Pseudoacids. II. 2-Acylbenzoic Acid Derivatives

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Abstract

Structures of derivatives of cyclic *o*-acylbenzoic acids, including the chloride, endo- and exocyclic amides, esters and anhydrides, are examined. 3-Chloro-1(3*H*)-isobenzofuranone (1), orthorhombic, *Pbca*, a = 11.616 (5), b = 8.120 (3), c = 15.640 (9) Å; 3-methoxy-3-phenyl-1(3*H*)-isobenzofuranone (3), orthorhombic, $P2_12_12_1$, a = 6.923 (2), b = 8.291 (4), c = 21.551 (8) Å; 3-hydroxy-3-phenyl-*N*-propyl-1(3*H*)-isoindolone (4), orthorhombic, $P2_12_12_1$, a = 8.662 (4), b = 9.551 (7), c = 17.649 (14) Å; 3-(*N*-morpholino)-1(3*H*)-isobenzofuranone (5), triclinic, $P\bar{1}$, a = 6.172 (4), b = 11.163 (7), c = 17.33 (2) Å, α = 105.91 (6), β = 99.85 (6), γ = 97.57 (5)°; 3-(2'-benzoylbenzoyloxy)-3-phenyl-1(3*H*)-isobenzofuranone (7), triclinic, $P\bar{1}$, a = 9.694 (3), b = 10.505 (4), c = 11.163 (4) Å, α = 80.58 (3), β = 80.41 (3), γ = 76.49 (3)°; bis[1(3*H*)-isobenzofuranone-3-yl]ether (8), monoclinic, $I2/a$, a = 15.31 (2), b = 6.111 (12), c = 28.30 (5) Å, β = 101.61 (12)°. An open oxoacid tertiary amide is also described: *N*-morpholino 2'-benzoylbenzamide (6): monoclinic, $P2_1/c$, a = 6.844 (4), b = 15.696 (8), c = 14.154 (7) Å, β = 99.43 (4)°. Pseudoacid derivatives form planar isobenzofuran and isoindole rings, and the former aldehyde/ketone carbon–heteroatom endocyclic and exocyclic bond distances show bond length variations which correlate with the relative basicities of the attached groups. Structures of both endocyclic and exocyclic nitrogen pseudoamides are reported as well as examples of the normal–pseudoanhydride and the dipseudoanhydride.

1. Introduction

Pseudoacids are the cyclic forms of 4- and 5-oxocarboxylic acids. Oxoacids with structures bringing the carboxyl and aldehyde/ketone groups into proximity are more likely to form cyclic pseudoacid forms in solution and in the solid state (Langlois & Wolff, 1948; Mowry, 1950). Therefore, 4-oxopentanoic acid (levulinic acid) is entirely in its open form in solution at room temperature (Pascual *et al.*, 1964). Dehydration of levulinic acid has long been known to produce α-angelicalactone [5-methyl-2(3*H*)-furanone (Wolff, 1885; Bredt, 1886)] putatively through the lactol (pseudoacid). Levulinic acid derivatives levulinoyl chloride and levulinamide are likely in their cyclic forms in solution

over a range of temperatures (Sterk, 1968). Sterk (1968) additionally determined that the lactamol or pyrollidone form of the amide was the likely form of the cyclic amide rather than the aminolactone or furanone form. Probably the first pseudoester to be identified was that of opianic acid (Wegscheider, 1892).

A related system in which the formation of the cyclic pseudoacid is sensitive to substitution is the 2-alkanoyl-(Tyman & Najam, 1977) and 2-benzoylbenzoic acids (Bhatt & Kamath, 1968). 2-Formyl and 2-ethanoylbenzoic acids are clearly in their cyclic forms, while 2-benzoylbenzoic acid favors the open form in solution and the solid state (Lalancette *et al.*, 1990). The present contribution dwells on the derivatives of some 2-acyl benzoic acids for which the prospects were improved that they might be readily characterized in the solid state. The synthesis of esters in this series (Newman & McCleary, 1941) proceeds through the pseudoacid halide and results in both the normal and pseudoesters
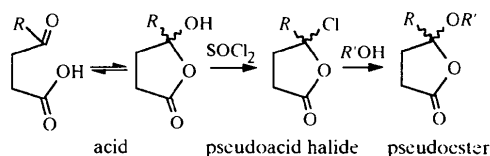

where R is bulky. The reaction of the acid chloride with primary and secondary amines apparently produces the normal amides, the former of which may form the hydroxylactam (Wawzonek *et al.*, 1944). If R is small,
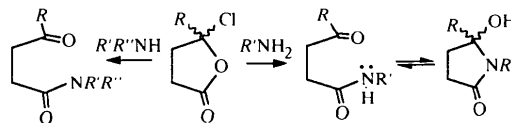
then the nucleophilic displacement of chloride becomes more likely, leading to the formation of the amino-lactone. A facile route to certain aminolactones lies through nucleoside esters of 2-(dibromomethyl)benzoic acid, which can be hydrolyzed to the corresponding aldehyde. On treatment of the normal aldehydoester with morpholine, the nucleoside alcohol is released, forming the aminolactone as a byproduct (Chattopadhyaya *et al.*, 1979). Finally, it is possible to dehydrate
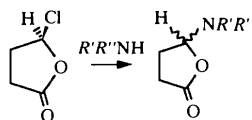
oxoacids to form the dipseudoanhydride (Schreiber & Wermuth, 1965) or to produce the mixed pseudo–normal anhydrides by nucleophilic substitution from the pseudoacid halide.

dipseudoanhydride   normal–pseudo-
anhydride
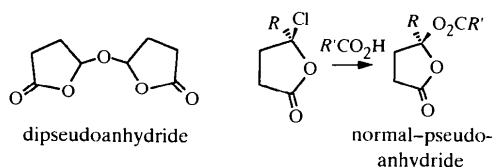
Oxoacids and their derivatives are not uncommon in natural product chemistry. Examples of pseudoacid halides include intermeditates on the route to 20(S)-camptothecin (Corey et al., 1975) and a derivative of marasmic acid (Cradwick & Sim, 1971), of pseudoesters include Ginkgo biloba ginkgolide B (Corey et al., 1988), qinghaosu or arteannuin (Schmid & Hofheinz, 1983), the weed germination stimulant strigol (Dailey Jr, 1987; Coggin et al., 1973), the isolactarane sterepolide from Stereum purpurea (Trost & Cheng, 1985), marasmic acid and its intermediates (Boeckman & Ko, 1980), the intermediates on the route to complement inhibitor K-76 (Corey & Das, 1982), and of a normal–pseudoanhydride include the O-pivaloyl isobilobalide (Weinges et al., 1987). Of the pseudoesters of aryl oxoacids, the chemistry is described in a variety of sources, of which Bowden & Malik (1993) and Bhatt & Kamath (1968) are useful sources.

Springing from our interest in C(sp^3)—O bond length disparity as it relates to molecular systems capable of open-cyclic tautomerism (Ruggiero et al., 1990; Valente et al., 1979), we sought to study a consistent open-cyclic oxoacid system with variable exocyclic substituents. In the somewhat diverse examples of oxoacid derivatives examined heretofore, C—O length differences have been found (Brooks et al., 1985; Qinghaosu Research Group, 1980; Weinges et al., 1987). The present communication examines the formation and structures
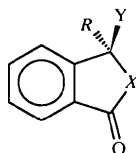
	R	X	Y
(1)	H	O	Cl
(2)	C_6H_5	O	Cl
(3)	C_6H_5	O	OCH_3
(4)	C_6H_5	$N(C_3H_7)$	OH
(5)	H	O	N(morpholine)

of 2-arylbenzoic pseudoacid derivatives primarily in the isobenzofuranone system. It includes the pseudoacid halide (1), pseudoester (3), pseudoamides (4) and (5), normal oxoamide (6), normal–pseudoanhydride (7) and the dipseudoanhydride (8).
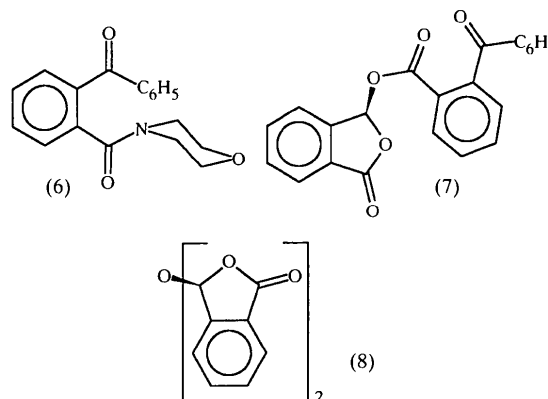
2. Experimental

Reagents were of the best commercially available purity. IR spectra were recorded on a Perkin–Elmer 1600 FTIR spectrometer, 2.0 cm^{-1} resolution. Differential scanning calorimetry was used to establish melting points and purity on 1.0 mg samples using a Shimadzu DSC-5, heating rate 10 min^{-1}, under N_2, standardized to 99.9999% tin and indium metals.

