Synthesis of βγ-Unsaturated α-Amino-acids †

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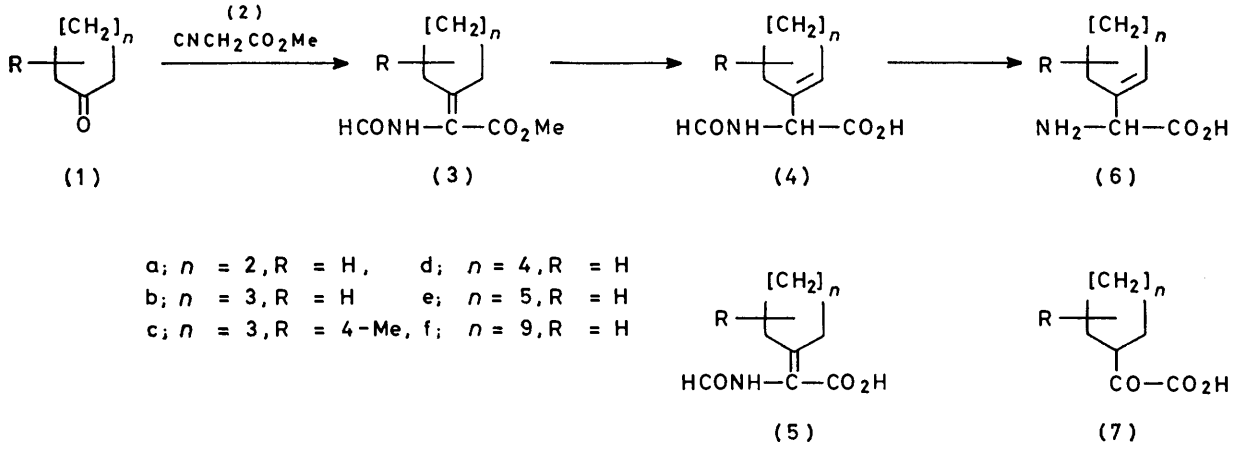
Saponification of methyl *N*-formylcycloalkylideneglycinates (3) gave *N*-formylcycloalk-1-enylglycines (4) through migration of the double bond. The compounds (4) were converted into cycloalk-1-enylglycines (6) by acid hydrolysis. On the results of mechanistic studies it is supposed that the migration is initiated by intramolecular proton abstraction by the carboxylate ion at the γ-position. The method was extended to the synthesis of cycloalk-1-enylglycines containing heteroatoms in the ring [compounds (15)] and isodehydrovaline (17) in high yields.

βγ-UNSATURATED α-amino-acids have been receiving much attention as some of the naturally occurring amino acids which possess potent biological activities both as antibiotics [1] and as irreversible inhibitors of amino acid metabolizing enzymes.[2] In particular, cyclic βγ-unsaturated α-amino-acids such as cyclohex-1-enylglycine, having a similar structure to phenylglycine, are an important class of amino-acids as intermediates for the synthesis of penicillin and cephalosporin derivatives.[3] Only a few methods for synthesis of cyclic βγ-unsaturated α-amino-acids have hitherto been reported; the Strecker or Bücherer methods using cyclohex-1-enecarbaldehyde,[4] the nitrosation of cyclohex-1-enyl acetate, followed by reduction with metals,[4] and a partial hydrogenation of cyclohexa-1,4-dienylglycine.[3a] These methods, however, are effective only for the synthesis of cyclohex-1-enylglycine and are unavailable for the synthesis of many types of cyclic βγ-unsaturated α-amino-acids.

In studies on the synthesis of amino-acids and related compounds,[5] we have found that migration of the αβ-double bond to the βγ-position proceeded smoothly during the saponification of methyl *N*-formylcycloalkylideneglycinates. In this study, to formulate a new synthesis of βγ-unsaturated α-amino-acids, we have investigated in detail the synthesis of cycloalk-1-enylglycines of various ring sizes and/or with heteroatoms such as sulphur or nitrogen in the ring. Moreover, the mechanism of migration of the double bond has been investigated and the reaction has been further extended to the synthesis of aliphatic βγ-unsaturated α-amino-acids.

