Reaction of *N*-t-Butoxycarbonylamino Acid Anhydrides with Tertiary Amines and Carbodi-imides. New Precursors for 2-t-Butoxy-oxazol-5(4*H*)-one and *N*-Acylureas

By N. LEO BENOITON* and FRANCIS M. F. CHEN

(*Department of Biochemistry, University of Ottawa, Ottawa, Ontario* K1N 9A9, *Canada*)

Summary *N*-t-Butoxycarbonylamino acid anhydrides react with tertiary amines to give 2-t-butoxyoxazol-5(4*H*)-ones, and with *N*,*N*′-dialkylcarbodi-imides to give the oxazol-5(4*H*)-ones and the *N*-acyl-*N*,*N*′-dialkylureas.

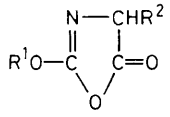
2-ALKOXYOXAZOL-5(4*H*)-ONES (**3**), whose existence was first reported by Jones and Witty,[1] can be obtained from *N*-alkoxycarbonylamino acids (**1**) and a soluble carbodi-imide.[2] They react smoothly with (**1**) to give the anhydrides (**2**).[2] Their immediate precursor is believed to be the *O*-acylisourea (**7**).[2] We now report that 2-t-butoxyoxazol-5(4*H*)-ones (**3a**) also arise from the *N*-t-butoxycarbonylamino acid anhydrides (**2a**)[3] if a tertiary amine base is present. Thus the addition of triethylamine to a solution of *N*-t-butoxycarbonylvaline anhydride (**2b**) in deuteriochloroform led to the formation of 2-t-butoxy-4-isopropyloxazol-5(4*H*)-one (**3b**). The amount of (**3b**) present in a solution of (**2b**) and the tertiary amine in deuteriochloroform and heptadeuteriodimethylformamide is illustrated in Figures 1 and 2 respectively.† In $CDCl_3$, triethylamine caused the gradual

† Determined by 60 MHz ^{1}H n.m.r. spectroscopy by integration of the unique t-butyl resonance (δ 1·60) of the 2-t-butoxyoxazol-5(4*H*)-one.

formation of the oxazolone, the amount increasing over 24 h. Pyridine and *p*-dimethylaminopyridine caused a more rapid conversion into the oxazolone, the amount reaching a maximum at 1 h, after which it levelled off or decreased. Some oxazolone appeared even in the absence of base. In [$^2H_7$]dimethylformamide, formation was more rapid, but the amount also decreased more rapidly. However, in no case did the spectroscopic evidence indicate that the decrease in the amount of oxazolone in solution was accompanied by decomposition.

$R^1OCO{\cdot}NH{\cdot}CHR^2{\cdot}CO_2H$ (1)

$(R^1OCO{\cdot}NH{\cdot}CHR^2{\cdot}CO)_2O$ (2)



(3)

$R^3N{=}C{=}NR^3$ (4)

$R^1OCO{\cdot}NH{\cdot}CHR^2{\cdot}CO{\cdot}N(R^3){\cdot}CO{\cdot}NHR^3$ (5)

$R^3NH{\cdot}CO{\cdot}NHR^3$ (6)

$R^1OCO{\cdot}NH{\cdot}CHR^2{\cdot}CO_2{\cdot}C(=NR^3){\cdot}NHR^3$ (7)

a; $R^1 = Bu^t$
b; $R^1 = Bu^t$, $R^2 = Pr^i$, $R^3 = Pr^i$
c; $R^1 = PhCH_2$, $R^2 = Pr^i$, $R^3 = Pr^i$
d; $R^1 = Bu^t$, $R^2 = Pr^i$, R^3 = cyclo-C_6H_{11}

Confirming evidence for the formation from (**2b**) and triethylamine of an activated form of (**1b**) was obtained as follows. A solution of (**2b**) (0·5 mmol) and triethylamine (0·6 mmol) in chloroform was left for 24 h and then washed with water which removes liberated acid (**1b**) as its triethylammonium salt. After drying and evaporating the solution, methylamine in dichloromethane was added. Only a trace of the methylammonium salt of (**1b**) precipitated out, indicating the absence of the anhydride (**2b**) in the solution. Work-up of the solution gave 75 mg of the methylamide of (**1b**), m.p. 112—113 °C, lit.[2] m.p. 113—114 °C.

Anhydrides of the butoxycarbonyl derivatives of alanine (**2a**; R^2 = Me) and leucine (**2a**; R^2 = Bu^s) also gave the oxazolones, but the amounts could not be determined quantitatively. The anhydride from phenylalanine (**2a**; $R^2 = PhCH_2$) with triethylamine in $CDCl_3$ gave 100% of the oxazolone (**3a**; $R^2 = PhCH_2$) at 30 min. No oxazolone could be detected after the addition of triethylamine to *N*-benzyloxycarbonylvaline anhydride (**2c**), but a reaction did occur.

In the presence of 1 equiv. of *N*,*N*′-di-isopropylcarbodi-imide (**4b**) in $CDCl_3$, (**2b**) gave a 65% yield of (**3b**) after 22 h, the *N*-acyl-*N*,*N*′-dialkylurea (**5b**) appearing as the second product instead of the salt of the acid (**1b**). The yields (isolated) of the oxazolone (**3**) and *N*-acylurea (**5**) obtained for reactions carried out on a 1 mmol scale in chloroform are given in Table 1. The yields of *N*-acylurea are so high that its formation by this reaction is incontestable. The possibility that carbodi-imides might react with anhydrides had been suggested by the results obtained upon closer examination of the reaction of acid (**1d**) with one equiv. of *N*,*N*′-dicyclohexylcarbodi-imide (**4d**).[4] The results of this study appear in Table 2. It is evident that small amounts of both the oxazolone and the *N*-acylurea are present after 15 min, and that the amounts increase with time at the expense of the anhydride and the carbodi-imide.