2.1. 3-Chloro-1(3H)-isobenzofuranone (1)

By the method of Newman & McCleary (1941), o-formylbenzoic acid and a molar excess of thionyl chloride were mixed under N_2, and the stirred mixture heated to reflux for 1 h. After cooling, the excess thionyl chloride was removed in vacuo and (1) was sublimed at 318 K and 300 mTorr from the resulting solid and deposited as large colorless crystals. The solid was unstable in moist air; m.p. 332.2 K (DSC peak); IR: 1777 cm^{-1} (νC=O).

2.2. 3-Methoxy-3-phenyl-1(3H)-isobenzofuranone (3)

o-Benzoylbenzoyl chloride (2) was prepared by a procedure analogous to that for (1) from o-benzoylbenzoic acid. To a solution of (2) in dry ether, a mixture of pyridine and methanol (2 equiv. each) was introduced dropwise with stirring. Pyridinium hydrochloride precipitated immediately and after the reaction was allowed to stir for 1 h, the solution was filtered to remove the salt and the solvent of the filtrate was removed in vacuo. The remaining solid was recrystallized from dry methanol; m.p. 355 K (DSC peak); IR: 1773 cm^{-1} (νC=O). Literature m.p. 354–355 K; IR: 1765 cm^{-1} (Bhatt & Kamath, 1968); m.p. 354.4–355.4 K (Newman & McCleary, 1941).

2.3. 3-Hydroxy-3-phenyl-N-propyl-1(3H)-isoindolone (4)

To a solution of (2) in CH_2Cl_2 was slowly added a solution containing 2 equiv. of propanamine in CH_2Cl_2. The precipitated propylammonium chloride was removed by filtration and the solvent was removed from the filtrate *in vacuo*. The solid (4) obtained was recrystallized from ethyl ethanoate as fine needles; m.p. 417.9 K (DSC peak); IR: 3100 (νO$-$H), 1672 cm^{-1} (νC$=$O).

2.4. 3-Morpholino-1(3H)-isobenzofuranone (5)

To a solution of (1) in CH_2Cl_2 was slowly added a solution containing 2 equiv. of morpholine in CH_2Cl_2. The precipitated morpholinium chloride was removed by filtration and the solvent was removed from the filtrate *in vacuo*. The solid obtained was recrystallized from ethyl ethanoate; m.p. 400.5 K (DSC peak); IR: 1753 cm^{-1} (νC$=$O).

2.5. N-Morpholino-2-benzoylbenzamide (6)

To a solution of (2) in CH_2Cl_2 was slowly added a solution of 2 equiv. of morpholine dissolved in CH_2Cl_2. The precipitated morpholinium chloride was removed by filtration and the solvent was removed from the filtrate *in vacuo*. The solid obtained was recrystallized from ethyl ethanoate; m.p. 372.2 K (DSC peak); IR: 1630 (νC$=$O, amide), 1672 cm^{-1} (νC$=$O, ketone).

2.6. 3-(2'-Benzoylbenzoyloxy)-1(3H)-isobenzofuranone (7)

To a solution of (2) in CH_2Cl_2 was added a mixture containing 1 equiv. of o-benzoylbenzoic acid and 1 equiv. of pyridine dissolved in CH_2Cl_2. After stirring at ambient temperature for 5 h, the mixture was filtered to remove the pyridinium hydrochloride, the solvent was removed *in vacuo* and the resulting solid was recrystallized from CH_3OH, affording colorless crystals; m.p. 414.6 K (DSC peak); IR: 1775 (νC$=$O, lactone), 1723 (νC$=$O, open ester), 1675 cm^{-1} (νC$=$O, ketone).

2.7. Bis[1(3H)-isobenzofuranone-3-yl]ether (8)

A sample of o-formylbenzoic acid (1 g) was heated *in vacuo* (300 mTorr) in a short path-length distillation apparatus using a heating mantle. The solid melted at ~373 K and began to reflux at ~543 K with the loss of water. On removing the heating mantle, the somewhat yellowed contents of the flask and lower part of the condenser immediately crystallized. The flask and lower condenser contents were collected, the color largely removed by flash chromatography (silical gel, ethyl

ethanoate), and the product was recrystallized from ethyl ethanoate as thin colorless needles; m.p. 494 K (DSC peak); IR: 1776 cm^{-1} (νC$=$O).

2.8. Crystallography

A summary of the crystal data, data collection and refinements for (1), (3)–(8) are given in Table 1. In each case the structures were discovered with the application of direct methods (Sheldrick, 1985). Models including coordinates and anisotropic displacement parameters for all non-H atoms were refined by full-matrix least-squares minimizing F^2 differences (Sheldrick, 1993). Hydrogen contributions to the scattering [with the exception of hydroxy H in (4)] were modeled by placing them at calculated positions, riding on the non-H atoms to which they are attached, and with isotropic displacement parameters fixed at 120% of the equivalent isotropic displacement parameters of the attached atoms. All data were used in the refinements. The hydroxy H atom in (4) was found in a difference Fourier map and the coordinates refined through a torsional parameter. In most cases an extinction correction was applied, but absorption corrections were not made. Methyl H atoms in (3) were modeled as disordered over alternate trigonal positions with the major conformer representing 74 (2)%.

For (8), needle-like crystals grew as incommensurately scattering pairs or multiples, although the crystals appeared optically as individuals. After examination of several specimens with X-radiation, a body-centered monoclinic cell could be identified, after which careful data collection proceeded on a fourth specimen. The diffraction record was carefully screened for reflections which were adversely affected by the crystal multiplicity, requiring the elimination of 22 reflections (out of 1959) for this reason.

Selected structural metrics associated with the five-ring cycle and its substituents are given in Table 2. Atom coordinates and equivalent isotropic displacement parameters for the structures are given in Tables 3–9.†

3. Discussion

The chemistry of pseudoacids has both similarities and differences from that of normal carboxylic acids. Both acids form derivatives of the typical classes (halides, esters, amides and anhydrides), but pseudoacids may form two types of amides and two types of anhydrides.

Formation of the pseudoacid chloride 3-chloro-1(3H)-isobenzofuranone (1) from 2-methanoylbenzoic

