International Journal of Pharmaceutics, 25 (1985) 27–39
Elsevier

IJP 00832

Allopurinol prodrugs. III. Water-soluble N-acyloxymethyl allopurinol derivatives for rectal or parenteral use

Hans Bundgaard and Erik Falch

Royal Danish School of Pharmacy, Departments of Pharmaceutical Chemistry AD and Chemistry BC, DK-2100 Copenhagen (Denmark)

(Received December 4th, 1984)
(Accepted January 7th, 1985)

Key words: allopurinol – prodrugs – N-acyloxymethyl derivatives of allopurinol – amino acid esters – stability – enzymatic hydrolysis – solubility – partition coefficients

Summary

Nine amino acid esters of 1-(hydroxymethyl)allopurinol were synthesized and evaluated as potential water-soluble prodrugs of allopurinol with the aim of developing preparations suitable for parenteral and/or rectal administration. Hydrochloride or hydrobromide salts of all the N_1-acyloxymethyl derivatives exhibited a water-solubility greater than 20%. The kinetics of hydrolysis of the compounds was studied in aqueous solution and in human plasma solutions at 37°C. Complete reversion to allopurinol was observed in all cases, the maximum stability of the derivatives occurring at pH < 4. The susceptibility of the derivatives to undergo enzymatic hydrolysis varied widely, the observed half-lives in 80% human plasma ranging from 3 to 140 min. It was concluded that N_1-acyloxymethyl derivatives of allopurinol containing an amino group in the acyl moiety are potentially useful as parenteral delivery forms of the parent drug. Furthermore, compounds containing a weakly basic amino group (pK_a 6–7.5) may be useful as prodrugs to enhance the rectal absorption of allopurinol as assessed on the basis of the water-solubility and lipophilicity of the derivatives.

Correspondence: H. Bundgaard, Royal Danish School of Pharmacy, Department of Pharmaceutical Chemistry AD, 2 Universitetsparken, DK-2100 Copenhagen, Denmark.

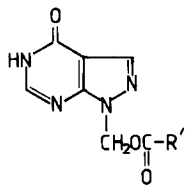
Introduction

Allopurinol (I) is only slightly soluble in water (0.5 mg · ml^{-1}) and therefore, it is only possible to deliver therapeutically sufficient amounts of the drug by infusion (Kann et al., 1968; Brown et al., 1970; Donnenberg et al., 1974). The infusion fluids used contain the sodium salt of allopurinol ($pK_a \sim 10.2$) at a concentration of 0.5–1% and are strongly alkaline (pH about 10.5–11.5); consequently, the administration may cause thrombophlebitis or perivascular inflammation. This poor water-solubility as well as the similarly poor lipid solubility of the drug may be the predominant factors (Bundgaard and Falch, 1985a) responsible for the much diminished absorption of the drug following rectal administration (Chang et al., 1981; Appelbaum et al., 1980, 1982).

A promising solution to these parenteral and rectal delivery problems may be to develop prodrugs of allopurinol with more desirable physicochemical properties. In previous papers (Bundgaard and Falch, 1985a and b), various acyl and acyloxymethyl derivatives of allopurinol were prepared and assessed as possible prodrug forms. While these derivatives showed adequate conversion rates to the parent drug under conditions similar to those prevailing in vivo and also exhibited greatly enhanced lipophilicity relative to allopurinol, the water-solubility of most derivatives was

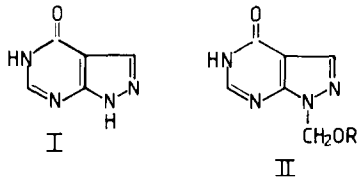
TABLE 1

CHEMICAL STRUCTURE AND ^{1}H-NMR DATA OF VARIOUS 1-ACYLOXYMETHYL DERIVATIVES OF ALLOPURINOL INVESTIGATED IN THIS STUDY



Compound	R′	^{1}H-NMR (δ) [a]	
		H (3)	H (6)
IIa, HCl	$-CH_2NH_2$	8.27	8.32
IIb, HBr	$-CH(CH_3)NH_2$	8.38	8.42
IIc, HBr	$-CH(C_6H_5)NH_2$	8.15	8.20
IId, HBr	$-CH(CH_2C_6H_5)NH_2$	8.28	8.30
IIe, HBr	$-CHCH_2CH(CH_3)_2$ $\vert$ NH_2	8.32	8.36
IIf, HCl	$-CH_2N(CH_3)_2$	8.28	8.34
IIg, HCl	$-CH_2N(C_2H_5)_2$	8.27	8.32
IIh, HCl	$-CH_2N(C_3H_7)_2$	8.34	8.40
IIi, HCl	$-CH(CH_3)N(C_2H_5)_2$	8.36	8.45
IIj, HCl	$-CH_2CH_2CH_2N(CH_3)_2$	8.29	8.35

[a] The NMR spectra were run in D_2O.



