Total Synthesis of Analogues of the β-Lactam Antibiotics. Part 4.[1] 4-t-Butoxycarbonyl-8-oxo-1,3,4-triazabicyclo[4.2.0]oct-2-ene-2-carboxylates[2]

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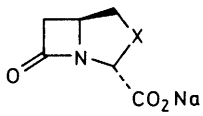
t-Butyl hydroxy(4-iodomethyl-2-oxoazetidin-1-yl)acetate (**6a**) was transformed into t-butyl 4-t-butoxycarbonyl-8-oxo-1,3,4-triazabicyclo[4.2.0]oct-2-ene-2-carboxylate (**9a**) by sequential reactions involving thionyl chloride [to give the chloroacetate (**7a**)], t-butyl carbazate [to give the 2-t-butoxycarbonylhydrazinoacetate (**5a**)], and silver(I) oxide. In the last reaction, the 2-t-butoxycarbonylhydrazonoacetate (**18a**) is a likely intermediate. The structure of compound (**9a**) was supported by its conversion into methyl 1-t-butoxycarbonyl-3-methoxycarbonyl-1,4,5,6-tetrahydro-1,2,4-triazin-5-ylacetate (**11b**) by the action of sodium hydroxide followed by iodomethane, and confirmed by a single crystal *X*-ray analysis. The *p*-nitrobenzyl and benzyl esters of the triazabicyclo-octene, *i.e.* compounds (**9c,d**), were prepared from the carbinols (**6b,c**) by a similar reaction sequence. Hydrogenolysis of the benzyl ester (**9d**) gave the acid (**9b**), the sodium salt of which lacked antibacterial activity.

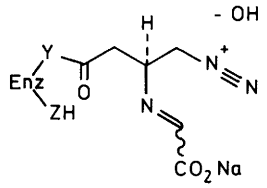
For some time, we have been interested in the synthesis and biological evaluation of compounds of type (**1**; X = heteroatomic substituent). To date, we have prepared the representatives (**1a**),[3] (**1b**),[4] and (**1c**)[4] but none of the compounds was endowed with β-lactamase inhibitory or antibacterial properties. Since double covalent binding of β-lactamases (HY-Enz-ZH) with their substrates is believed to be important for irreversible inhibition,[5] the bicycle (**1d**) attracted our attention. It was envisaged that, if the compound fulfilled the role of a substrate, a species of type (**2**) might be generated. The loss of nitrogen from such an intermediate might be accompanied by the formation of a species of type (**3**) and water; such an event might result in an irreversible inhibition of the enzyme.

In one approach to the target (**1d**), we decided to evaluate compounds of type (**4**) as forerunners. The unexpected emergence of the title compounds, during attempts to prepare such precursors, is the subject of this paper.

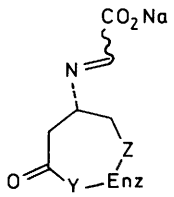


(**1**)

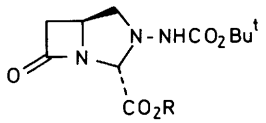
a; X = O
b; X = S
c; X = SO_2
d; X = N-N=O



(**2**)



(**3**)



(**4**)

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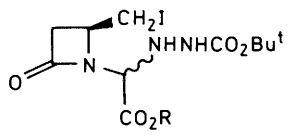
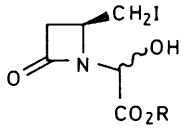
Discussion

It was presumed that compounds of type (**4**) would be accessible from azetidinones of type (**5**) under appropriate basic conditions. In turn, hydrazides of type (**5**) were expected to be derivable from carbinols of type (**6**) by way of chlorides of type (**7**).



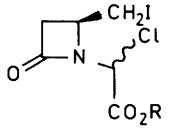
(**5**)

a; R = Bu^t
b; R = $CH_2C_6H_4NO_2$-*p*
c; R = CH_2Ph



(**6**)

a; R = Bu^t
b; R = $CH_2C_6H_4NO_2$-*p*
c; R = CH_2PH



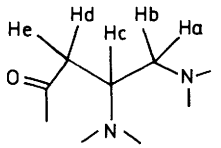
(**7**)

a; R = Bu^t
b; R = $CH_2C_6H_4NO_2$-*p*
c; R = CH_2Ph

Treatment of the carbinol (**6a**)[3] in tetrahydrofuran (THF) at −20 °C with 2,6-dimethylpyridine followed by thionyl chloride gave the chloride (**7a**) which was immediately converted into the hydrazide (**5a**) by the action of t-butyl carbazate in dichloromethane. The hydrazide (**5a**), which was isolated in 60% yield (after SiO_2 chromatography) as a syrupy 1:1 mixture of diastereoisomers, was transformed into non-β-lactam products under a variety of basic conditions. In the hope of providing electrophilic assistance to the iodine displacement, the crude hydrazide (**5a**) was stirred in acetonitrile with silver(I) oxide. Following work-up and recrystallisation of the crude

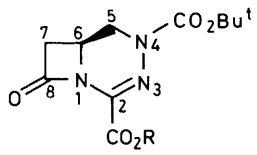
product, a material with the constitution $C_{15}H_{23}N_3O_5$ was isolated [49% yield based upon (**6a**)]. The material, designated compound **A**, was clearly derived from its precursor (**5a**) by an oxidative elimination, *i.e.* loss of the elements of hydrogen and hydrogen iodide.