Table 1. *Experimental details*

|	(1)	(3)	(4)
Crystal data			
Chemical formula	$C_8H_5ClO_2$	$C_{15}H_{12}O_3$	$C_{17}H_{17}NO_2$
Chemical formula weight	168.57	240.25	267.32
Cell setting	Orthorhombic	Orthorhombic	Orthorhombic
Space group	*Pbca*	$P2_12_12_1$	$P2_12_12_1$
a (Å)	11.616 (5)	6.923 (2)	8.662 (4)
b (Å)	8.120 (3)	8.291 (4)	9.551 (7)
c (Å)	15.640 (9)	21.551 (8)	17.649 (14)
V (Å^3)	1475.2 (12)	1237.0 (8)	1460.1 (17)
Z	8	4	4
D_x (Mg m^{-3})	1.518	1.290	1.216
Radiation type	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$
Wavelength (Å)	0.71073	0.71073	0.71073
No. of reflections for cell parameters	49	35	30
θ range (°)	30–54	12.5–20.0	10–17.5
μ (mm^{-1})	0.455	0.090	0.080
Temperature (K)	294 (2)	294 (2)	294 (2)
Crystal form	Prism	Plate	Needle
Crystal size (mm)	0.80 × 0.40 × 0.40	0.40 × 0.40 × 0.20	0.25 × 0.10 × 0.10
Crystal color	Colorless	Colorless	Colorless
Data collection			
Diffractometer	Scintillation counter	Scintillation counter, pH analysis	Scintillation counter, pH analysis
Data collection method	ω scans	ω scans	ω scans
Absorption correction	None	None	None
No. of measured reflections	2684	1728	1704
No. of independent reflections	2153	1421	1135
No. of observed reflections	1204	1003	387
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R_{int}	0.0195	0.0102	0.0486
θ_{max} (°)	30.00	27.50	22.50
Range of h, k, l	$0 \rightarrow h \rightarrow 16$	$0 \rightarrow h \rightarrow 5$	$0 \rightarrow h \rightarrow 9$
	$0 \rightarrow k \rightarrow 11$	$0 \rightarrow k \rightarrow 10$	$0 \rightarrow k \rightarrow 10$
	$-22 \rightarrow l \rightarrow 0$	$-27 \rightarrow l \rightarrow 27$	$0 \rightarrow l \rightarrow 19$
No. of standard reflections	3	3	3
Frequency of standard reflections	Every 97 reflections	Every 97 reflections	Every 97 reflections
Intensity decay (%)	0.0 (20)	−0.0 (10)	−0.0 (35)
Refinement			
Refinement on	F^2	F^2	F^2
$R[F^2 > 2\sigma(F^2)]$	0.0435	0.0253	0.0583
$wR(F^2)$	0.1164	0.0581	0.1131
S	1.139	1.019	1.211
No. of reflections used in refinement	2153	1421	1135
No. of parameters used	101	165	182
H-atom treatment	H atoms fixed, calculated	H atoms fixed, calculated	H atoms fixed, calculated
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0731P)^2 + 0.0000P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0372P)^2 + 0.0000P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0577P)^2 + 0.0000P]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	0.001	0.000	0.000
$\Delta\rho_{max}$ (e Å^{-3})	0.250	0.077	0.211
$\Delta\rho_{min}$ (e Å^{-3})	−0.201	−0.077	−0.166
Extinction method	*SHELXL*93 (Sheldrick, 1993)	*SHELXL*93 (Sheldrick, 1993)	None
Extinction coefficient	0.0162 (26)	0.0139 (18)	—
Source of atomic scattering factors	*International Tables for Crystallography* (1992, Vol. C)	*International Tables for Crystallography* (1992, Vol. C)	*International Tables for Crystallography* (1992, Vol. C)
Computer programs			
Data collection	*P3/PC* (Siemens, 1989*a*)	*P3/PC* (Siemens, 1989*a*)	*P3/PC* (Siemens, 1989*a*)
Cell refinement	*P3/PC* (Siemens, 1989*a*)	*P3/PC* (Siemens, 1989*a*)	*P3/PC* (Siemens, 1989*a*)
Data reduction	*XDISK* (Siemens, 1989*b*)	*XDISK* (Siemens, 1989*b*)	*XDISK* (Siemens, 1989*b*)
Structure solution	*SHELXS*86 (Sheldrick, 1985)	*SHELXS*86 (Sheldrick, 1985)	*SHELXS*86 (Sheldrick, 1985)

Table 1 (cont.)

Structure refinement	(1) SHELXL93 (Sheldrick, 1993)	(3) SHELXL93 (Sheldrick, 1993)	(4) SHELXL93 (Sheldrick, 1993)
Preparation of material for publication	SHELXL93 (Sheldrick, 1993)	SHELXL93 (Sheldrick, 1993)	SHELXL93 (Sheldrick, 1993)

|	(5)	(6)	(7)	(8)
Crystal data				
Chemical formula	$C_{12}H_{13}NO_3$	$C_{18}H_{17}NO_3$	$C_{28}H_{18}O_5$	$C_{16}H_{10}O_5$
Chemical formula weight	219.23	295.33	434.42	282.24
Cell setting	Triclinic	Monoclinic	Triclinic	Monoclinic
Space group	$P\bar{1}$	$P2_1/c$	$P\bar{1}$	$I2/a$
a (Å)	6.172 (4)	6.844 (4)	9.694 (3)	15.308 (22)
b (Å)	11.163 (7)	15.696 (8)	10.505 (4)	6.111 (12)
c (Å)	17.332 (15)	14.154 (7)	11.163 (4)	28.299 (45)
α (°)	105.91 (6)		80.58 (3)	
β (°)	99.85 (6)	99.43 (4)	80.41 (3)	101.61 (12)
γ (°)	97.57 (5)		76.49 (3)	
V (Å^3)	1111.2 (13)	1499.9 (14)	1080.6 (7)	2593.1 (75)
Z	4	4	2	8
D_x (Mg m^{-3})	1.311	1.308	1.335	1.446
Radiation type	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$
Wavelength (Å)	0.71073	0.71073	0.71073	0.71073
No. of reflections for cell parameters	40	30	30	40
θ range (°)	12.5–20.0	15.0–25.0	12.5–20.0	12.5–20.0
μ (mm^{-1})	0.095	0.090	0.092	0.109
Temperature (K)	293 (2)	293 (2)	294 (2)	295 (2)
Crystal form	Rhomb	Prism	Needle	Needle
Crystal size (mm)	0.40 × 0.20 × 0.10	0.50 × 0.40 × 0.20	0.30 × 0.20 × 0.10	1.00 × 0.06 × 0.04
Crystal color	Colorless	Colorless	Colorless	Colorless
Data collection				
Diffractometer	Scintillation counter, pH analysis	Scintillation counter, pH analysis	Scintillation counter, pH analysis	Scintillation counter, pH analysis
Data collection method	ω scans	ω scans	ω scans	ω scans
Absorption correction	None	None	None	None
No. of measured reflections	5784	3705	5293	1937
No. of independent reflections	5092	3433	4984	1680
No. of observed reflections	2282	1417	2137	404
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R_{int}	0.0274	0.0390	0.0210	0.1166
θ_{max} (°)	27.52	27.49	27.52	22.51
Range of h, k, l	$0 \rightarrow h \rightarrow 8$ $-14 \rightarrow k \rightarrow 14$ $-22 \rightarrow l \rightarrow 22$	$0 \rightarrow h \rightarrow 8$ $0 \rightarrow k \rightarrow 20$ $-18 \rightarrow l \rightarrow 18$	$0 \rightarrow h \rightarrow 12$ $-13 \rightarrow k \rightarrow 13$ $-14 \rightarrow l \rightarrow 14$	$0 \rightarrow h \rightarrow 16$ $0 \rightarrow k \rightarrow 6$ $-30 \rightarrow l \rightarrow 29$
No. of standard reflections	3	3	3	3
Frequency of standard reflections	Every 97 reflections	Every 97 reflections	Every 97 reflections	Every 97 reflections
Intensity decay (%)	-2.4 (20)	-1.7 (33)	-1.4 (15)	$+6$ (4)
Refinement				
Refinement on	F^2	F^2	F^2	F^2
$R[F^2 > 2\sigma(F^2)]$	0.0481	0.0431	0.0350	0.0678
$wR(F^2)$	0.1175	0.0906	0.0599	0.1431
S	1.127	1.018	0.947	1.297
No. of reflections used in refinement	5092	3433	4984	1674
No. of parameters used	290	200	299	190
H-atom treatment	H atoms fixed, calculated	H atoms fixed, calculated	H atoms fixed, calculated	H atoms fixed, calculated
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0740P)^2 + 0.0000P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0485P)^2 + 0.0000P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0198P)^2 + 0.0000P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0650P)^2 + 0.0000P]$, where $P = (F_o^2 + 2F_c^2)/3$

Table 1 (cont.)

