2-Isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline as a Coupling Reagent in Peptide Synthesis

By YOSHIAKI KISO and HARUAKI YAJIMA*

(*Faculty of Pharmaceutical Sciences, Kyoto University, Kyoto, Japan*)

Summary 2-Isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline and two analogous compounds have been used as coupling reagents for peptide synthesis.

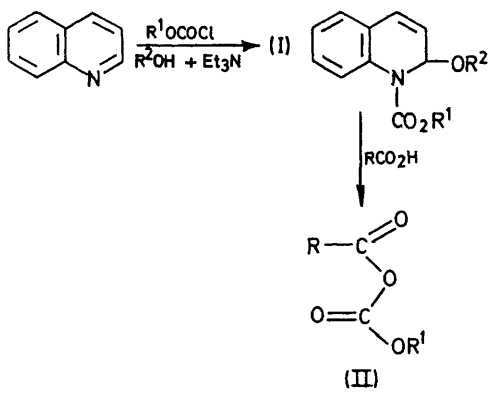
THE formation of peptide bonds using 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (I; $R^1 = R^2 = Et$),[1] appears to proceed *via* the intermediate carbonic carboxylic anhydride (II; $R^1 = Et$). To prepare such a mixed anhydride for peptide synthesis, isobutyl chloroformate[2] is preferable to ethyl chloroformate.[3,4] With this in mind, we prepared 2-isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline (I; $R^1 = R^2 = Bu^i$) and two other analogous compounds, (I; $R^1 = Bu^i$, $R^2 = Me$) and (I; $R^1 = Bu^i$, $R^2 = Et$). All can be conveniently used for peptide synthesis.

(I; $R^1 = R^2 = Bu^i$) was prepared in the same way as (I; $R^1 = R^2 = Et$),[5] with only minor modifications (see Scheme). The product was obtained as a liquid, b.p. 144—145°/0·5 mm (55%). (I; $R^1 = Bu^i$, $R^2 = Me$), b.p. 147—148°/0·8 mm (50%) and (I; $R^1 = Bu^i$, $R^2 = Et$), b.p. 143—144°/0·2 mm (55%) were prepared similarly. The compounds were characterised by elemental analysis and i.r. and n.m.r. spectroscopy.

As a model experiment, the coupling of Z·Ala·OH† with H·Tyr·OMe was performed using each reagent in dimethyl-

† Abbreviations used are those recommended by IUPAC–IUBC Commission on Biochemistry Nomenclature: *Biochem.*, **1966**, **5**, 2485; *ibid.*, **1967**, **6**, 362. Z = benzyloxycarbonyl, Z(OMe) = *p*-methoxybenzyloxycarbonyl, Bzl = benzyl. Optically active amino acids are of the L-form.

formamide at room temperature for 24 h. Yields of Z·Ala·Tyr·OMe[6,7] were 88% with (I; $R^1 = R^2 = Bu^t$), 79% with (I; $R^1 = Bu^t$, $R^2 = Me$), and 77% with (I; $R^1 = Bu^t$, $R^2 = Et$), respectively. Since (I; $R^1 = R^2 = Bu^t$) seemed superior to the others in its reactivity, Z·Gln·Thr·OMe[6] (84%), Z·Ser·



SCHEME

Ala·OMe[6,8] (80%), and Z(OMe)·Asn·Ala·OMe (95%, m.p. 172—174°, $[\alpha]_D^{26}$ − 8·5° in dimethylformamide) were also prepared with this reagent. These compounds were isolated analytically pure without masking the side functional groups of the parent amino-acids.

The use of (I; $R^1 = R^2 = Bu^t$) for solid phase peptide synthesis was also examined. For example, it was used for the coupling of Z(OMe)·Asp(OBzl)·Phe·Cys(Bzl)·Leu·Glu(OBzl)·Pro·OH with H·Gly·Ala·resin (four molar equivalents of an amino-component attached to a copolymer of styrene and 2% divinylbenzene.)[9] Amino-acid ratios in an acid hydrolysate of the peptide resin obtained after 48 h were $Asp_{0.90}Phe_{0.94}Leu_{0.89}Glu_{0.92}Pro_{0.95}Gly_{1.00}Ala_{1.05}$. The result indicated that the coupling reaction was nearly complete under these conditions. Thus (I; $R^1 = R^2 = Bu^t$) seems to be a useful reagent, like (I; $R^1 = R^2 = Et$)[6], for the condensation reaction of a peptide fragment on a polymer support.

For the racemization test, the system of Bodanszky and Conklin[10] was used. Ac·Ile·OH was coupled with H·Gly·OMe by (I; $R^1 = R^2 = Bu^t$) at 20° for 18 h and the racemate, *allo*-D-Ile, was determined, after acid hydrolysis, by Spackman–Stein–Moore method[11] of quantitative amino-acid analysis. Under these conditions, (I; $R^1 = R^2 = Bu^t$) gave a racemate in 4·1%, while dicyclohexylcarbodi-imide gave 27·4%.

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