Compound **A** showed absorptions at 1 790, 1 735, and 1 705 cm^{-1} in the i.r. region and a band at 287 nm (ε 14 500) in the u.v. spectrum. The presence of two t-butoxy groups (δ 27.8, 27.9 and 83.1, 83.6), two methylene moieties (δ 44.2 and 45.4), a methine function (δ 41.1), an imine entity (δ 129.4), and three carbonyl groups (δ 152.0, 157.9, and 162.2) was established by 90 MHz ^{13}C n.m.r. spectroscopy ($CDCl_3$). In addition to corroborating the presence of two t-butyl groups (δ 1.54 and 1.56), 360 MHz ^1H n.m.r. spectroscopy ($CDCl_3$) indicated that compound **A** incorporated the partial structure (**8**). Thus the spectrum

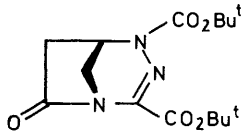


(**8**)

contained one-proton double doublets at δ 2.68 (*J* 12.5 and 8.5 Hz) and 4.87 (*J* 12.5 and 4 Hz), assigned to H_a and H_b, a one-proton multiplet at δ 2.92—3.00, due to H_e, and a two-proton multiplet at δ 3.55—3.62, attributed to H_c and H_d. An unusual feature of the spectrum, which exhibited second-order characteristics, was the chemical shift difference of 2.19 p.p.m. of the hydrogen atoms attributed to the NCH_2 group. On the basis of the spectroscopic evidence, compound **A** was considered to possess either the structure (**9a**) or (**10**).



(**9**)

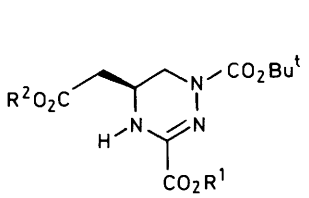


(**10**)

a; R = Bu^t
b; R = H
c; R = $CH_2C_6H_4NO_2$-*p*
d; R = CH_2Ph
e; R = Na
f; R = Me

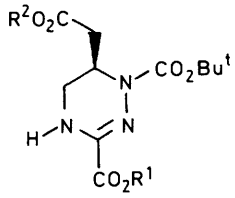
In principle, a differentiation between compounds (**9a**) and (**10**) is possible after cleavage of the amide linkage. Thus it was envisaged that a hydrolysis-methylation sequence would transform compounds (**9a**) and (**10**) into the respective tetrahydrotriazines (**11a**) and (**12a**) [the tautomeric structures (**13**) and (**14**) were considered to be less likely contenders because of their reduced conjugation] which should be distinguishable by ^1H n.m.r. spectroscopy.

Treatment of compound **A** with sodium hydroxide (2 mol equiv.) (the use of 1 mol equiv. of the reagent resulted in the recovery of *ca.* 50% of the starting material) gave a disodium salt which reacted with iodomethane in *N*,*N*-dimethylformamide (DMF) to give a dimethyl ester. The product, isolated in 52% yield as a pale-yellow syrup after silica-gel purification, was considered to be compound (**11b**) on the basis of ^1H n.m.r. spectroscopy. Thus the 300 MHz spectrum ($CDCl_3$) incorporated a one-proton multiplet at δ 3.98—4.03 for the methine hydrogen atom and a one-proton broad signal at δ 6.14 for the NH moiety; after addition of deuterium oxide, the former signal sharpened and the latter disappeared. Evidently, the methine hydrogen atom and the NH moiety were coupled, suggesting that the groups possessed a vicinal relationship. Clearly, the dimethyl ester possessed structure (**11b**) and the disodium salt structure (**11c**). Compound **A** was therefore the triazabicyclo-octene (**9a**).



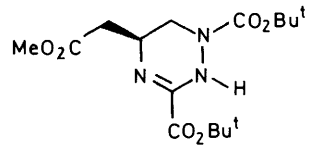
(**11**)

a; R^1 = Bu^t, R^2 = Me
b; R^1 = R^2 = Me
c; R^1 = R^2 = Na
d; R^1 = Bu^t, R^2 = $COCF_3$

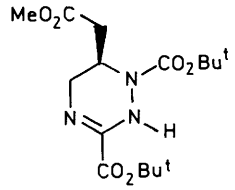


(**12**)

a; R^1 = Bu^t, R^2 = Me
b; R^1 = R^2 = Me

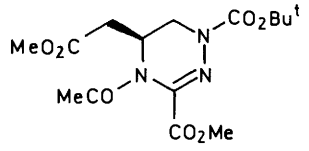


(**13**)

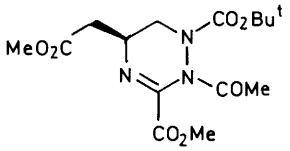


(**14**)

In contrast with those of its precursor (**9a**), the hydrogen atoms of the NCH_2 group of compound (**11b**) appeared as one-proton double doublets at δ 3.56 (*J* 12.5 and 5 Hz) and 3.75 (*J* 12.5 and 3.5 Hz). To determine the effect of an *N*-acyl group upon the chemical shift difference, attempts were made to prepare the *N*-acetyl derivative (**15**). Although the (**11b**)→(**15**) transformation was not effected by acetic anhydride and pyridine, it was achieved in THF by sodium hydride followed by acetyl chloride. Following silica-gel purification, an acetyl derivative was isolated in 40% yield as a colourless syrup. That the product possessed structure (**15**), rather than (**16**), was indicated by u.v. spectroscopy [$\lambda_{max.}$(EtOH) 267 nm (ε 15 000)]. In the 300 MHz ^1H n.m.r. spectrum ($CDCl_3$), the NCH_2 group appeared as one-proton double doublets at δ 3.37 (*J* 13 and 4 Hz) and 4.41 (*J* 13 and 1 Hz). Clearly, the acetyl group had increased the chemical shift difference between the diastereotopic hydrogen atoms of the NCH_2 entity but the effect did not match that observed in the triazabicyclo-octene (**9a**).