Cycloalk-1-enylglycines.—The starting materials, methyl *N*-formylcycloalkylideneglycinates (3), were easily prepared by the reaction of methyl isocyanoacetate (2) with cycloalkanones (1) according to the method of Schöllkopf *et al.*[6] Saponification of these compounds (3) with 2N-potassium hydroxide in methanol was carried out at 50 °C, resulting in the formation of the desired *N*-formylcycloalk-1-enylglycines (4) in high yields. The results suggested that the reaction proceeds through migration of the αβ-double bond to the βγ-position. The structure of the products (4) was confirmed by ^{1}H n.m.r. spectroscopy in $(CD_3)_2SO$: the α-methine proton (δ 4.71—4.96) was coupled with a NH proton and changed to a singlet upon exchange with D_2O, an olefinic proton appearing at δ 5.4—5.8 (Table 1). Subsequently, deformylation of (4) using hydrochloric acid in tetrahydrofuran was carried out to give the corresponding cycloalk-1-enylglycines (6) in good yields (Table 2). In the case of (1b), (1c), and (1f), the *N*-formylcycloalkylideneglycines (5b), (5c), and (5f), in which double-bond migration did not take place, were also formed (*ca.* 20% yields) in addition to (4b), (4c), and (4f). However, these by-products were easily removed as the α-keto-acid derivatives (7b), (7c), and (7f) by



SCHEME 1

† Preliminary communication, M. Suzuki, K. Nunami, and N. Yoneda, *J.C.S. Chem. Comm.*, 1978, 270.

TABLE 1

Yields, physical, and analytical data of (4)

Compound	Yield (%)	M.p.(°C) (decomp.)	^{1}H n.m.r.[a] α-CH	>C=CH–	HCO	NH	$\nu_{max.}$(Nujol) cm^{-1}	Molecular formulae	Analysis (%) [b] C	H	N
(4a)	87	149—151	4.96	5.66	8.02	8.50	3 370, 1 720, 1 610	$C_8H_{11}NO_3$	56.8 56.6	6.55 6.45	8.25 8.25
(4b)	80 [c]		4.75	5.72	8.03	8.48	3 250, 1 730, 1 620	$C_9H_{13}NO_3$	59.0 58.85	7.15 7.05	7.65 7.65
(4c)	87 [c]		4.73	5.75	7.98	8.42	3 250, 1 730, 1 620	$C_{10}H_{15}NO_3$	60.9 60.8	7.65 7.7	7.1 7.0
(4d)	90	175—177	4.71	5.80	7.98	8.40	3 260, 1 725, 1 620	$C_{10}H_{15}NO_3$	60.9 60.8	7.65 7.55	7.1 7.1
(4e)	79	144—145	4.87	5.61	7.98	8.42	3 350, 1 718, 1 625	$C_{11}H_{17}NO_3$	62.55 62.4	8.1 7.95	6.65 6.55
(4f)	95 [c]		4.81	5.40	8.00	8.40	3 300, 1 710, 1 620	$C_{15}H_{25}NO_3$	67.4 67.25	9.45 9.5	5.25 5.2

[a] δ Values. $(CD_3)_2SO$ as solvent. [b] Upper line ' required '; lower line ' found.' [c] (4b), (4c), and (4f) were obtained as mixtures with (5b), (5c), and (5f), respectively.

TABLE 2

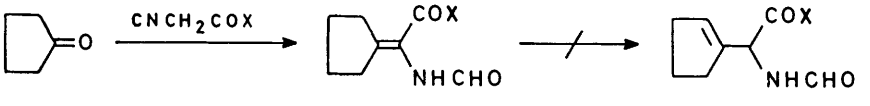
Yields, physical, and analytical data of (6)

Compound	Yield (%)	M.p.(°C) (decomp.)	^{1}H N.m.r.[a] α-CH	>C=CH–	$\nu_{max.}$(KBr) cm^{-1}	Molecular formulae	Analysis (%) [b] C	H	N
(6a)	90	232—234	5.06	6.20	2 100, 1 660, 1 630, 1 580 [c]	$C_7H_{11}NO_2$	59.55 59.35	7.85 7.75	9.9 9.65
(6b)	55	259—260 [d]	4.75	6.20	2 120, 1 610, 1 590	$C_8H_{13}NO_2$	61.9 61.65	8.45 8.5	9.05 9.0
(6c)	49	216—217	4.70	6.15	2 140, 1 600	$C_9H_{15}NO_2$	63.9 63.7	8.95 9.0	8.3 8.05
(6d) [e]	92	237—238	4.81	6.35	1 690, 1 630, 1 608, 1 580	$C_9H_{17}NO_3$	57.75 57.6	9.15 9.0	7.5 7.35
(6e)	93	217—218	4.78	6.13	2 080, 1 665, 1 570 [c]	$C_{10}H_{17}NO_2$	65.55 65.35	9.35 9.25	7.65 7.45
(6f)	58	191—194	4.77	5.85	1 660, 1 625, 1 595	$C_{14}H_{25}NO_2$	70.25 70.15	10.55 10.65	5.85 5.7

[a] δ Values. CF_3CO_2D as solvent. [b] Upper line ' required '; lower line ' found.' [c] Measured in Nujol. [d] Lit.,[4] 242—243 °C (decomp.). [e] Hydrate.

subsequent acid hydrolysis [7] (see Experimental section).

