Synthesis of Racemic 4-t-Butoxycarbonyl-8-oxo-1,3,4-triazabicyclo[4.2.0]oct-2-ene-2-carboxylates: a Novel Class of β-Lactam Derivatives

Chandra M. Pant,[a] Richard J. Stoodley,*[a] Andrew Whiting,[a] and David J. Williams[b]

[a] *Department of Organic Chemistry, The University, Newcastle upon Tyne NE1 7RU, U.K.*

[b] *Department of Chemistry, Imperial College of Science and Technology, London SW7 2AZ, U.K.*

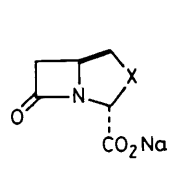
Representatives of the title compounds have been prepared and the *X*-ray structure of the t-butyl ester has been determined.

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**),[1] (**1b**),[2] and (**1c**)[2] but none of the compounds acted as β-lactamase inhibitors or antibacterial agents. Since double covalent binding of β-lactamases with their substrates is believed to be important for irreversible inhibition,[3] the bicycle (**1d**) attracted our attention. It was envisaged that, if the compound fulfilled the role of a substrate, a diazonium intermediate of type (**2**) might be generated. The loss of nitrogen from such an intermediate might result in the formation of a species of type (**3**) or (**4**) and, perhaps, in irreversible inhibition of the enzyme. In the hope that they would act as precursors of compound (**1d**), compounds of type (**5**) were selected as synthetic targets. The unexpected emergence from these studies of bicycles of type (**6**) is the subject of this communication.

It was presumed that compounds of type (**7**), which should be readily prepared from azetidinones of type (**8**), would undergo a base-induced cyclisation to bicycles of type (**5**). Conversion of the hydroxy-amide (**8a**)[1] into the hydrazide (**7a**), as a 1:1 mixture of diastereoisomers, was achieved by sequential reactions with thionyl chloride–2,6-lutidine (tetrahydrofuran, −20 °C) and t-butyl carbazate (CH_2Cl_2). However, attempts to convert the hydrazide (**7a**) into the bicycle (**5a**) under a variety of basic conditions afforded non-β-lactam products. With a view to providing electrophilic assistance to the halide ionisation, the hydrazide (**7a**) was treated with silver(I) oxide in acetonitrile. Following recrystallisation of the crude product, a material, m.p. 152—153 °C, with the constitution $C_{15}H_{23}N_3O_5$ and designated compound (A), was isolated in 50% yield [based on (**8a**)]. Clearly, an oxidative elimination, *i.e.* $-H_2$ and −HI, was involved in the production of compound (A) from its precursor (**7a**).

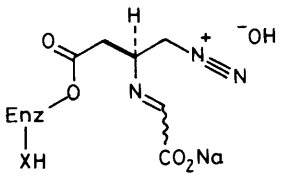
Compound (A) showed strong absorptions at 1 790, 1 735, and 1 705 cm^{-1} in the i.r. region (KBr disc) and a band at 287 nm (ε 14 500) in the u.v. spectrum (EtOH). The presence of two t-butoxy groups (δ 27.8, 27.9 and 83.1, 83.6), two methylene moieties (δ 44.2 and 45.4), a methine moiety (δ 41.1), an imine function (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), 300 MHz ^1H n.m.r. spectroscopy implicated the partial structure (**9**). Thus the spectrum ($CDCl_3$) 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 double doublet with fine structure at δ 2.95 (separations 18 and 4.5 Hz), 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 protons attributed to the N-CH_2 group. On the basis of the spectroscopic evidence, compound (A) was considered to possess either the structure (**6a**) or (**10**).

