Simple and Condensed β-Lactams. Part 13.[1] Synthesis of Some 1-(3-Acylamino-2-oxoazetidin-1-yl)-cyclopentane- and -cyclohexanecarboxylic Acids

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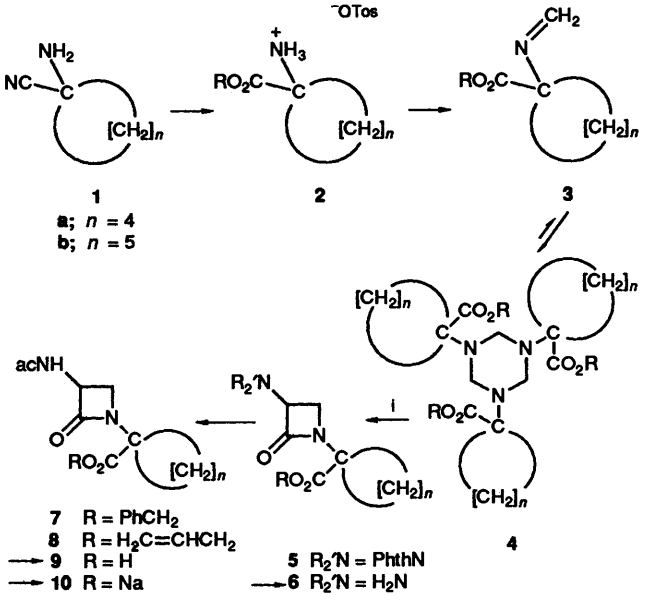
The synthesis of the title compounds **9a, b, c', f** and of the sodium salts **10d, e, g** starting with phthaloylglycyl chloride and the trimers **4a–d** of methyleneamino-cyclopentane and -cyclohexane-carboxylic esters **3a–d** is described. The products were devoid of any antibacterial activity.

We report the synthesis of novel β-lactams of types **9** and **10** (n = 4, 5). The method of synthesis of these compounds is outlined in Scheme 1. The toluenesulphonate salts **2**, obtained from cyclopentanone and cyclohexanone, respectively, *via* the cyano amines **1**, were treated with aq. formaldehyde in the presence of base to afford the corresponding 1-(methylene-amino)cycloalkanecarboxylic esters **3**, various analogues of which have been known[2] to exist mainly in form of their trimers containing 1,3,5-triazine rings. The same was found now to be true for the esters **3**. Reaction of the trimers **4** with phthaloylglycyl chloride in the presence of boron trifluoride–diethyl ether and pyridine following Kamiya's method[2] furnished the β-lactam derivatives **5**. Dephthaloylation of the latter with methylhydrazine gave the amino lactams **6**, which were subsequently *N*-acylated to afford compounds **7a–d, f** and **8d, e, g**. The benzyl esters **7a** and **7b** were hydrogenolysed to give the free acids **9a** and **9b**, respectively. Similar treatment of ester **7c** led, with concomitant opening of the isoxazole ring, to

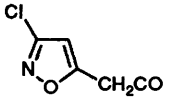
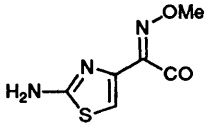
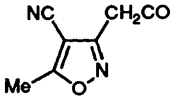
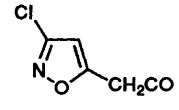
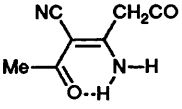
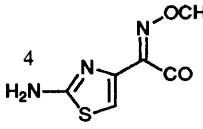
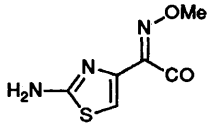


Scheme 1 Synthesis of 1-(3-acylamino-2-oxoazetidin-1-yl)-cyclopentane- and -cyclohexanecarboxylic acids **9** and their salts **10** (n = 4, 5, respectively). All compounds are racemic. PhthN = phthalimido. *Reagents and conditions:* i, $PhthNCH_2COCl$, $BF_3{\cdot}Et_2O$, pyridine, CH_2Cl_2, −70 °C.

Compounds **2–6**

	n	R		n	R
a;	4	$PhCH_2$	**c**;	5	PhCH
b;	4	$H_2C{=}CHCH_2$	**d**;	5	$H_2C{=}CHCH_2$

Compounds **7–10**

	n	ac		n	ac
a;	4	$PhCH_2CO$			
b;	4		**e**;	4	
c;	4		**f**;	5	
c;	4				
d;	4		**g**;	5	

compound **9c'** whose structure is supported by IR and NMR data. Thus, the presence of an α,β-unsaturated ketone grouping is reflected by the band at 1675 cm^{-1} in the IR, as well as by the signal at δ_C 191.6 ppm in the ^{13}C NMR spectrum. The expected NH_2 bands are also present in the IR spectrum. The chemical non-equivalence and the large shift difference of the amino hydrogen atoms (δ_H 9.1 and 10.35) are due to an intramolecular hydrogen-bond with the acetyl group. Ester **7d**, on the other hand, exhibited, probably due to the presence of the sulfur-containing ring, resistance to attempted hydrogenolytic debenzylation. A further attempt at the preparation of compound **9d** by cleavage of the benzyl ester moiety of the free amino derivative **6a** and subsequent *N*-acylation also failed because, in addition to hydrogenolysis of the ester group of compound **6a**, cleavage of the β-lactam ring also took place.

