowered by the unfavourable steric effect as noted in model systems [27]. The activation parameters for **13e** confirm the nature of the pathway.

The neutral or water-catalysed hydrolysis of 2-formyl or 2-acylphenyl esters has not been previously reported [8–10], which is probably due to the previous studies of hydrolysis being conducted under more alkaline conditions where the neutral or water-catalysed reaction is overwhelmed by the alkaline contribution. Neutral or water-catalysed hydrolysis has been observed for very reactive phenyl esters [11]. However, as it is *not* observed for 4-formylphenyl esters, it is very likely to follow an intramolecular route which is outlined in Scheme 4 [27]. The enthalpies of activation for the neutral or water-catalysed hydrolysis are relatively modest, but significantly greater than those for alkaline hydrolysis, as shown in Table 3. The large negative entropies of activation appear to indicate that two molecules of water are involved in the transition state for the neutral or water-catalysed hydrolysis.

The values of $t_{1/2}$ at pH 7.52 at 37°C in 30% aqueous dioxane for the esters are shown in Table 2. The increased anti-flammatory activity of the 2-formylphenyl esters **11a** and **13a**, compared with the parent NSAID, could be due to better transport characteristics of the esters, as they are relatively rapidly hydrolysed to the parent NSAID. The 4-formyphenyl ester **11b** would not be expected to be hydrolysed rapidly non-enzymatically and the anti-inflammatory activity may arise from the activity of the ester in its own right. The failure of the 2-trifluoroacetylphenyl ester **13e** to elicit an anti-inflammatory response is surprising. Further studies will be required to elucidate these points.



Scheme 3.



Scheme 4.

Acknowledgements

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