I II

rather poor. The previously described N_1-acyl derivatives formed with amino acids were highly water-soluble as salts but such prodrugs were considered to be less suitable as parenteral delivery forms due to a very limited stability in aqueous solution (Bundgaard and Falch, 1985a).

Based on the earlier work on N_1-acyloxymethyl allopurinol derivatives (II) (Bundgaard and Falch, 1985b) it was thought that the introduction of an ionizable amino group in the ester moiety of such derivatives would make it possible to obtain more water-soluble prodrug forms suitable for injection. Furthermore, if only slightly basic amino functions, i.e. with a pK_a of 6–7.5, were selected it should also be feasible to obtain derivatives with adequate lipophilicities at pH 7–8 and hence with good rectal absorption characteristics. In the present work a series of such N_1-acyloxymethyl derivatives (Table 1) have been prepared and evaluated as potentially useful prodrug forms.

Materials and Methods

Apparatus

High-performance liquid chromatography (HPLC) was done with a Spectra-Physics Model 3500B instrument equipped with a variable-wavelength UV detector and a 10-μl loop injection valve. A column, 250 × 4 mm, packed with LiChrosorb RP-8 (7 μm particles) (E. Merck, Darmstadt) was used. Readings of pH were carried out on a Radiometer Type PHM 26 meter at the temperature of study. ^{1}H-NMR spectra were run on a Varian 360L instrument. Melting points were taken in capillary tubes and are not corrected. Microanalyses were performed by G. Cornali, Microanalytical Laboratory, Leo Pharmaceutical Products, Ballerup, Denmark and were within ±0.4% of the theoretical values.

Synthesis of acyloxymethyl derivatives of allopurinol (IIa–j and IV)

Method A

The compounds IIa–e all containing a primary amino group were prepared by reaction of 1-(hydroxymethyl)allopurinol (III) (prepared as described by Bansal et al. (1981)) with an amino acid where the amino function is protected with a benzyloxycarbonyl (Z) or a *t*-butyloxycarbonyl (BOC) group. The reactions were performed in pyridine with N,N′-dicyclohexylcarbodiimide as condensing agent. The

amino groups were deprotected with hydrobromic acid in acetic acid or with 1 N hydrochloric acid.

General procedure—1-(DL-alanyloxymethyl)allopurinol (IIb). A mixture of 1-(hydroxymethyl)allopurinol (III) (1.66 g; 10 mmol), DL-N-benzyloxycarbonylalanine (2.23 g; 10 mmol), N,N′-dicyclohexylcarbodiimide (2.06 g; 10 mmol), and 4-toluenesulfonic acid (150 mg) in pyridine (60 ml) was stirred at room temperature for 20 h. Methylene chloride (100 ml) was added and the mixture was filtered. The filtrate was evaporated in vacuo and the residue was extracted with boiling methylene chloride (3 × 50 ml). The methylene chloride was evaporated and the residue was recrystallized from ethyl acetate–ethanol. To the crude N-protected compound was added a 33% solution of hydrobromic acid in acetic acid (8 ml). The mixture was stirred at room temperature for 7 min and ethyl acetate (50 ml) was added. The precipitate (520 mg, 16%) was collected and recrystallized from methanol. The title compound crystallized with 2/3 mole of water, m.p. 195–198°C (dec).

1-(Glycyloxymethyl)allopurinol hydrochloride (IIa). From III (0.8 g; 5 mmol) and N-*t*-butyloxycarbonyl)glycine (0.88 g; 5 mmol). The amino group was deprotected with 1 N hydrochloric acid. Yield: 173 mg (13%), m.p. 192–195°C (dec.) (from 2-propanol-ether).

1-(DL-Phenylglycyloxymethyl)allopurinol hydrobromide (IIc). From III (2.49 g; 15 mmol) and DL-N-(benzyloxycarbonyl)phenylglycine (4.28 g; 15 mmol). The amino group was deprotected with a 33% solution of hydrobromic acid in acetic acid. Yield: 1.27 g (22%), m.p. 192–195°C (dec.) (from methanol–ether).

1-(DL-Phenylalanyloxymethyl)allopurinol hydrobromide (IId). From III (1.66 g; 10 mmol) and DL-N-(benzyloxycarbonyl)phenylalanine (2.99 g; 10 mmol). Deprotection was carried out with hydrobromic acid in acetic acid. Yield: 1.37 g (34%), m.p. 204–205°C (dec.) (from methanol).

