# Synthesis of γ-Aminobutyric Acid Analogues of Restricted Conformation. Part 2.[1] The 2-(Aminomethyl)cycloalkanecarboxylic Acids †

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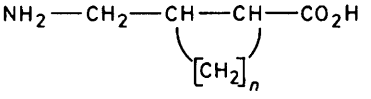
The syntheses of analogues with restricted rotation about the C(2)–C(3) bond of γ-aminobutyric acid, namely *cis*- and *trans*-2-(aminomethyl)-cyclopropane and -cyclobutanecarboxylic acids and *trans*-2-(aminomethyl)cyclohexanecarboxylic acid are described.



In the preceding paper we reported [1] the synthesis of 2-aminocycloalkylacetic acids as analogues of the inhibitory neutrotransmitter, γ-aminobutyric acid (GABA) (1). These represent the GABA molecule with restricted rotation about the C(3)–C(4) bond. The present paper describes the synthesis of the 2-(aminomethyl)cycloalkanecarboxylic acids (2) where free rotation about the

$NH_2CH_2CH_2CH_2CO_2H$

(1)



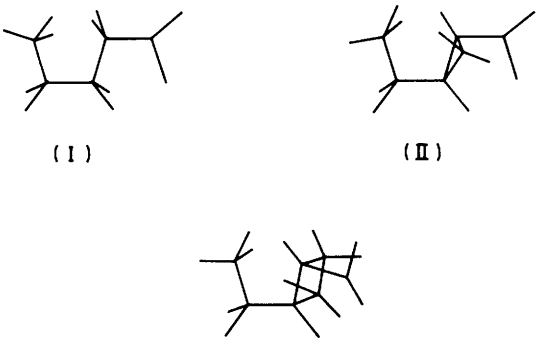
(2)

| | *n* | isomer |
|---|---|---|
| a | 1 | *cis* |
| b | 1 | *trans* |
| c | 2 | *cis* |
| d | 2 | *trans* |
| e | 4 | *cis* |
| f | 4 | *trans* |

C(2)–C(3) bond of GABA is restricted by incorporating this bond into a cycloalkane ring. The configurational isomers of these simple amino-acids can be expected to adopt a variety of conformations resulting from the free rotation of the aminomethyl substituent with respect to the carbocyclic ring and in the cyclobutane and cyclohexane derivatives the added factor of the conformational mobility of these rings. This partial ' conformational freedom,' it was hoped, would permit these molecules the optimum conformation necessary for binding to the GABA receptor.

Dreiding stereomodels of the 2-(aminomethyl)cycloalkanecarboxylic acids indicate that conformations are available to the *trans*-isomers (2b), (2d), and (2f) that are a close ' fit ' to the ' active conformation ' suggested by Nicholson *et al.*[2] which the GABA molecule adopts when binding to its receptor. Figure 1 illustrates such conformations for the cyclopropyl and cyclobutyl amino-acids (2b) and (2d) respectively. For the cyclohexyl amino-acids, whilst the *cis*-isomer (2e) cannot mimic the conformation (I) of GABA depicted in Figure 1, the *trans*-isomer (2f) in the unfavourable conformation with

† Abstracted from the Ph.D. thesis presented by S. S. Matharu, 1980, to the City University, London.



(I) (II) (III)

FIGURE 1 Dreiding stereomodel drawings of the ' active conformation ' of GABA (I) as proposed by Nicholson *et al.*[2] and the simulated conformations of *trans*-amino-acids (2b) (II) and (2d) (III). In both (II) and (III) the nitrogen, the methylene carbon, and the C(2) and C(1) atoms of the carbocyclic ring lie in a plane with the carboxylate carbon atom out of this plane

1,2-diaxial substituents (Figure 2) almost perfectly adopts such a conformation.

Unlike the *trans*-isomers, the *cis*-amino-acids (2a) and (2c) are unable to assume the GABA conformation (I) in Figure 1 and on this basis may be predicted to be devoid of GABA-mimetic activity.