Deallylation [$Pd(OAc)_2$, $(EtO)_3P$-, *N*-methylpyrrolidine, MeCN][3] of the allyl esters **8d** and **8e**, on the other hand, led to the *N*-methylpyrrolidinium salts of the desired acids **9d** and **9e**, respectively, which were then converted into the sodium salts **10d** and **10e**. Similarly obtained were the acid **9f** and the sodium salt **10g** by cleavage of the ester groups of benzyl ester **7f** and allyl ester **8g**, respectively.

The spectral data of the products are shown in Tables 1 and 2. The following comments should be added. Owing to the prochiral nature of C-1 of the carbocycles, the C-2 and C-5, and C-3 and C-4 atoms of the cyclopentane and the C-2 and

C-6, and C-3 and C-5 atoms of the cyclohexane rings are pairwise diastereotopic; as a result, they yield two pairs of very close lines in the ^{13}C NMR spectra.

None of the carboxylic acids **9a**, **b**, **c'**, **f** nor any of the sodium salts **10d**, **e**, **g** displayed any antibacterial activity.

Experimental

M.p.s are uncorrected and were determined in glass capillaries or on hot plates. IR spectra, unless otherwise stated, were run in KBr discs on a Bruker IFS-113v vacuum optic spectrometer, equipped with an Aspect 2000 computer. ^1H and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ or $(CD_3)_2SO$ solution in 5 or 10 mm tubes, unless otherwise stated, on a Bruker WM-250 FT spectrometer, controlled by an Aspect 2000 computer, at 250 and 63 MHz, respectively, using the deuterium signal of the solvent as the lock and $SiMe_4$ as the internal standard. Measuring parameters: spectral widths 5 and 15 kHz; pulse widths 1 (^1H) and 7 μs (^{13}C) (flip angle ~20° and 30°); acquisition time 1.64 and 1.02 s; computer memory 16 K. Complete proton noise decoupling was used (~3 W) for the ^{13}C NMR spectra, and Lorentzian exponential multiplication for signal-to-noise enhancement with line widths of 0.7 (^1H) and 1.0 Hz (^{13}C), respectively. DEPT spectra[4] were run in the usual way,[5] using only the θ 135° pulse to separate CH/Me and CH_2 lines phased 'up' and 'down', respectively. Typical acquisition data: number of scans 128–12K; relaxation delay for protons 3 s, 90° pulse widths 10.8 and 11.8 μs for ^{13}C and ^1H nuclei, respectively. The estimated J(C, H)-values resulted after a 3.7 ms delay for polarization. Some ^1H NMR spectra were recorded at 60 MHz with a Perkin-Elmer R 12 spectrometer, and some IR spectra were run on a Specord 75 instrument (Zeiss, Jena).

(1-Allyloxycarbonylcyclopentyl)ammonium Toluene-4-sulfonate **2b**.—A mixture of (1-carboxycyclopentyl)ammonium chloride[6] (12 g, 72 mmol), allyl alcohol (40 g, 690 mmol), toluene-4-sulfonic acid monohydrate (16 g, 84 mmol) and benzene (90 cm^3) was refluxed for 10 h and continuously stirred in a flask equipped with a condenser and a water-separator. The hot mixture was filtered and evaporated to dryness at reduced pressure. The residue was triturated with diethyl ether (80 cm^3) to afford a *crystalline product* (22.3 g, 89%), m.p. 140–142 °C (from chloroform–diethyl ether) (Found: N, 3.9; S, 8.9. $C_{16}H_{23}NO_5S$ requires N, 4.1; S, 9.4%).

(1-Allyloxycarbonylcyclohexyl)ammonium Toluene-4-sulfonate **2d**.—This *compound*, m.p. 155–156 °C (from chloroform–diethyl ether) (Found: N, 3.7; S, 8.8. $C_{17}H_{25}NO_5S$ requires N, 3.95; S, 9.0%), was obtained in 60% yield in an essentially similar way starting with (1-carboxycyclohexyl)ammonium chloride.[7]