Mechanistic Studies on the Double-bond Migration.— From the results of the above reaction, it is likely that saponification of the methyl ester of (3) probably causes the successive double-bond migration. In order to clarify this assumption, reactions using t-butyl *N*-formylcyclopentylideneglycinate (8a) and *N*-formylcyclopentylideneglycinylpyrrolidine (8b), which are hardly saponified in the usual alkaline solution, were carried out under the same conditions as above. As expected, the reaction did not proceed for either compound, starting materials only being recovered. In order to examine the possibility of migration by proton abstraction at the γ-position [8] without saponification occurring, even when other strong bases such as sodium hydride or sodium methoxide were used, the desired double-bond migration did not occur. These results

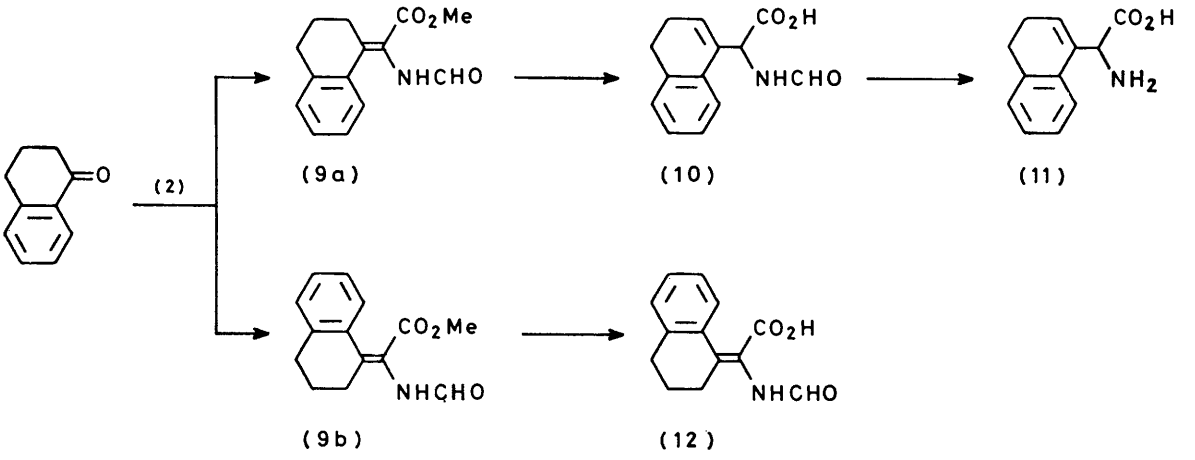


(8) a; X = OBu^t

b; X = N

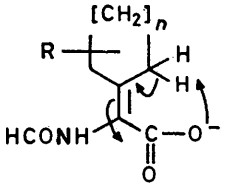
SCHEME 2

apparently show that the conversion of the methyl ester to a carboxylate ion is essential for migration of the αβ-double bond of (3) to the βγ-position. Furthermore, we have investigated the orientation of double-bond migration. A typical experiment involved condensation of 1,2,3,4-tetrahydronaphthalen-1-one (1-tetralone) and methyl isocyanoacetate (2) to afford a mixture of the *Z*- and *E*-isomers of methyl *N*-formyl-1,2,3,4-tetrahydro-1-naphthylideneglycinate (9a and 9b). The isomers were separated and purified by column chromatography, followed by recrystallization. The ^{1}H n.m.r. spectrum of the first fraction in $CDCl_3$ showed a signal for the ester methyl group at δ 3.79 while the formyl proton absorbed at δ 8.00. Another fraction showed corresponding signals at δ 3.60 and 8.14, respectively. However, CPK models of these compounds showed that a group located *cis* across the double bond to the benzene ring would be deshielded by the co-planar ring current; *i.e.*, the methyl protons of the *E*-isomer should appear at lower field than those of the *Z*-configuration with the formyl proton of the *Z*-isomer appearing at lower field. It was thus confirmed that the first fraction was the *E*-isomer (9b) and the other the *Z*-isomer (9a). Each isomer was saponified with 2N-potassium hydroxide in methanol at 50 °C. As a result, the *Z*-isomer gave *N*-formyl-3,4-dihydro-1-naphthylglycine (10) *via* migration of the double bond; this was then hydrolysed with hydrochloric acid to afford 3,4-dihydro-1-naphthylglycine (11) in 61% yield. On the other hand, in the case of the *E*-isomer. saponification of the ester occurred only without migration of the double bond, resulting in the formation of *N*-formyl-1,2,3,4-tetrahydro-1-naphthylideneglycine (12). These facts reveal that the location of the carb-