1-(L-Leucyloxymethyl)allopurinol hydrobromide (IIe). From III (1.66 g; 10 mmol) and L-N-(benzyloxycarbonyl)leucine (2.65 g; 10 mmol). Deprotection with hydrobromic acid in acetic acid. Yield: 809 mg (21%) of the monohydrate of the title compound. M.p. 215–217°C (dec.) (from methanol–acetonitrile).

2,5-bis(DL-Alanyloxymethyl)allopurinol dihydrobromide (IV). From 2,5-bis(hydroxymethyl)allopurinol (Bundgaard and Falch, 1985b) (1.96 g; 10 mmol), DL-N-(benzyloxycarbonyl)alanine (1.46 g; 20 mmol), and N,N′-dicyclohexylcarbodiimide (4.28 g; 20 mmol). The amino groups were deprotected with hydrobromic acid in acetic acid. Yield: 975 mg (19%), m.p. 190–192°C (dec.) (from methanol). The compound crystallized with 0.5 mole of methanol.

Method B

The compounds IIf–i were synthesized by reacting 1-(hydroxymethyl)allopurinol (III) with an amino acid or in the case of IIg with an amino acid hydrochloride in the presence of N,N′-dicyclohexylcarbodiimide.

General procedure—1-(N,N-dimethylglycyloxymethyl)allopurinol hydrochloride (IIf). A mixture of III (2.0 g; 12 mmol), N,N-dimethylglycine (1.25 g; 12 mmol), N,N′-dicyclohexylcarbodiimide (2.5 g; 12 mmol), and 4-toluenesulfonic acid (150 mg) in pyridine (40 ml) was stirred at room temperature for 48 h. Methylene

chloride (80 ml) was added. The mixture was filtered and the filtrate was evaporated in vacuo. The residue was extracted with two 50-ml portions of boiling methylene chloride, and the extracts were evaporated. The residue was recrystallized from ethyl acetate. The crude compound obtained was suspended in ethanol (20 ml) and a 2 N solution of hydrochloric acid in ethyl acetate (8 ml) was added followed by ethyl acetate (20 ml). The precipitate was collected and recrystallized from methanol–ether yielding 1.32 g (38%), m.p. 203–206°C (dec.).

1-(N,N-Dipropylglycyloxymethyl)allopurinol hydrochloride (IIh). From III (2.0 g; 12 mmol) and N,N-dipropylglycine (1.91 g; 12 mmol). Yield: 1.29 g (31%), m.p. 195–198°C (dec.) (from ethanol).

1-(DL-N,N-Diethylalanyloxymethyl)allopurinol hydrochloride (IIi). From III (4.76 g; 28.7 mmol) and DL-N,N-diethylalanine (4.16 g; 28.7 mmol). Yield 3.47 g (37%), m.p. 168–170°C (dec.) (from ethanol–ether).

1-(N,N-Diethylglycyloxymethyl)allopurinol hydrochloride (IIg). A mixture of III (10.3 g; 62 mmol), N,N-diethylglycine hydrochloride (10.4 g; 62 mmol), N,N-dicyclohexylcarbodiimide (12.8 g; 62 mmol), and 4-toluenesulfonic acid (500 mg) in pyridine (185 ml) was stirred at room temperature for 24 h. Methylene chloride (185 ml) was added to the reaction mixture and the precipitate was collected. The precipitate was stirred for 15 min with water (75 ml) to which 2 N hydrochloric acid was added to maintain pH at 3. The insoluble compound was filtered off, and the filtrate was evaporated in vacuo. The residue was recrystallized from a mixture of methanol and ethanol (1 : 1) yielding 10.3 g (54%), m.p. 196–198°C.

When 2 M sodium hydroxide was added to a solution of IIg hydrochloride (7.9 g; 25 mmol) in water (30 ml) until the pH was 7.6, 1-(N,N-diethylglycyloxymethyl)allopurinol (IIg) in free base form precipitated. Yield: 6.13 g (88%), m.p. 155–156°C (from ethyl acetate).

The compounds IIa–IIj showed a λ_{max} at 251 nm in pH 5.0 buffer solutions whereas λ_{max} for compound IV occurred at 259 nm in agreement with the assigned structures, cf. Bundgaard and Falch (1985b). The pertinent NMR data of the compounds are shown in Table 1. For compound IV the signals for H(3) and H(6) were observed at 8.51 and 8.97 ppm. The consistency of these data with the position of substitution in allopurinol was discussed previously (Bundgaard and Falch, 1985b).

