

Not the Alkoxy-carbonylamino-acid O-Acylisourea

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

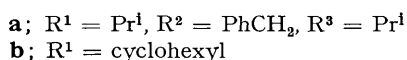
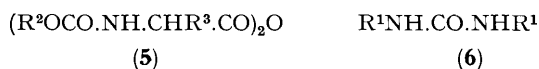
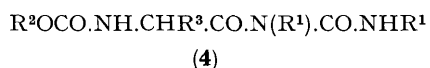
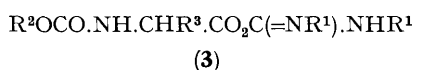
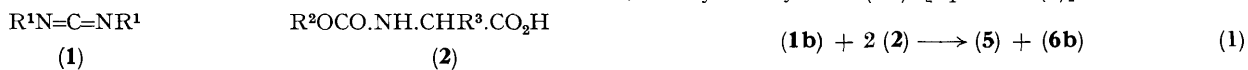
(Department of Biochemistry, University of Ottawa, Ottawa, Ontario K1N 9A9, Canada)

Summary The reaction of equivalent amounts of *N*-benzyl-oxycarbonyl-L-valine and *N,N'*-di-isopropylcarbodi-imide in deuteriochloroform gives an equimolar mixture of the

symmetrical anhydride of the *N*-protected amino-acid, *N,N'*-di-isopropylurea, and unchanged carbodi-imide and not the *O*-acylisourea adduct as reported in the literature.

BATES *et al.*¹ reported that the addition of 1 equiv. of *N,N'*-di-isopropylcarbodi-imide (**1a**) to *N*-benzyloxycarbonyl-L-valine (**2a**) in deuteriochloroform leads to rapid, clean, and complete reaction with formation of *O*-(*N*-benzyloxycarbonyl-L-valyl)-*N,N'*-di-isopropylisourea (**3a**). The identity of the product was established on the basis that its ¹H n.m.r. (300 MHz) spectrum was different from that of the

isomeric and unreactive *N*-acylurea (**4a**). The spectrum of the recognised but heretofore elusive *O*-acylisourea remained unchanged for 9 h. On the other hand, when 0.5 equiv. of *N,N'*-dicyclohexylcarbodi-imide (**1b**) [or *N*-ethyl-*N'*-(γ -dimethylaminopropyl)carbodi-imide] is treated with an *N*-alkoxycarbonylamino-acid (**2**) in dichloromethane, the product is the symmetrical anhydride (**5**) and *N,N'*-dicyclohexylurea (**6b**) [equation (1)].^{2,3}



Carbodi-imide (1a)

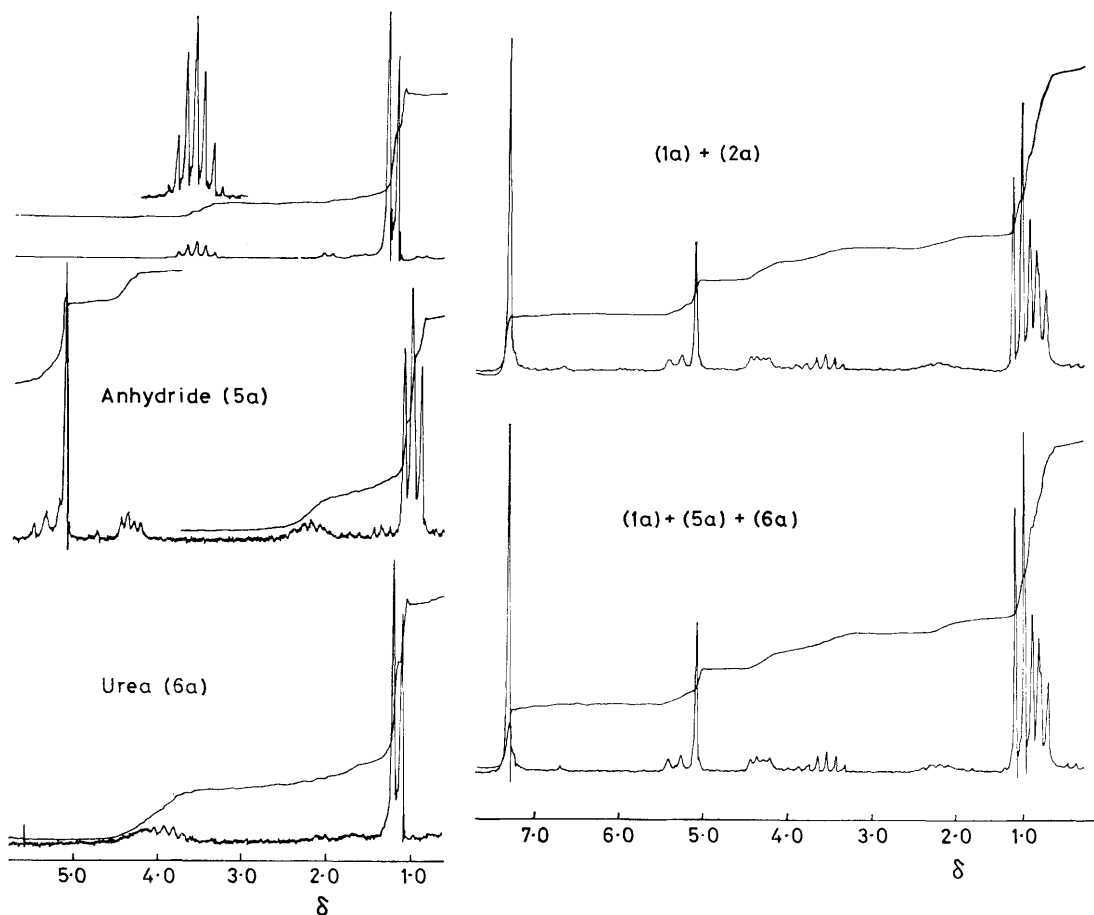
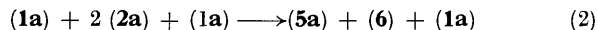


