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MECHANISMS OF ACYLATION OF 2,3-DIHYDROBENZOXAZOL-2-ONE AND 2*H*-1,4-BENZOXAZIN-3(4*H*)-ONE

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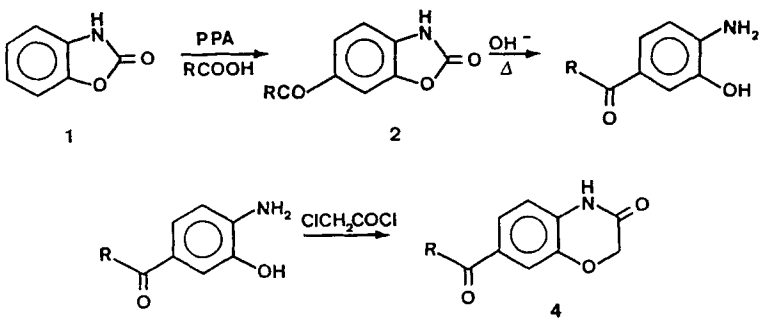
The kinetics of the acylation of 2,3-dihydrobenzoxazol-2-one with dodecanoic acid in polyphosphoric acid were investigated. Two competitive reactions occurred at the 3- and 6-positions. The acylation reactions in polyphosphoric acid of 2,3-dihydrobenzoxazol-2-one and 2*H*-1,4-benzoxazin-3(4*H*)-one give 6- and 7-acyl derivatives. 4-Acetyl-2*H*-1,4-benzoxazin-3(4*H*)-one rearranged in polyphosphoric acid exclusively to the 7-acetyl derivative. Two mechanisms are proposed to explain the different reaction sites for the acylation of 2*H*-1,4-benzoxazin-3(4*H*)-one.

INTRODUCTION

Recently, 7-acyl-2*H*-1,4-benzoxazin-3(4*H*)-ones (**4**) were found to exhibit interesting normolipaemic properties.[1–4] These derivatives were prepared from 6-acyl-2,3-dihydrobenzoxazol-2-ones (**2**) in a two-step procedure which gave high yields (Scheme 1). Unfortunately, it was not always possible to obtain compounds **2** satisfactorily, the yield of the acylation with carboxylic acid or acyl halides in polyphosphoric acid (PPA)[5,6] depending on the nature of the acyl group and the substitution on the heterocyclic N atom. The yield of the acylation of 3-methyl-2,3-dihydrobenzoxazol-2-one is generally higher and the reaction conditions milder than those with 2,3-dihydrobenzoxazol-2-one (**1**).

The benzoyl migration observed in PPA for benzanilide and *N*-benzoyltoluidide[7] similarly to the photochemically induced rearrangement of 3-acyl-2,3-dihydrobenzoxazol-2-ones[8] prompted us to investigate the mechanism of the acylation of 2,3-dihydrobenzoxazol-2-one and to compare it with the acylation of 2*H*-1,4-benzoxazin-3(4*H*)-one.

In this paper, we report the kinetics and mechanistic



Scheme 1

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studies of the reaction of acylation of 2,3-dihydrobenzoxazol-2-one and 2*H*-1,4-benzoxazin-3(4*H*)-one.

RESULTS AND DISCUSSION

Acylation of 2,3-dihydrobenzoxazol-2-one

In order to simplify the kinetic investigations, the acylation reaction was carried out with dodecanoic acid in polyphosphoric acid at 120 °C. Dodecanoic acid was chosen because it is similarly insoluble in aqueous acidic medium as the two products of the reaction, i.e. the 6- and 3-acyl derivatives, and so they are easily obtained as a mixture by filtration after hydrolysis. Moreover, the 6- and 3-dodecanoyl derivatives are unreactive in aqueous acidic medium whereas the 3-acyl derivatives, with a shorter alkyl chain, are easily hydrolysed at room temperature to carboxylic acid and compound **1** (Table 1). The reaction temperature was fixed at 120 °C because then the 3,6-didodecanoyl derivative **5** was not detected (in the ^{1}H NMR spectrum there were no signals at 8·17, 7·92 and 3·15 ppm; see Experimental) even after 2 h of reaction (Table 2). The resulting mixture was analysed in ^{1}H NMR in CD_2Cl_2 by

Table 1. Hydrolysis of **3** (**3** → **1**) in ethanol or water with hydrochloric acid

R[a]	Temperature (°C)	Solvent	Time (min)	Yield of **1** (%)
CH_3	25	Water	60	100
	25	Ethanol	10	100
C_4H_9	25	Water	60	80
	25	Ethanol	10	40
	80	Ethanol	30	100
$C_{11}H_{23}$	25	Water	60	0
	25	Ethanol	10	0
	80	Ethanol	30	20
	80	Ethanol	180	100

[a] See Scheme 2.