Kinetic measurements

The conversion of the N-acyloxymethyl derivatives to allopurinol was studied in 80% human plasma solutions of pH 7.4 as well as in various aqueous buffer solutions at 37°C. The buffers used were hydrochloric acid, formate, acetate, phosphate, borate and carbonate; a constant ionic strength (μ) of 0.5 was maintained for each buffer by adding a calculated amount of potassium chloride. The rates of hydrolysis were followed by monitoring the disappearance of the derivatives or the appearance of allopurinol using reversed-phase HPLC procedures. Mobile phase systems of 15–70% v/v methanol in 0.02 M phosphate buffer of pH 7.0 were used for analyzing the derivatives, the concentration of methanol being adjusted for each compound to give an appropriate retention time (3–10 min). The flow rate was

1.2 ml · min^{-1} and the column effluent was monitored at 251 nm. Quantitation of the compounds was done by measuring the peak heights in relation to those of standards chromatographed under the same conditions. The initial concentration of the derivatives was in the range 0.02–0.05 mg · ml^{-1}. Pseudo-first-order rate constants for the hydrolysis were determined from the slopes of linear plots of the logarithm of residual allopurinol derivative against time. Allopurinol was determined by using a mobile phase system consisting of 5% v/v methanol in 0.01 M acetate buffer of pH 4.5. Other procedures such as analysis of plasma samples were as described in the foregoing paper (Bundgaard and Falch, 1985b).

Determination of aqueous solubility and partition coefficients

This was performed as previously described (Bundgaard and Falch, 1985a and b). For determination of the partition coefficients an octanol–0.05 M borate buffer (pH 8.0) system was used.

Results and Discussion

Enzymatic hydrolysis of the N-acyloxymethyl derivatives

For the derivatives IIa–j to behave as true prodrugs of allopurinol, they must revert rapidly to allopurinol under in vivo conditions. To give an indication as to their in vivo behaviour the rates of hydrolysis of the compounds were studied in human plasma solutions at 37°C. At initial concentrations of 0.02–0.1 mg · ml^{-1} all the derivatives underwent complete hydrolysis as indicated by the quantitative formation of allopurinol (cf. Fig. 1), and in all cases the disappearance of derivative or appearance of allopurinol exhibited strict first-order kinetics for several half-lives at constant pH. The half-lives for the conversion in 80% human plasma solutions are given in Table 2 along with the corresponding data for hydrolysis in absence of plasma.

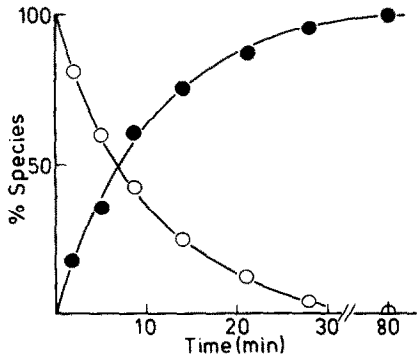


Fig. 1. The time-course of degradation of 1-(N,N-dimethylglycyloxymethyl)allopurinol (IIf) (○) and the concomitant formation of allopurinol (●) in a 80% human plasma solution (pH 7.4) at 37°C.

TABLE 2

RATE DATA FOR THE HYDROLYSIS OF VARIOUS N-ACYLOXYMETHYL DERIVATIVES (II) OF ALLOPURINOL IN AQUEOUS SOLUTION AND IN 80% HUMAN PLASMA AT 37°C

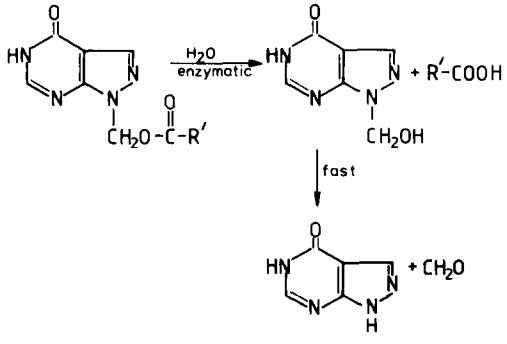
Compound		$t_{1/2}$ (min)		
No.	R in II	pH 4.0	pH 7.40	80% human plasma
IIa	Glycyl	–	26	9
IIb	DL-Alanyl	14.6 h	15	11
IIc	DL-Phenylglycyl	8.9 h	20	3
IId	DL-Phenylalanyl	–	40	9
IIe	L-Leucyl	–	17	6
IIf	N,N-Dimethylglycyl	21.4 h	72	7
IIg	N,N-Diethylglycyl	28.9 h	49	10
IIh	N,N-Dipropylglycyl	29.5 h	50	12
IIi	DL-N,N-Diethylalanyl	32.5 h	21	17
IIj	4-(N,N-Dimethylamino)butyryl	–	145	140

Inspection of the rate data shows that all derivatives except the 4-(N,N-dimethylamino)butyryloxymethyl derivative (IIj) are rapidly hydrolyzed in plasma. The hydrolysis of the alanyl derivatives IIb and IIi is catalyzed to only a minor extent whereas the N,N-dialkylglycyl derivatives (IIf–h) appear to be relatively good substrates for the hydrolyzing enzymes.