Tribenzyl 1,1',1''-(Hexahydro-1,3,5-triazine-1,3,5-triyl)tris(cyclopentanecarboxylate) **4a**.—1 mol dm^{-3} NaOH (3 cm^3) and, subsequently, 37% aq. formaldehyde (2.1 cm^3) were added to a stirred suspension of compound **2a**[8] (1.17 g, 3 mmol) in a mixture of water (2.7 cm^3) and benzene (5.2 cm^3) at 5–10 °C. The mixture was stirred for a further 2.5 h at this temperature until, according to TLC, the starting compound **2a** had been used up. The two phases were separated, and the aq. phase was extracted with ethyl acetate (2 × 3 cm^3). The combined organic phases were washed with water (2 × 10 cm^3), dried ($MgSO_4$), filtered, and evaporated to dryness at reduced pressure to afford a crystalline mass (0.55 g, 80%), which was recrystallized from diethyl ether to give a crystalline product, m.p. 71 °C; ν_{max}(Specord; KBr)/cm^{-1} 1710, 1200 and 1040; δ_H(60 MHz; $CDCl_3$) 1.4–2.6 (m, 3 × $[CH_2]_4$), 3.65 (s, 3 × NCH_2), 5.0 (s, 3 × $PhCH_2O$) and 7.3 (s, 3 × Ph), which was used without further purification for the preparation of compound **5a** (see below).

Triallyl 1,1',1''-(Hexahydro-1,3,5-triazine-1,3,5-triyl)tris(cyclopentanecarboxylate) **4b**.—This product was obtained in 69% yield as an oil in an essentially similar way starting with compound **2b** (17 g, 50 mmol); ν_{max}(Specord; film)/cm^{-1} 1725, 1220 and 1060; δ_H(60 MHz; $CDCl_3$) 1.5–2.4 (m, 3 × $[CH_2]_4$), 3.6 (s, 3 × NCH_2), 4.6 (d, 3 × OCH_2CH), 5.0–5.5 (m, 3 × $CH{=}CH_2$) and 5.5–6.3 (m, 3 × $CH{=}CH_3$). The product was, according to its ^1H NMR spectrum, not completely pure. Since all attempts at its purification failed, the crude product was used for the preparation of compound **5b** (see below).

Tribenzyl **4c** *and Triallyl 1,1',1''-(Hexahydro-1,3,5-triazine-1,3,5-triyl)tris(cyclohexanecarboxylates)* **4d**.—Aq. formaldehyde (20 cm^3, 250 mmol) was added to suspensions of compound **2c**[8] (10.1 g, 25 mmol) and compound **2d** (8.85 g, 25 mmol) in mixtures of water and toluene (40 cm^3, each). The mixtures were cooled to 0 °C. Aq. (20 cm^3) NaOH (1 g, 25 mmol) was added dropwise at this temperature. The mixtures were stirred for 2 h at 5–10 °C and kept for 30 min at room temperature. The phases were separated and the aq. phase was extracted with ethyl acetate (2 × 60 cm^3). The combined organic phases were washed with water (20 cm), dried ($MgSO_4$), filtered, and evaporated to dryness at reduced pressure to obtain the title compounds as crude products which could not be purified and were therefore converted in crude form into compounds **5c** and **5d**, respectively (see below).

Benzyl 1-(2-Oxo-3-phthalimidoazetidin-1-yl)cyclopentanecarboxylate **5a**.—Anhydrous pyridine (1.9 cm^3, 23.4 mmol) and, subsequently, a mixture of compound **4a** (2.65 g, 3.8 mmol), dry CH_2Cl_2 (47 cm^3), and boron trifluoride–diethyl ether (1.4 cm^3, 11.4 mmol) were added dropwise to a solution of phthaloylglycyl chloride (5.1 g, 22.9 mmol) in dry CH_2Cl_2 (85 cm^3) at −78 °C. The mixture was stirred for 3 h at this temperature, kept overnight in a refrigerator, and evaporated to dryness at reduced pressure. The residue was triturated with ethyl acetate (5 × 30 cm^3), each supernatant being decanted from the insoluble residue. The combined organic solutions were evaporated to dryness at reduced pressure and the residue was purified by chromatography [Kieselgel G; CH_2Cl_2–acetone (10:1)] at reduced pressure. The oily main fractions crystallized when triturated with diethyl ether to afford the *title compound* (2.7 g, 36%), m.p. 115 °C (Found: C, 68.7; H, 5.55; N, 6.65. $C_{24}H_{22}N_2O_5$ requires C, 68.9; H, 5.3; N, 6.7%). For spectral data, see Tables 1 and 2.