	(5)	(6)	(7)	(8)
$(\Delta/\sigma)_{max}$	0.000	0.000	0.000	0.000
$\Delta\rho_{max}$ (e Å^{-3})	0.227	0.184	0.127	0.296
$\Delta\rho_{min}$ (e Å^{-3})	−0.225	−0.168	−0.151	−0.237
Extinction method	SHELXL93 (Sheldrick, 1993)	SHELXL93 (Sheldrick, 1993)	SHELXL93 (Sheldrick, 1993)	None
Extinction coefficient	0.0214 (24)	0.0163 (14)	0.0114 (7)	—
Source of atomic scattering factors	International Tables for Crystallography (1992, Vol. C)	International Tables for Crystallography (1992, Vol. C)	International Tables for Crystallography (1992, Vol. C)	International Tables for Crystallography (1992, Vol. C)
Computer programs				
Data collection	P3/PC (Siemens, 1989a)	P3/PC (Siemens, 1989a)	P3/PC (Siemens, 1989a)	P3/PC (Siemens, 1989a)
Cell refinement	P3/PC (Siemens, 1989a)	P3/PC (Siemens, 1989a)	P3/PC (Siemens, 1989a)	P3/PC (Siemens, 1989a)
Data reduction	XDISK (Siemens, 1989b)	XDISK (Siemens, 1989b)	XDISK (Siemens, 1989b)	XDISK (Siemens, 1989b)
Structure solution	SHELXS86 (Sheldrick, 1985)	SHELXS86 (Sheldrick, 1985)	SHELXS86 (Sheldrick, 1985)	SHELXS86 (Sheldrick, 1985)
Structure refinement	SHELXL93 (Sheldrick, 1993)	SHELXL93 (Sheldrick, 1993)	SHELXL93 (Sheldrick, 1993)	SHELXL93 (Sheldrick, 1993)
Preparation of material for publication	SHELXL93 (Sheldrick, 1993)	SHELXL93 (Sheldrick, 1993)	SHELXL93 (Sheldrick, 1993)	SHELXL93 (Sheldrick, 1993)

Table 2. Selected bond lengths (Å), angles (°) and torsion angles (°) in 4-oxoacid pseudoacid esters, amides and anhydrides (parentheses: [heteroatoms], e.s.d.'s)

	C=O	=C−X [X]	X−C	C−Y [Y]	X−C−Y	τC−X−C−Y
(1)	1.196 (2)	1.371 (2) [O]	1.405 (2)	1.791 (2) [Cl]	109.6 (1)	−118.7 (1)
(3)	1.198 (2)	1.363 (2) [O]	1.466 (2)	1.386 (3) [O]	109.3 (2)	−127.3 (2)
(4)	1.264 (11)	1.351 (12) [N]	1.497 (11)	1.412 (10) [O]	110.0 (8)	−128.8 (8)
(5)	1.210 (3)	1.360 (3) [O]	1.501 (3)	1.415 (3) [N]	112.8 (2)	−127.4 (2)
	1.211 (3)	1.364 (3) [O]	1.490 (3)	1.427 (3) [N]	112.2 (2)	125.2 (2)
(7)	1.200 (2)	1.385 (2) [O]	1.453 (2)	1.444 (2) [O]	107.7 (1)	118.0 (1)
(8)	1.167 (12)	1.393 (12) [O]	1.460 (11)	1.424 (11) [O]	108.2 (8)	−118.5 (8)
	1.170 (11)	1.371 (11) [O]	1.451 (11)	1.398 (11) [O]	111.0 (8)	−116.0 (8)
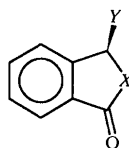
acid and thionyl chloride proceeds quickly and quantitatively at room temperature. Crystals of (1) hydrolyze in moist air. A diagram of the structure is shown in Fig. 1. With the exception of the H and Cl on C3, the non-H atoms of the molecular structure are almost planar [mean deviation 0.013 (10) Å]. There are no unusual intermolecular contacts. The C−Cl [1.791 (2) Å] is longer than in a comparable alkyl halide (Bart et al., 1979; Bürgi & Dunitz, 1994), but not quite as long as in benzyl chlorides (Carrell, 1993; Zacharias, 1977). The (endocyclic) C3−O2 bond is 1.405 (2) Å and considerably shorter than the typical C−O length in pseudoacids (1.46 Å; Valente et al., 1998). Since chloride is a somewhat better leaving group than carboxylate from C3, lengthening of the C−Cl bond and contraction of the C−O bond may be expected. This may be rationalized by the participation of resonance structure A, where Y = Cl⁻.
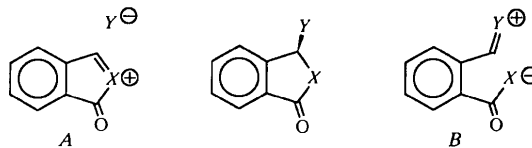
Using the acid halide (2), reaction with methanol in the presence of a base can produce almost quantitative yields of the pseudoester (3). The structure of (3) is shown in Fig. 2. Only the phenyl and methoxy groups are out of the plane described by the remaining non-H atoms for which the mean deviation from the plane is 0.014 (15) Å. Since the methoxy is a much poorer leaving group than carboxylate, the endocyclic C−O bond is lengthened to 1.466 (2) Å, while the exocyclic C−O is shortened to 1.386 (3) Å. This may be modeled by participation in the ground state by resonance structures more like B.

Table 3. *Fractional atomic coordinates and equivalent isotropic displacement parameters ($\mathring{A}^2$) for (1)*

$U_{eq} = (1/3)\Sigma_i\Sigma_j U^{ij}a^ia^j\mathbf{a}_i.\mathbf{a}_j.$

	x	y	z	U_{eq}
Cl	0.28256 (5)	0.09827 (7)	0.80148 (3)	0.0796 (2)
O1	−0.06586 (12)	0.3491 (2)	0.83822 (10)	0.0872 (5)
O2	0.06026 (11)	0.1532 (2)	0.80272 (6)	0.0630 (4)
C1	0.00561 (14)	0.2525 (2)	0.86085 (10)	0.0540 (4)
C3	0.14249 (15)	0.0531 (2)	0.84315 (9)	0.0539 (4)
C3A	0.13495 (13)	0.0955 (2)	0.93616 (9)	0.0428 (4)
C4	0.1960 (2)	0.0379 (3)	1.00543 (12)	0.0675 (6)
C5	0.1685 (2)	0.1069 (3)	1.08462 (12)	0.0851 (8)
C6	0.0841 (2)	0.2239 (3)	1.09338 (10)	0.0799 (7)
C7	0.0247 (2)	0.2785 (2)	1.02432 (10)	0.0619 (5)
C7A	0.05244 (12)	0.2137 (2)	0.94554 (8)	0.0418 (4)

Table 4. *Fractional atomic coordinates and equivalent isotropic displacement parameters ($\mathring{A}^2$) for (3)*

$U_{eq} = (1/3)\Sigma_i\Sigma_j U^{ij}a^ia^j\mathbf{a}_i.\mathbf{a}_j.$

	x	y	z	U_{eq}
O1	0.2505 (3)	0.3226 (2)	0.52870 (6)	0.1073 (7)
O2	0.1019 (2)	0.26090 (13)	0.61759 (6)	0.0698 (5)
O3	−0.1326 (2)	0.1143 (2)	0.67051 (6)	0.0676 (4)
C1	0.1950 (4)	0.2210 (3)	0.56402 (9)	0.0743 (7)
C3	0.0620 (4)	0.1178 (2)	0.65547 (8)	0.0545 (6)
C3A	0.1304 (3)	−0.0182 (2)	0.61420 (8)	0.0496 (6)
C4	0.1234 (3)	−0.1824 (2)	0.62384 (9)	0.0620 (6)
C5	0.1985 (4)	−0.2816 (3)	0.57865 (10)	0.0742 (7)
C6	0.2801 (4)	−0.2179 (3)	0.52590 (11)	0.0803 (8)
C7	0.2888 (4)	−0.0540 (3)	0.51599 (10)	0.0764 (7)
C7A	0.2102 (3)	0.0440 (3)	0.56143 (8)	0.0579 (6)
C11	0.1728 (3)	0.1295 (2)	0.71561 (8)	0.0494 (6)
C12	0.1251 (3)	0.0290 (2)	0.76420 (9)	0.0599 (6)
C13	0.2297 (4)	0.0306 (3)	0.81858 (9)	0.0700 (7)
C14	0.3819 (4)	0.1325 (3)	0.82529 (10)	0.0819 (8)
C15	0.4292 (4)	0.2337 (3)	0.77742 (12)	0.0892 (8)
C16	0.3272 (4)	0.2322 (3)	0.72276 (10)	0.0718 (7)
C17	−0.2638 (4)	0.0851 (3)	0.62066 (9)	0.0853 (8)

Table 5. *Fractional atomic coordinates and equivalent isotropic displacement parameters ($\mathring{A}^2$) for (4)*