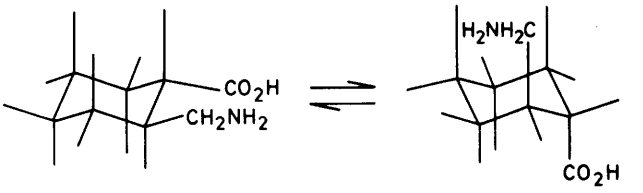
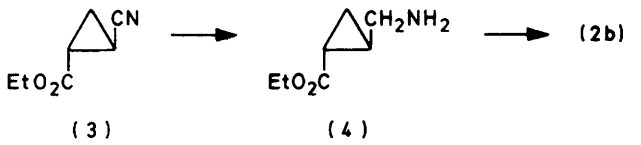


FIGURE 2 The interconvertible forms of the amino-acid (2f)

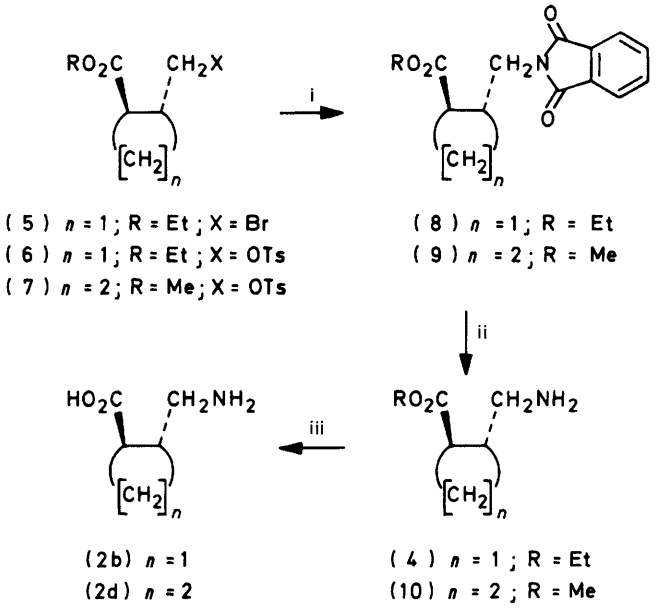
## RESULTS AND DISCUSSION

The synthesis of the *trans*-cyclopropyl amino-acid (2b) has previously been described [3] and involves reduction of the *trans*-cyano-ester (3) by high-pressure hydrogenation at elevated temperatures over Raney nickel followed by base hydrolysis of the *trans*-amino-ester (4). More recently Allan *et al.*[4] reported the synthesis of both the *trans*- and *cis*-amino-acids (2b) and (2a) by essentially the same route. A similar approach was adopted by Inoue and Sato [5] for the preparation of the esters of the *trans*-cyclobutylamino-acid (2d). In the present study




(3) (4)

both the *trans*-cyclopropyl amino-acid (2b) and its homologue (2d) were prepared by the Gabriel synthesis outlined in Scheme 1. Thus treatment of the bromide (5) [1] or the tosylate (6) [1] with potassium phthalimide afforded the *trans*-ester (8) whilst the cyclobutyl analogue (9) was obtained from the *trans*-tosylate (7) [1] by an identical method. Dephthaloylation of (8) in ethanolic methylamine solution [6] yielded the *trans*-amino-ester (4)




(5) $n$ = 1; R = Et; X = Br
(6) $n$ = 1; R = Et; X = OTs
(7) $n$ = 2; R = Me; X = OTs

(8) $n$ = 1; R = Et
(9) $n$ = 2; R = Me

(2b) $n$ = 1
(2d) $n$ = 2

(4) $n$ = 1; R = Et
(10) $n$ = 2; R = Me

Ts = *p*-$MeC_6H_4SO_2$

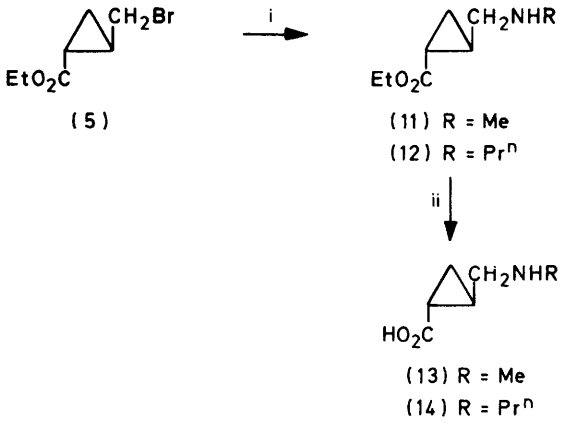
SCHEME 1 i, potassium phthalimide–dimethylformamide (DMF); ii, $MeNH_2$–EtOH; iii, NaOH–aq. EtOH