Allyl 1-(2-Oxo-3-phthalimidoazetidin-1-yl)cyclopentanecarboxylate **5b**, *and Benzyl* **5c** *and Allyl 1-(2-Oxo-3-phthalimidoazetidin-1-yl)cyclohexanecarboxylates* **5d**.—These compounds were obtained by a slightly modified procedure. Thus, (*a*) the crude compounds **4c** and **4d** (see above) were dissolved in dry dichloromethane (75 cm^3). Boron trifluoride–diethyl ether (3.1 cm^3, 25 mmol) was added. The resulting solutions were added dropwise to a stirred mixture of phthaloylglycyl chloride (8.3 g, 37.5 mmol), anhydrous pyridine (3.6 cm^3, 44.5 mmol) and dry dichloromethane (125 cm^3) at −75 °C under nitrogen. The mixtures were stirred for 3 h at −75 °C, kept overnight in a refrigerator, and evaporated to dryness at reduced pressure. The residues were triturated with ethyl acetate (3 × 150 cm^3), the supernatants being decanted from the insoluble residues. The combined organic solutions were washed with water (2 × 25 cm^3), dried ($MgSO_4$), and evaporated to dryness at reduced pressure. The residues were purified by chromatography (Kieselgel 60, 0.063–0.2 mm, 50 g; CH_2Cl_2) at reduced pressure and the crude products were crystallized by trituration with

Table 1 ^{1}H NMR data [δ(SiMe$_4$) = 0 ppm], in $CDCl_3$ or $(CD_3)_2SO$ solution at 250 MHz, of compounds **5a–d, 6a, b, d, 7a, c, d, f, 8e, g, 9a, b, c′, f** and **10d, e, g** and their IR carbonyl bands (cm^{-1}, KBr discs)[a]

Compound	3-H (1 H, m)[b]	4-H (2 H, m)[c]	CH_2 (alicycle) (8/10 H, m)[d]	OCH_2 (2 H, m)[e]	ArH (m or s)[f]	Me (s, ac)	CH_2 (s, ac)	NH_2 (2 H, br)	NH[g] (1 H, d)	ν(C=O) lactam	ν(C=O) ester	ν(C=O) amide[h]
5a	5.34	~3.65	1.85–2.25 (7 H), ~2.9	5.22	7.80					1749	1713	1764
5b	5.40	~3.7	1.8–2.1 (7 H), ~2.9	4.68	7.80					1735	1713	1759
5c	5.35	~3.7	1.2–2.0 (9 H), ~2.7	5.22	7.80					1740	1725	1759
5d	5.40	~3.7	~1.35, 1.6–2.0 (8 H), ~2.65	4.68	7.80					1735	1728	1758
6a	4.02	2.90 3.50	1.6–2.5 (8 H)	5.16						1735	1735	
6b[i]	3.57	3.05 4.10	~1.8 (4 H), 2.0–2.5 (4 H)	4.65				2.25		~1755	1730	
6d	3.57	3.05 4.10	1.2–2.2 (10 H)	4.65				2.35		1750	1735	
7a	4.80	3.16 3.54	~1.8 (4 H), ~2.1 (2 H), ~2.35 (2 H)	5.14			3.52		6.25	1762	1730	1650
7c	4.88	3.25 3.61	~1.8 (4 H), ~2.1 (2 H), ~2.3 (2 H)	5.16		2.60	3.70[j]		7.25	1755	1737	1688
7d	~5.0	3.36 3.64	1.6–2.4 (8 H)	5.17[k]	6.96	1.46[l]		~5.7	8.20	1750	1728	1685
7f	4.75	3.20 3.50	1.2–1.8 (8 H), ~2.0, ~2.28	5.16	6.67		3.84		~8.9	1754	1730	1690
8e	5.25[m]	3.45 3.75	~1.8 (4 H), ~2.1 (4 H)	4.61	6.67	3.92		5.83[n]	~8.9	1747	1730	1670
8g	5.30	3.45 3.75	~1.3, ~1.6 (5 H), ~1.85 (2 H), ~2.15, ~2.35	4.60	6.67	3.92		5.90	~8.9	1752	1730	1675
9a	4.8	3.3 ~3.5[o]	~1.8 (4 H), ~2.18 (3 H), ~2.4				3.57[o]			1737[p]	1737[p]	1675
9b	4.77	3.20 3.53	~1.75 (4 H), ~1.95 (2 H), ~2.15, ~2.4		6.67		3.84		10	1740	1692[q]	1665
9c′[r]	4.78	3.20 3.53	~1.75 (4 H), ~1.95 (2 H), ~2.15,[o] ~2.4			2.18[o]	3.43[s]	9.1[t]	~8.9	1740[p]	1700[p,q]	1635
9f	4.80	3.18 3.52	1.1–1.8 (8 H), ~1.98, ~2.22		6.67		3.84		~8.9	1730	1690[q]	1661
10d	4.85	3.25 3.55	~1.7 (4 H), ~1.9 (2 H), ~2.05, ~2.5		6.74	1.43[l]	4.56	7.25	9.2	1744[u]	1615[v]	
10e	4.80	3.15 3.5[p]	~1.6 (4 H), ~1.9 (4 H)		6.74	3.83		7.25	9.2	1731	1589[v]	1664
10g	4.82	3.10 3.55	1.1–1.8 (9 H), ~2.25		6.75	3.83		7.25	9.2	1736	1591[v]	1661