$U_{eq} = (1/3)\Sigma_i\Sigma_j U^{ij}a^ia^j\mathbf{a}_i.\mathbf{a}_j.$

	x	y	z	U_{eq}
O1	0.2532 (7)	0.7603 (8)	0.0769 (4)	0.080 (2)
O3	−0.0089 (5)	0.5682 (8)	−0.1192 (4)	0.083 (2)
N2	0.1709 (8)	0.6186 (10)	−0.0196 (4)	0.056 (2)
C7A	0.2021 (10)	0.8443 (14)	−0.0517 (6)	0.057 (3)
C7	0.2313 (10)	0.9896 (15)	−0.0500 (7)	0.075 (3)
C6	0.2092 (11)	1.0626 (13)	−0.1168 (9)	0.090 (4)
C5	0.1567 (12)	0.9977 (16)	−0.1814 (7)	0.083 (3)
C4	0.1307 (10)	0.8527 (15)	−0.1821 (7)	0.077 (3)
C3A	0.1551 (9)	0.7792 (12)	−0.1150 (7)	0.056 (3)
C1	0.2163 (10)	0.7438 (14)	0.0082 (7)	0.061 (3)
C3	0.1378 (10)	0.6250 (13)	−0.1028 (6)	0.064 (3)
C11	0.2521 (10)	0.5414 (11)	−0.1455 (6)	0.064 (3)
C12	0.2125 (10)	0.4459 (11)	−0.2017 (6)	0.073 (3)
C13	0.3175 (13)	0.3717 (11)	−0.2435 (6)	0.093 (3)
C14	0.4762 (12)	0.3997 (12)	−0.2343 (7)	0.091 (4)
C15	0.5163 (11)	0.4926 (13)	−0.1775 (6)	0.092 (4)
C16	0.4128 (9)	0.5683 (12)	−0.1361 (6)	0.078 (3)
C21	0.1577 (11)	0.4891 (11)	0.0265 (6)	0.080 (3)
C22	0.3073 (11)	0.4208 (14)	0.0438 (6)	0.114 (4)
C23	0.2834 (14)	0.3015 (11)	0.1019 (6)	0.137 (5)

Table 6. *Fractional atomic coordinates and equivalent isotropic displacement parameters ($\mathring{A}^2$) for (5)*

$U_{eq} = (1/3)\Sigma_i\Sigma_j U^{ij}a^ia^j\mathbf{a}_i.\mathbf{a}_j.$

	x	y	z	U_{eq}
O1A	0.7628 (3)	0.34313 (15)	0.37245 (9)	0.0674 (5)
O2A	0.4063 (2)	0.25061 (13)	0.35836 (8)	0.0551 (4)
O3A	0.0086 (3)	−0.15695 (14)	0.33348 (9)	0.0630 (4)
N1A	0.1448 (3)	0.11026 (15)	0.39933 (10)	0.0467 (4)
C1A	0.6082 (4)	0.3201 (2)	0.40383 (14)	0.0521 (5)
C3A	0.2451 (3)	0.2378 (2)	0.41265 (12)	0.0466 (5)
C3AA	0.3864 (3)	0.3058 (2)	0.49695 (12)	0.0438 (5)
C4A	0.3305 (4)	0.3246 (2)	0.57235 (13)	0.0547 (6)
C5A	0.4942 (4)	0.3969 (2)	0.64135 (14)	0.0641 (7)
C6A	0.7051 (4)	0.4473 (2)	0.63449 (15)	0.0628 (6)
C7A	0.7611 (4)	0.4270 (2)	0.55924 (14)	0.0543 (6)
C7AA	0.5978 (3)	0.3551 (2)	0.49076 (12)	0.0444 (5)
C8A	−0.0193 (4)	0.0523 (2)	0.32153 (14)	0.0616 (6)
C9A	−0.1410 (4)	−0.0741 (2)	0.3223 (2)	0.0681 (7)
C10A	0.1702 (4)	−0.0999 (2)	0.40779 (14)	0.0626 (6)
C11A	0.2982 (4)	0.0253 (2)	0.41023 (14)	0.0574 (6)
O1B	0.8788 (3)	0.9692 (2)	0.11150 (10)	0.0691 (5)
O2B	0.5334 (2)	0.89174 (13)	0.12089 (8)	0.0542 (4)
O3B	0.2020 (3)	0.52142 (13)	0.16648 (8)	0.0557 (4)
N1B	0.2397 (3)	0.70642 (15)	0.08345 (9)	0.0446 (4)
C1B	0.6911 (4)	0.9119 (2)	0.07713 (14)	0.0510 (5)
C3B	0.3185 (3)	0.8185 (2)	0.06432 (12)	0.0469 (5)
C3AB	0.3731 (3)	0.7962 (2)	−0.01927 (13)	0.0453 (5)
C4B	0.2406 (4)	0.7331 (2)	−0.09616 (14)	0.0586 (6)
C5B	0.3365 (5)	0.7303 (2)	−0.16318 (15)	0.0699 (7)
C6B	0.5557 (5)	0.7891 (2)	−0.1535 (2)	0.0703 (7)
C7B	0.6880 (4)	0.8512 (2)	−0.07719 (15)	0.0592 (6)
C7AB	0.5918 (3)	0.8537 (2)	−0.01036 (13)	0.0469 (5)
C8B	0.1608 (4)	0.7311 (2)	0.16049 (13)	0.0530 (5)
C9B	0.0527 (4)	0.6080 (2)	0.16826 (14)	0.0574 (6)
C10B	0.2804 (4)	0.4972 (2)	0.09235 (13)	0.0539 (6)
C11B	0.3923 (4)	0.6179 (2)	0.08145 (13)	0.0518 (5)

Table 7. *Fractional atomic coordinates and equivalent isotropic displacement parameters ($\mathring{A}^2$) for (6)*

$U_{eq} = (1/3)\Sigma_i\Sigma_j U^{ij}a^ia^j\mathbf{a}_i.\mathbf{a}_j.$

	x	y	z	U_{eq}
O1	0.0857 (2)	0.68780 (9)	0.34798 (9)	0.0639 (4)
O2	0.5063 (2)	0.61810 (8)	0.28108 (9)	0.0635 (4)
O3	0.0642 (2)	0.60511 (9)	0.02932 (9)	0.0687 (4)
N	0.0696 (2)	0.71200 (10)	0.18929 (10)	0.0485 (4)
C1	0.3191 (3)	0.78411 (11)	0.30599 (11)	0.0407 (5)
C2	0.2890 (3)	0.87106 (12)	0.29754 (13)	0.0545 (5)
C3	0.4390 (4)	0.92786 (13)	0.33078 (14)	0.0633 (6)
C4	0.6201 (4)	0.89820 (13)	0.37420 (13)	0.0626 (6)
C5	0.6540 (3)	0.81173 (12)	0.38346 (12)	0.0528 (5)
C6	0.5055 (3)	0.75402 (11)	0.34960 (11)	0.0417 (5)
C7	0.1505 (3)	0.72340 (11)	0.28241 (13)	0.0443 (5)
C8	0.5452 (3)	0.66040 (12)	0.35380 (13)	0.0441 (5)
C9	0.6309 (3)	0.62083 (11)	0.44695 (12)	0.0434 (5)
C10	0.7097 (3)	0.53901 (13)	0.44724 (15)	0.0562 (5)
C11	0.7792 (3)	0.49871 (15)	0.5339 (2)	0.0688 (7)
C12	0.7686 (3)	0.5394 (2)	0.6185 (2)	0.0758 (7)
C13	0.6929 (4)	0.6202 (2)	0.61930 (14)	0.0726 (7)
C14	0.6241 (3)	0.66067 (12)	0.53285 (13)	0.0536 (5)
C15	0.1604 (3)	0.73926 (13)	0.10802 (13)	0.0585 (6)
C16	0.2237 (3)	0.66299 (15)	0.05642 (14)	0.0692 (7)
C17	−0.0139 (3)	0.57745 (13)	0.11097 (14)	0.0642 (6)
C18	−0.0886 (3)	0.65027 (12)	0.16307 (14)	0.0571 (6)

Table 8. *Fractional atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for (7)*

