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THE USE OF VINYLENE HOMOLOG OF MIXED ANHYDRIDE FOR THE CARBOXYL-ACTIVATION. A NEW SYNTHESIS OF PEPTIDES

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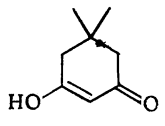
Several dimedone enol esters of N-benzyloxycarbonylamino acids have been prepared in excellent yields. It has also been indicated that the esters accounted as a vinylene homolog of mixed anhydride were easily aminolyzed by free amino esters or amino acids to give the corresponding dipeptides.

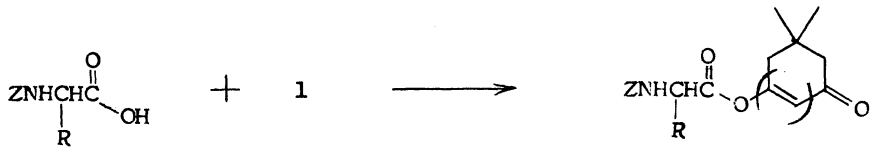
Varieties of the mixed anhydrides of N-protected amino acids with other acids have served as a valuable acylating agent on the peptide synthesis for a long time.

This letter will deal with the preparation of the β-diketone enol ester of N-protected amino acids, which will also be examined to see if it does acylate desirably the amino acid derivatives as well as the mixed anhydrides do. 5,5-Dimethylcyclohexane-1,3-dione(Dimedone) was selected as a reasonable β-diketone providing an alcohol component as required, because of its certain enolized form (IR: two bands in dimedone with conjugated chelation in the range 1640-1540 cm^{-1}, and UV: strong absorption in the 230-260 nm region to the $\pi \rightarrow \pi^*$ in the s-trans enone system) (1).

Thus, N-benzyloxycarbonyl(Z)glycine was allowed to react with dimedone by the aid of dicyclohexylcarbodiimide(DCC) in an anhydrous organic solvent at 0 °C for 2-4 hr to give the dimedone enol ester (2) (Scheme I: R = H). Usual work-up and subsequent recrystallization from ethyl acetate and petroleum ether gave Z-glycine dimedone ester melting at 84-85 °C in 95% yield. Anal. Found: C, 65.14; H, 6.41; N, 4.11%. Calcd. for $C_{18}H_{21}O_5N$: C,65.24; H, 6.39; N, 4.23%. In this condensation, tetrahydrofuran or ethyl acetate was used as a suitable solvent and the use of slightly less amount of dimedone to Z-glycine (e.g. Z-glycine: DCC: dimedone = 1.05: 1.00: 1.00) was favored for the isolations of the products. Similarly, the dimedone esters of Z-L-proline



(1)



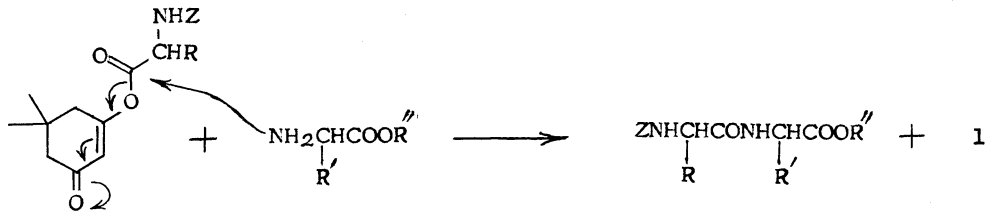
Z : $-OCOCH_2C_6H_5$

(2)

Scheme I

(mp 57-59 °C, $[\alpha]_D^{27}$ -63.6°(c 0.66 in EtOH)), Z-L-valine(colorless oil), and Z-L-methionine(colorless oil) were also obtained each in high yield.

With all of these esters, the free amino esters could readily be acylated (Scheme II), in such organic solvents as ethyl acetate, tetrahydrofuran, and dioxane, to produce the desired protected dipeptides in high yield: on the preparation of ethyl Z-glycylglycinate, Z-glycine dimedone ester was added in one



R'' : $-C_2H_5$, -H (or Na)

(2) (3)

Scheme II

portion to a solution of ethyl glycinate hydrochloride containing an equimolar amount of triethylamine at 0-5 °C and the reaction was continued for another 2 hr, while being stirred efficiently. The progress of the reaction could be followed by TLC. Protected dipeptides thus obtained are summarized in Table I. The acylation using this ester could also proceed with free amino acid, at 0 °C, in its aqueous solution containing the same volume of a miscible organic solvent such as acetonitrile in the presence of an equimolar amount of sodium hydrogencarbonate. Table II shows the dipeptides obtained from the reaction mixture through the appropriate operations for each product, dipeptide. In the isolations of the former two compounds shown in Table II, each dipeptide deposited in almost pure form by only neutralization of the aqueous phase with 6M hydrogen chloride, after washing the reaction mixture with ethyl acetate. As shown in Table I and II, the optical rotation values of the products obtained here are compatible with

Table I

Z-dipeptide	yield (%)	mp (°C)	$[\alpha]_D$(deg)	Lit. mp (°C)	Lit. $[\alpha]_D$(deg)
Gly-GlyOEt	95	82-83		82-83[2,3]	
Gly-DL-PheOEt	93	92		91-92[2,3]	
L-Pro-L-LeuOEt	84	68-69	-45.0 (in DMF)	68-69[2]	
L-Val-L-LeuOEt	86	103-105	-41.0 (in EtOH)	103-105[3]	-42 (in EtOH)[3]
L-Met-GlyOEt	80	98-99	-19.5 (in EtOH)	95-96[2]	-20.0 (in EtOH)[2]

Table II

Z-dipeptide	yield (%)	mp (°C)	$[\alpha]_D$(deg)	Lit. mp (°C)	Lit. $[\alpha]_D$(deg)
Gly-GlyOH	90	178		178[2,3]	
Gly-DL-AlaOH	86	177-178		176[2]	
Gly-L-AlaOH	86	119-120	- 9.6 (in EtOH)	119.5[2] 130-131[3]	- 9.1 (in EtOH)[3]
Gly-L-PheOH	84	126	+41.3 (in EtOH)	126[2]	+41.9 (in EtOH)[2]
Gly-L-SerOH	68	125-127	+ 4.8 (in DMF)	124[2]	- 5 (in DMF)[3)a)]
L-Pro-L-AlaOH	83	159-160	-58.0 (in EtOH)	161-162[3]	-59 (in EtOH)[3]

a) The value is for the D-serine isomer.

those reported in the literatures. The advantages as an acylating agent of the dimedone enol ester are shown in its stability for the possible storage of the ester in a tightly capped bottle, and in its use for direct N-acylation of free amino acids including hydroxy amino acid(serine) without any protection in aqueous conditions.

Since the chemical structure(2) is considered as an amino acid mixed anhydride vinylog[4] in which a vinylene group is inserted into the mixed anhydride bond, the above-described reactivity of 2 as the acylating agent may be ascribed to the activation of the amino acyl moiety of the vinylog through the substantially similar mechanism(Scheme II) to that for the usual mixed anhydride form.

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References

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4) Vinylene group being under consideration is parenthesized in formula 2.

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