SCHEME 3

oxylate ion is an important factor in the migration of the αβ-double bond to the βγ-position and that the migration is initiated by intramolecular proton abstraction by the carboxylate ion at the γ-position (13).



(13)

Other βγ-Unsaturated α-Amino-acids.—The above reaction was extended to the preparation of pharmacolo-

TABLE 3

Yields, physical, and analytical data of (15)

Compound	Yield (%)	M.p.(°C) (decomp.)	^{1}H n.m.r.[a] α-CH	–CH=C–	Other	$\nu_{max.}$(KBr) cm^{-1}	Molecular formulae	Analysis (%)[b] C	H	N	Cl	S
(15a)[c]	62	222—224	5.01	6.30	2.8—4.3 (6 H, m, $3CH_2$), 3.13 (3 H, s, CH_3)	2 000, 1 630	$C_8H_{15}ClN_2O_2$	46.5 46.2	7.3 7.2	13.55 13.4	17.15 17.35	
(15b)[c]	57	217—219	5.02	6.29	2.7—3.2 (2 H, m, CH_2), 3.7—4.1 (4 H, m, $2CH_2$) 4.50 (2 H, s, CH_2Ph), 7.51 (5 H, s, ArH)	2 120, 1 600	$C_{14}H_{19}ClN_2O_2$	59.45 59.2	6.75 6.9	9.9 9.8	12.55 12.8	
(15c)	75	241—243	4.79	6.39	2.3—2.7 (2 H, m, CH_2), 2.75—3.1 (2 H, m, CH_2), 3.2—3.5 (2 H, m, CH_2)	2 130, 1 600	$C_7H_{11}NO_2S$	48.55 48.4	6.4 6.5	8.1 8.0		18.5 18.25
(15d)	54	196—200	5.03	6.97	3.0—4.1 (2 H, m, CH_2), 3.96 (3 H, s, OCH_3), 5.34 (1 H, s, CH), 7.00 (2 H, d, *J* 8 Hz, ArH) 7.44 (2 H, d, *J* 8 Hz, ArH)	2 120, 1 600	$C_{13}H_{15}NO_3S_2$	52.5 52.3	5.1 5.2	4.7 4.6		21.55 21.3

[a] δ Values. CF_3CO_2D as solvent. [b] Upper line ' required '; lower line ' found.' [c] Hydrochloride.

TABLE 4

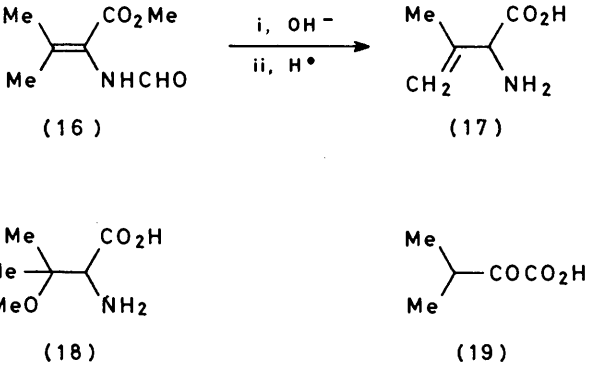
Yields, physical, and analytical data of starting materials