$U_{eq} = (1/3)\Sigma_i \Sigma_j U^{ij} a^i a^j \mathbf{a}_i . \mathbf{a}_j.$

	x	y	z	U_{eq}
O1	0.07288 (13)	0.79465 (12)	0.07835 (11)	0.0692 (4)
O2	0.27166 (11)	0.64225 (10)	0.11408 (9)	0.0442 (3)
O3	0.34128 (10)	0.42189 (9)	0.19863 (9)	0.0422 (3)
O4	0.10568 (12)	0.44374 (10)	0.18574 (11)	0.0563 (3)
O5	0.35401 (13)	0.21825 (12)	0.41496 (11)	0.0667 (4)
C1	0.1402 (2)	0.7202 (2)	0.1517 (2)	0.0483 (4)
C3	0.3276 (2)	0.55677 (14)	0.21899 (13)	0.0368 (4)
C3A	0.2196 (2)	0.59646 (14)	0.32632 (14)	0.0385 (4)
C4	0.2181 (2)	0.5496 (2)	0.44958 (15)	0.0501 (4)
C5	0.1032 (2)	0.6056 (2)	0.5293 (2)	0.0616 (5)
C6	−0.0078 (2)	0.7024 (2)	0.4875 (2)	0.0641 (5)
C7	−0.0063 (2)	0.7486 (2)	0.3644 (2)	0.0570 (5)
C7A	0.1106 (2)	0.69406 (15)	0.28487 (15)	0.0428 (4)
C11	0.4789 (2)	0.57172 (14)	0.21966 (13)	0.0367 (4)
C12	0.5053 (2)	0.65736 (15)	0.29087 (15)	0.0498 (4)
C13	0.6428 (2)	0.6765 (2)	0.2866 (2)	0.0571 (5)
C14	0.7538 (2)	0.6112 (2)	0.2118 (2)	0.0568 (5)
C15	0.7287 (2)	0.5255 (2)	0.1413 (2)	0.0574 (5)
C16	0.5923 (2)	0.5064 (2)	0.14454 (14)	0.0498 (4)
C20	0.2239 (2)	0.3768 (2)	0.18746 (13)	0.0418 (4)
C21	0.2655 (2)	0.23482 (15)	0.16888 (14)	0.0405 (4)
C22	0.1950 (2)	0.1947 (2)	0.08811 (15)	0.0517 (4)
C23	0.2330 (2)	0.0667 (2)	0.0597 (2)	0.0609 (5)
C24	0.3426 (2)	−0.0214 (2)	0.1120 (2)	0.0620 (5)
C25	0.4134 (2)	0.0174 (2)	0.1922 (2)	0.0535 (5)
C26	0.3745 (2)	0.1444 (2)	0.22383 (14)	0.0425 (4)
C27	0.4358 (2)	0.17419 (15)	0.3284 (2)	0.0475 (4)
C28	0.5924 (2)	0.14323 (15)	0.3293 (2)	0.0452 (4)
C29	0.6455 (2)	0.1204 (2)	0.4403 (2)	0.0604 (5)
C30	0.7906 (2)	0.0977 (2)	0.4431 (2)	0.0773 (6)
C31	0.8834 (2)	0.0997 (2)	0.3359 (2)	0.0788 (6)
C32	0.8330 (2)	0.1218 (2)	0.2256 (2)	0.0731 (6)
C33	0.6869 (2)	0.1428 (2)	0.2222 (2)	0.0579 (5)

Table 9. *Fractional atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for (8)*

$U_{eq} = (1/3)\Sigma_i \Sigma_j U^{ij} a^i a^j \mathbf{a}_i . \mathbf{a}_j.$

|	x	y	z	U_{eq}
O3	0.0697 (3)	0.1392 (11)	0.3587 (2)	0.041 (2)
O1	0.2320 (4)	0.6724 (12)	0.3242 (3)	0.064 (2)
O2	0.1916 (4)	0.3676 (11)	0.3574 (2)	0.043 (2)
C1	0.1967 (6)	0.5025 (20)	0.3184 (4)	0.059 (3)
C3	0.1492 (6)	0.1604 (17)	0.3403 (3)	0.046 (3)
C3A	0.1295 (5)	0.1790 (16)	0.2877 (3)	0.035 (2)
C4	0.0855 (6)	0.0285 (17)	0.2530 (4)	0.053 (3)
C5	0.0781 (6)	0.0994 (19)	0.2047 (4)	0.057 (3)
C6	0.1084 (7)	0.2910 (21)	0.1915 (4)	0.064 (3)
C7	0.1505 (7)	0.4397 (18)	0.2267 (4)	0.062 (3)
C7A	0.1575 (6)	0.3785 (16)	0.2743 (3)	0.038 (2)
O1A	0.1024 (5)	−0.4111 (13)	0.4575 (3)	0.065 (2)
O2A	0.1299 (3)	−0.0976 (11)	0.4223 (2)	0.045 (2)
C1A	0.0772 (7)	−0.2412 (19)	0.4411 (4)	0.050 (3)
C3BA	0.0828 (6)	0.1058 (17)	0.4085 (4)	0.048 (3)
C3AA	−0.0061 (6)	0.0756 (16)	0.4223 (3)	0.038 (3)
C4A	−0.0792 (6)	0.2112 (18)	0.4160 (3)	0.057 (3)
C5A	−0.1555 (6)	0.1363 (20)	0.4318 (3)	0.056 (3)
C6A	−0.1562 (7)	−0.0694 (21)	0.4524 (3)	0.064 (4)
C7BA	−0.0820 (7)	−0.2057 (18)	0.4583 (3)	0.056 (3)
C7AA	−0.0080 (6)	−0.1310 (15)	0.4423 (3)	0.034 (2)

On reaction with the primary amine propanamine, the pseudoacid halides may produce hydroxylactams. This would seem to proceed from the open form of the acid halide, which is available in the reaction solution depending on the equilibrium and reaction rate. Thus, *o*-benzoylbenzoyl chloride, which in solution exists ∼90% in the open form, produces the *N*-propyl-3-hydroxy-1(3*H*)-isobenzofuranone (4) in high yield (where 2 equiv. of amine are used).
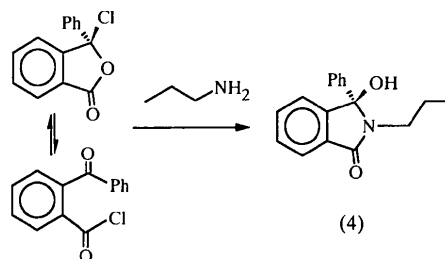
The structure of (4) is shown in Fig. 3. The non-H atoms of the isoindole rings (including the trigonal N) are essentially planar, with a mean deviation from the plane of 0.020 (14) Å. Since the amide is a weaker base than water, the endocyclic C3—N2 bond is lengthened to 1.497 (11) Å relative to that typical of γ-lactams (1.460 Å; Bürgi & Dunitz, 1994). Correspondingly, the exocyclic C3—O3 length is shortened to 1.412 (10) Å. Additionally, the passage of charge from nitrogen to the better acceptor carbonyl oxygen in a resonance contributor such as *B* would involve contributions more likely from C atoms and the carbonyl C1—O1 bond is lengthened to 1.264 (11) Å again compared with typical γ-lactams (1.225 Å). The hydroxy H atom is hydrogen bonded to O1 of a neighboring molecule with H···O 1.78 (1) Å, the angle at H 174 (1)° (after normalizing
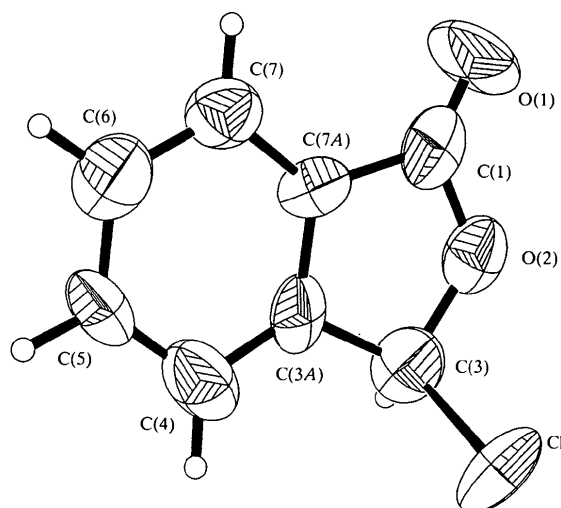
Fig. 1. Thermal ellipsoid plot (50%) for 3-chloro-1(3*H*)-isobenzofuranone (1).