Table 2. Reaction of **1** with dodecanoic acid in PPA

			Yield (%)		
Entry	Temperature (°C)	Time (min)	**2**	**3**	**5**
1	120	120	17·5	48·5	0
2	120	360	16	52	17
3	150	120	26	26	15
4	150	360	29	36	25

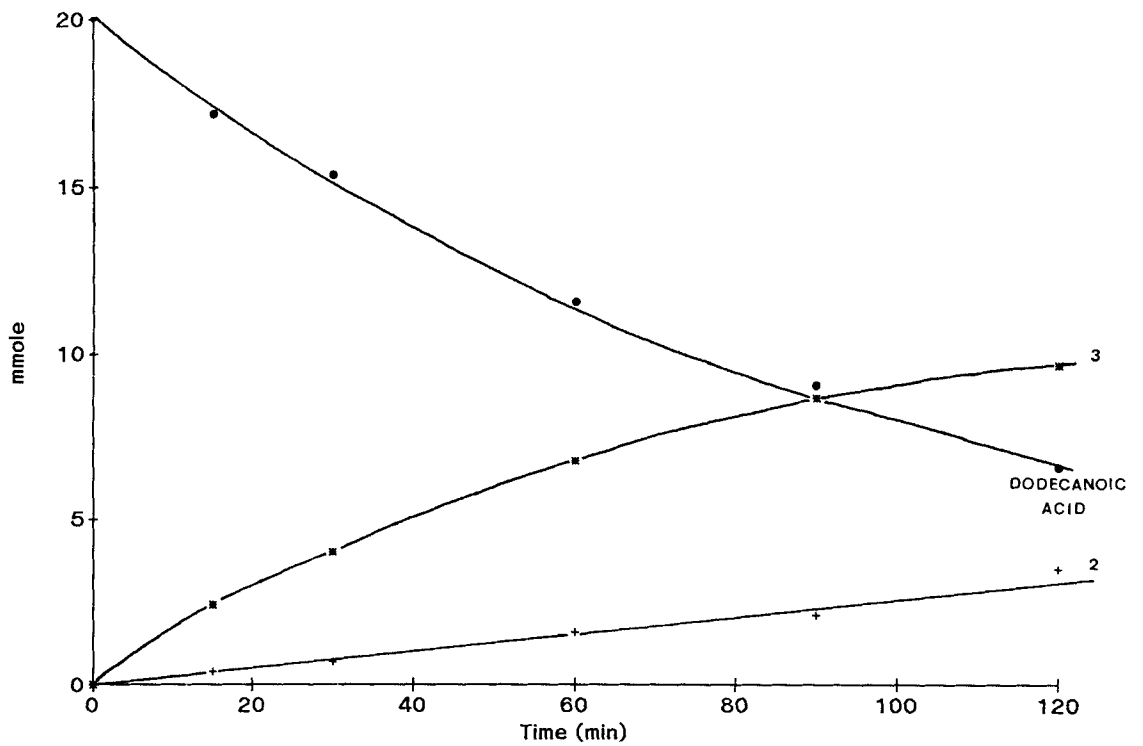


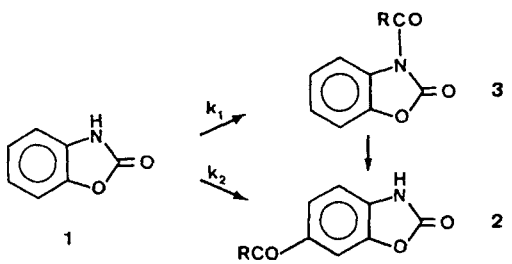
Figure 1. Reaction of **1** with dodecanoic acid at 120 °C in PPA: composition of the mixture at different times. (•) Dodecanoic acid; (+) compound **2**; (*) compound **3**

Table 3. Kinetics of reaction of **1** with dodecanoic acid at 120 °C in PPA

Time (min)	0	15	30	60	90	120
Dodecanoic acid (mmol)	20	17·2	15·4	11·6	9·1	6·6
2 (mmol)	0	0·4	0·7	1·6	2·1	3·5
3 (mmol)	0	2·4	4·0	6·8	8·7	9·7

integration of the triplets of $COCH_2$ which appeared at 2·30, 2·96 and 3·10 ppm for dodecanoic acid and the 6-dodecanoyl and 3-dodecanoyl compounds, respectively [verification of these integrations were obtained from the other signals (aromatic and aliphatic)]. The validity of this method was tested by three consecutive assays.