Compound	Yield (%)	M.p.(°C) (Recryst. solv.)	^{1}H n.m.r.[a] HCO	^{1}H n.m.r.[a] NH	$\nu_{max.}$(Nujol) cm^{-1}	Molecular formulae	Analysis (%)[b] C	H	N
(3a)	78	95—98 (AcOEt–hexane)	8.17	7.25[c]	3 240, 1 720, 1 665, 1 640	$C_9H_{13}NO_3$	59.0 59.0	7.15 7.15	7.65 7.75
(3b)	78	105—107 (AcOEt–hexane)	8.00	9.40[d]	3 240, 1 720, 1 650, 1 620	$C_{10}H_{15}NO_3$	61.0 61.05	7.65 7.45	7.1 7.1
(3c)	69	78—79.5 (AcOEt–hexane)	8.04	9.50[d]	3 270, 1 720, 1 665, 1 640	$C_{11}H_{17}NO_3$	62.55 62.55	8.1 8.2	6.65 6.6
(3d)	72	66—68 (AcOEt–hexane)	8.03	9.30[d]	3 250, 1 715, 1 680, 1 650	$C_{11}H_{17}NO_3$	62.55 62.45	8.1 7.95	6.65 6.65
(3e)	64	Syrup[e]	8.12	7.93[c]	3 270, 1 720,[f] 1 670, 1 650	$C_{12}H_{19}NO_5$			
(3f)	73	133—134 (AcOEt)	7.98	9.39[d]	3 240, 1 710, 1 690, 1 660	$C_{16}H_{27}NO_3$	68.3 68.3	9.65 9.55	5.0 4.95
(14a)	68	121—123 (Benzene)	8.11	7.63[c]	3 240, 1 720, 1 655, 1 620	$C_{10}H_{16}N_2O_3$	56.6 56.6	7.6 7.5	13.2 13.25
(14b)	68	67.5—70 (AcOEt–hexane)	8.09	7.41[c]	3 270, 1 720,[g] 1 665, 1 650	$C_{16}H_{20}N_2O_3$	66.65 66.5	7.0 7.05	9.7 9.7
(14c)	88	135—137 (AcOEt–hexane)	8.13	7.24[c]	3 300, 1 720, 1 665, 1 640	$C_9H_{13}NO_3S$	50.2 50.35	6.1 6.2	6.5[h] 6.5
(14d)	60	213—214 (Acetone)	8.07	9.81[d]	3 260, 1 720, 1 660, 1 640	$C_{15}H_{17}NO_4S_2$	53.1 52.9	5.05 5.15	4.15[i] 4.05
(16)	71	67—69 (AcOEt–hexane)	8.00	9.30[d]	3 270, 1 720, 1 645	$C_7H_{11}NO_3$	53.5 53.65	7.05 7.1	8.9 8.9

[a] δ Values. [b] Upper line 'required'; lower line 'found.' [c] $CDCl_3$ as solvent. [d] $(CD_3)_2SO$ as solvent. [e] Purified by column chromatography ($CHCl_3$–AcOEt 10 : 1). [f] Taken by film. [g] Taken in KBr. [h] Required: S, 14.9. Found: S, 14.55. [i] Required S, 18.9, Found S, 18.6.

gically interesting cyclic βγ-unsaturated α-amino acids containing heteroatoms in the ring. Saponification of the methyl *N*-formylcycloalkylideneglycinates (14a—d) derived from *N*-substituted 4-piperidone, 4-oxothian, and 5-oxo-1,3-dithian derivatives was carried out in a similar way. Subsequently, acid hydrolysis without isolation of the *N*-formylcycloalk-1-enylglycines was performed to afford the corresponding βγ-unsaturated α-amino-acids (15a—d) in high yields (Table 3). The ^{1}H n.m.r. spectra in CF_3CO_2D showed characteristic signals for the methine (δ 4.79—5.03) and the olefinic protons (δ 6.29—6.97).

We also attempted the synthesis of isodehydrovaline, an important intermediate in the biosynthesis of cephalosporins.[8a] Thus methyl *N*-formylisopropylideneglycinate (16), prepared by condensation of methyl isocyanoacetate (2) and acetone, was saponified as above, followed by acid hydrolysis, to afford isodehydrovaline. However, a by-product, showing peaks at δ 1.20 (3 H, s, Me), 1.42 (3 H, s, Me), 3.25 (3 H, s, OMe), and 3.75 (1 H, s, CH), in the ^{1}H n.m.r. spectrum



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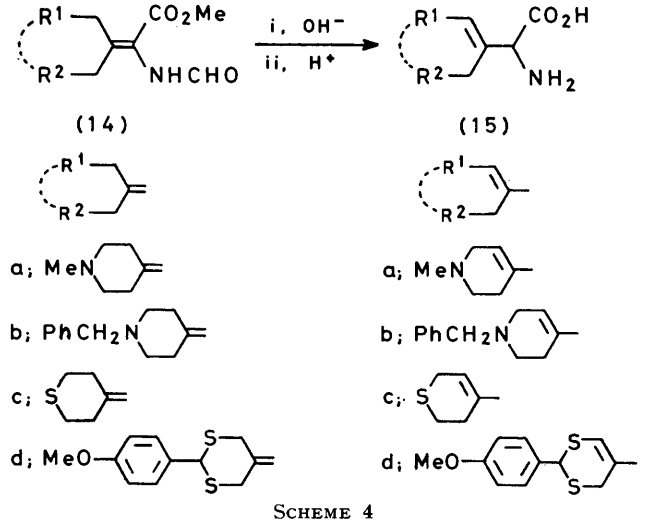