(**15**)



(**16**)

That compound **A** was indeed the triazabicyclo-octene (**9a**) was confirmed by an *X*-ray analysis (see Experimental section for crystal data and other information). The molecular structure is shown in Figure 1 together with its crystallographic numbering. Refined atomic co-ordinates are included in the

Table. Fractional atomic co-ordinates ($\times 10^4$) and temperature factors ($Å^2 \times 10^3$), with estimated standard deviations in parenthesis, of the triazabicyclo-octene (**9a**)

Atom	*x*	*y*	*z*
N(1)	2 559	4 593(2)	4 732
C(2)	2 691(1)	3 136(2)	4 652(2)
N(3)	2 353(1)	2 437(2)	3 562(2)
N(4)	1 903(1)	3 234(2)	2 421(2)
C(5)	2 086(2)	4 762(2)	2 413(2)
C(6)	2 033(2)	5 444(2)	3 541(2)
C(7)	2 610(2)	6 741(2)	4 243(2)
C(8)	3 116(2)	5 741(2)	5 383(2)
O(8)	3 743(1)	5 803(2)	6 431(2)
C(9)	3 187(1)	2 354(2)	5 918(2)
O(9)	3 179(1)	2 734(2)	6 905(1)
O(10)	3 606(1)	1 255(2)	5 799(1)
C(11)	4 149(2)	315(2)	6 949(2)
C(12)	4 840(2)	1 196(3)	8 018(3)
C(13)	4 526(2)	−708(3)	6 351(3)
C(14)	3 591(2)	−447(3)	7 402(3)
C(15)	1 390(2)	2 532(2)	1 252(2)
O(15)	1 045(1)	3 163(2)	216(1)
O(16)	1 331(1)	1 151(2)	1 448(2)
C(17)	752(2)	199(3)	350(2)
C(18)	1 000(2)	193(4)	−730(3)
C(19)	−156(2)	674(4)	−141(3)
C(20)	932(3)	−1 242(3)	1 028(3)

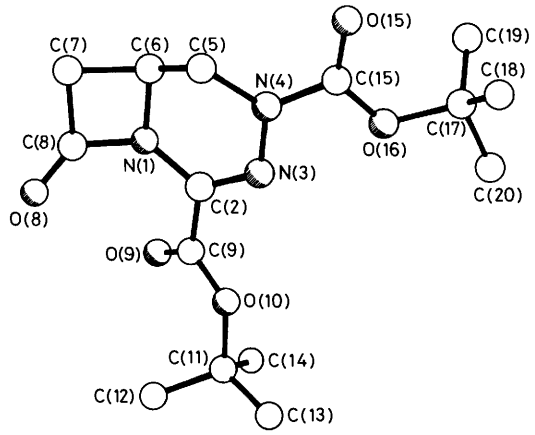
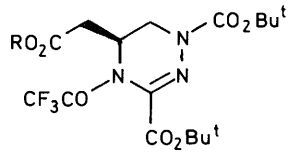


Figure 1. The molecular structure of the triazabicyclo-octene (**9a**).

Table, while bond lengths, bond angles, and thermal parameters are available as a separate publication (see Experimental section).

In the crystal state, the six-membered ring exists in a sofa-like conformation and the β-lactam nitrogen is non-planar [the sum of the bond angles around N(1) is 347.4° and the distance of N(1) from the plane defined by the substituents is 0.28 Å, values that are similar to those observed in cephalosporins[6]]. The *X*-ray structure also provides a possible explanation for the large chemical shift difference between the 5α- and 5β-hydrogen atoms, alluded to earlier. Thus the 5α-hydrogen atom, *i.e.* H_b, appears to lie in the deshielding zone of the carbazate carbonyl group whereas the 5β-hydrogen atom, *i.e.* H_a, may be shielded by the β-lactam carbonyl group.

In an attempt to prepare the acid (**9b**) for biological evaluation, compound (**9a**) was treated in deuteriochloroform with trifluoroacetic acid. Following esterification with diazomethane and purification of the product by silica-gel chromatography, the tetrahydrotriazine (**11a**) was isolated in 88% yield as a syrup. Presumably, trifluoroacetic acid reacts with the triazabicyclo-octene (**9a**) to give the mixed anhydride (**11d**) which rearranges to the *N*-acylated tetrahydrotriazine (**17a**). Diazomethane then reacts with the last-cited compound to give the methyl ester (**17b**) which undergoes deacylation during



(**17**)

a; R = H

b; R = Me

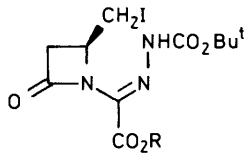
chromatography. Although analogous reactions (without the deacylation step) have been observed with β-lactams fused to five-membered rings, *e.g.* 3-oxa-1-azabicyclo[3.2.0]heptan-7-ones,[3] 3-thia- and 4-thia-1-azabicyclo[3.2.0]heptan-7-ones,[4] and 1-azabicyclo[3.2.0]hept-3-en-7-ones,[1] they do not usually occur with β-lactams fused to six-membered rings. Thus 4-carboxylic acid derivatives of 1-azabicyclo[4.2.0]oct-2-en-8-ones,[7] 5-thia-1-azabicyclo[4.2.0]oct-2-en-8-ones,[8] 5-oxa-1-azabicyclo-[4.2.0]oct-2-en-8-ones,[9] and 1,5-diazabicyclo[4.2.0]oct-2-en-8-ones[10] can be liberated from their t-butyl esters by the action of trifluoroacetic acid. Evidently, the β-lactam linkage of the bicycle (**9a**) is endowed with a high chemical reactivity.

Starting with the carbinols (**6b,c**),[3] it was possible to prepare the bicycles (**9c,d**) by way of the chlorides (**7b,c**) and the hydrazides (**5b,c**). The former product was isolated as a crystalline solid in 47% yield after silica-gel chromatography; the latter product was obtained in 45% yield after crystallisation. In the 360 MHz ^1H n.m.r. spectrum ($CDCl_3$) of compound (**9d**), the 5β-hydrogen atom appeared as a double doublet (*J* 12.5 and 9 Hz) at δ 2.71 and the 5α-hydrogen atom as a double doublet (*J* 12.5 and 4 Hz) at δ 4.90.