The results (Figure 1, Table 3) indicated that the reaction followed a pseudo-first-order law (compound **1**) was in substantial excess) and at 120 °C gave rate constants for two competitive reactions (Scheme 2) of $k_1 = 1{\cdot}1 \times 10^{-4}\,s^{-1}$ and $k_2 = 4{\cdot}0 \times 10^{-5}\,s^{-1}$. Compound **3** did not rearrange into **2** under these conditions, as established by heating a solution of **3** in PPA at 120 °C for 2 h, when **3** was recovered in 97% yield. However, we have shown that 3-acyl-2,3-dihydrobenzoxazol-2-ones rearranged into 6-acyl derivatives with good yields[9] (higher than those from the direct acylation of **1**). The general mechanism of the acylation can be described as a competitive acylation (in the 3- or 6-position) plus a rearrangement of the acyl group from the 3- to the 6-position (Scheme 2). The lower yields encountered in the direct acylation are explained by the formation of 3-acyl compounds, which gave **1** after hydrolysis. This was verified by analysing the crude product of the acylation of **1** with butanoic acid, when we found 6-butanoyl, 3-butanoyl and 3-6-dibutanoyl derivatives [83, 9 and 8% respectively, calculated from ^{1}H NMR spectrum of the crude product (56% yield)].



Scheme 2

Rearrangement of 4-acetyl-2*H*-1,4-benzoxazin-3(4*H*)-one

In order to compare the reactivities of **1** and 2*H*-1,4-benzoxazin-3(4*H*)-one(**6**), we prepared 4-acetyl-2*H*-1,4-benzoxazin-3(4*H*)-one from acetic anhydride and **6**. The 4-acetyl derivative rearranged in PPA exclusively but in low yield (40%) into the 7-acetyl derivative (50% of **6** was recovered). The acylation of **6** with acetic acid in PPA gave 6- and 7-acetyl derivatives (85 and 15%, respectively) in good yield (79%) whereas in dichloromethane with aluminium chloride and acetyl chloride, the 6-acetyl derivative was obtained selectively.[10] Because the method of structure determination in the cited patent[10] was inadequately unambiguous and the physical data (melting point) were nearly the same for the 6- and 7-acetyl derivatives, we investigated the ^{1}H NMR data of these compounds. To confirm the position of the acetyl group, we irradiated the 4-methyl signal of the 6-acetyl-4-methyl-2*H*-1,4-benzoxazin-3(4*H*)-one[10] and observed an Overhauser effect only on H-5 (26%). On a 400-MHz NMR spectrometer, we were able to differentiate the signals of 6- and 7-acetyl derivatives (Table 4) and calculate the relative proportion of each isomer.

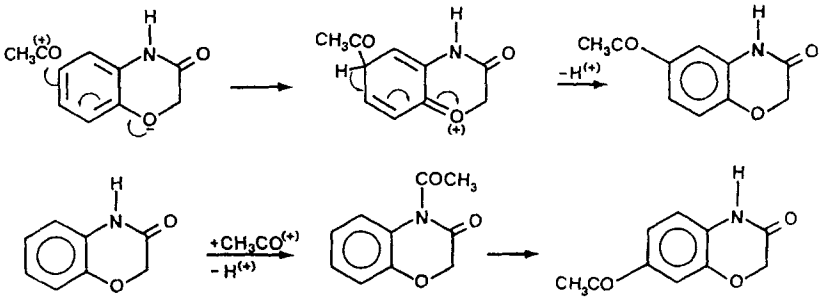
The predominant formation of the 6-acetyl derivative, which appears to result from a direct acylation, can be explained by an increased reactivity at this position owing to the oxygen donor effect, whereas the 7-acetyl derivative probably comes from an *N*-acylation followed by a Chattaway migration[11] [the 7-acetyl derivative is the sole product of the rearrangement of 4-acetyl-2*H*-1,4-benzoxazin-3(4*H*)-one in PPA (Scheme 3)].

We performed INDO calculations to confirm the regioselective attack of **1** and **6** by electrophiles. The calculations were carried out on HOMO electron density. The results are given in Table 5.