which could be purified by distillation at low pressure. Hydrolysis of (4) and isolation by ion-exchange chromatography afforded the *trans*-amino-acid (2b) as the monohydrate.

For the cyclobutane series, although t.l.c. evidence indicated that the dephthaloylation of (9) proceeded satisfactorily, all attempts to isolate the amino-ester (10) resulted in polymeric viscous oils. The polymerisation of esters of 2-(aminomethyl)cyclobutanecarboxylic acid has previously been reported.[7] The *trans*-amino-acid (2d) [8] could however be obtained by treatment of the phthalimide (9) with ethanolic methylamine solution followed by hydrolysis of the crude reaction mixture and isolation by ion-exchange chromatography.

In terms of biological activity the *trans*-amino-acid (2b) proved to be potent in GABA receptor binding studies. This finding prompted us to investigate the effect of an *N*-alkyl substituent in (2b) on biological activity. Scheme 2 outlines the synthesis of two such derivatives of (2b). The bromide (5),[1] when treated with methylamine and propylamine, yielded the *trans*-amino-esters (11) and (12) respectively, base hydrolysis of which afforded the *trans*-amino-acids (13) and (14).

The synthesis of the *cis*-cyclopropyl amino-acid (2a)



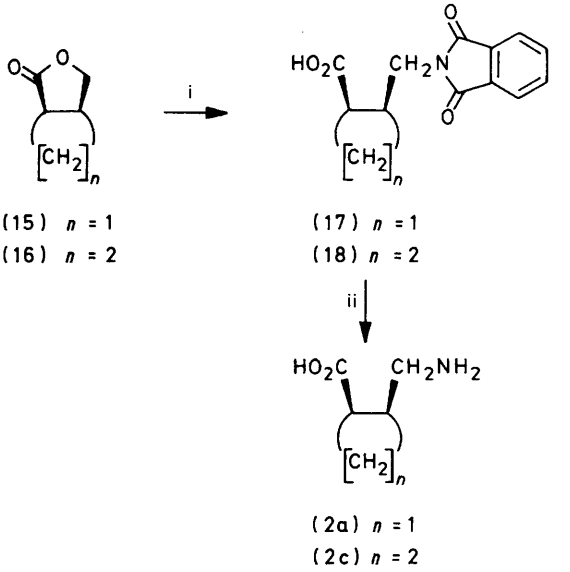

(5)

(11) R = Me
(12) R = $Pr^n$

(13) R = Me
(14) R = $Pr^n$

SCHEME 2 i, $RNH_2$–PhMe or EtOH; ii, NaOH–aq. EtOH

and its homologue (2c) is outlined in Scheme 3 and involved the reaction of lactones (15) [9,10] and (16) [9,11] with potassium phthalimide to give the *cis*-acids (17) and (18) respectively. Such lactone ring opening by the phthalimide anion has previously been reported [12] for a phenyl substituted cyclopropane derivative. Dephthaloylation




