Characterization of a Methoxylated Oxazol-5-one Derivative: an Unexpected By-product in a Dehydropeptide Synthesis

Alvin C. Bach, II, Alysia A. Baldwin, Lila M. Gierasch,* and Arnold L. Rheingold

Department of Chemistry, University of Delaware, Newark, DE 19716, U.S.A.

During the synthesis of the oxazol-5-one derivative (**2**) of t-butoxycarbonyl-glycyl-2,3-didehydrophenylalanine, the unexpected side product the 2-methoxyoxazol-5-one (**3**) was isolated and subsequently characterized by n.m.r., i.r., and single-crystal *X*-ray diffraction analysis.

Synthesis of the α,β-didehydrodipeptide, t-butoxycarbonyl-glycyl-2,3-didehydrophenylalanine (**1**), starting from the saturated dipeptide using the method of Konno and Stammer,[1] gave rise to two crystalline products: the desired oxazol-5-one[2] derivative (**2**), and an unexpected product (**3**) which has a methoxy group added to C-2 of the oxazolone ring [C(7) in Figure 1]. The identity of these products has been confirmed by observation of the appropriate ^{1}H n.m.r. and i.r. spectral parameters, by high resolution mass spectrometry of (**2**), and by a single crystal *X*-ray analysis of (**3**).† The unexpected product (**3**) was isolated as racemic monoclinic crystals (m.p. 142—145 °C) from ethyl acetate–light petroleum (b.p. 40—60 °C) (1:2); a crystal of (**3**) was then subjected to an *X*-ray analysis.

Crystal data: (23 °C), $C_{17}H_{22}N_2O_4$, monoclinic, space group $C2/c$, a = 16.138(4), b = 11.891(3), c = 21.499(5) Å, β = 116.70(2)°, U = 3685.9(14) Å^3, Z = 8. Of 2938 reflections collected ($4 \leqslant 2\theta \leqslant 50°$) using a Nicolet R3 diffractometer (Mo-K_α radiation), 2709 were unique, and 2141 that were considered as observed [$3\sigma(I)$ cutoff] were used in the solution and refinement of the structure. The successful structure solution was obtained by direct methods (SHELXTL-SOLV) after making adjustments in parity group representation in the starting set of reflections. All hydrogen atoms except those contained in the thermally-active t-butoxy group were located and refined; the hydrogen atoms in the t-butoxy group were positioned in idealized locations [d(C–H) = 0.96 Å]. All non-hydrogen atoms were refined with anisotropic temperature factors. After corrections for secondary extinction, R_F = 0.0465, R_{wF} = 0.0537, and goodness of fit = 1.409.‡

The molecular geometry and labelling scheme for (**3**) is shown in Figure 1. (**3**) crystallizes as discrete molecules with significant intermolecular hydrogen bonding [shortest contact, N(2)–H(N2) · · · O(2) 3.000 Å]. The oxazol-5-one ring is nearly planar; maximum deviation from planarity occurs at N(2). A deviation from coplanarity of the two rings [torsion

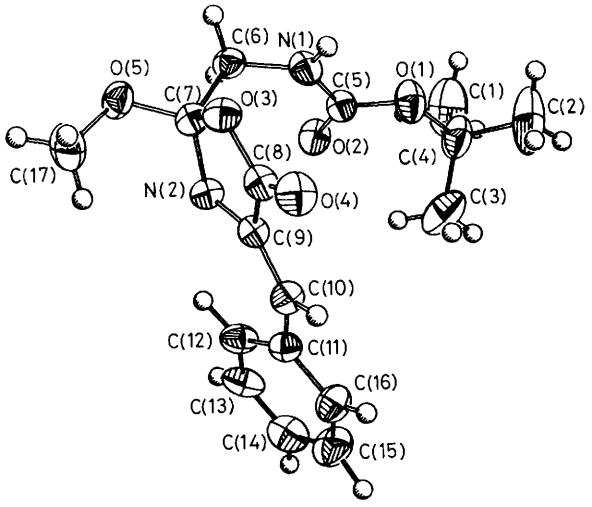
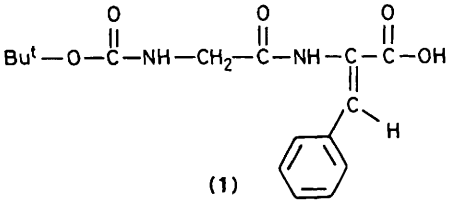
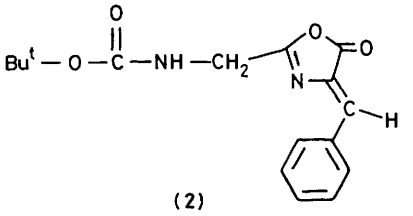