The calculations indicate that the order of the HOMO electron density of the ring carbons of **1** is 6 > 7a > 4 > 5 > 7 > 3a, whereas for **6** the order is

Table 4. ^{1}H NMR data for 6-acetyl- and 7-acetyl-2*H*-1,4-benzoxazin-3(4*H*)-ones ($CDCl_3$, TMS)

	Chemical shifts (ppm)							Coupling constants (Hz)			
	H-2	H-4	H-5	H-6	H-7	H-8	CH_3	$^3J_{H\text{-}5,H\text{-}6}$	$^4J_{H\text{-}5,H\text{-}7}$	$^4J_{H\text{-}6,H\text{-}8}$	$^3J_{H\text{-}7,H\text{-}8}$
6-Acetyl	4·66	10·75	7·63	—	7·50	7·01	2·49	—	2·00	—	8·30
7-Acetyl	4·63	10·96	6·99	7·50	—	7·64	2·50	8·20	—	1·70	—



Scheme 3

Table 5. Positional reactivities estimated by INDO calculations of **1** and **6**

Position	HOMO electron density of **1**	Position	HOMO electron density of **6**
4	0·1341	5	0·1144
3a	0·0046	4a	0·0445
7a	0·1576	8a	0·0021
7	0·0187	8	0·0456
6	0·1579	7	0·0315
5	0·0522	6	0·2160

6 > 5 > 8 > 4a > 7 > 8a. This is consistent with the observed results.

CONCLUSION

These reinvestigations on the acylation of **1** in PPA give a new view on the mechanism of the reaction and the reactivity of **1**. Comparison with **6** indicates a selective rearrangement of 4-acetyl-2*H*-1,4-benzoxazin-3(4*H*)-one which gives an alternative synthetic route to 7-acyl-2*H*-1,4-benzoxazin-3(4*H*)-ones.

EXPERIMENTAL

Melting points were obtained on a Büchi 510 capillary apparatus and are uncorrected. Elemental analysis were performed by CNRS (Vernaison) and were within 0·4% of the theoretical value. Infrared spectra were obtained on a Perkin-Elmer 297 spectrometer on KBr paths. NMR spectra were recorded on WP80 and AM400WB Brüker spectrometers in an appropriate deuterated solvent with tetramethylsilane as internal reference. Thin-layer chromatography (TLC) was performed on 3 × 10 cm plastic sheets precoated with a 0·2 mm layer of silica gel $60F_{254}$ (Merck), using ethyl acetate–hexane (2 : 3) as the solvent system.

Kinetics. In a three-necked flask, 27 g (200 mmol) of 2,3-dihydrobenzoxazol-2-one, 4 g (20 mmol) of dodecanoic acid and 100 g of polyphosphoric acid were heated at 120 °C for various periods. The mixture was poured into 1000 ml of ice–water with vigorous stirring. The precipitate was filtered, washed with water until neutral (pH7) and dried. A powder containing 6-dodecanoyl- and 3-dodecanoyl-2,3-dihydrobenzoxazol-2-ones and unreacted acid was analysed by ^{1}H NMR in CD_2Cl_2. A pure sample of 3-dodecanoyl derivative was prepared by a known method.[9] 6-Dodecanoyl and 3,6-didodecanoyl derivatives were isolated from the crude product of direct acylation (Table 2, entry 4) by fractional crystallization from acetone.

6-Dodecanoyl-2,3-dihydrobenzoxazol-2-one, m.p. 166–168 °C: ^{1}H NMR (DMSO-d_6), 10·00(NH), 7·83(dd, H5), 7·79(d, H7), 7·16(d, H4), 2·96(t, $COCH_2$), 1·60(m, $COCH_2CH_2$), 1·24[m, $CO(CH_2)_2(CH_2)_8$], 0·85(t, CH_3); IR, 3340–3100 cm^{-1} (NH), 1740 cm^{-1} (C=O ring), 1675 cm^{-1} (C=O). Analysis calculated for $C_{19}H_{27}NO_3$. C 71·89, H 8·56, N 4·41; found, C 71·90, H 8·51, N 4·38%.

3,6-Didodecanoyl-2,3-dihydrobenzoxazol-2-one, m.p. 126–127 °C: ^{1}H NMR ($CDCl_3$), 8·17(d, H4), 7·92(dd, H5), 7·84(d, H7), 3·15(t, $NCOCH_2$),

2·98(t, $COCH_2$), 1·80(quint, $NCOCH_2CH_2$), 1·76(quint, $COCH_2CH_2$), 1·29[m, $NCO(CH_2)_2(CH_2)_8$ and $CO(CH_2)_2(CH_2)_8$], 0·90(t, $2CH_3$); IR, 1830 cm^{-1} (C=O ring), 1725 cm^{-1} (NC=O), 1675 cm^{-1} (C=O). Analysis: calculated for $C_{31}H_{49}NO_4$, C 74·51, H 9·88, N 2·80; found, C 74·17, H 9·83, N 2·77%.