The triazabicyclo-octenes (**9c,d**) were both subjected to hydrogenolytic conditions but the best results were achieved using the latter material. When stirred under a hydrogen atmosphere with 5% palladium–charcoal in ethyl acetate–ethanol (1:1), compound (**9d**) was transformed into the acid (**9b**) in essentially quantitative yield. The derived sodium salt (**9e**), which was stable in deuterium oxide over a period of 24 h, showed no significant antibacterial activity and it did not act as an ampicillin synergist against β-lactamase-producing bacteria. The acid (**9b**) and the sodium salt (**9e**) were characterised by their spectral properties and by their conversion into the crystalline methyl ester (**9f**).

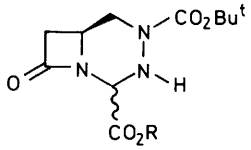
The transformation of the hydrazides (**5a**—**c**) into the triazabicyclo-octenes (**9a,c,d**) may involve the intermediacy of the hydrazones (**18a**—**c**) and/or the triazabicyclo-octanes (**19a**—**c**). We favour the former possibility. Thus when treated with lead(IV) acetate in dichloromethane, the hydrazide (**5a**) was converted into the hydrazone (**18a**) (58% yield after SiO_2 chromatography) which reacted with silver(I) oxide in acetonitrile to give the bicycle (**9a**) in 68% yield.

Compounds (**9a**—**f**) are the first members of the 1,3,4-triazabicyclo[4.2.0]oct-2-en-8-one family of β-lactam derivatives; a few examples of the 1,3,4-triazabicyclo[4.2.0]octan-8-one group, *e.g.* (**20**), have been described.[11] Related systems include 1,3-diazabicyclo[4.2.0]oct-2-en-8-ones,[12] 1,4-diazabicyclo[4.2.0]oct-2-en-8-ones,[13] 5-thia-1,3-diazabicyclo[4.2.0]oct-2-en-8-ones,[14] and 5-thia-1,4-diazabicyclo[4.2.0]oct-2-en-8-ones.[15]



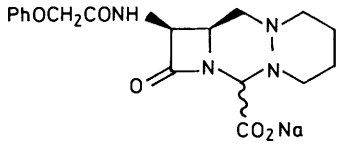
(18)

a; R = Bu^t
b; R = $CH_2C_6H_4NO_2$-*p*
c; R = CH_2Ph



(19)

a; R = Bu^t
b; R = $CH_2C_6H_4NO_2$-*p*
c; R = CH_2Ph



(20)

Experimental

Dry solvents referred to in the ensuing experiments were prepared as follows: THF was dried over calcium hydride or lithium aluminium hydride and, immediately prior to use, distilled; 2,6-dimethylpyridine was stored over sodium hydroxide pellets; dichloromethane was stored over calcium chloride; acetonitrile and DMF were stored over 4 Å molecular sieves. Light petroleum refers to that fraction boiling in the range 40—60 °C. Silver(I) oxide was prepared by the method of Vogel[16] and dried *in vacuo* over phosphorus pentaoxide. Ethereal diazomethane was prepared[17] by adding a solution of Diazald in diethyl ether to potassium hydroxide in aqueous ethanol at *ca.* 60 °C. For chromatographic and instrumental details, see Parts 1,[3] 2,[4] and 3.[1]

Preparation of t-Butyl 4-*Iodomethyl*-2-*oxoazetidin*-1-*yl*(2-*t-butoxycarbonylhydrazino*)*acetate* (**5a**).—To a cooled (CCl_4–solid CO_2) stirred solution of the carbinol (**6a**)[3] (0.220 g, 0.64 mmol) in dry THF (5 cm^3) was added dry 2,6-dimethylpyridine (0.15 cm^3, 1.28 mmol) followed by thionyl chloride (0.093 cm^3, 1.28 mmol). After 30 min, the mixture was filtered through Hyflo and the filtrate evaporated. The resultant crude chloride (**7a**) was immediately dissolved in dry dichloromethane (5 cm^3) and to the stirred solution under nitrogen was added t-butyl carbazate (0.092 g, 0.70 mmol). After 24 h, the mixture was diluted with dichloromethane and washed twice with aqueous potassium hydrogen carbonate. Evaporation of the dried ($MgSO_4$) organic layer and purification of the product by silica-gel chromatography [light petroleum–EtOAc (1:9) as eluant] gave the title compound (**5a**) (0.176 g, 60%) as a syrupy 1:1 mixture of diastereoisomers; $\nu_{max.}$(film 3 320 (NH), 1 760 (β-lactam C=O), and 1 740br cm^{-1} (ester and carbazate C=O); δ(60 MHz; $CDCl_3$) 1.48 and 1.50 (each 9 H, s, together 2 × CMe_3), 2.48—4.50 (6 H, m, 3 × β-lactam-H, CH_2I, and CHN*H*NH), 5.10 and 5.18 (each 0.5 H, s, together $NCHCO_2$), and 6.65br (1 H, s, NHN*H*CO_2) (addition of D_2O caused the signal at δ 6.65 to disappear); *m/z* 399 ($M^+ - C_4H_8$) and 57 ($C_4H_9^+$, base peak).