As discussed previously (Bundgaard and Falch, 1985b), the conversion of the N-acyloxymethyl derivatives is expected to take place via the formation of an unstable 1-hydroxymethyl intermediate (III) with the cleavage of the ester moiety being the rate-determining step in both the enzymatic and non-enzymatic hydrolysis (Scheme 1).

Kinetics of degradation in aqueous solution

To provide information on the chemical stability of the compounds in aqueous solution the kinetics of hydrolysis of some representative derivatives (IIc, IIf and IIg) was studied in aqueous buffer solutions over the pH range 1–10.5.



Scheme 1

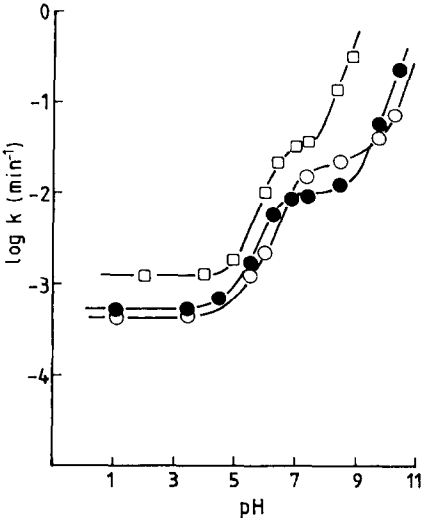


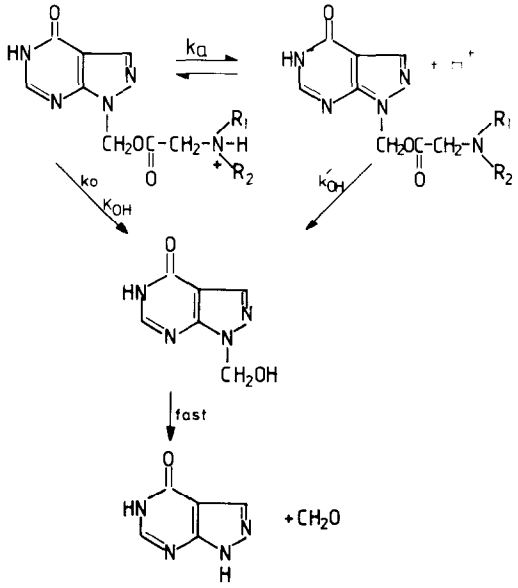
Fig. 2. The pH–rate profiles for the hydrolysis of the N-acyloxymethyl allopurinol derivatives IIc (□), IIf (●) and IIg (○) in aqueous solution ($\mu = 0.5$) at 37°C.

At all pH values studied, the derivatives hydrolyzed to yield allopurinol quantitatively as evidenced by HPLC analysis. The rates of hydrolysis were subject to catalysis by most of the buffer substances used to maintain constant pH. Plots of the observed pseudo-first-order rate constants at each pH value (k_{obs}) against the total buffer concentration were linear over at least 3 buffer concentrations (0.02–0.1 M). Values of the buffer-independent pseudo-first-order rate constants (k) were obtained from the intercepts of such linear plots.

The effect of pH on the rates of hydrolysis at 37°C of the compounds IIe, IIf and IIg is shown in Fig. 2 in which the logarithm of k has been plotted against pH. At pH > 5 the pH rate profiles show two linear segments with slopes of unity with a plateauing occurring around pH 7. At low pH the rates of hydrolysis become independent of pH. This pattern indicates that the free base and the protonated forms of the amino esters undergo hydrolysis with different rates and that the hydrolysis can be described in terms of specific base-catalyzed reactions of these species along with a spontaneous (pH-independent) reaction of the protonated ester (Scheme 2):

$$k = k_0 \cdot \frac{a_H}{a_H + K_a} + k_{OH} a_{OH} \cdot \frac{a_H}{a_H + K_a} + k'_{OH} a_{OH} \cdot \frac{K_a}{a_H + K_a} \qquad (1)$$

where a_{OH} and a_H refer to the hydroxide ion and hydrogen ion activity, respectively, $a_H/(a_H + K_a)$ and $K_a/(a_H + K_a)$ are the fractions of total ester in the protonated and free base form, respectively, and K_a is the apparent ionization constant of the protonated amino group in the esters. The rate constant k_0 refers to the pH-inde-