[a] Solvent $CDCl_3$ (**5a–d, 6a, b, d, 7a, c, d, 8e, g** and **9a**), $(CD_3)_2SO$ (**7f, 9b, c′, f** and **10d, e, g**). Further signals: phenyl group, 5 H, m, for **5a, c, 6a, 7c, d, f, 9a** and 10 H for **7a**): ~7.35. Allyl group (**5b, d, 6b, d** and **8e, g**) =CH_2, 2 dd (2 × 1 H): ~5.3, =CH, (1 H, m), ~5.9. [b] dd (*J* 5.5 and 3.0 Hz) for **5a, 6a**, t (*J* ~5 Hz) for **5b, 6b, d** and **9a**. [c] dd (*J* ~5.5 and ~2.5 Hz) and t (*J* ~5.5 Hz) with coalesced lines, except for **7a, c** and **9b**. The two signal overlap for **5a–d**. [d] 1–4 m of 8 H- (**5a, b, 6a, b, 7a, c, d, 8e, 9a, b, c′** and **10d, e**) or 10 H-total intensity (**5c, d, 6d, 7f, 8g, 9f** and **10g**). Intensity of the separated signals is 1 H or given in parentheses. [e] ~s (AB spin system near to the A_2 limiting case) for benzyl esters and dd for allyl esters. [f] AA′BB′ multiplet (4 H) for **5a–d**, ΔδAB ~0.1 ppm, *J* (A,B) ~8 Hz; s (1 H) for **7d, f, 8e, g, 9b, f** and **10d, e, g**. [g] 3-NH group, *J* ~8 Hz. [h] Amide-I band (**7–10**); δ_{as} C=O imide band for **5a–d**; the ν_s C=O band is in overlap with the ester ν C=O band. [i] Approx. shift data from the spectrum of crude product. [j] Centrum of an AB spectrum near to the A_2 limiting case, ΔδAB ~0.1 ppm, *J*(A, B) ~16 Hz. [k] Benzyloxycarbonyl group, δ 4.68 for the oxime ester group. [l] 9 H, Bu^t group. [m,n] In overlap with the =CH_2/=CH multiplet of the allyl group. [o,p] Overlapping signals. [q] ν C=O band of carboxylic group. [r] ν C=O band of the ketone group 1675 cm^{-1}. [s] Hidden by the signal of water content in the solvent. [t] Two signals (1–1 H intensity) with the second maximum at δ 10.35. [u] Overlapping bands of the β-lactam and ester carbonyl groups. [v] Δ_{as} CO_2^- band.

Table 2 ^{13}C NMR chemical shifts [$\delta(SiMe_4)$ 0 ppm] of compounds **5a–d**, **6d**, **7a**, **c**, **f**, **8e**, **g**, **9b**, **c′**, **f** and **10d**, **e**, **g** in $CDCl_3$ or $(CD_3)_2SO$ solution at 63 MHz[a]

	Azetidin-2-one			Alicycle						Phthalimide/heterocycle (ac)					
Compound	C=O	C-3	C-4	C-1	C-2	C-3	C-4	CO_2R^b	CH_2 R^c	C=O[d]	C-1, -2, C-3[e]	C-3, -6 C-4	C-4, -5 C-5	CH_2 C=N (ac)	Me OMe (ac)
5a	167.0	52.2	45.1	69.5	35.0 35.6	23.9		172.6	67.4	164.4	131.8	123.6	134.4		
5b[f]	167.0	52.2	45.1	69.4	35.1 35.6	23.9		172.4	66.2	164.4	131.8[g]	123.6	134.4		
5c	167.0	52.2	44.5	63.5	31.4 31.9	21.7	24.9	172.4	67.2	164.7	131.8	123.6	134.4		
5d	167.0	52.2	44.5	63.5	31.4 32.0	21.7	25.0	172.4	66.1	164.7	131.8[g]	123.6	134.4		
6d	171.5[h]	57.7	48.1	62.7	30.9	21.3 21.4	24.3	172.2[h]	65.5						
7a	167.1	54.8	47.6	67.4[g]	35.2 35.5	24.1		172.7	67.4[g]	171.3				43.3	
7c[f]	166.9	54.7	47.6	69.2	35.2 35.5	24.1 24.2		172.6	67.5	166.4	157.9	92.6	177.4	32.3	12.5
7f	167.8[h]	56.0	47.3	64.0	32.7 32.8	23.1	26.1	172.1	68.3	168.4[h]	154.9	106.0	173.7	35.4	
8e[f]	167.4	53.6	47.4	69.3	35.0 35.4	23.7		172.2	66.1	168.7	162.8	142.0	111.3	147.9	62.3
8g	167.9[h]	53.7	46.9	62.4	31.2 31.5	21.6	24.6	172.2	66.1	168.5[h]	162.9	142.3	111.3	148.0	63.4
9b[f]	167.8[h]	55.8	48.1	70.1	36.3 36.4	25.4		175.9		168.1[h]	154.5	106.1	172.7	35.4	
9c′	167.9[h]	55.8	48.1	70.2	36.3 36.5	25.5		176.0		168.1[h]	169.7[h]	84.0	191.6	30.1	26.4
9f	167.8[h]	55.9	47.4	63.9	32.6 32.8	23.2	26.3	175.9		168.4[h]	154.5	106.1	172.2	35.5	
10d	167.8	55.5	47.9	70.1	36.2 36.5	25.4		175.9		170.4[h]	163.9	144.2	112.2	151.9	29.7
10e	167.8	54.9	48.0	73.1	36.2 36.8	25.9		177.0		170.0	164.2	144.7	112.2	151.3	63.9
10g	167.9	55.0	47.3	63.9	33.3 33.9	24.0 24.2	27.2	177.0		170.4	164.2	144.7	112.2	151.3	66.4