the OH distance to 0.96 Å) and O3⋯O1 2.74 (1) Å. The hydrogen-bonding motif consists of chains of hydrogen-bonded molecules down the a (screw) axis.
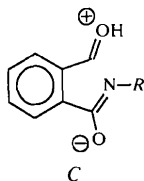
Reaction of the open acid halide (2) with secondary amines such as morpholine generates the normal tertiary amide (6), while with the cyclic o-formylbenzoyl chloride (1) the pseudoamide (5) is produced. The structures of (5) and (6) are shown in Figs. 4 and 5, respectively. The pseudoamide (5) has two molecules in

the asymmetic unit; their structures and conformations are equivalent with distances, angles and torsion angles rarely differing by more than three e.s.d.'s. Non-H atoms of the isobenzofuranone are essentially planar with mean deviations of 0.011 (9) and 0.013 (6) Å for the two molecules in the asymmetric unit. The exocyclic morpholino nitrogen is pyramidal, as indicated from the sum of the interbond angles at nitrogen, which are 340.0 and 339.0°. Since carboxylate is a much better leaving group than morpholine, the endocyclic C3—O2 bond is lengthened considerably (average 1.495 Å) compared with the typical γ-lactone (1.464 Å; Bürgi & Dunitz, 1994). The endocyclic C—O bond is among the longer known for nominally neutral C—O's. The adjacent exocyclic C—N is shortened (average 1.421 Å) compared with that found for normal pyramidal tertiary nitrogen (1.469 Å). A model accounting for this
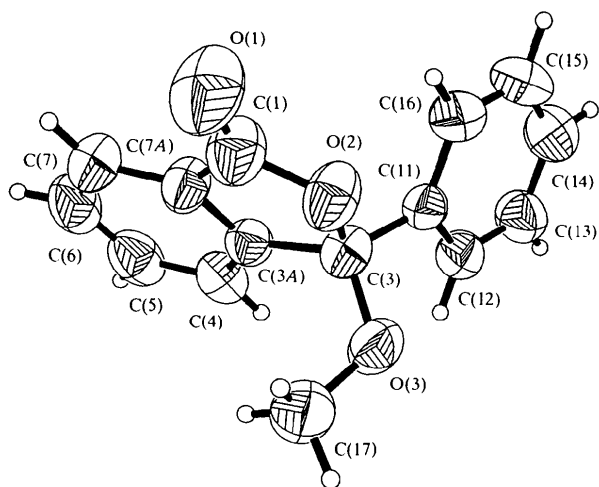
Fig. 2. Thermal ellipsoid plot (50%) for the major conformer of 3-methoxy-3-phenyl-1(3H)-isobenzofuranone (3).
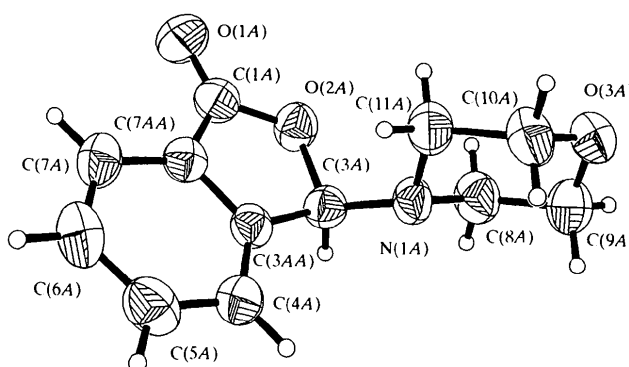

Fig. 4. Thermal ellipsoid plot (50%) for one of the two molecules in the asymmetric unit of 3-(N-morpholino)-1(3H)-isobenzofuranone (5).

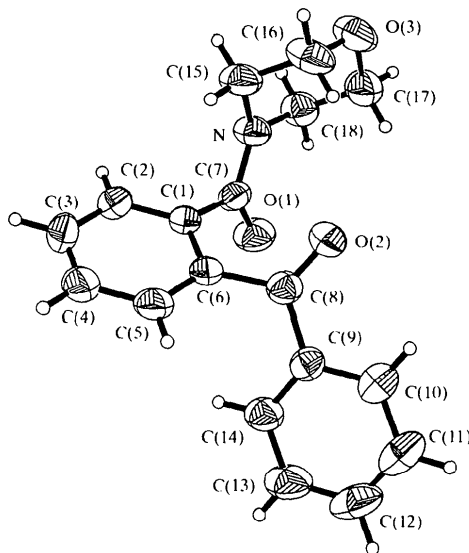Fig. 3. Thermal ellipsoid plot (50%) for 3-hydroxy-3-phenyl-N-propyl-1-isoindolone (4).

Fig. 5. Thermal ellipsoid plot (50%) for N-morpholino 2-benzoylbenzamide (6).

involves resonance contibutors such as *B* being in the ground state. Exceptional hydrolytic reactivity of (5) has been ascribed to just such contributions (Bender & Silver, 1962; Bender *et al.*, 1965; Chattopadhyaya *et al.*, 1979).

In contrast, the normal tertiary morpholinamide (6) has the shortened C(=O)—N distance of 1.355 (2) Å, typical for acyclic amides. Amide nitrogen is planar and the six atoms of the tertiary amide group have a mean deviation from planarity of 0.05 (4) Å. All other molecular structural features are normal.

Structures for both classes of anhydrides have been examined: the pseudo–normal anhydride (7) and the dipseudoanhydride (8). The former was made by displacement of the chloride from (2) by a carboxylate. The structure of (7) is shown in Fig. 6. The non-H atoms of the isobenzofuran are essentially planar and the mean deviation from the plane is 0.012 (11) Å in (7) and 0.015 (10) and 0.016 (11) Å in the two rings of (8). With both the endocyclic and exocyclic leaving groups being carboxylate in (7), the C3—O2 and C3—O3 bond distances may be expected to be similar. They are observed to be 1.453 (3) and 1.444 (2) Å, respectively. In (8) (Fig. 7) the exocyclic leaving group is the pseudoacid anion. Owing to the symmetry of the structure, two examples of each key C—O distance are observed in the molecule. The average endocyclic C—O distance (C3—O2 and C3*BA*—O(2*A*)) is 1.455 Å and the average exocyclic C—O distance (C3—O3 and C3*BA*—O3) is 1.413 Å, suggesting that the pseudoacid anion, which is attached through a lactol oxygen, is a poorer leaving group than carboxylate.

Now it is a well established feature of lactones that the CC(=O)OC group is planar unless the molecule has considerable steric strain (Sim, 1967). In fused aryl γ-lactones the benzofuranone planar geometry favors

resonance contributors such as *A* and *B*. Merlino (1971) showed that contributors in lactones from structures such as *B* have a significant influence on C—O bond lengths, representing models in which the exocyclic group is poorer than carboxylate. The resonance contributions from ions act to reduce the normal ionic contribution, which serves to shorten C—O covalent bonds by ~0.09 Å (Schomaker & Stevenson, 1941).

Leaving-group tendencies of the exocyclic groups in the isobenzofuranones (1), (3), (5) and (7) span a range of ~35 p*K* units (−2 to +33). It is not clear, for the moment, how to treat the exocyclic leaving group in (8). Over this p*K* range the endocyclic C—O bond length, which is common to the structures, varies by nearly 0.09 Å and lengthens as the leaving-group ability decreases. It would be instructive to compare the C(sp^3)—O bond length trends in these pseudoacid derivatives with those in the pyranoid warfarin ketals (Ruggiero *et al.*, 1990) and tetrahydropyranyl ethers (Briggs *et al.*, 1984). In the present series the carboxylate endocyclic leaving group is better than in the pyranoid series (enolate and alkoxide), being derived from a more acidic component. Some cautions should be noted in advance, because in contrast to the uniform endocyclic systems of the pyranoids, the pseudoacid derivatives are formed from 2-formyl- and 2-benzoyl-benzoic acids, aromatic systems whose acidities are similar but not the same (Bowden & Taylor, 1971). The difference cannot be disregarded because a certain amount of resonance stabilization can be expected between the *ortho* substituents through conjugation with the intervening aromatic system which is known to be influenced by steric effects in their acyl groups. In addition, it is not clear how to assess the p*K*a's of the conjugate acids to the endocyclic leaving groups since steric and resonance (and, in solution, solvent) effects are active, as judged by the wide applicability of substituent influences modeled in aryl Hammett relationships (Shorter, 1982). For consistency, the endocyclic system may be taken to be the open 2-acylbenzoic acids. Estimation of the p*K*a's may be further complicated by the effect of the normal–pseudoacid equilibrium (Pascual *et al.*, 1964). Finally, the plausible contributions of resonance structures *A* or *B* to the
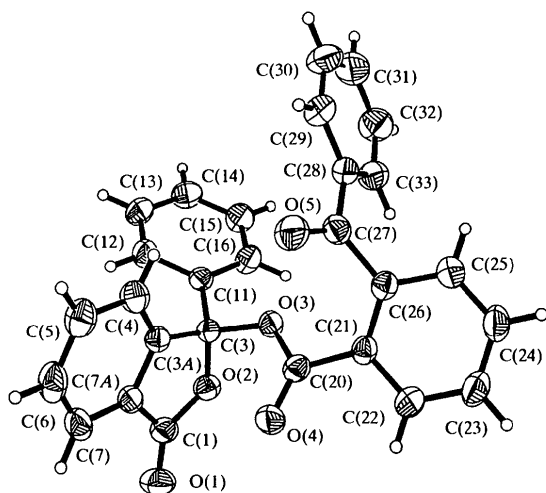

