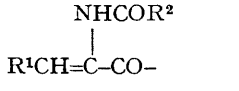
Configuration of Dehydroleucine Derivatives; *X*-Ray Crystal Structure of *N*-Boc-Δ^{α}-leucine

By VIRANDER S. CHAUHAN, CHARLES H. STAMMER,* LEIF NORSKOV-LAURITZEN, and M. GARY NEWTON*
(*Chemistry Department, University of Georgia, Athens, Georgia* 30602)

Summary Crystalline *N*-Boc-Δ^{α}-leucine (**2**), prepared by the *N*-chlorination procedure, has been subjected to single-crystal *X*-ray diffraction analysis; the double bond has the *Z*-configuration, while $\phi = -55$, $\psi = 162$, and $\omega = -8°$.

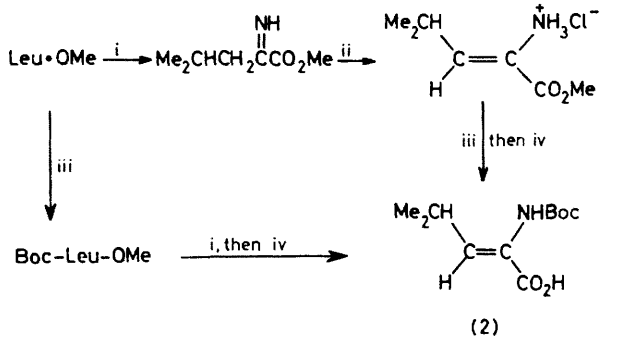
RECENT interest[1] in the synthesis of dehydro amino-acids and peptides† has increased the need to establish absolutely the configuration of the double bond in the dehydro residue so that its influence on bioactivity may be determined. The stereochemistry of the aromatic dehydro amino-acid residues (**1a**) has been well established[2] by *X*-ray crystallography and n.m.r. spectroscopy. It has been found that



(**1**) **a**; R^1 = aryl
b; R^1 = alkyl

compounds in the (**1a**) series invariably have the *Z*-configuration, particularly when either the dehydrogenation method[1e,3] or the Erlenmeyer–Plöchl condensation[4] is used in their preparation.‡ The assignment of configuration to the aliphatic dehydro amino-acid residues (**1b**), however, has been made only on the basis of the chemical shifts of the alkyl protons and/or vinyl protons[5] in (**1b**). It was found that the vinyl proton shifts were sensitive to the nature of the *N*-acyl group and to the presence of an *N*-methyl grouping, the proton *cis* to the *N*-methyl group (*E*-isomer) being shifted upfield significantly. In our recent work on dehydroleucine derivatives we have obtained only one isomer of the dehydroleucine residue and even though *N*-methylation of the methyl ester caused essentially no upfield shift of the vinyl proton, indicating the *Z*-isomer,[5] we needed confirmation of this assignment. The *N*-t-butoxycarbonyl-Δ^{α}-leucine (**2**) was prepared by two reaction sequences, each of which used the *N*-chlorination method[1c] to introduce the double bond (Scheme). The same isomer was obtained in either case as a crystalline solid, m.p. 152—153 °C, ^{1}H n.m.r. ($CDCl_3$) δ 6·53 (vinyl H), 5·16 (br, N-H), 1·58 (br, δ-H), 1·40 (Boc), and 0·97 p.p.m. [m, $(CH_3)_2CH$]; ^{13}C n.m.r. (25 MHz, $CDCl_3$) δ 169·8 (CO_2H), 154·8 (Boc C=O), 146·0 (C_α), 123·9 (C_β), 81·0 (Boc C), 28·2 (Boc CH_3), 27·5 ($C\gamma$), and 21·6 p.p.m. (C_δ). The fact that the same dehydroleucine configuration was obtained whether *N*-acylation was accomplished before or after the introduction of the double bond is important in the synthesis of dehydroleucine peptides.

A crystal of the dehydroleucine derivative was subjected to single-crystal *X*-ray diffraction analysis. Diffraction data were collected on an Enraf-Nonius CAD-4 diffractometer using Cu-K_α radiation with a graphite monochromator. The system was found to be triclinic with $a = 11·040(1)$, $b = 11·858(1)$, $c = 12·049(2)$ Å, $\alpha = 109·720(9)$, $\beta = 97·689(9)$, and $\gamma = 108·391(7)°$, with $Z = 4$. The space group was determined from the structure analysis to be $P\bar{1}$ with two independent molecules per asymmetric unit. The structure was solved by direct method using MULTAN. In all, 2650 unique, non-zero reflections were used in the analysis; full-matrix least-squares refinement gave a final $R = 0·046$ ($R_w = 0·047\%$).§



SCHEME. Boc = Bu^{t}OC(:O)–, DBU = 1,5-diazabicyclo-[5.4.0]undec-5-ene. i, Bu^{t}OCl–DBU; ii, dry HCl; iii, $(Boc)_2O$; iv, MeOH–NaOH.