[a] Solvent: $CDCl_3$: **5a–d**, **6d**, **7a**, **c** and **8e**, **g**, $(CD_3)_2SO$: **7f**, **9b**, **c′**, **f** and **10d**, **e**, **g**. Further signals: **5a**: phenyl C-1: 135.6, C-2, -6: 128.7, C-3, -5: 128.1, C-4: 128.5; **5b**: allyl $=CH_2$: 118.7, =CH: 131.8;[g] **5c**, phenyl C-1: 135.7, C-2, -6: 128.7, C-3, -5: 128.1, C.4: 128.4; **5d**: allyl $=CH_2$: 118.7, =CH: 131.8;[g] **6d**, allyl $=CH_2$: 118.2, =CH: 131.4; **7a**: phenyl. C-1: 134.3, 135.5, C-2, -3, -5, -6: 128.1, 128.5, 128.8, 129.0, C-4: 127.4, 129.4; **7c**, phenyl C-1: 135.5, C-2, -3, -5, -6: 128.2, 128.8, C-4: 128.6; **7f**, phenyl C-1: 137.8, C-2, -6: 130.3, C-3, -5: 129.6, C-4: 130.0; **8e**, allyl $=CH_2$: 118.0, =CH: 131.4; **8g**: allyl $=CH_2$: 118.6, =CH: 131.6; **10d**, $C_{quat}(Bu^t)$: 72.9, OCH_2: 83.0, C=O (ester): 170.2.[h] [b] On C-1 of alicycle. [c] In benzyl group (**a**, **c**, **f**) or in allyl group (**b**, **d**, **e**, **g**). [d] Imide **5** or amide **6–10**. [e] C-2 for **8e**, **g**, **10d**, **e**, **g** and C-3 for **7c**, **f**, **9b**, **c′**, **f**. [f] Assignments were confirmed by DEPT measurements. [g] Two overlapping lines. [h] Interchangeable assignments.

diethyl ether to obtain *compounds* **5c** (2.0 g, 18.4%), m.p. 110–113 °C (Found: C, 69.15; H, 5.7; N, 6.1. $C_{25}H_{24}N_2O_5$ requires C, 69.45; H, 5.6; N, 6.5%) and **5d** (1.8 g, 18.8%), m.p. 108–110 °C (Found: C, 65.5; H, 6.05; N, 7.4. $C_{21}H_{22}N_2O_5$ requires C, 65.95; H, 5.8; N, 7.35%) (yields are overall yields, based on the amounts of toluene-4-sulfonates **2c** and **2d**, respectively, introduced). For spectral data, see Tables 1 and 2.

(*b*) By the same procedure the crude compound **4b** (see above) (4.15 mmol) was converted in 64% yield into compound **5b** (m.p. 80 °C) (Found: C, 64.9; H, 5.4; N, 7.25. $C_{20}H_{20}N_2O_5$ requires C, 65.2; H, 5.45; N, 7.6%). For spectral data, see Tables 1 and 2.

Benzyl **6a**, **c** *and Allyl* 1-(3-*Amino*-2-*oxoazetidin*-1-*yl*)*cycloalkanecarboxylates* **6b**, **d**.—Mixtures of the phthaloyl derivatives **5a** (1.4 g, 3.3 mmol) or **5b–d** (15 mmol), dry CH_2Cl_2 (~6 cm^3/mmol of compound **5**), and methylhydrazine (2.2–2.5 mol equiv.) were stirred for 8 h at room temperature under nitrogen. The crystals of the resulting cyclic hydrazide were filtered off. The filtrates were evaporated to dryness at reduced pressure and the residues were taken up in ethyl acetate. The small amounts of insoluble material were filtered off and the filtrates were worked up by chromatography (Kieselgel 60, 0.063–0.2 mm; EtOAc) at reduced pressure to afford *compounds* **6a** (0.73 g, 78%) (Found: C, 66.4; H, 6.75; N, 9.55. $C_{16}H_{20}N_2O_3$ requires C, 66.65; H, 7.0; N, 9.7%), **6b** (2.5 g, 70%), **6c** (3.6 g, 79%), and **6d** (1.6 g, 42%) as oils. The last three products were not completely pure and were used without further purification for the subsequent reactions.

