Nuclear Magnetic Resonance Evidence of Conformational Isomerism in Substituted Prolines

By R. GARNER* and W. B. WATKINS

(*The Dyson Perrins Laboratory, South Parks Road, Oxford* OX1 3QY)

Summary Hindered rotation in the urethane link of *N*-benzyloxycarbonyl- and *N*-t-butoxycarbonyl-L-proline esters is revealed by n.m.r. spectroscopy.

THE use of n.m.r. spectroscopy to study torsional barriers in amides,[1] acylhydrazines,[2] acylhydroxylamines,[3] amidines,[4] *etc.* has been well established.[5] We now report that the normal-temperature n.m.r. spectra of several *N*-benzyloxycarbonyl- (I; $R^1 = PhCH_2{\cdot}O{\cdot}CO{\cdot}$) and *N*-t-butoxycarbonyl-(I; $R^1 = Bu^tO{\cdot}CO$) -L-proline esters, commonly used as intermediates in peptide synthesis show the presence of two conformers brought about by restricted rotation about the N–CO bond. For example, the spectrum at 30°; (Figure, a) of *N*-benzyloxycarbonyl-L-proline *p*-nitrophenyl ester[6] (I; $R^1 = PhCH_2{\cdot}O{\cdot}CO{\cdot}$, $R^2 = p\text{-}C_6H_4NO_2$) shows that equal quantities of the two forms (II) and (III) are present. Bands are tentatively assigned to (II) at τ 4·92 (2H, s, CH_2Ph), 2·78 and 1·84 (4H, A_2X_2 pattern, J_{ax} 9 c./sec., $C_6H_4NO_2$); and to (III) at τ 4·86 and 5·02 (2H, AB pair of doublets, J_{ab} 12·2 c./sec., CH_2Ph), 3·0 and 1·91 (4H, A_2X_2 pattern, J_{ax} 9 c./sec., $C_6H_4{\cdot}NO_2$). The α-CH proton appears at approximately τ 5·5 as two overlapping X of ABX patterns. As the temperature is increased to 54° (Figure, b) the bands are seen almost to have coalesced, and at 72° (Figure, c) the spectrum is that of a single compound with bands at τ 4·93 (2H, s, CH_2Ph), 5·49 (1H, X part of ABX pattern, NC*H*CO) and *ca.* 2·8 and 1·9 (4H, A_2X_2 pattern, J 9 c./sec., $C_6H_4{\cdot}NO_2$).

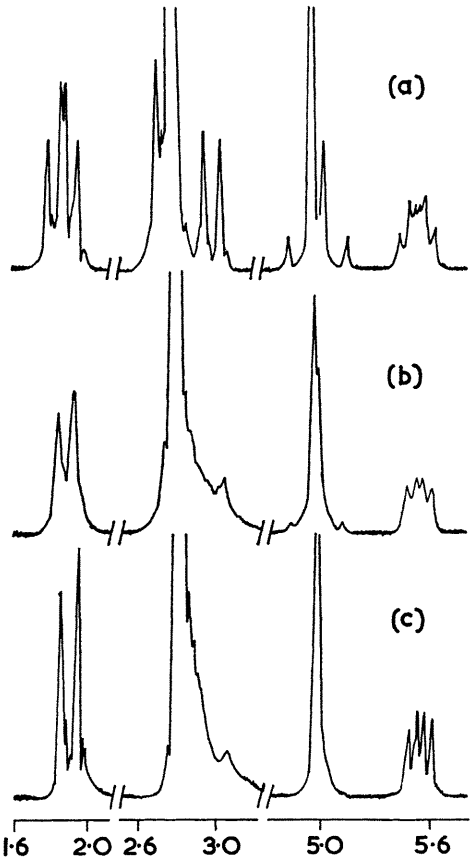
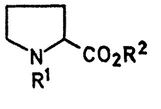
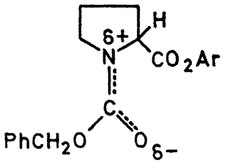
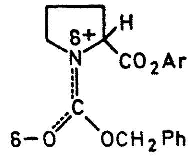


FIGURE. *The 100 MHz. n.m.r. spectrum of the aromatic, benzyl methylene, and α-methine protons of* N-*benzyloxycarbonyl*-L-*proline* p-*nitrophenyl ester in* $(CD_3)_2SO$ (a) *at* 30°, (b) *at* 54°, (c) *at* 72°.

Magnetic nonequivalence of protons in the benzyl methylene group in (III) probably arises through nonbonded interactions involving the bulky ester group; the free acid (I; $R^1 = PhCH_2{\cdot}O{\cdot}CO{\cdot}$, $R^2 = H$) shows no spectral anomalies. It is of interest to note, in addition to changes in the benzyl and α-methine groups, considerable differences in chemical shift for the protons of the ester group in the two conformers.


(I)


(II)


(III)

$(Ar = C_6H_4\text{-}p\text{-}NO_2)$

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