Scheme 2

pendent hydrolysis of the protonated form of the esters (equal to k at pH < 3) while k_{OH} and k'_{OH} are the second-order rate constants for the apparent attack of hydroxide ion on the protonated and unprotonated ester species, respectively. The lines drawn for the pH–rate profiles in Fig. 2 were constructed from Eqn. 1 and the appropriate rate and ionization constants given in Table 3. It is recognized that a kinetically equivalent reaction to the k_{OH}-reaction is a spontaneous or water-catalyzed reaction of the free base form of the esters. As seen from Table 3 the kinetically obtained values of pK_a compared well with the values determined by potentiometric titration of the compounds at 37°C and $\mu = 0.5$.

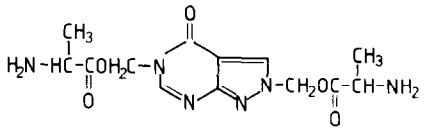
The sigmoidal pH–rate profiles observed are similar to those of various other amino acid esters (e.g. Kirby and Lloyd, 1976; Kovach et al., 1981; Bundgaard et al.,

TABLE 3

RATE AND IONIZATION CONSTANTS FOR THE HYDROLYSIS OF THE N-ACYLOXYMETHYL ALLOPURINOL DERIVATIVES IIc, IIf AND IIg IN AQUEOUS SOLUTION ($\mu = 0.5$) AT 37°C

Compound	k_0 (min^{-1})	k_{OH} ($M^{-1} \cdot min^{-1}$)	k'_{OH} ($M^{-1} \cdot min^{-1}$)	pK_a [a]
IIc	1.3×10^{-3}	4.2×10^{5}	2.2×10^{4}	6.6 (6.6)
IIf	5.4×10^{-4}	1.7×10^{5}	3.9×10^{2}	6.5 (6.5)
IIg	4.0×10^{-4}	8.0×10^{4}	1.3×10^{2}	7.1 (7.0)

[a] The values given in parenthesis were obtained by potentiometric titration; the other values were determined kinetically.



IV

1984; Varia et al., 1984) and possible mechanisms accounting for the large differences in the susceptibility of the unprotonated and protonated ester species to undergo hydrolysis have been discussed in these references.

A 2,5-bis(acyloxymethyl)allopurinol derivative with an amino group in the side-chains was prepared using DL-alanine. The compound IV proved to be very unstable in aqueous solution, the half-life at pH 6.0 and 22°C being 30 min and that at pH 7.4 and 37°C less than 2 min. This behaviour is in accord with the previous findings (Bundgaard and Falch, 1985b) of 2,5-bis(acetoxymethyl)allopurinol being 6 times as unstable as 1-(acetoxymethyl)allopurinol in neutral and basic solutions.

Solubility and stability

The hydrochloride or hydrobromide salts of the various amino group-containing N_1-(acyloxymethyl)allopurinol derivatives displayed, as expected, high solubilities in water. For all compounds the water-solubility was higher than 20% w/v (Table 4), the pH of 1–20% w/v solutions being in the range pH 3–4.

TABLE 4

PARTITION COEFFICIENTS (P), HPLC CHROMATOGRAPHIC CAPACITY FACTORS (k') AND WATER-SOLUBILITIES (S) OF ALLOPURINOL AND VARIOUS N_1-ACYLOXYMETHYL DERIVATIVES (IIa–IIi) OF ALLOPURINOL

Compound			log P [a]	k' [b]	S [c]
No.	R in II	salt			(mg·ml^{-1})
I	Allopurinol		−0.55	0.63	0.50
IIa	Glycyl	HCl	–	0.89	> 500
IIb	DL-Alanyl	HBr	–	1.37	> 200
IIc	DL-Phenylglycyl	HBr	−0.15	6.3	> 200
IId	DL-Phenylalanyl	HBr	0.40	14.5	> 200
IIe	L-Leucyl	HBr	0.19	–	> 400
IIf	N,N-Dimethylglycyl	HCl	−0.49	4.0	> 500
IIg	N,N-Diethylglycyl	HCl	0.20	12.0	> 500
		free base	0.20	12.0	4.5
IIh	N,N-Dipropylglycyl	HCl	1.27	> 60	> 400
IIi	DL-N,N-Diethylalanyl	HCl	0.72	17.1	> 400

[a] Partition coefficients between octanol and 0.05 M borate buffer of pH 8.0 at 22°C.
[b] Mobile phase: 0.02 M phosphate buffer pH 7.4–methanol (4:1 v/v).
[c] At 22°C.