SCHEME 4

(D_2O), was also formed. This compound was presumed to be 2-amino-3-methoxy-3-methylbutyric acid (18), formed by Michael-type addition of a methoxide anion to the double bond of compound (16). However, removal of this by-product was very difficult. Upon repeating the experiment, the saponification of (16) was performed using 50% v/v water–tetrahydrofuran instead of methanol as solvent. Consequently, isodehydrovaline (17) was obtained in 42% yield. In this reaction, 2-oxoisovaleric acid (19) was also formed in 50% yield. This result suggests that attack of the carboxylate ion to a proton at the γ-position is restrained due to the higher flexibility of the methyl group in comparison with cyclic derivatives.

EXPERIMENTAL

M.p.s were measured with a Yamato melting point apparatus. I.r. spectra were recorded with a Shimadzu

IR-27G spectrophotometer and ^1H n.m.r. spectra with a Hitachi–Perkin-Elmer R-20A high resolution n.m.r. spectrometer using tetramethylsilane as internal standard. Column chromatography was carried out on silica gel (Kieselgel, 0.063—0.200 mm, Merck).

Starting Materials (3a—f), (14a—d), *and* (16).—The appropriate ketones were condensed with methyl isocyanoacetate [9] (2) in the presence of sodium hydride according to the method of Schöllkopf *et al.*[7] Yields, physicochemical properties, and analytical data of these compounds are summarized in Table 4.

N-*Formylcycloalk*-1-*enylglycines* (4a—f).—*General procedure*. To a stirred solution of potassium hydroxide (2.24 g, 0.04 mol) in methanol (20 ml) was added the ester (3) (0.02 mol). After stirring had been continued for 10 h at 50 °C, water (10 ml) was added and the solvent was removed *in vacuo*. The residue was adjusted to pH 3 with 10% hydrochloric acid under ice-cooling and the resultant precipitates were filtered off under suction and washed with water. Recrystallization from ethyl acetate gave the N-*formylcycloalk*-1-*enylglycines* (4a—f) as crystals. The results are summarized in Table 1. In the formation of (4b), (4c), and (4f), the products were contaminated with the N-*formylcycloalkylideneglycines* (5b), (5c), and (5f), respectively, $\delta[(CD_3)_2SO]$ (5b), 9.26 (1 H, br s, NH); (5c), 9.23 (1 H, br s, NH); (5f), 9.23 (1 H, br s, NH).

Cycloalk-1-*enylglycines* (6a—f).—*General procedure*. Compound (4) (0.01 mol) dissolved in a mixture of tetrahydrofuran (20 ml) and concentrated hydrochloric acid (4 ml) was stirred for 6 h at 50 °C when the tetrahydrofuran was removed *in vacuo*. The residue was extracted with ether and the aqueous layer concentrated to dryness. The residue was dissolved in 30% v/v ethanol–water and the solution was adjusted to pH 6 with 10% w/v sodium hydroxide–water. The resultant crystals were isolated by suction and washed with ethanol and ether to afford the *cycloalk*-1-*enylglycines* (6a—f) as summarized in Table 2. In the case of (6b), (6c), and (6f), the corresponding α-keto-acids [(7b), (7c), and (7f), respectively] were obtained as by-products upon evaporation of the ethereal layers. (7b), 18% yield from (3b), showed $\nu_{max.}$ (film) 1 720 cm^{-1}; (7c), 16% from (3c), had $\nu_{max.}$ (film) 1 720 cm^{-1}; and (7f), 21% from (3f), showed $\nu_{max.}$ (film) 1 715 cm^{-1}. The keto-acids were analysed as their dicyclohexylammonium salts; *e.g.*, *cyclohexylglyoxylic acid* (7b) *dicyclohexylammonium salt* had m.p. 198—200 °C (decomp.), $\nu_{max.}$ (Nujol) 1 702 and 1 625 cm^{-1} (Found: C, 71.55; H, 10.75; N, 4.0. $C_{20}H_{35}NO_3$ requires C, 71.15; H, 10.45; N, 4.15%).