TABLE 1. Yields (%) of products from the reaction of the anhydrides (**2**) with the carbodi-imides (**4**).

(**2**)	(**4**)	Time/h	Oxazolone (**3**)	*N*-Acylurea (**5**)
(**2b**)	(**4b**)	22	(**3b**) 66	(**5b**) 90
(**2c**)	(**4c**)	96	(**3c**) 50	(**5c**) 90
(**2d**)	(**4d**)	18	(**3d**) 70	(**5d**) 80

TABLE 2. Yields (%) of products from the reaction of the acid (**1d**) with the carbodi-imide (**4d**)[a].

	Anhydride (**2d**)	Oxazolone (**3d**)	*N*-Acylurea (**5d**)	Di-imide (**4d**)	Urea (**6d**)
15 min	80	3	6	40	53
24 h	12	38	40	0	60

[a] Recoveries correspond to *ca.* 90% for the amino acid components and *ca.* 100% for the di-imide–urea components.

The fact that oxazolones (**3**) are generated by the action of tertiary amines on symmetrical anhydrides (**2**) has implications for the possible stereochemical course of some reactions in organic synthesis. It is known that these oxazolones racemise partially when coupled in the presence of triethylamine.[2] It follows that couplings of symmetrical anhydrides, or reactants which generate the anhydride, in the presence of tertiary amines are likely to be accompanied by racemisation unless the coupling is much faster than the conversion into oxazolone. Ironically, it is when couplings are not rapid that one resorts to the addition of such basic catalysts to accelerate reactions. Typical examples of this are the use of the very basic *p*-dimethylaminopyridine to enhance the esterification of the acid (**1**) to resin supports in

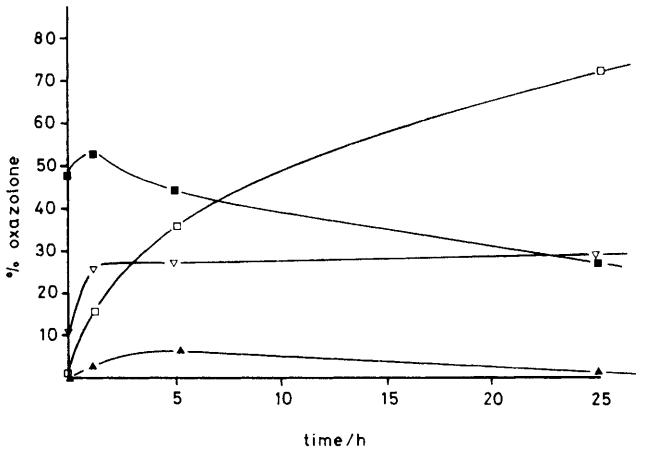


FIGURE 1. Amount of 2-alkoxyoxazol-5(4*H*)-one (**3b**) present in a solution of the anhydride (**2b**) and amine (1·2 equiv.) in deuteriochloroform at various times. □, Triethylamine; ■, *p*-dimethylaminopyridine; ▽, pyridine; ▲, no base.

peptide synthesis[5,6] and to hydroxy-acids in depsipeptide synthesis.[7] This compound causes immediate formation of the oxazolone from the anhydride (Figures 1 and 2), and some racemisation has indeed been shown to occur in the former case.[8]

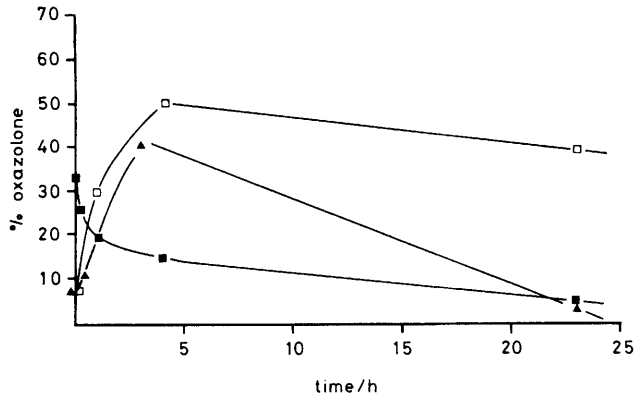


FIGURE 2. As in Figure 1, in [$^2H_7$]dimethylformamide.

The reaction of the anhydrides (**2**) with carbodi-imides has not been reported previously[9] despite some closely related studies.[10] The basic properties of carbodi-imides are known,[10,11] so their reaction with (**2**) is consistent with the raction of (**2**) with tertiary amines. Acetic anhydride does not react with the carbodi-imide (**4d**), nor with the urea (**6d**).[10] This, combined with the known reactions of *O*-alkylisoureas, has been taken as the basis for the accepted tenet that *N*-acylurea side-products in peptide synthesis arise from the *O*-acylisourea (**7**) by an O → N acyl shift.[9] Our results indicate that *N*-acylurea can indeed arise from the reaction of the anhydride and carbodi-imide. Moreover, they introduce the intriguing possibility that this is the source of the *N*-acylurea which is commonly encountered in peptide synthesis. This hypothesis which does not run contrary to experimental observations, is supported by some,[12] and would explain some puzzling observations such as the fact that when *N*-acylurea is prepared by reaction of the acid (**1**) with the carbodi-imide (**4d**) in the presence of triethylamine, the yield does not exceed 50%. The new reaction also poses the question as to whether it is the source of the 2-alkoxyoxazol-5(4*H*)-one isolated from other carbodi-imide-mediated reactions.[2] Attempts to clarify these points are in progress.

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