That compound (A) was the bicyclic β-lactam (**6a**) was revealed by a single-crystal *X*-ray analysis; the molecular structure is shown in Figure 1. *Crystal 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 = 1.29 g cm^{-3}. 1159 Independent observed reflections [$|F_o| > 3\sigma(|F_o|)$, $\theta \leq 58°$] were measured with

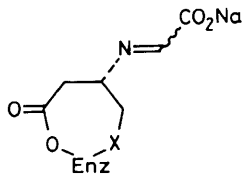


(1)

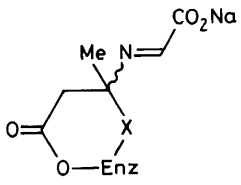
a; X = O
b; X = S
c; X = S(=O)$_2$
d; X = NN(=O)



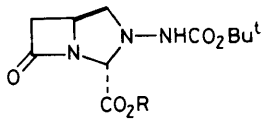
(2)



(3)

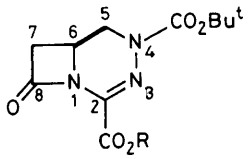


(4)



(5)

a; R = Bu^t



(6)

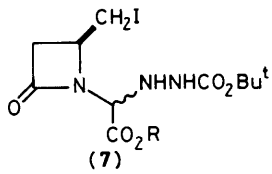
a; R = Bu^t
b; R = H
c; R = CH$_2$Ph
d; R = Me
e; R = Na

Cu-K_α radiation (graphite monochromator) on a Nicolet R3m diffractometer using ω-scans. The structure was solved by direct methods and the non-hydrogen atoms were refined anisotropically. The bridgehead hydrogen atom was refined isotropically. All the other hydrogen atoms were placed at calculated positions, and the methyl groups were refined as rigid bodies. Refinement converged to give $R = 0.024$, $R_w = 0.027$.†

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 its substituents is 0.28 Å, values that are similar to those observed in cephalosporins[4]]. The *X*-ray structure also provides a possible explanation for the large chemical shift difference between the 5α- and 5β-protons, alluded to earlier. Thus the 5α-proton, *i.e.* H$_b$, appears to lie in a deshielding zone of the urethane carbonyl group whereas the 5β-proton, *i.e.* H$_a$, may be shielded by the β-lactam carbonyl group.

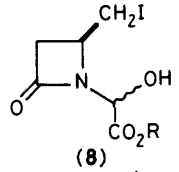
With the intention of deriving the acid (**6b**) for biological evaluation, compound (**6a**) was treated in deuteriochloroform with trifluoroacetic acid. Following esterification (CH_2N_2) and silica gel purification, the tetrahydrotriazine (**11**) was isolated in 72% yield. Since 2-carboxylic acid derivatives of

† The atomic co-ordinates are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K. Any request should be accompanied by the full literature citation for this communication.



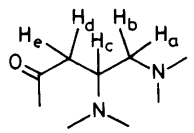
(7)

a; R = Bu^t
b; R = CH$_2$Ph

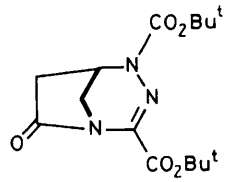


(8)

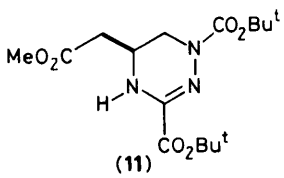
a; R = Bu^t
b; R = CH$_2$Ph



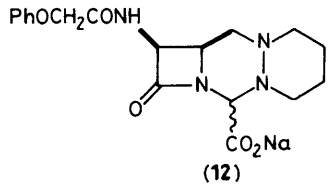
(9)



(10)



(11)



(12)

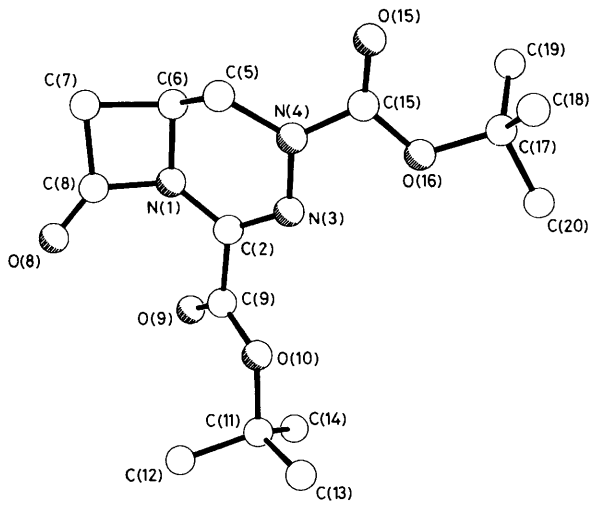


Figure 1. The molecular structure of compound (**6a**). Bond lengths (e.s.d.s in parentheses): N(1)–C(2) 1.391(3), C(2)–N(3) 1.284(3), N(3)–N(4) 1.386(2), N(4)–C(5) 1.463(3), C(5)–C(6) 1.495(4), C(6)–N(1) 1.471(2), N(1)–C(8) 1.407(3), C(7)–C(8) 1.510(3), C(6)–C(7) 1.541(3) Å.