t-Butyl N-*Formylcyclopentylideneglycinate* (8a).—To sodium hydride (65% suspension in oil; 0.7 g, 0.019 mol) in tetrahydrofuran (17 ml) was added dropwise a mixture of cyclopentanone (1.43 g, 0.017 mol) and t-butyl isocyanoacetate [9] (2.4 g, 0.017 mol) in tetrahydrofuran (17 ml) at 30—40 °C. The mixture was treated as before. The oil obtained was purified by chromatography on silica gel (70 g), using chloroform–ethyl acetate (5 : 1) as eluant, to give (8a) as a syrup (2.7 g, 71%), $\nu_{max.}$ (film) 3 260, 2 920, 1 710, and 1 500 cm^{-1}; δ ($CDCl_3$) 1.52 (9 H, s, 3 Me), 1.5—2.0 (4 H, m, $2CH_2$), 2.2—2.95 (4H, m, $2CH_2$), 7.24 (1 H, br s, NH), and 8.12 (1 H, s, HCO).

N-*Formylcyclopentylideneglycinylpyrrolidine* (8b).—To sodium hydride (65% suspension in oil; 0.81 g, 0.022 mol) in dimethylformamide (20 ml) was added dropwise a mixture of cyclopentanone (1.68 g, 0.02 mol) and pyrrolidinylisocyanoacetamide [10] (2.76 g, 0.02 mol) in dimethylformamide (20 ml) at 30—40 °C and the mixture treated as before. Recrystallization from ethyl acetate–hexane gave (8b) as *prisms* (2.3 g, 52%), m.p. 142—143 °C; $\nu_{max.}$ (Nujol) 3 150, 1 690, 1 670, and 1 600 cm^{-1}; $\delta(CDCl_3)$ 1.50—2.10 (8 H, m, $4CH_2$) 2.10—2.50 (4 H, m, $2CH_2$), 3.40—4.80 (4 H, m, $2CH_2$), 8.00 (1 H, d, *J* 2 Hz, HCO), and 9.25 (1 H, br s, NH) (Found: C, 65.2; H, 8.15; N, 12.6. $C_{12}H_{18}N_2O_2$ requires C, 64.85; H, 8.15; N, 12.6%).

(Z-) *and* (E)-*Methyl* N-*Formyl*-1,2,3,4-*tetrahydro*-1-*naphthylideneglycinate* (9a, b).—The reaction of 1,2,3,4-tetrahydronaphthalen-1-one (11.7 g, 0.08 mol) with methyl isocyanoacetate (2) (7.9 g, 0.08 mol) was carried out according to the general method. The resulting oily products [a mixture of (9a) and (9b)] were subjected to column chromatography (150 g) using chloroform–ethyl acetate (6 : 1) as eluant. The separated isomers were purified by recrystallization from ethyl acetate–hexane. The *Z-isomer* (9a) (8.20 g, 42%) had m.p. 135.5—137 °C; $\nu_{max.}$ (Nujol) 3 360, 1 725, and 1 685 cm^{-1}; $\delta(CDCl_3)$ 1.6—2.1 (2 H, m, CH_2), 2.3—2.9 (4 H, m, $2CH_2$), 3.60 (3 H, s, OMe), 7.10 (4 H, s, ArH), 7.81 (1 H, br s, NH), and 8.14 (1 H, s, HCO) (Found: C, 68.35; H, 6.25; N, 5.7. $C_{14}H_{15}NO_3$ requires C, 68.55; H, 6.15; N, 5.7%). The E-*isomer* (9b) (2.89 g, 15%) had m.p. 146—148 °C; $\nu_{max.}$ (Nujol) 3 210, 1 710, and 1 655 cm^{-1}; $\delta(CDCl_3)$ 1.65—2.1 (2 H, m, CH_2), 2.5—3.1 (4 H, m, $2CH_2$), 3.79 (3 H, s, OMe), 7.0—7.7 (5 H, m, ArH and NH), and 8.00 (1 H, s, HCO) (Found: C, 68.4; H, 6.25; N, 5.7. $C_{14}H_{15}NO_3$ requires C, 68.55; H, 6.15; N, 5.7%).

Saponification and Hydrolysis of (9a).—Compound (9a) (4.9 g, 0.02 mol) was treated with potassium hydroxide (2.24 g, 0.04 mol) in methanol as before to give *N*-formyl-3,4-dihydro-1-naphthylglycine (10) contaminated with a small amount of (*Z*)-*N*-formyl-1,2,3,4-tetrahydro-1-naphthylideneglycine. The mixture was treated with concentrated hydrochloric acid (6 ml) in tetrahydrofuran (30 ml) as before giving 3,4-*dihydro*-1-*naphthylglycine* (11) as leaflets [2.47 g, 61% from (9a)], m.p. 233—235 °C (decomp.); $\nu_{max.}$ (KBr) 3 420, 1 620, and 1 595 cm^{-1}; $\delta(CF_3CO_2D)$ 2.2—3.1 (4 H, m, $2CH_2$), 5.44 (1 H, s, CH), 6.49 (1 H, t, *J* 5 Hz, C=CH–), and 7.25 (4 H, s, ArH) (Found: C, 70.85; H, 6.5; N, 6.75. $C_{12}H_{13}NO_2$ requires C, 70.9; H, 6.45; N, 6.9%).