Fig. 6. Thermal ellipsoid plot (50%) for 3-(2′-benzoylbenzoyloxy)-3-phenyl-1(3*H*)-isobenzofuranone (7).
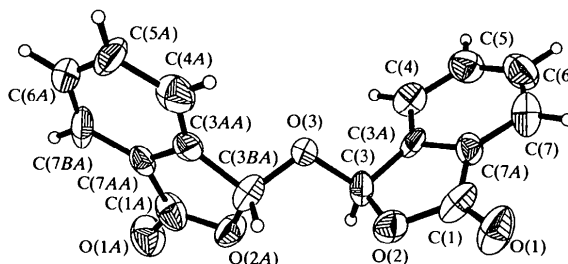

Fig. 7. Thermal ellipsoid plot (50%) for bis[1(3*H*)-isobenzofuranone-3-yl]ether (8).

ground state structure depend on the varying disparity of the comparative leaving-group tendencies. Dominance of one over the other may imply mechanistic changes which could compromise a linear free-energy treatment.

In water at 298 K the pK_a's of o-formyl- and o-benzoylbenzoic acids are measured to be 4.37 and 3.53, respectively (Bray et al., 1957; Bowden & Taylor, 1971); other pK_a's are taken from March (1985). A linear regression between the differences in pK_a's of the conjugate acids to the exocyclic and endocyclic leaving groups and the endocyclic C—O lengths in (1), (3), (5), (7) and 2-formylbenzoic pseudoacid (Valente et al., 1998) is poor ($R = 0.92$). Examination of the trend (Fig. 8) shows that the chloride leaving-group tendency would be greatly underestimated by a linear analysis. Compound (1) is a benzyl chloride for which the exocyclic leaving group (chloride) is much better than the endocyclic leaving group (carboxylate). Compared with alkyl and allyl halides, benzyl halides have increased reactivity characterized by increasing S_N1 (E1) participation, for which A is a model contribution to the ground state (Isaacs, 1995). Developing positive charge is more easily delocalized within the large isobenzofuranonium ion (as in A). Evidence can be found in (1) in the shortened endocyclic $C(sp^3)$—O distance compared with similar bonds in furanoses, esters and γ-lactones (Bürgi & Dunitz, 1994). Since the

electronic stabilization of the cation augments the dissociation implied by A in this system and effectively in (1), a case in which the exocyclic leaving group is superior to the endcyclic leaving group, departure from linearity between leaving-group ability (modeled by pK_a) and C—O lengths is rational. The C—Cl bond in (1) is intermediate between axial and equatorial since the furanone ring is planar, so the slightly increased C—Cl length is also consistent with a contribution by A.

Where only second-row atom-leaving groups are treated, the linear correlation is improved ($R = 0.95$, $N = 5$, $P = 0.01$) over a range of 29 pK_a units for the endocyclic C—O giving $d(C—O)_n$ (Å) $= 1.451 + 0.001498 \times pK_a$ (conjugated acid of the leaving group). The slope is less than half (42%) that for the endocyclic C—O in the warfarin dihydropyranyl ketals (Ruggiero et al., 1990), a decreased sensitivity consistent with the smaller ring size. The corresponding relationship for the exocyclic C—O lengths of (3), (7) and o-formylbenzoic pseudoacid for the relationship spanning 11 pK units ($R = 0.99$, $N = 3$, $P = 0.08$) is $d(C—O)_x$ (Å) $= 1.444 - 0.005240 \times pK_a$ (conjugated acid of the leaving group). Here, the slope is 82% that in the warfarin ketals. While the regressions are based on relatively few data, the trends implied are consistent with the decreased basicity of the endocyclic leaving group compared with those in the pyranoid systems. The 'crossover' pK_a in the isobenzofuranones is 2.4 [pK of leaving (oxygen) group, for which endocyclic and exocyclic C—O lengths are equal], normalized to the o-benzoylbenzoic acid case (7) for which ΔpK_a is taken to be 0. This is 4.60 pK units lower than in the warfarin dihydropyranyl ketals in which the endocyclic leaving group is the conjugate base of an enol and 10.3 pK units lower than in the α-tetrahydropyranyl acetals, in which the endocyclic leaving group is the conjugate base of an alkyl alcohol (Briggs et al., 1984). Such differences are roughly in conformity with the difference in relative acidities of carboxylic acids ($pK \simeq 5$), phenols/enols ($pK \simeq 10$) and alkyl alcohols ($pK \simeq 16$).

Based on the above relationships, an estimate of the pK_a of the exocyclic pseudocarboxylate leaving group in (8) can be made by solving the regression lines with the C—O bond lengths. The observation that the exocyclic are less than the endocyclic C—O bond lengths is evidence that the pseudocarboxylate is a much better base than carboxylate. The average pK_a for pseudo-o-formylbenzoate is found to be 8.1(±3.8), with considerable uncertainty owing to the poorer quality of the bond metrical results in (8). Nevertheless, this is not very different from the average value expected for a lactol-like secondary/benzyl alcohol ($pK_a \simeq 16$) and an o-acyl benzoic acid ($pK_a \simeq 4$). In solution, contributions to the oxoacid open $\rightleftharpoons$ cyclic equilibrium (K_e) by a cyclic pseudoacid act to diminish the observed pK_a by removing the more acidic component. For o-acylbenzoic acids (Bowden & Taylor, 1971) and aliphatic 4-oxoacids
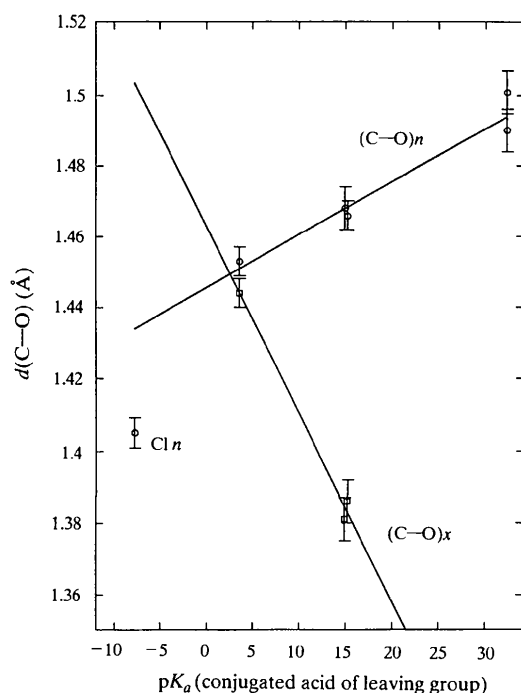

Fig. 8. Plot of endocyclic and exocyclic C—O bond lengths (Å) in 2-acylbenzoic acid derivatives as a function of exocyclic leaving-group ability [pK_a (conjugate acid of leaving group)].

(Pascual *et al.*, 1964; Sheffold & Dubs, 1967), K_e ranges from <6 to >100 and depends on the solvent. The implied pK_a reduction of <1 to >3 pK units follows from a modification of the observed pK_a by the factor $-\log(1 + K_e)$. In the structure of (8) the (cyclic 3-lactoxide) pseudocarboxylate leaving group is 'unsolvated'. The $C-O$ bond lengths suggest that pseudocarboxylate is a poorer leaving group than the open carboxylate by $\sim$3.7 pK units, implying $K_e > 500$, which is consistent with its cyclic structure.

4. Summary

Derivatives of cyclic 2-acylbenzoic acids forming planar five-membered rings and corresponding to the pseudoacid halide, ester, amides and anhydrides are found to exhibit structural variations consistent with the differences between the basicities of the exocyclic (leaving) groups and the endocyclic carboxylate function. The trends are qualitatively similar to those found in six-membered oxygen heterocycles in which the endocyclic leaving groups are poorer.

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