For the ^1H NMR and IR spectra of compounds **6a**, **6b** and **6d**, see Table 1, and for the ^{13}C NMR spectrum of compound **6d** see Table 2.

Benzyl **7** *and Allyl* 1-(3-*Acylamino*-2-*oxoazetidin*-1-*yl*)*cycloalkanecarboxylates* **8**.—(*a*) Phenylacetyl chloride or (3-chloroisoxazol-5-yl)acetyl chloride freshly prepared from (3-chloroisoxazol-5-yl)acetic acid[9] (1.1 mol equiv.), dissolved in CH_2Cl (3 cm^3), were added dropwise to a stirred mixture of compound **6a** (0.58 g, 2 mmol), CH_2Cl_2 (12 cm^3), and triethylamine (1.1–1.25 mol equiv.) cooled in ice–water. The mixtures were stirred for 30 min at room temperature, washed with water (2 portions), dried ($MgSO_4$), and evaporated to dryness at reduced pressure. The residues were worked up by chromatography [Kieselgel G; CH_2Cl_2–acetone (10:0.5)] at reduced pressure to give *compound* **7a** (0.58 g, 70%) (Found: C, 70.85; H, 6.3; N, 7.0. $C_{24}H_{26}N_2O_4$ requires C, 70.9; H, 6.45; N, 6.9%) as an oil and *compound* **7b** (0.55 g, 64%), m.p. 94 °C (from diethyl ether) (Found: Cl, 7.95; N, 9.65. $C_{21}H_{22}ClN_3O_5$ requires Cl, 8.2; N, 9.75), respectively.

(*b*) A mixture of compound **6a** (0.58 g, 2 mmol), CH_2Cl_2 (14 cm^3), (4-cyano-5-methylisoxazol-3-yl)acetic acid[10] (0.32 g, 2 mmol), and dicyclohexylcarbodiimide (DCC) (0.43 g, 2.1 mmol) was stirred at room temperature until compound **6a** was used up. The resulting dicyclohexylurea was filtered off and the filtrate was worked up by chromatography [Kieselgel G; CH_2Cl_2–acetone (10:0.5)] to afford *compound* **7c** (0.82 g, 94%) (Found: C, 63.55; H, 5.65; N, 12.75. $C_{23}H_{24}NO_5$ requires C, 63.35; H, 5.55; N, 12.85%).

(*c*) *S*-Benzothiazol-2-yl (*Z*)-(2-aminothiazol-4-yl) (*t*-butoxycarbonylmethoxyimino)thioacetate[3] (0.5 g, 1.1 mmol) was added to a precooled mixture of compound **6b** (0.24 g, 1.0 mmol), dichloromethane (10 cm^3), and triethylamine (0.16 cm^3; 1.1 mmol) cooled in ice. The mixture was stirred for 2 h at room temperature and worked up by chromatography [Kieselgel G; CH_2Cl_2–acetone (7:1)] at reduced pressure to afford *compound* **8d** (0.43 g, 85%), m.p. 174–178 °C (Found: N, 13.55; S, 6.45. $C_{23}H_{31}N_5O_7S$ requires N, 13.40; S, 6.15%).

(*d*) By applying the method described in (*c*) to the benzyl ester **6a**, compound **7d** was obtained (85%). Although this compound could not be purified completely, some unsuccessful attempts at cleavage of its ester group by hydrogenolysis were carried out.

(*e*) A mixture of DCC (1 g, 5 mmol) and 1-hydroxybenzotriazole (0.78 g, 5 mmol) was added to a solution of compound **6c** (1.5 g, 5 mmol) and (3-chloroisoxazol-5-yl)acetic acid[9] (0.9 g, 5 mmol) in anhydrous dimethylformamide (DMF) (25 cm^3) under nitrogen. The mixture was stirred for 1–2 days. The resulting dicyclohexylurea was filtered off and the filtrate was evaporated to dryness at reduced pressure. The residue was taken up in ethyl acetate (50 cm^3). The small amount of insoluble material was filtered off and the filtrate was extracted with 5% aq. $NaHCO_3$ (3 × 5 cm^3), washed with water (5 cm^3), dried ($MgSO_4$), and evaporated to dryness at reduced pressure. The residue was worked up by chromatography [Kiesegel 60, 0.063–0.2 mm, 30 g; hexane–ethyl acetate (1:1 → 1:3)] at reduced pressure. Heptane, hexane, and pentane (30 cm^3, each) were successively added to and distilled from the residue but *compound* **7f** (1.5 g, 68%) (Found: C, 57.15; H, 5.65; Cl, 7.45; N, 8.85. $C_{22}H_{24}ClN_3O_5 \cdot H_2O$ requires C, 56.95; H, 5.65; Cl, 7.65; N, 9.05%) could not be induced to crystallize.