Preparation of t-Butyl 4-*t-Butoxycarbonyl*-8-*oxo*-1,3,4-*triazabicyclo*[4.2.0]*oct*-2-*ene*-2-*carboxylate* (**9a**).—The carbinol (**6a**)[3] (5.32 g, 15.6 mmol) was transformed into the crude hydrazide (**5a**) as described in the previous experiment. The material was immediately dissolved in dry acetonitrile (30 cm^3) and stirred with silver(I) oxide (8.95 g, 38.6 mmol). After 12 h, the mixture was filtered and the filtrate concentrated. The resultant residue was dissolved in ethyl acetate and the solution was washed with brine (× 2). Evaporation of the dried ($MgSO_4$) organic phase and recrystallisation of the resultant yellow solid from dichloromethane–diethyl ether gave the *title compound* (**9a**) (2.49 g, 49%) as a white solid, m.p. 152—153 °C; $\nu_{max.}$(KBr) 1 790 (β-lactam C=O), 1 735 (unsaturated ester C=O), and 1 705 cm^{-1} (carbazate C=O); $\lambda_{max.}$(EtOH) 213 (ε 5 300), 230 (3 900), and 287 nm (14 500); δ_H(360 MHz; $CDCl_3$) 1.54 and 1.56 (each 9 H, s, together 2 × CMe_3), 2.68 (1 H, dd, *J* 12.5 and 8.5 Hz, 5β-H), 2.92—3.00 (1, m, 7α-H), 3.55—3.62 (2 H, m, 7β- and 6-H), and 4.87 (1 H, dd, *J* 12.5 and 4 Hz, 5α-H); δ_C(90 MHz; $CDCl_3$; ^1H decoupled) 27.8 and 27.9 [2 × C(CH_3)$_3$], 41.1 (6-C), 44.2 and 45.4 (5- and 7-C), 83.1 and 83.6 [2 × O*C*(CH_3)$_3$], 129.4 (2-C), 152.0 and 157.9 (2 × CO), and 162.2 (8-C); *m/z* 325 (M^+), 269 ($M^+ - C_4H_8$), 225 ($M^+ - C_5H_8O_2$), 169 ($M^+ - C_9H_{16}O_2$), and 57 ($C_4H_9^+$, base peak) (Found: C, 55.3; H, 7.0; N, 12.8. $C_{15}H_{23}N_3O_5$ requires C, 55.35; H, 7.1; N, 12.9%).

X-*Ray Crystal Structure Data*.—$C_{15}H_{23}N_3O_5$, M = 325.4. Monoclinic, a = 17.823(3), b = 9.329(2), c = 11.580(3) Å, β = 118.80(2), U = 1 687 $Å^3$, space group Cc, Z = 4, D_c = 1.28 g cm^3. Refined unit-cell parameters were obtained by centring 15 reflections on a Nicolet R3m diffractomer. 1 165 Independent reflections (Θ < 58°) were measured with Cu-K_α radiation (graphite monochromator) using the ω-scan measuring routine. Of these 1 159 had $|F_o| > 3\sigma(|F_o|)$ and were considered to be observed. The net count of the two check reflections (the 1,3,−1 and the 3,−1,−3), measured every 50 reflections during the data collection, did not change significantly, indicating that no deterioration of the crystal had occurred. The data were brought to a uniform arbitrary scale and Lorentz and polarisation corrections applied; no absorption correction was applied.

The structure was solved by a combination of direct methods and ΔE map recycling. The non-hydrogen atoms were refined anisotropically. The proton on C(6) was located from a ΔF map and refined isotropically subject to a C–H distance constraint (0.96 Å). The positions of the remaining hydrogen atoms were idealised, C–H = 0.96 Å, assigned isotropic thermal parameters, U(H) = 1.2U_{eq}(C), and allowed to ride on their parent carbon atoms. The methyl groups were refined as rigid bodies. Refinement was by block-cascade, full-matrix least-squares to R = 0.024, R_w = 0.027 [$w^{-1} = \sigma^2(F) + 0.00019F^2$]. The maximum residual electron density in the final ΔF map was 0.10 e $Å^{-3}$. Computations were carried out on an Eclipse S140 using the SHELXTL program system.[18]

The fractional co-ordinates of the hydrogen atoms and their isotropic thermal parameters, the bond lengths and bond angles, and the anisotropic thermal parameters of the non-hydrogen atoms are available, on request, from the Cambridge Crystallographic Data Centre.*

Preparation of Methyl 1-*t-Butoxycarbonyl*-3-*methoxycarbonyl*-1,4,5,6-*tetrahydro*-1,2,4-*triazin*-5-*ylacetate* (**11b**).—1M Sodium hydroxide (2.10 cm^3, 2.1 mmol) was added to a stirred solution of the triazabicyclo-octene (**9a**) (0.325 g, 1.0 mmol) in THF (5 cm^3). After 3 h, the solution was evaporated and the residue was dried [by evaporation from EtOH (× 3) followed by CCl_4 (× 2)]. The resultant foam was dissolved in dry DMF (5 cm^3) and iodomethane (0.311 cm^3, 5.0 mmol) was added to the stirred solution. After 12 h, the mixture was diluted with ethyl acetate and washed with brine (× 5). Evaporation of the dried ($MgSO_4$) organic layer and purification of the residue by silica-gel chromatography [light–petroleum EtOAc (1:1) as eluant] gave the *title compound* (**11b**) (0.164 g, 52%) as a chromato-

* For details of the Scheme, see 'Instructions for Authors (1989)' in *J. Chem. Soc., Perkin Trans. 1*, 1989, Issue 1.

graphically homogeneous pale-yellow syrup; $\nu_{max.}$(film) 3 400 (NH), 1 720br (ester and carbazate C=O), and 1 630 cm^{-1} (C=N); $\lambda_{max.}$(EtOH) 212 (ε 3 200) and 293 nm (5 400); δ(300 MHz; $CDCl_3$) 1.55 (9 H, s, CMe_3), 2.51 (1 H, dd, *J* 17 and 9 Hz, COC*H*HCH), 2.60 (1 H, dd, *J* 17 and 5 Hz, COCH*H*CH), 3.56 (1 H, dd, *J* 12.5 and 5 Hz, NC*H*HCH), 3.74 (3 H, s, OMe), 3.75 (1 H, dd, *J* 12.5 and 3.5 Hz, NCH*H*CH), 3.87 (3 H, s, OMe), 3.98—4.03 (1 H, m, NHC*H*), and 6.14br (1 H, s, NH) (addition of D_2O caused the broad singlet at δ 6.14 to disappear and the multiplet at δ 3.98—4.03 to sharpen); *m/z* 315 (M^+), 300 ($M^+ - CH_3$), and 57 ($C_4H_9^+$, base peak) (Found: M^+, 315.1460. $C_{13}H_{21}N_3O_6$ requires *M*, 315.1430).