(15) $n$ = 1
(16) $n$ = 2

(17) $n$ = 1
(18) $n$ = 2

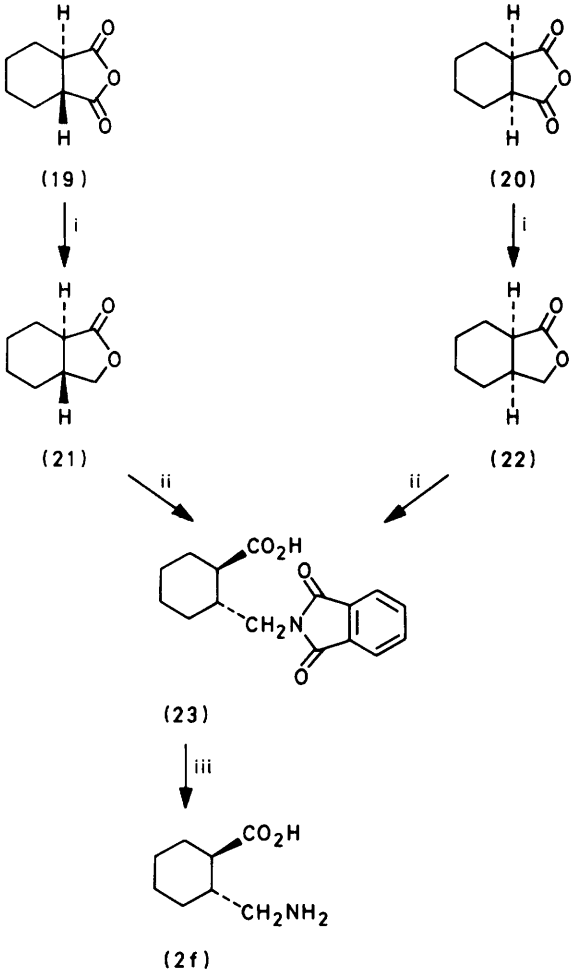
(2a) $n$ = 1
(2c) $n$ = 2

SCHEME 3 i, potassium phthalimide–DMF; ii, $MeNH_2$–EtOH

of the phthalimides (17) and (18) was accomplished in ethanolic methylamine solution [6] and the *cis*-amino-acids (2a) and (2c) were obtained as crystalline solids.

The ease of lactone ring cleavage in (15) and (16) on treatment with potassium phthalimide prompted us to synthesise the cyclohexyl derivatives (2e) and (2f) by analogous routes. Thus the *trans*- and *cis*-anhydrides (19) and (20) (Scheme 4) were reduced to the corresponding lactones (21) and (22) according to the method of Bailey and Johnson.[13] Treatment of the *trans*-lactone

(21) with potassium phthalimide in DMF at 140—150 °C yielded the *trans*-cyclohexyl acid (23), dephthaloylation of which by the usual method afforded the *trans*-amino-acid (2f). However, when the *cis*-lactone (22) was treated with potassium phthalimide under identical conditions, the product after purification was




SCHEME 4 i, $NaBH_4$–(tetrahydrofuran) THF; ii, potassium phthalimide–DMF; iii, $MeNH_2$–EtOH

found to be identical to the *trans*-isomer (23) (m.p., t.l.c., and i.r., $^1H$ n.m.r. and mass spectra). Furthermore, dephthaloylation of this product gave an amino-acid identical to the *trans*-amino-acid (2f). This type of base-induced isomerisation *via* an enolate intermediate has previously been reported [14] for other cyclohexanecarboxylic acids.

A further extension to the preparation of the 2-(aminomethyl)cyclobutanecarboxylic acids was the synthesis of the 2-aminocyclobutanecarboxylic acids which lack the ' GABA structure element '. Scheme 5 outlines the synthetic route to (24) and (25). The *N*-cyclobutylcarbamates (26) and (27) were prepared by a lead tetra-acetate-induced rearrangement of the *cis*- and *trans*-amido-esters (28) and (29) respectively according to the method of Cannon *et al.*[15] Concomitant base hydrolysis of the ester groups followed by decarboxylation by acid treatment yielded the amino-acids (24) and (25) after isolation by ion-exchange chromatography. Hydrolysis of the amides (28) and (29) with sodium hydroxide (1 mol equiv.) in aqueous ethanol furnished the previously unknown water-soluble amido-acids (30) and (31) respectively, both isolated by regeneration from the corresponding sodium salts by treatment with ion-exchange resin.