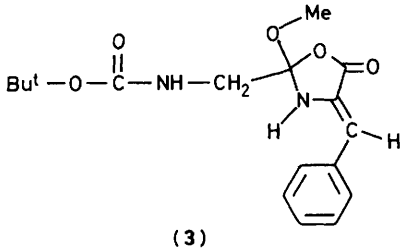
Figure 1. ORTEP diagram and labelling scheme for (**3**) with 40% probability thermal ellipsoids. Selected bond distances and angles are: O(1)–C(5), 1.334(3); O(2)–C(5), 1.208(3); C(5)–N(1), 1.346(4); N(1)–C(6), 1.429(3); C(6)–C(7), 1.519(3); C(7)–O(5), 1.373(3); C(7)–O(3), 1.451(3); O(3)–C(8), 1.362(3); C(8)–O(4), 1.201(3); C(8)–C(9), 1.473(4); C(9)–N(2), 1.383(3); N(2)–C(7), 1.443(4); C(9)–C(10), 1.335(4) Å; O(1)–C(5)–N(1), 109.8(2); C(5)–N(1)–C(6), 123.3(2); C(6)–C(7)–O(5), 106.2(2); C(6)–C(7)–N(2), 113.2(2); C(6)–C(7)–O(3), 109.9(2); O(5)–C(7)–O(3), 109.6(2); O(5)–C(7)–N(2), 114.4(2); N(2)–C(7)–O(3), 103.5(2); C(7)–O(3)–C(8), 110.7(2); C(8)–C(9)–N(2), 105.7(2); C(9)–N(2)–C(7), 111.2(2); C(8)–C(9)–C(10), 121.6(2); N(2)–C(9)–C(10), 132.7(2); and C(9)–C(10)–C(11), 129.4(2)°.



(**1**)



(**2**)



(**3**)

† *Note added in proof:* the structure of (**2**) has also been confirmed by a single-crystal *X*-ray analysis.

‡ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication. The structure factor table is available as Supplementary Publication No. SUP 23787 (15 pp.) from the British Library Lending Division. See Instructions for Authors, *J. Chem. Soc., Perkin Trans.* 1, 1983, issue 1, p. xvii.

angle around the Phe C_β–C_γ bond $-11.5(0.3)°$] is likely to be a result of steric interactions. A C=C double bond exists at C(9)–C(10) [1.338(4) Å].

As previously observed,[1] the aromatic ring in the dehydroamino-acid moiety is in the *Z*-configuration. The ϕ,ψ angles of the Δ^{α}-Phe [$\phi = 31.4\ (2.1)°$, $\psi = -3.0\ (0.3)°$] are similar to those found in other crystals of dehydropeptides,[3] where ϕ is significantly different from zero, while ψ is near zero. In this case, constraints imposed by the oxazolone ring contribute to the observed geometry.

Gas chromatographic analysis of the dimethoxyethane (DME) solvent used in the oxidation of the saturated oxazol-5-one showed that methanol was present at $<0.5\%$ v/v. This is believed to be the source of the methoxy group in (**3**). To our knowledge there have been no previous reports of a side product analogous to (**3**) when using the Konno and Stammer synthesis. This facile addition of methanol across the C=N bond is a side reaction which may be minimized by purification of the DME solvent. A similar addition of water across the C=N double bond has been demonstrated to be the initial step in the mechanism of hydrolysis of the oxazol-5-one ring.[4] In contrast to the present case, in the hydrolytic reaction the tetrahedral adduct is not isolated, and undergoes rapid ring opening to the product acid.

This work was supported in a part by a N.I.H. grant (to L. M. G.). A. C. B., II, thanks the Upjohn Co. for a graduate fellowship. The National Science Foundation supported the acquisition of the *X*-ray diffractometer.

Received, 22nd August 1983; Com. 1141

References

1 S. Konno and C. H. Stammer, *Synthesis*, 1978, 598. This procedure first forms a saturated oxazol-5-one by internal condensation of the *C*-terminal carbonyl with the preceding carbonyl of an *N*-terminal protected dipeptide. Second, the exocyclic double bond is formed by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in the presence of pyridine using DME as solvent.

2 For a general review of oxazolones and the ring numbering scheme see: R. Filler and Y. S. Rao in 'Advances in Heterocyclic Chemistry,' vol. 21, eds. A. R. Katritzky and A. J. Boulton, New York, Academic Press, 1977, pp. 175—201.

3 D. Ajo, G. Granozzi, E. Tondello, and A. Del Pra, *Biopolymers*, 1980, **19**, 469.

4 W. Steglich, V. Anstel, and A. Prox, *Angew. Chem., Int. Ed. Engl.*, 1968, **7**, 726.