Preparation of Methyl 4-*Acetyl*-1-*t-butoxycarbonyl*-3-*methoxycarbonyl*-1,4,5,6-*tetrahydro*-1,2,4-*triazin*-5-*ylacetate* (**15**).—Sodium hydride (0.025 g, 1.04 mmol) followed by acetyl chloride (0.037 cm^3, 0.52 mmol) were added to a stirred ice-cooled solution of the triazine (**11b**) (0.090 g, 0.29 mmol) in dry THF (2 cm^3). After 2 h, acetic acid was added and the mixture was diluted with ethyl acetate and washed with brine and aqueous sodium hydrogen carbonate. Evaporation of the dried ($MgSO_4$) organic phase left a yellow syrup which was purified by silica-gel column chromatography (light petroleum–EtOAc; gradient elution) to give the *title compound* (**15**) (0.041 g, 40%) as a chromatographically homogeneous colourless syrup; $\nu_{max.}$(film) 1 740br (ester C=O) and 1 690 cm^{-1} (amide C=O); $\lambda_{max.}$(EtOH) 210 (ε 4 500) and 267 nm (15 000); δ (300 MHz; $CDCl_3$) 1.55 (9 H, s, CMe_3), 2.20 (3 H, s, NCOMe), 2.40 (1 H, dd, *J* 16.5 and 7.5 Hz, COC*H*HCH), 2.49 (1 H, dd, *J* 16.5 and 7 Hz, COCH*H*CH), 3.37 (1 H, dd, *J* 13 and 4 Hz, NC*H*HCH), 3.72 and 3.88 (each 3 H, s, 2 × OMe), 4.41 (1 H, dd, *J* 13 and 1 Hz, NCH*H*CH), and 4.93—5.10 (1 H, m, NCH_2CH); *m/z* 357 (M^+), 315 ($M^+ - C_2H_5O$), and 57 $C_4H_9^+$, base peak) (Found: M^+, 357.1545. $C_{15}H_{23}N_3O_7$ requires *M*, 357.1536).

Reaction of the Triazabicyclo-octene (**9a**) *with Trifluoroacetic Acid followed by Diazomethane.*—Trifluoroacetic acid (1 drop) was added to a solution of the triazabicyclo-octene (**9a**) (0.032 g, 0.098 mmol) in deuteriochloroform (0.5 cm^3). After 2 h, when the starting material had disappeared (^1H n.m.r. spectroscopy), the solvent was evaporated. After addition of carbon tetrachloride to the residue and re-evaporation (repeated × 3), the crude acid (**17a**) was dissolved in dichloromethane (2 cm^3) and treated with an excess of diazomethane in diethyl ether. Evaporation and purification of the residue by silica-gel column chromatography ($CHCl_3$ as eluant) gave *methyl* 1,3-*di-t-butoxycarbonyl*-1,4,5,6-*tetrahydro*-1,2,4-*triazin*-5-*ylacetate* (**11a**) (0.031 g, 88%) as a chromatographically homogeneous pale yellow syrup; $\nu_{max.}$(film) 3 400br (NH), 1 730 (ester C=O), 1 710 (carbazate C=O), and 1 630 cm^{-1} (C=N); $\lambda_{max.}$(EtOH) 212 (ε 6 800), 275 (7 400), and 283 nm (7 600); δ(360 MHz; $CDCl_3$) 1.53 and 1.54 (each 9 H, s, 2 × CMe_3), 2.49 (1 H, dd, *J* 17 and 9 Hz, NCHC*H*HCO), 2.57 (1 H, dd, *J* 17 and 5 Hz, NCHCH*H*CO), 3.51 (1 H, dd, *J* 12.5 and 5 Hz, CHC*H*HN), 3.67—3.74 (4 H, m, OMe and CHCH*H*N), 3.94—3.98 (1 H, m, C*H*CH_2N), and 6.1br (1 H, s, NH); *m/z* 357 (M^+), 297 ($M^+ - C_5H_8O_2$), and 57 ($C_4H_9^+$, base peak) (Found: M^+, 357.1900. $C_{16}H_{27}N_3O_6$ requires *M*, 357.1900).

Preparation of p-*Nitrobenzyl* 4-*t-Butoxycarbonyl*-8-*oxo*-1,2,4-*triazabicyclo*[4.2.0]*oct*-2-*ene*-2-*carboxylate* (**9c**).—Dry 2,6-dimethylpyridine (0.55 cm^3, 4.72 mmol) followed by thionyl chloride (0.34 cm^3, 4.66 mmol) were added to a stirred cooled (CCl_4–solid CO_2) solution of the carbinol (**6b**)[3] (1.00 g, 2.38 mmol) in dry THF (15 cm^3). After 30 min, the mixture was filtered through Hyflo and the filtrate evaporated. The resultant crude chloride (**7b**) was immediately dissolved in dry dichloromethane (15 cm^3) and to the stirred solution under nitrogen was added t-butyl carbazate (0.345 g, 2.61 mmol). After 24 h, the mixture was diluted with dichloromethane and washed with aqueous potassium hydrogen carbonate (× 2). Evaporation of the dried ($MgSO_4$) organic layer left the crude hydrazide (**5b**) which was dissolved in dry acetonitrile (5 cm^3) and stirred with silver(I) oxide (0.550 g, 2.37 mmol). After 12 h, the mixture was filtered and the filtrate concentrated. Purification of the residue by silica-gel chromatography (EtOAc as eluant) gave the *title compound* (**9c**) (0.450 g, 47%) as a white solid. After recrystallisation from chloroform, the sample possessed m.p. 176—178 °C; $\nu_{max.}$(KBr) 1 800 (β-lactam C=O) and 1 725br cm^{-1} (ester and carbazate C=O); $\lambda_{max.}$(EtOH) 210 (ε 4 500) and 285 nm (7 000); δ(60 MHz; $CDCl_3$) 1.53 (9 H, s, CMe_3), 2.60—3.90 (4 H, m, 5β- and 6-H, and 7-H_2), 4.84—5.10 (1 H, m, 5α-H), 5.48 (2 H, s, $OCH_2C_6H_4$), and 7.62 and 8.22 (each 2 H, d, *J* 8 Hz, together C_6H_4); *m/z* 404 (M^+) and 57 ($C_4H_9^+$, base peak) (Found: C, 53.2; H, 4.9; N, 13.7; M^+, 404.1349. $C_{18}H_{20}N_2O_7$ requires C, 53.45; H, 5.0; N, 13.85%; *M*, 404.1332).