1-azabicyclo[4.2.0]oct-2-en-8-ones,[5] 5-thia-1-azabicyclo-[4.2.0]oct-2-en-8-ones,[6] 5-oxa-1-azabicyclo[4.2.0]oct-2-en-8-ones,[7] and 1,5-diazabicyclo[4.2.0]oct-2-en-8-ones[8] can usually be liberated from their t-butyl esters by the action of trifluoroacetic acid, the β-lactam linkage of the bicycle (**6a**) is evidently endowed with a high chemical reactivity.

Starting with the azetidinone (**8b**),[1] it was possible to derive the hydrazide (**7b**) which reacted with silver(I) oxide in acetonitrile to give the bicycle (**6c**), m.p. 137.5—139 °C, in 45% overall yield after recrystallisation. Hydrogenolysis of the benzyl ester (**6c**) (H_2–Pd, EtOH) provided the acid (**6b**) which was converted into the sodium salt (**6e**), m.p. 210 °C (decomp.), by the action of sodium 2-ethylhexanoate. The salt (**6e**), which was stable in deuterium oxide over a 24 h period,

showed no significant antibacterial activity and did not act as an ampicillin synergist against β-lactamase-producing bacteria.

Compounds (**6a**)—(**6e**) 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.* (**12**), have been described.[9] Related systems include 1,4-diazabicyclo-[4.2.0]oct-2-en-8-ones,[10] 5-thia-1,3-diazabicyclo[4.2.0]oct-2-en-8-ones,[11] and 5-thia-1,4-diazabicyclo[4.2.0]oct-2-en-8-ones.[12]

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References

1 J. Brennan, G. Richardson, and R. J. Stoodley, *J. Chem. Soc., Perkin Trans. 1*, 1983, 649.
2 C. M. Pant and R. J. Stoodley, *J. Chem. Soc., Chem. Commun.*, 1980, 928; P. H. Crackett, C. M. Pant, and R. J. Stoodley, *J. Chem. Soc., Perkin Trans. 1*, in the press.
3 D. G. Brenner, J. R. Knowles, and G. Rihs, *Biochemistry*, 1981, **20**, 3680; C. Kemal and J. R. Knowles, *ibid.*, 1981, **20**, 3688; R. L. Charnas and J. R. Knowles, *ibid.*, 1981, **20**, 3214.
4 R. M. Sweet and L. F. Dahl, *J. Am. Chem. Soc.*, 1970, **92**, 5489.
5 M. Hatanaka and T. Ishimaru, *Tetrahedron Lett.*, 1983, **24**, 4837.
6 I. Ernest, A. J. Main, and R. B. Woodward, *Helv. Chim. Acta*, 1981, **64**, 1303.
7 C. L. Branch and M. J. Pearson, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2268.
8 M. J. Pearson, *J. Chem. Soc., Perkins Trans. 1*, 1981, 2544.
9 J. Finkelstein, K. D. Holden, R. Sneed, and C. D. Perchonock, *Tetrahedron Lett.*, 1977, 1855.
10 T. W. Doyle, B.-Y. Luh, D. T.-W. Chu, and B. Belleau, *Can. J. Chem.*, 1977, **55**, 2719; T. W. Doyle, J. L. Douglas, B. Belleau, T. T. Conway, C. F. Ferrari, D. E. Horning, G. Lim, B.-Y. Luh, A. Martel, M. Menard, and L. R. Mossis, *ibid.*, 1981, **58**, 2508; M. J. Pearson, *J. Chem. Soc., Chem. Commun.*, 1981, 947; C. L. Branch, S. C. Finch, and M. J. Pearson, *Tetrahedron Lett.*, 1982, **22**, 4381.
11 M. Aratani and M. Hashimoto, *J. Am. Chem. Soc.*, 1980, **102**, 6171.
12 G. Johnson and B. C. Ross, *J. Chem. Soc., Chem. Commun.*, 1981, 1269.