Synthesis of Cycloalk-1-enylglycines

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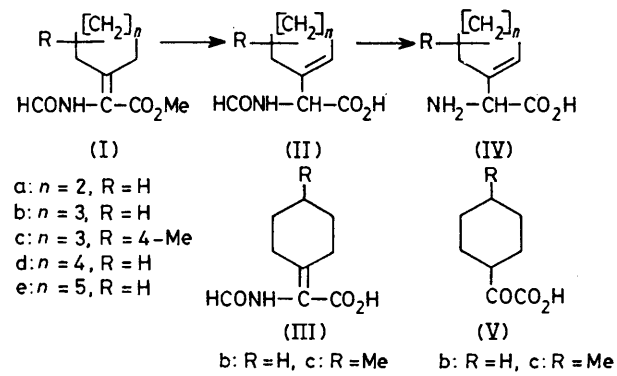
Summary Saponification of methyl *N*-formylcycloalkylideneglycinates (I) leads to migration of the double bond to afford *N*-formylcycloalk-1-enylglycines (II), which are converted into cycloalk-1-enylglycines (IV) by acid hydrolysis.

SOME aliphatic $\beta\gamma$-unsaturated α-amino acids[1] possess potent biological activity.[2] In particular, cyclic $\beta\gamma$-unsaturated amino acids such as cyclohex-1-enylglycine have recently received much attention as intermediates for synthesis of penicillin and cephalosphorin derivatives.[3] Only a few methods have been reported for their synthesis, *e.g.* the Strecker syntheses using cyclohex-1-enecarbaldehyde[4] and the nitrosation of cyclohex-1-enyl acetate followed by reduction.[4] However, these methods lack versatility for synthesis of many types of cyclic amino acids.

We now report a method for the synthesis of cycloalk-1-enylglycines from cycloalkylideneglycine derivatives. The starting cycloalkylidene derivatives (Ia—e) were easily prepared by the reaction of methyl isocyanoacetate with cycloalkanones according to the method reported by Schöllkopf *et al.*[5]

Saponification of the cycloalkylidene derivatives (Ia—e) with potassium hydroxide in methanol at 50 °C proceeded



easily giving high yields of the required *N*-formylcycloalk-1-enylglycines (IIa—e) as a result of migration of the $\alpha\beta$-double bond to the $\beta\gamma$-position. The structure of the resultant products (IIa—e) was confirmed by ^{1}H n.m.r. spectroscopy in $(CD_3)_2SO$: the α-methine proton (δ 4·7—5·0) was coupled with the NH proton and changed to singlet upon exchange with D_2O; the vinyl proton appeared at δ 5·6—5·8. Deformylation of (IIa—e) using hydrochloric

TABLE

	(II)		(IV)			
Substrate	Yield (%)	M.p./°C (decomp.)	Yield (%)	M.p./°C (decomp.)	^{1}H n.m.r.[a] α-CH	Vinyl-CH
(Ia)	87	149—151	90	232—234	5·06	6·20
(Ib)	80[b]	—	55	259—260	4·75	6·20
(Ic)	87[b]	—	49	216—217	4·70	6·15
(Id)	90	175—177	92	237—238	4·81	6·35
(Ie)	79	144—145	93	217—218	4·78	6·13

[a] δ values from Me_4Si internal standard for solutions in CF_3CO_2D. [b] (IIb)' and (IIc) were obtained as mixtures with (IIIb) and (IIIc), respectively.

acid in tetrahydrofuran in the usual manner gave the corresponding cycloalk-1-enylglycines (IVa—e) in high yields (Table). In the case of (Ib) and (Ic), compounds (IIIb) and (IIIc), in which double bond migration had not taken place, were also formed (20—30% yields) in addition to (IIb) and (IIc), as shown by ^{1}H n.m.r. spectroscopy. However, these by-products were easily separated as the keto acid derivatives[6] (Vb) and (Vc) by acid hydrolysis.

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