Preparation of Benzyl 4-*t-Butoxycarbonyl*-8-*oxo*-1,3,4-*triazabicyclo*[4.2.0]*oct*-2-*ene*-2-*carboxylate* (**9d**).—The carbinol (**6c**)[3] (0.740 g, 1.97 mmol) was sequentially treated with thionyl chloride, t-butyl carbazate. and silver(I) oxide, as described for compound (**9a**). Work-up as before gave a yellow foam which was crystallised from dichloromethane–diethyl ether to give the *title compound* (**9d**) (0.320 g, 45%) as a white powder; m.p. 137—139 °C; $\nu_{max.}$(KBr) 1 795 (β-lactam C=O), 1 720 (unsaturated ester C=O), and 1 705 cm^{-1} (carbazate C=O); $\lambda_{max.}$(EtOH) 211 (ε 8 300), 229 (3 600), and 288 nm (11 900); δ(360 MHz; $CDCl_3$) 1.55 (9 H, s, CMe), 2.71 (1 H, dd, *J* 12.5 and 9 Hz, 5β-H), 2.95—3.01 (1 H, m, 7α-H), 3.56—3.64 (2 H, m, 7β- and 6-H), 4.90 (1 H, dd, *J* 12.5 and 4 Hz, 5α-H), 5.35 (2 H, AB q, *J* 12.5 Hz, separation of inner lines 7 Hz, OCH_2Ph), and 7.31—7.45 (5 H, s, C_6H_5); *m/z* 359 (M^+), 259 ($M^+ - C_5H_8O_2$), and 57 ($C_4H_9^+$, base peak) (Found: C, 60.0; H, 5.8; N, 11.7. $C_{18}H_{21}N_3O_5$ requires C, 60.15; H, 5.9; N, 11.7%).

Preparation of 4-*t-Butoxycarbonyl*-8-*oxo*-1,3,4-*triazabicyclo*-[4.2.0]-*oct*-2-*ene*-2-*carboxylic Acid* (**9b**).—A stirred mixture of the triazabicyclo-octene (**9d**) (0.320 g, 0.89 mmol) and 5% palladium–carbon (1.28 g, 4 mass equiv.) in ethyl acetate (10 cm^3) and ethanol (10 cm^3) was saturated with hydrogen for 15 min. The mixture was then filtered through Hyflo and the filtrate concentrated. Carbon tetrachloride was added to the residue and the solvent was evaporated (repeated × 3) to give the *title compound* (**9b**) (0.235 g, 98%) as a glassy foam; $\nu_{max.}$(film) 3 300br (OH), 1 785 (β-lactam C=O), and 1 710 cm^{-1} (acid and carbazate C=O); $\lambda_{max.}$(EtOH) 208 (ε 4 100) and 279 nm (7 900); δ(300 MHz; $CDCl_3$) 1.57 (9 H, s, CMe_2), 2.78 (1 H, dd, *J* 12 and 8 Hz, 5β-H), 3.00—3.06 (1 H, m, 7α-H), 3.66—3.74 (2 H, m, 7β- and 6-H), and 4.88 (1 H, dd, *J* 12 and 4 Hz, 5α-H); *m/z* 225 ($M^+ - CO_2$), 210 ($M^+ - C_2H_3O_2$), 168 ($M^+ - C_5H_8O_2$), and 57 ($C_4H_9^+$), base peak) (Found: $M^+ - CO_2$, 225.1117. $C_{10}H_{15}N_3O_3$ requires *m/z* 225.1113).

Preparation of Sodium 4-*t-Butoxycarbonyl*-8-*oxo*-1,2,4-*triazabicyclo*[4.2.0]*oct*-2-*ene*-2-*carboxylate* (**9e**).—A solution of sodium 2-ethylhexanoate in a mixture of butan-1-ol and diethyl ether was added in drops to a solution of the acid (**9b**) (0.098 g, 0.36 mmol) in acetone (1 cm^3) until no further precipitation occurred. After filtration, the solid was recrystallised from acetone–diethyl ether to yield the title compound (**9e**) (0.066 g, 62%) as a white-solid; m.p. 210 °C (decomp.); $\nu_{max.}$(KBr) 1 785 (β-lactam C=O), 1 710 (carbazate C=O), and 1 640 cm^{-1} (carboxylate C=O); δ(300 MHz; D_2O) *inter alia* 1.53 (9 H, s, CMe_3), 3.08 (1 H, dd, *J* 16.5 and 2.5 Hz, 7β-H), 3.56—3.64 (1 H, m, 7α-H), and 3.67—3.77 (1 H, m, 6-H) [the signals for the 5β-hydrogen atoms were presumed to be obscured by the triplet

at δ 2.90 (due to the CH_2SO_2 signals of $Me_3SiCH_2CH_2CH_2SO_2Na$ which was added as an internal reference) and the broad singlet of δ 4.80 (due to HOD)].

