An Oxazol-5(4*H*)-one Derived from a Benzyloxycarbonylamino-acid

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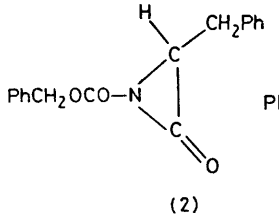
Summary The cyclodehydration of benzyloxycarbonyl-L-phenylalanine does not give an alkoxycarbonylaziridinone as claimed by Miyoshi: the product is in fact 2-benzyloxy-4-benzyloxazol-5(4*H*)-one.

MIYOSHI[1] has described the cyclodehydration of benzyloxycarbonylamino-acids (**1**) to give activated heterocycles which react rapidly with amino-esters to yield, after appropriate isolation procedures including recrystallisation, optically pure peptides (Scheme). An alkoxycarbonylaziridinone structure (**2**) was confidently assigned to the

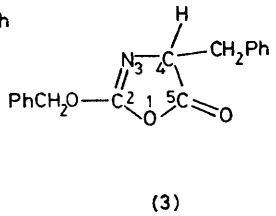
$$PhCH_2OCONHCHR^1CO_2H \xrightarrow{i,\ ii} ? \xrightarrow{iii} PhCH_2OCONHCHR^1CONHCHR^2CO_2R^3$$

(**1**) (**2**) or (**3**)

SCHEME. Reagents: i, $COCl_2$, $SOCl_2$, or $POCl_3$ in tetrahydrofuran at −20 °C; ii, Et_3N; iii, $NH_2CHR^2CO_2R^3$.



(**2**)



(**3**)

easily isolated activated intermediate derived from benzyloxycarbonyl-L-phenylalanine (**1**, $R^1 = PhCH_2$) following a detailed study of its i.r., ^1H n.m.r., and mass spectra. However, all Miyoshi's spectroscopic evidence for (**2**) is also consistent with the 2-benzyloxy-oxazol-5(4*H*)-one structure (**3**) and the ambiguity is not easily resolved as no sufficiently close analogy for (**2**) or (**3**) has been described. It appears that Miyoshi favoured (**2**) largely on the grounds that aminolysis gave optically active peptides, this being held to rule (**3**) out because the intervention of oxazol-5(4*H*)-ones in peptide bond formation commonly leads to racemisation. This is a *non sequitur*, however: whether racemisation occurs will depend on the ratio of the rates of racemisation and ring opening[2] and there is no reason to suppose that (**3**) would necessarily be the same as previously encountered oxazol-5(4*H*)-ones in this respect. Indeed, comparison[3,4] of the properties of 2-alkyl- and 2-alkoxy-thiazol-5(4*H*)-ones suggests that a 2-alkoxy group may diminish the ease of ionisation at position 4 considerably in this type of heterocyclic system. We now present unambiguous evidence supporting structure (**3**) for the cyclodehydration product from benzyloxycarbonyl-L-phenylalanine (**1**, $R^1 = PhCH_2$). We prepared the compound as described by Miyoshi only with some difficulty and therefore developed an improved method. Compound (**1**, $R^1 = PhCH_2$) (1 equiv.) in ether (1·5 ml g^{-1}) was treated with a 10% excess of phosphorous pentachloride in an ice–salt bath for 25 min. Evaporation and trituration with light petroleum followed by redissolution of the solid in ether and treatment with triethylamine (1 equiv.) in an ice–salt bath for 30 min gave, after

removal of triethylamine hydrochloride, evaporation, and recrystallisation, material which was identical in every respect with the compound Miyoshi thought to be (**2**). The ^{13}C n.m.r. spectrum† of this compound showed signals at δ 37·5 and 71·6 (each s, benzylic carbons, 66·7 (s, C-4), 135·5—127·0 (complex m, aromatic carbons, 158·3 (s, C-2), and 175·2 (s, C-5); the spectrum of the corresponding DL-[^{15}N]-labelled compound was unchanged except that the C-2 and C-4 singlets at 158·3 and 66·7 became doublets, J 6·1 and 2·4 Hz, respectively. These results eliminate structure (**2**) from consideration but confirm (**3**) since only two ^{13}C–^{15}N couplings are observed;[5] whereas (**3**) has two carbon atoms directly bonded to nitrogen, (**2**) has three. The oxazol-5-(4*H*)-one (**3**) is the first derived from an alkoxycarbonylamino-acid to be recognised.

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† Spectra were recorded at 300 K for solutions of *ca.* 50% concentration in $CDCl_3$ on a Bruker WH90 instrument at 22·6 MHz with complete proton decoupling; chemical shifts are in p.p.m. from Me_4Si internal reference.

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