FIGURE. Comparison of the ¹H n.m.r. spectrum of the mixture of (**1a**), (**5a**), and (**6a**) with that of a mixture of (**1a**) and (**2a**), and with spectra of (**1a**), (**5a**), and (**6a**).

† Based on a control experiment showing that *N,N'*-di-isopropylcarbodi-imide in deuteriochloroform survives the washes with dilute aqueous solutions.

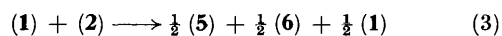
N,N'-di-isopropylurea (**6a**) as well. Finally, when an n.m.r. spectrum was taken in deuteriochloroform[‡] of an equimolar mixture of the anhydride (**5a**),² carbodi-imide (**1a**), and urea (**6a**),§ the spectrum was indistinguishable from that exhibited by an equimolar mixture of acid (**2a**) and carbodi-imide (**1a**) (Figure). Furthermore, n.m.r. spectra taken separately of (**1a**), (**5a**), and (**6a**) (Figure) when superimposed gave a curve identical with the other two spectra.

We conclude that the reaction between equimolar amounts of (**1a**) and (**2a**) in deuteriochloroform is the same as in equation (1) except that one half of the carbodi-imide is not involved in the reaction [equation (2)].



All proton assignments made by Bates *et al.*¹ attributed to structure (**3a**) can be applied to the corresponding protons in the mixture of (**1a**), (**5a**), and (**6a**), the only difference in structure being $-\text{CH}\cdot\text{NH}\cdot\text{C}(=\text{N})\text{O}-$ in (**3a**) *vs.* $-\text{CH}\cdot\text{NH}\cdot\text{C}(=\text{O})\cdot\text{N}-$ in (**6a**). The reported stability in

deuteriochloroform for 9 h of the activated amino-acid derivative formed from (**1a**) and (**2a**) is consistent with the known properties of (**5a**)² which is stable in this solvent at 50 °C for 3 h. Supporting evidence for the validity of equation (2) is provided by the observation that an equimolar mixture of *N,N'*-dicyclohexylcarbodi-imide (**1b**) and *N*-benzyloxycarbonyl-L-valine (**2a**) or *N*-t-butoxycarbonyl-*N*-methyl-L-valine in dichloromethane gives a 50% yield of *N,N'*-dicyclohexylurea (**6b**) when filtered after 15 min. The implication is that equation (3) is the general reaction in these solvents.



Added in proof: Dr. J. H. Jones has expressed his agreement with the conclusions of this submission.

This work was financially supported by the Medical Research Council.

(Received, 2nd February 1981; Com. 121.)

‡ The 60 MHz ¹H n.m.r. spectra of 0.05 M solutions in CDCl₃ gave the following data: δ (**1a**): 3.57 (septet, 1H, Me₂CH) and 1.23 (d, 6H, Me₂CH); δ (**5a**): 7.35 (s, 5H, ArH), 5.25 (d, 1H, PhCH₂OCONH), 5.10 (s, 2H, PhCH₂), 4.35 (dd, 1H, NHCHCO), 2.20 (m, 1H, CHMe₂), and 1.05 and 0.95 (2 × d, 6H, Me₂CH); δ (**6a**): 3.6–4.5 (m, 2H, Me₂CHNH and Me₂CHNH) and 1.14 (d, 6H, Me₂CHNH). Same assignments for the mixtures. Some urea (**6a**) precipitated out of the solutions of the mixtures.

§ M.p. 190–192 °C, prepared by evaporating a solution of (**1a**) in aqueous tetrahydrofuran containing a drop of hydrochloric acid.

¹ H. S. Bates, J. H. Jones, and M. J. Witty, *J. Chem. Soc., Chem. Commun.*, 1980, 773.

² F. M. F. Chen, K. Kuroda, and N. L. Benoiton, *Synthesis*, 1978, 928, and references therein.

³ N. L. Benoiton and F. M. F. Chen, *Can. J. Chem.*, 1981, **59**, 384.