Preparation of Methyl 4-t-Butoxycarbonyl-8-oxo-1,3,4-triazabicyclo[4.2.0]oct-2-ene-2-carboxylate (**9f**).—(*a*) A solution of the acid (**9b**) (0.112 g, 0.42 mmol) in dichloromethane (5 cm^3) was treated with an excess of diazomethane in diethyl ether. Evaporation and recrystallisation of the residue from dichloromethane-diethyl ether gave the *title compound* (**9f**) (0.060 g, 51%) as a white solid, m.p. 178—181 °C; $\nu_{max.}$(KBr) 1 795 (β-lactam C=O) and 1 710br cm^{-1} (unsaturated ester and carbazate C=O); $\lambda_{max.}$(EtOH) 210 (ε 4 500), 232 (4 400), and 286 nm (17 800); δ(360 MHz; $CDCl_3$) 1.56 (9 H, s, CMe_3), 2.73 (1 H, dd, *J* 12.5 and 9 Hz, 5β-H), 2.99 (1 H, dd, *J* 18 and 4.5 Hz, 7α-H), 3.60—3.66 (2 H, s, 7β- and 6-H), 3.92 (3 H, s, OMe), and 4.90 (1 H, dd, *J* 12.5 and 3.5 Hz, 7β-H); *m/z* 283 (M^+), 210 ($M^+ - C_4H_9O$), 183 ($M^+ - C_5H_8O_2$), and 57 ($C_4H_9^+$, base peak) (Found: C, 50.9; H, 5.9; N, 14.6. $C_{12}H_{17}N_3O_5$ requires C, 50.9; H, 6.05; N, 14.85%).

(*b*) A solution of the sodium salt (**9e**) (0.028 g, 0.096 mmol) in deuterium oxide (0.5 cm^3) was left for 24 h, after which time little change was observed by ^1H n.m.r. spectroscopy. The solid obtained after evaporation was dried [by addition of EtOH and re-evaporation (repeated ×2) and addition of CCl_4 and re-evaporation (repeated ×2)], dissolved in dry DMF (2 cm^3) and treated with iodomethane (0.030 cm^3, 0.48 mmol). After 24 h, the mixture was diluted with ethyl acetate and washed with brine (×5). Evaporation of the dried ($MgSO_4$) organic phase and recrystallisation of the residue from dichloromethane–diethyl ether gave a white solid (0.010 g, 37%), m.p. 180—181 °C, which was identical with the ester (**9f**) (^1H n.m.r. and i.r. spectroscopy).

Preparation of t-Butyl 2-t-Butoxycarbonylhydrazono(4-iodomethyl-2-oxoazetidin-1-yl)acetate (**18a**).—Dry 2,6-dimethylpyridine (1.50 cm^3, 12.9 mmol) followed by thionyl chloride (0.93 cm^3, 12.7 mmol) were added to a stirred cooled (CCl_4–solid CO_2) solution of the carbinol (**6a**)[3] (2.20 g, 6.45 mmol) in dry THF (50 cm^3) under nitrogen. After 30 min, the mixture was filtered through Hyflo and the filtrate evaporated. The resultant crude chloride (**7a**) was dissolved in dry dichloromethane (50 cm^3) and to the stirred solution under nitrogen was added t-butyl carbazate (0.921 g, 6.97 mmol). After 24 h, the mixture was diluted with dichloromethane and washed with aqueous potassium hydrogen carbonate (×2). Evaporation of the dried ($MgSO_4$) organic phase left the crude hydrazide (**5a**) which was dissolved in dry dichloromethane (50 cm^3) and treated at 0 °C with lead(IV) acetate (3.11 g, 7.01 mmol). After filtration, the solution was washed with aqueous potassium hydrogen carbonate (×2). Evaporation of the dried ($MgSO_4$) organic layer gave an orange syrup which was purified by silica-gel column chromatography (light petroleum–EtOAc; gradient solution) to give the title compound (**18a**) (1.27 g, *ca.* 58%) as a slightly impure yellow syrup; $\nu_{max.}$(film) 3 200 (NH), 1 750br (β-lactam and ester C=O), and 1 715 cm^{-1} (carbazate C=O); $\lambda_{max.}$(EtOH) 212 (ε 7 400) and 280 nm (8 000); δ(300 MHz; $CDCl_3$) 1.45 and 1.49 (each 9 H, s, 2 × CMe_3), 2.75 (1 H, dd, *J* 16 and 3 Hz, COC*H*HCH), 3.13 (1 H, dd, *J* 16 and 5.5 Hz, COCH*H*CH), 3.17 (1 H, t, *J* 10.5 and 10.5 Hz, CHC*H*HI), 3.44 (dd, *J* 10.5 and 3.5 Hz, CHCH*H*I), 4.53—4.61 (1 H, m, C*H*CH_2I), and 10.0br (1 H, s, CONH); *m/z* 397 ($M^+ - C_4H_8$), 341 ($M^+ - C_8H_{16}$), and 57 ($C_4H_9^+$, base peak) (Found: $M^+ - C_4H_8$, 397.0168. $C_{11}H_{16}IN_3O_5$ requires *m/z* 397.0136).

Reaction of the Hydrazone (**18a**) *with Silver(I) Oxide.*—Silver(I) oxide (0.282 g, 1.22 mmol) was added to a stirred solution of the hydrazone (**18a**) (0.500 g, 1.10 mmol) in dry acetonitrile (10 cm^3). After 12 h, the mixture was filtered through Hyflo and the filtrate concentrated. Recrystallisation of the residue from dichloromethane–diethyl gave a white solid (0.245 g, 68%), m.p. 149—151 °C, that was identical to the triazabicyclo-octene (**9a**) by ^1H n.m.r. spectroscopy.

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