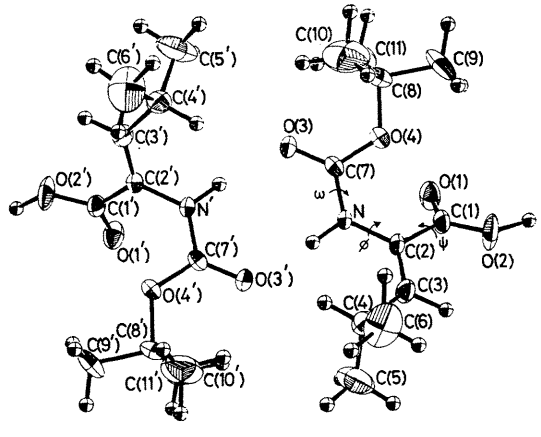


FIGURE. ORTEP drawing of (**2**).

† In the context of this paper, a dehydro amino-acid residue is one having a double bond between the α- and β-carbon atoms (Δ^{α}).

‡ Only the method of Rich *et al.*,[1a] in which sulphoxide pyrolysis is used to introduce the double bond, gives both the *E*- and *Z*-isomers.

§ 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.

Results of the structure determination clearly confirm the assignment of the *Z*-configuration for the double bond. An ORTEP plot of the asymmetric unit is shown in the Figure. The packing of the molecules presents an interesting H-bonding scheme. The two independent molecules are related by an approximate non-crystallographic two-fold axis which is nearly parallel to the a^* direction. Hydrogen bonding between N'-H · · · O(3) [and N-H · · · O(3')] results in an intermolar approach distance of 2·88 Å between N · · · O(3). The CO_2H groups form H-bonds to CO_2H groups related to each other through crystallographic inversion centres with an average O(1) · · · H-O(2) approach distance of 2·64 Å between O(1) · · · O(2). Dihedral angles ϕ[6] [C(1)–C(2)–N–C(7)], ψ[6] [O(2)–C(1)–C(2)–N], and ω[6] [H–N–C(7)–O(3)] were as follows: $\phi = -55$, $\psi = 162$, and $\omega = -8°$ (average values for the two units). It is interesting to note that the peptide linkage has essentially an *s-cis* ($\omega = 0$) conformation, contrary to the usual *s-trans* arrangement, and that the ϕ dihedral angle is equal to that found for ϕ_1 in Ac–ΔPhe–ΔPhe.OH by Pieroni, *et al.*[7] It appears that the *Z*-configuration may be the more stable arrangement for the aliphatic dehydro amino-acids (**1b**) as well as for the aromatic series (**1a**). A recent report[8] (without crystallographic details) indicated that (**1b**) [R^1 = (phthaloyl)$NHCH_2CH_2$, R^2 = Me] also had the *Z*-configuration.

We gratefully acknowledge the financial support of the National Heart, Lung and Blood Institute and the College of Arts and Sciences, University of Georgia.

(*Received*, 19*th January* 1979; *Com.* 055.)

[1] (a) D. H. Rich, P. Bhatnagar, P. Mathiaparanam, J. A. Grant, and J. P. Tam, *J. Org. Chem.*, 1978, **43**, 296; (b) A. Srinvasan, R. W. Stephenson, and R. K. Olsen, *ibid.*, 1977, **42**, 2253, 2256; (c) H. Poisel and U. Schmidt, *Chem. Ber.*, 1977, **110**, 942; (d) U. Schmidt and E. Ohler, *Angew. Chem. Internat. Edn*, 1976, **16**, 327; (e) S. Konno and C. H. Stammer, *Synthesis*, 1978, 598; (f) M. L. English and C. H. Stammer, *Biochem. Biophys. Res. Comm.*, 1978, **83**, 1464.

[2] A. G. Brown and T. C. Smale, *J.C.S. Perkin I*, 1972, 65; A. P. Morganstern, C. Schutij, and W. Th. Nanta, *Chem. Comm.*,1969, 321.

[3] S. Konno and C. H. Stammer, *Internat. J. Peptide Protein Res.*, 1978, **12**, 222.

[4] H. E. Carter, 'Organic Reactions,' Vol. 3, Wiley, New York, 1947, pp. 198—239; Y. S. Rao and R. Filler, *Synthesis*, 1975, 749.

[5] See A. Srinivasan, K. D. Richards, and R. K. Olsen, *Tetrahedron Letters*, 1976, 891 and references therein.

[6] G. D. Fasman, 'Handbook of Biochemistry and Molecular Biology,' Vol. I, 1976, p. 59.

[7] O. Pieroni, G. Montagnoli, A. Fissi, S. Merlino, and F. Ciardelli, *J. Amer. Chem. Soc.*, 1975, **97**, 6820.

[8] D. D. Keith, R. Yang, J. A. Tortora, and M. Weigele, *J. Org. Chem.*, 1978, **43**, 3713.