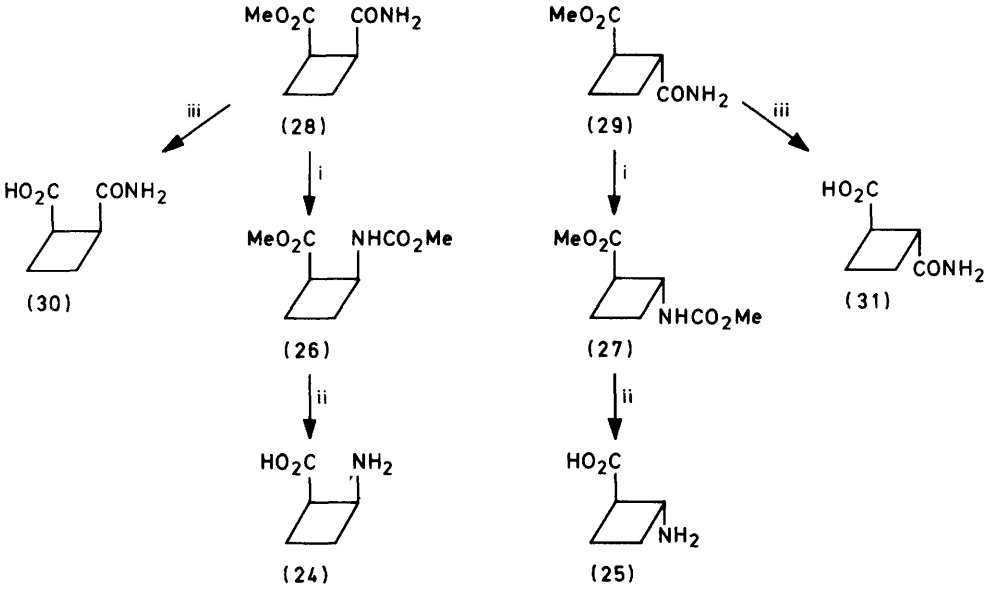
A similar sequence of reactions was followed in the *trans*-cyclopropane series (Scheme 6). Thus the *trans*-*N*-cyclopropyl-carbamate (32) [9] was treated with aqueous base in an attempt to prepare the amino-acid (33). Only a complex mixture of products resulted. This probably highlights the difference in the behaviour of the cyclopropane and cyclobutane systems and the ease with which ring-opening of activated cyclopropanes [16] can occur. Hydrolysis of the *trans*-amido-ester (34) afforded the previously unknown water-soluble *trans*-amido-acid (35).

As was the case with the 2-aminocycloalkylacetic acids,[1] the stereochemical assignments of the amino-acids (2a—d, 2f) were based on their stereoselective syntheses. Further proof of structural assignment of these compounds was provided by mass spectroscopy. Again, the ($M$ — 18) fragment was relatively abundant in the spectra of the *cis*-amino-acids (2a) and (2c) and also in the *trans*-amino-acid (2f), consistent with loss of water and formation of a bicyclic lactam. This ion was not significant in the mass spectra of the *trans*-amino-acids (2b) and (2d) in which lactam formation is not expected.