Saponification of (9b).—Compound (9b) (1.96 g, 0.008 mol) was dissolved in a solution of potassium hydroxide (0.9 g, 0.016 mol) in methanol (8 ml) and the mixture treated as before. Recrystallization from ethyl acetate–hexane gave (E)-N-*formyl*-1,2,3,4-*tetrahydro*-1-*naphthylideneglycine* (12) as needles (1.18 g, 63%), m.p. 173—175 °C (decomp.); $\nu_{max.}$ (Nujol) 3 320, 1 690, 1 665, and 1 615 cm^{-1}; $\delta[CDCl_3 + (CD_3)_2SO]$ 1.6—2.1 (2 H, m, CH_2), 2.5—3.1 (4 H, m, $2CH_2$), 7.0—7.7 (4 H, m, ArH), 8.02 (1 H, s, HCO), 8.36 (1 H, br s, NH), and 11.0 (1 H, br s, CO_2H) (Found: C, 67.45; H, 5.75; N, 5.95. $C_{13}H_{13}NO_3$ requires C, 67.5; H, 5.65; N, 6.05%).

Cycloalk-1-*enylglycines containing Heteroatoms in the Rings* (15a—d).—*General procedure*. After saponification of compounds (14a—d) (0.02 mol) as described before, the solution was concentrated to dryness *in vacuo*. The residue was treated with a mixture of tetrahydrofuran (36 ml) and concentrated hydrochloric acid (12 ml) for 6 h at 50 °C. The solution was concentrated to dryness *in vacuo*, ethanol was added to the residue, and the insoluble material was filtered off. The filtrate was concentrated to 10 ml *in vacuo* and adjusted to pH 6 with 28% aqueous ammonia. The crystals obtained were isolated by suction and washed

with ethanol and ether to afford (15a—d). These results are summarized in Table 3.

Isodehydrovaline (17).—To a solution of potassium hydroxide (2.24 g, 0.04 mol) in 50% v/v tetrahydrofuran–water (20 ml) was added the ester (16) (3.14 g, 0.02 mol) and the solution was stirred for 10 h at room temperature. The solution was concentrated to dryness *in vacuo* and the residue was dissolved in a mixture of tetrahydrofuran (36 ml) and concentrated hydrochloric acid (12 ml). After the solution had been stirred for 6 h at 50 °C, water (10 ml) was added and the tetrahydrofuran was evaporated off *in vacuo*. The residue was extracted with ether and the aqueous layer concentrated to dryness. To the residue was added ethanol and the insoluble materials were filtered off. The filtrate was concentrated to dryness *in vacuo* and the residue was triturated with ether to give isodehydrovaline hydrochloride as crystals (1.27 g, 42%), m.p. 204—207 °C (decomp.) [lit.,[8a] 206—208 °C (decomp.)]. The hydrochloride was treated by the method of Baldwin *et al.*[8a] to afford isodehydrovaline (17) (0.69 g, 72%), m.p. 211—214 °C (decomp.) [lit.,[8a] 212—215 °C (decomp.)]; $\nu_{max.}$ (KBr) 2 100 and 1 580—1 660 cm^{-1}; $\delta(D_2O)$ 1.79 (3 H, d, *J* 2 Hz, Me), 4.24 (1 H, s, CH), and 5.12 (2 H, br s, CH_2=) (Found: C, 51.9; H, 7.95; N, 12.1. $C_5H_9NO_2$ requires C, 52.1; H, 7.9; N, 12.15%). On evaporation of the ether extract, 2-oxoisovaleric acid (19) was obtained as a crude oil (1.16 g, 50%); $\nu_{max.}$ (film) 1 720 cm^{-1}; the *dicyclohexylammonium salt* had m.p. 178—180 °C (decomp.); $\nu_{max.}$ (Nujol) 1 710 and 1 630 cm^{-1} (Found: C, 68.6; H, 10.6; N, 4.6. $C_{17}H_{31}NO_3$ requires C, 68.65; H, 10.5; N, 4.7%).

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