TABLE 5

APPARENT ZERO-ORDER INITIAL RATES OF FORMATION OF ALLOPURINOL (A) FROM ITS PRODRUG IIg AND TIMES FOR A TO BEGIN PRECIPITATION (t_{pt}) FROM SOLUTIONS OF IIg AS CALCULATED FROM EQN. 2 (AT 23°C)

Concentration of IIg, HCl salt ($mg \cdot ml^{-1}$)	$(d[A]/dt)_i$ ($mg \cdot ml^{-1} \cdot h^{-1}$)	t_{pt} (min)
25	0.175	171
50	0.35	86
100	0.70	43
200	1.40	21
300	2.10	14

In considering the stability of concentrated solutions of the prodrugs to be used for parenteral administration it may be important to recognize not only the loss of prodrug per se but also the gradual formation of allopurinol and its subsequent precipitation as the saturation solubility of the drug is reached. The formation of a saturated solution of allopurinol will be a function of the initial concentration of the ester, $[II]_0$, so the initial rate of formation of allopurinol (A) would be:

$$\left(\frac{d[A]}{dt}\right)_i = k[II]_0 \qquad (2)$$

where k is the pseudo-first-order rate constant for the hydrolysis of II to allopurinol under the designated experimental conditions. At pH 3–4.5, corresponding to the pH range of 1–20% aqueous solutions of the hydrochloride salts of IIf–h, and at 23°C, k was determined to be approximately 7×10^{-3} h^{-1}. The time for allopurinol to potentially begin nucleating from solutions of e.g. IIg (t_{pt}) can be calculated from Eqn. 2, knowing that the solubility of allopurinol is 0.5 $mg \cdot ml^{-1}$. Table 5 gives the calculated zero-order rates of formation of allopurinol as a function of the initial ester concentration at 23°C. Since $t_{10\%}$ for the derivative is 14 h at 23°C the results given in Table 5 indicate that the stability of aqueous solutions of the prodrug in the concentration range 2.5–30% will be limited solely by the potential precipitation of allopurinol formed upon hydrolysis and that solutions of IIg (or other similar compounds) might have quite short utilization times. However, it was repeatedly found experimentally that the time required for allopurinol precipitation to occur was much higher (more than 5–10 h) than the predicted figures. This discrepancy may possibly be due to the occurrence of super-saturation or that allopurinol is solubilized by the prodrug salt. Such phenomena have been shown to contribute to a similar lack of correlation between theoretical and experimental precipitation times for some water-soluble prodrugs of phenytoin (Varia et al., 1984).

Lipophilicity of the derivatives as free bases

Since the amino group-containing N_1-acyloxymethyl derivatives all have a pK_a value of less than 7.5 (except for compound IIj) they will be at least partly

unprotonated at pH values corresponding to those in the rectum (pH ~ 7.9) (Bitterman et al., 1967). The lipophilicity of the derivatives was evaluated in terms of partition coefficients (P) between octanol and borate buffer of pH 8.0 and HPLC chromatographic capacity factors (k') using a mobile phase of 25% v/v methanol in 0.02 M phosphate buffer of pH 7.4. As seen from the data given in Table 4 all the derivatives (IIa–i) are more lipophilic than the parent drug. The water-solubility of the free base form of IIg was found to be 4.5 $mg \cdot ml^{-1}$ which is 9 times as high as the solubility of allopurinol. Nevertheless, the log P and k' values for the derivative are seen to greatly exceed those of allopurinol. This further illustrates how decreased intermolecular hydrogen bonding in the crystal lattice as achieved by blocking the 1-NH group in allopurinol may lead to a derivative with both enhanced water-solubility and lipophilicity as discussed in the previous paper (Bundgaard and Falch, 1985b). In this work the following relationship between melting points, water-solubilities (S, in molar concentration) and octanol–water partition coefficients (P) for various N_1-acyl and N-acyloxymethyl allopurinol derivatives was derived:

$$\log S = -1.08(\pm 0.13) \log P - 0.0073(\pm 0.002)\text{m.p.} - 0.65(\pm 0.80)$$

$$n = 18;\ r = 0.918 \qquad (3)$$

The melting point of IIg (free base) is 155–156°C and from this and the log P value of 0.20, Eqn. 3 predicts a water-solubility of the compound of 0.010 M corresponding to 3.2 $mg \cdot ml^{-1}$. This figure is quite close to the experimentally observed solubility (4.5 $mg \cdot ml^{-1}$).