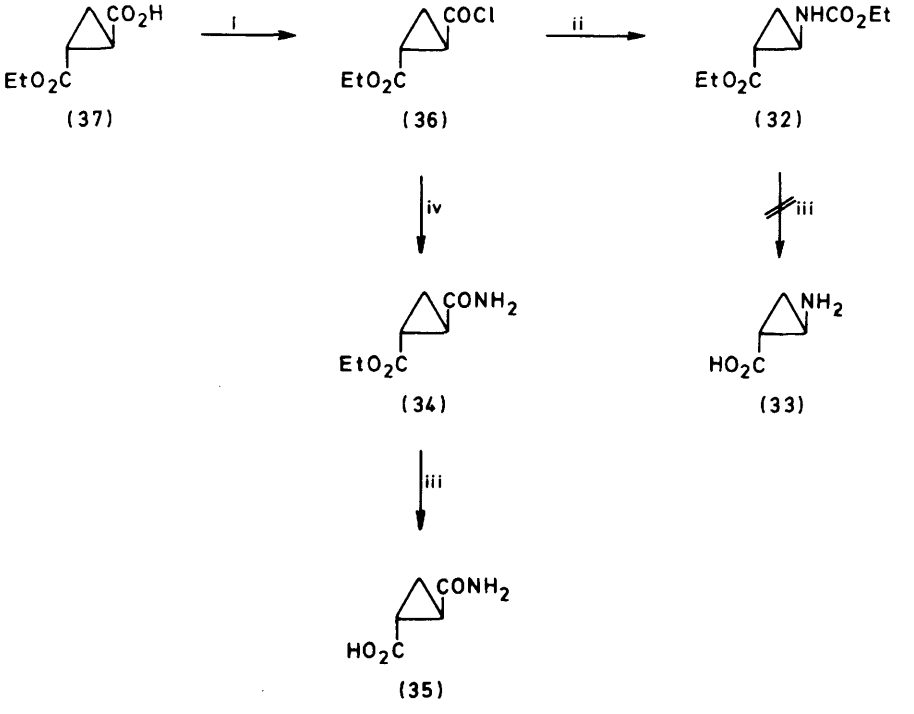
The proposed initial mass spectral fragmentation pathways for the amino-acids (2a) and (2b) and for the amino-acids (2c) and (2d) are shown in Figures 3 and 4, respectively. To confirm that the peak at $m/z$ 111 found in the spectrum of (2c) arises from the bicyclic lactam (38), this compound was prepared by thermolysis of the parent amino-acid (2c). Mass spectrometric analysis of (38) showed, as expected, a base peak at $m/z$ 111 corresponding to the molecular ion and a fragmentation pattern similar to that of (2c).

The mass spectrum of the *trans*-cyclohexyl amino-acid (2f) also showed an abundant $[M - H_2O]^{\cdot+}$ fragment at $m/z$ 139 consistent with bicyclic lactam formation. Furthermore, the more abundant ions, *e.g.* at $m/z$ 139, 84, 67, and 30, in the spectrum of (39), prepared by thermolysis of (2f) were also observed in the spectrum of the latter, thus reaffirming the belief that the $m/z$ 139 peak was due to an ion of (37).

In receptor binding studies, in accordance with expectation, only the *trans*-cyclopropane and -cyclobutane derivatives showed any significant biological activity. The amino-acid (2b) which represents the best ' fit ' to the ' active conformation ' of GABA [(I) in Figure 1] was found to be a potent inhibitor of [$^3H$]-muscimol binding in rat brain membranes ($IC_{50}$ 0.4 μM) while the cyclobutyl analogue (2d) was only weakly potent ($IC_{50}$ 25 μM). The details of these studies will be




SCHEME 5 i, $Pb(OAc)_4$–MeOH–PhMe; ii, (a) NaOH–aq. EtOH, (b) $H^+$; iii, NaOH–aq. EtOH




SCHEME 6 i, $SOCl_2$; ii, (a) $NaN_3$–$Me_2CO$–$H_2O$, (b) heat, (c) EtOH; iii, NaOH–aq. EtOH; iv, $NH_3$–PhMe

reported elsewhere.[17] For the cyclohexyl amino-acid (2f), the unfavourable 1,2-diaxial arrangement of substituents necessary to simulate conformation (I) in Figure 1 may be the over-riding factor for its inactivity. The amino-acids (13), (14), (24), and (25) and the amido-acids (30), (31), and (35) were inactive in the [$^3$H]muscimol binding assay. This finding further highlights the rigid structural requirement for interaction with GABA receptors in that any deviation from the ' GABA structure element ' leads to loss of activity.

All the amino-acids in the present study were found to be inactive ($IC_{50} > 100$ μM) as inhibitors of [$^3$H]GABA uptake.