Reaction of 3-dodecanoyl-2,3-dihydrobenzoxazol-2-one. A 3·2 g (10 mmol) amount of 3-dodecanoyl-2,3-dihydrobenzoxazol-2-one and 50 g of polyphosphoric acid were heated at 120 °C for 2 h and the mixture was poured into 500 ml of ice–water. The precipitate was filtered, washed with water until neutral (pH 7) and dried. The product was identical with the starting material.[9]

The acylation of **1** in polyphosphoric acid (110 °C, 90 min) with butanoic acid gave 6-butanoyl, 3-butanoyl and 3,6-dibutanoyl derivatives (83, 9 and 8%, respectively) with a yield of crude product of 56%. 6-Butanoyl and 3-butanoyl derivatives were prepared as described previously.[9]

3,6-Dibutanoyl-2,3-dihydrobenzoxazol-2-one. A 1·02 g (5 mmol) amount of 6-butanoyl-2,3-dihydrobenzoxazol-2-one was refluxed in 10 ml of butanoic anhydride for 3 h. 3,6-Dibutanoyl-2,3-dihydrobenzoxazol-2-one precipitated on cooling and was filtered. Crystallization from ethanol gave a pure sample (1·10 g, 80%), m.p. 141–142 °C: ^{1}H NMR ($CDCl_3$), 8·04(d, H4), 7·93(dd, H5), 7·91(d, H7), 3·02(t, $NCOCH_2$), 3·00(t, $COCH_2$), 1·68(m, $NCOCH_2CH_2$), 1·63(m, $COCH_2CH_2$), 0·97[t, $NCO(CH_2)_2CH_3$], 0·92[t, $CO(CH_2)_2CH_3$]; IR, 1810 cm^{-1} (C=O ring), 1720 cm^{-1} (NC=O), 1665 cm^{-1} (C=O). Analysis calculated for $C_{15}H_{17}NO_4$, C 65·44, H 6·22, N 5·09; found, C 65·37, H 6·04, N 5·06%.

4-Acetyl-2H-1,4-benzoxazin-3(4H)-one. A 1·49 g (10 mmol) amount of 2*H*-1,4-benzoxazin-3(4*H*)-one[12] was refluxed in 20 ml of acetic anhydride for 3 h. The solution was cooled and poured into 200 ml of ice–water. The aqueous solution was extracted with diethyl ether (3 × 50 ml). The organic solution was dried ($MgSO_4$) and evaporated. The product was crystallized from cyclohexane (1·05 g, 54%), m.p. 150–151 °C: ^{1}H NMR ($CDCl_3$), 8·05(dd, H5), 7·25–7·10(m, H6,H7,H8), 4·60(s, H2), 2·51(s, $COCH_3$); IR, 1725 cm^{-1} (C=O ring), 1700 cm^{-1} (C=O). Analysis calculated for $C_{10}H_9NO_3$, C 62·82, H 4·75, N 7·33; found, C 62·49, H 4·72, N 7·35%.

Rearrangement of 4-acetyl-2H-1,4-benzoxazin-3(4H)-one. A 1·91 g (10-mmol) amount of 4-acetyl-2*H*-1,4-benzoxazin-3(4*H*)-one and 50 g of polyphosphoric acid were heated at 110 °C for 1·5 h and the mixture was poured into 500 ml of ice–water. The precipitate was filtered, washed with water until neutral (pH 7) and dried. The crude product (40% yield) was analysed by ^{1}H NMR in $CDCl_3$ and its spectrum was compared with those of 6-acetyl- and 7-acetyl-2*H*-1,4-benzoxazin-3(4*H*)-ones [prepared as described previously (Refs 10 and 13, respectively)]. The product was identical with the 7-acetyl derivative.

Acylation of 2H-1,4-benzoxazin-3(4H)-one. In a three-necked flask, 1·49 g (10 mmol) of 2*H*-1,4-benzoxazin-3(4*H*)-one, 0·90 g (15 mmol) of acetic acid and 50 g of polyphosphoric acid were heated at 110 °C for 1·5 h. The mixture was poured into 500 ml of ice–water with vigorous stirring. The precipitate was filtered, washed with water until neutral (pH 7) and dried. The crude product was analysed by ^{1}H NMR in $CDCl_3$. 6-Acetyl (85%) and 7-acetyl (15%) derivatives were obtained with a yield of 79%.

INDO calculations. The INDO calculations on **1** and **6** were performed by using the CNDO/INDO program of Dobosh.[14]

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