(*f*) When the method described in (*e*) was applied to (*Z*)-(2-aminothiazol-4-yl)(methoxyimino)acetic acid[11] and the allyl esters **6b** and **6d** (5 mmol each), *compounds* **8e** (1.55 g, 73.5%) m.p. 82–84 °C (Found: N, 15.75; S, 7.15. $C_{18}H_{23}N_5O_5S \cdot H_2O$ requires N, 15.95; S, 7.3%) and **8g** (1.7 g, 78%), m.p. 162 °C (from toluene) (Found: C, 52.45; H, 5.8; N, 15.85; S, 6.85. $C_{19}H_{25}N_5O_5S$ requires C, 52.4; H, 5.8; N, 16.1; S, 7.35%), respectively, were obtained.

For the spectra of compounds **7a**, **c**, **d**, **f**, **8e** and **8g**, see Tables 1 and 2.

1-(3-*Acylamino*-2-*oxoazetidin*-1-*yl*)*cycloalkanecarboxylic Acids* **9**.—(*a*) The benzyl esters **7a** (0.8 mmol) and **7b** (1.3 mmol) were reduced in methanol (30 cm^3) in the presence of 10% Pd–C catalyst (0.1 g) within 10 min at room temperature. Conventional work-up afforded *compound* **9a** (100%) (Found: C, 64.6; H, 6.2; N, 8.8. $C_{17}H_{20}N_2O_4$ requires C, 64.55; H, 6.35; N, 8.85%) as a gum, and *compound* **9b** (94%), m.p. 137 °C (Found: Cl, 10.3; N, 12.05. $C_{14}H_{16}ClN_3O_5$ requires Cl, 10.4; N, 12.3%), which crystallized when triturated with diethyl ether.

(*b*) When the same procedure was applied to benzyl ester **7c** (0.8 g, 1.9 mmol), *compound* **9c′** (0.4 g, 61%), m.p. 76 °C (decomp.) (Found: N, 16.1. $C_{16}H_{20}N_4O_5$ requires N, 15.8%) was obtained.

(*c*) Ester **7f** (0.5 g, 1.1 mmol) was reduced in ethyl acetate (10 cm^3) to give, after conventional work-up, *carboxylic acid* **9f** (0.3 g, 77%), m.p. 149–152 °C (from ethyl acetate) (Found: C, 50.9; H, 5.45; Cl, 9.45; N, 11.45. $C_{15}H_{18}ClN_3O_5$ requires C, 50.65; H, 5.1; Cl, 9.95; N, 11.8%).

For spectral data, see Tables 1 and 2.

Sodium 1-(3-*Acylamino*-2-*oxoazetidin*-1-*yl*)*cycloalkanecarboxylates* **10**.—Mixtures of the allyl ester **8d**, **8e** or **8g** (2 mmol), acetonitrile (5 cm^3), *N*-methylpyrrolidine (0.21 cm^3, 2 mmol), triethyl phosphite (0.02 cm^3), and palladium(II) acetate (3.8 mg) were stirred for 5–12 h at room temperature. The resulting *N*-methylpyrrolidinium salt of the acid **9d** (1.44 g, 80%), m.p. 148–151 °C (crude), **9e** (0.9 g), or **9g** (0.75 g) was isolated by filtration.

These salts (0.9 g in the **d** series, the total amounts obtained in the **e** and **g** series) were stirred with a mixture of the ion-exchange resin Varion KS(Na^+) (20 cm^3), water (20 cm^3), and methanol (20 cm^3) for 12–20 at room temperature. The resin was filtered off and washed successively with water and methanol. The methanol was distilled off from the combined

filtrates. The aq. solutions were treated with Norite (**d** series), or filtered and extracted with CH_2Cl_2 (2 × 10 cm^3) (**e** and **g** series), respectively, and finally evaporated to dryness at reduced pressure. The residues were dried over P_2O_5 *in vacuo* to give the *salts* **10d** (0.6 g, 72%), m.p. 158–161 °C (decomp.) (Found: N, 13.4; S, 6.5. $C_{20}H_{26}N_5NaO_7$ requires N, 13.9; S, 6.35%), **10e** (0.24 g, 29%), m.p. 129 °C (decomp.) (Found: N, 17.65; S, 7.55. $C_{15}H_{18}N_5NaO_5S$ requires N, 17.35; S, 7.95%), and **10g** (0.54 g, 65%), m.p. 195 °C (decomp.) (Found: N, 16.5; S, 7.2. $C_{16}H_{20}N_5NaO_5S$ requires N, 16.8; S, 7.7%), respectively.

For spectral data see Tables 1 and 2.

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