New Synthesis of Selected Dehydroamino-acid Esters and Triazolidines

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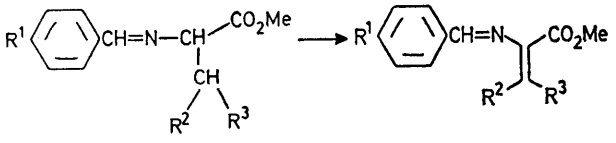
Summary Diethyl azodicarboxylate reacts with imines of α-amino-acid esters, probably by way of an ene-reaction, to give either imines of the corresponding dehydroamino-acid ester or triazolidines, depending on the structure of the α-amino-acid ester.

DEHYDROAMINO-ACIDS and their derivatives have attracted interest as synthetic precursors of L-amino-acids *via* asymmetric reduction,[1,2] and as possible biochemical intermediates in the conversion of L-amino-acid species into D-amino-acid species in microbial peptides.[3] We were interested in devising a method for converting L-amino-acid esters into the corresponding dehydroamino-acid esters and have studied the reaction of imines derived from various L-amino-acid esters and aromatic aldehydes with diethyl azodicarboxylate (DAD). The valine imine (**1a**) (1 mol) reacted (130 °C, 48 h) with DAD (1·3 mol) to give the imine of the dehydroamino-acid ester (**2a**) (74%) as a pale yellow oil, τ ($CDCl_3$) 1·86 (s, 1H, –CH=N–), 2·10—2·75 (m, 5H, ArH), 6·20 (s, 3H, OMe), and 7·93 and 8·02 (2 × s, 2 × 3H, $=CMe_2$). The *para*-substituted imines (**1**; R=OMe or NO_2, $R^1 = R^2$ = Me), under similar conditions, gave *ca.* 1:1 mixtures of starting material and product. The phenylalanine imine (**1b**) gave (160 °C, 2 h) the corresponding solid dehydro-derivative (**2b**) as a single isomer. The olefinic double bond of (**2b**) is provisionally assigned the *Z*-configuration by analogy with the known configuration of the related *N*-acyl dehydroamino-acid derivatives.[4] The isoleucine imine (**1c**) gave a mixture of both the *E*- (**2c**) and *Z*- (**2d**) dehydro-derivatives which were separated by preparative g.l.c. The corresponding leucine derivative has also been prepared and purified by preparative g.l.c.

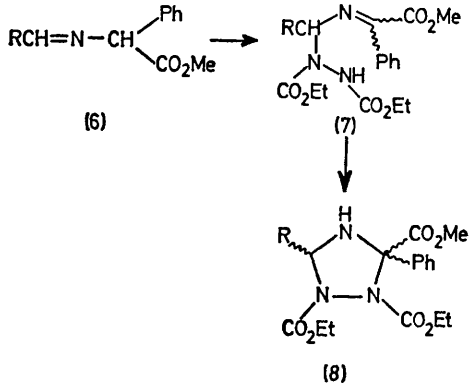
Isomerism about the –C=N– unit was not observed in any of the dehydroamino-acid imines or their precursor imines and the imine species is assigned the expected[5] *E*- or *anti*-configuration.



(1) (2)

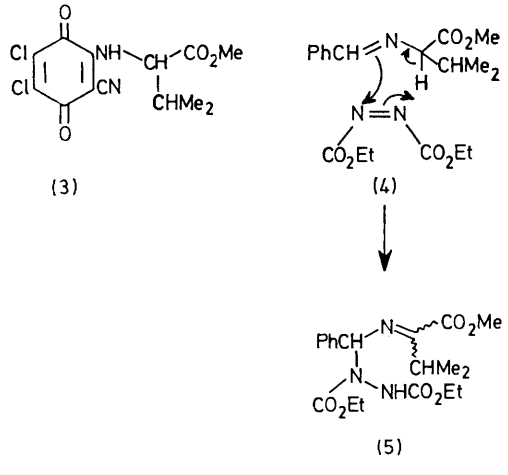
a; R^1 = H, R^2 = R^3 = Me
b; R^1 = R^2 = H, R^3 = Ph
c; R^1 = H, R^2 = Me, R^3 = Et

a; R^1 = H, R^2 = R^3 = Me
b; R^1 = R^3 = H, R^2 = Ph
c; R^1 = H, R^2 = Me, R^3 = Et
d; R^1 = H, R^2 = Et, R^3 = Me.



(6) (7) (8)

a; R = Ph
b; R = C_6H_4OMe-*p*
c; R = $C_6H_4NO_2$-*p*
d; R = 3-pyridyl
e; R = 2-furyl



(3) (4) (5)

Several mechanisms can be advanced for this dehydrogenation reaction. A direct one-step dehydrogenation, although favoured by orbital symmetry considerations, appears unlikely since the corresponding *N*-acylamino-acid esters do not undergo dehydrogenation with DAD. Attempt to dehydrogenate the imines (**1a**—**c**) with high potential quinones were also unsuccessful and led to amination of the quinone, *e.g.* (**1a**) and dichlorodicyanoquinone gave (**3**) by displacement of cyanide.

The conversion (**1** → **2**) is thought to involve an initial ene-reaction (**4** → **5**).† An analogous reaction has been reported for benzylidenebenzylamine.[6] Breakdown of (**5**) to give the product could then occur in several ways. One possible pathway involves cyclisation to a 1,2,4-triazolidine. We have been able to isolate triazolidines from reactions of DAD with imines incapable of dehydrogenation. Thus the imines of (±)-phenylglycine (**6a**—**e**) react with DAD in boiling benzene or toluene (0·5—24 h) to give stable

† We cannot, on our present evidence, rule out free radical or ylide mechanisms such as those proposed for the reactions of DAD with amines. See E. E. Smissman and A. Makriyannis, *J. Org. Chem.*, 1973, **38**, 1652 and refs. therein.

1:1 adducts (26—84%) formulated as the triazolidines (**8a**—**e**) on the basis of their spectral characteristics, *e.g.* (**8c**), ν_{max} (KBr disc) 3300 (NH); τ ($CDCl_3$ 1·70—2·65 (m, 9H, ArH), 4·39 [d, *J* 11 Hz, 1H, ArC*H*(N)N], 5·69 (q, 2H, CH_2Me), 5·92 (q, 2H, CH_2Me), 6·21 (d, *J* 11 Hz, 1H, NH), 6·33 (s, 3H, OMe), and 8·67 and 8·82 (2 × overlapping t, 6H, CH_2*Me*). Decoupling experiments established that the signals at τ 4·39 and 6·21 are coupled, and the doublet at τ 4·27 collapses to a singlet on shaking the sample with D_2O.

The triazolidines (**8a**—**e**) are obtained as single diastereoisomers and are thought to arise *via* an ene-reaction (**6** → **7**) followed by cyclisation (**7**→**8**).† The absence of a hydrogen atom β to the amine nitrogen prevents elimination of EtO_2CNH–$NHCO_2Et$.

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