Conclusions

The results obtained show that esterification of 1-(hydroxymethyl)allopurinol with amino acids is a potentially useful approach to obtain highly water-soluble prodrug forms of allopurinol for parenteral administration. It is possible to identify several such N-acyloxymethyl derivatives with facile enzymatic conversion in plasma and excellent solubility properties. In preliminary experiments it was found that intravenous administration of 1-(N,N-diethylglycyloxymethyl)allopurinol hydrochloride to rabbits afforded essentially the same plasma levels of allopurinol and its major metabolite oxipurinol as those obtained by administration of the equivalent amount of an alkaline solution of allopurinol (to be published). The compounds are not sufficiently stable for formulation as ready-to-use solutions but the stability at pH 3–5 is compatible with their use as formulations to be reconstituted as solutions within several hours prior to use. Some more lipophilic and weakly basic derivatives such as IIg, IIh and IIi have also been found to be well absorbed following rectal administration to rabbits and humans and may hence be useful as rectal allopurinol prodrug delivery forms. The results of such bioavailability studies will be the subject of a subsequent paper.

References

Appelbaum, S.J., Mayersohn, M., Perrier, D. and Dorr, R.T., Allopurinol absorption from rectal suppositories. Drug Intell. Clin. Pharm., 13 (1980) 789.

Appelbaum, S.J., Mayersohn, M., Dorr, R.T. and Perrier, D., Allopurinol kinetics and bioavailability. Intravenous, oral and rectal administration. Cancer Chemother. Pharmacol., 8 (1982) 93–98.

Bansal, P.C., Pitman, I.H. and Higuchi, T., N-Hydroxymethyl derivatives of nitrogen heterocycles as possible prodrugs II. Possible prodrugs of allopurinol, glutethimide and phenobarbital. J. Pharm. Sci., 70 (1981) 855–857.

Bitterman, W., Spencer, R.J., Huizenga, K.A. and Shorter, R.G., Measurement of contact pH in the human rectum in health and disease. Gastroeneterology, 53 (1967) 288–290.

Brown, C.H., Stashick, E. and Carbone, P.P., Chemical efficacy and lack of toxicity of allopurinol (NSC-1390) given intravenously. Cancer Chemother. Rep., 54 (1970) 125–129.

Bundgaard, H. and Falch, E., Allopurinol prodrugs. I. Synthesis, stability and physicochemical properties of various N_1-acyl allopurinol derivatives. Int. J. Pharm., 23 (1985) 223–237.

Bundgaard, H. and Falch, E., Allopurinol prodrugs. II. Synthesis, hydrolysis kinetics and physicochemical properties of various N-acyloxymethyl allopurinol derivatives. Int. J. Pharm., 24 (1985) 307–325.

Bundgaard, H., Larsen, C. and Arnold, E., Prodrugs as drug delivery systems XXVII. Chemical stability and bioavailability of a water-soluble prodrug of metronidazole for parenteral administration. Int. J. Pharm., 18 (1984) 79–87.

Chang, S.-L., Kramer, W.G., Feldman, S., Ballentine, R. and Frankel, L.S., Bioavailability of allopurinol from oral and rectal dosage forms. Am. J. Hosp. Pharm., 38 (1981) 365–368.

Donnenberg, A., Holton, C.P., Mayer, C.M.H. and Phillips, L.K., Evaluation of intravenous allopurinol (NSC-1390) in pediatric neoplasia. Cancer Chemother. Rep., 58 (1974) 737–739.

Kann, Jr., H.E., Wells, J.H., Gallelli, J.F., Schein, P.S., Cooney, D.A., Smith, E.R., Seegmiller, J.E. and Carbone, P.P., The development and use of an intravenous preparation of allopurinol. Am. J. Med. Sci., 256 (1968) 53–63.

Kirby, A.J. and Lloyd, G.J., Intramolecular general base catalysis in the hydrolysis of 3-dimethylaminopropionates. J. Chem. Soc. Perkin Trans. II, (1976) 1748–1752.

Kovach, I.M., Pitman, I.H. and Higuchi, T., Amino acid esters of phenols as prodrugs: synthesis and stability of glycine, β-aspartic acid, and α-aspartic acid esters of *p*-acetamidophenol. J. Pharm. Sci., 70 (1981) 881–885.

Varia, S.A., Schuller, S. and Stella, V.J., Phenytoin prodrugs IV. Hydrolysis of various 3-(hydroxymethyl)phenytoin esters. J. Pharm. Sci., 73 (1984) 1074–1080.