## EXPERIMENTAL

General experimental conditions were the same as outlined in Part 1.[1]

*Ethyl* trans-2-(*Phthalimidomethyl*)*cyclopropanecarboxylate* (8).—A stirred mixture of the *trans*-bromomethyl compound (5) [1] (5.18 g, 25 mmol) and potassium phthalimide (4.63 g,

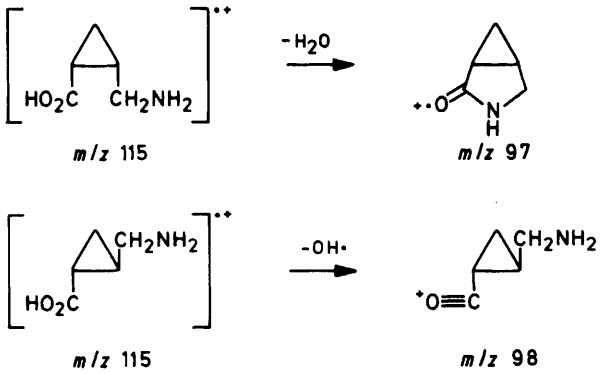



FIGURE 3 The proposed mass spectral breakdown pathways for amino-acids (2a) and (2b)

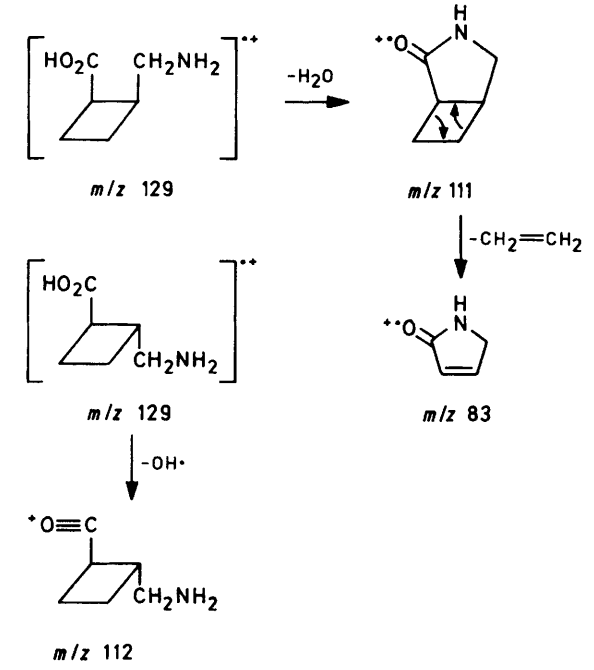
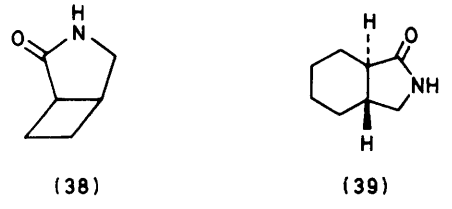



FIGURE 4 The proposed mass spectral fragmentation pathways for the amino-acids (2c) and (2d)




25 mmol) in dimethylformamide (DMF) (25 ml) was heated at 140—150 °C under an atmosphere of dry nitrogen for 1 h and then the cooled mixture poured on to ice (100 g). The precipitated solid was filtered off, washed thoroughly with water, and then dissolved in chloroform (100 ml). The chloroform solution was washed with 5% aqueous potassium hydroxide (50 ml) followed by water (50 ml), dried, and evaporated. The residual oil crystallised on trituration with cold light petroleum. The crystals of the trans-*phthalimide* (8) (3.0 g, 44%) were washed with light petroleum and dried, m.p. 76—78 °C (from light petroleum) Found: C, 65.9; H, 5.55; N, 5.1. $C_{15}H_{15}NO_4$ requires C, 65.95; H, 5.55; N, 5.15%); $\nu_{max.}$ (KBr) 2 980, 1 770, 1 720, 1 700, 1 400, 1 180, 1 065, and 715 $cm^{-1}$; $\tau(CDCl_3)$ 2.00—2.42 (4 H, m, ArH), 5.92 (2 H, q, *J* 7 Hz, $CH_2CH_3$), 6.39 (2 H, d, *J* 7 Hz, $CH_2N$), 8.02—8.50 (2 H, m, cyclopropyl-CHCH), 8.53—9.30 (2 H, m, cyclopropyl-$CH_2$), and 8.80 (3 H, t, *J* 7 Hz, $CH_2CH_3$); *m/z* 273 ($M^+$, 49%), 199 (68), 160 (100), 125 (74) ,and 113 (62).

*Ethyl* trans-2-(*Aminomethyl*)*cyclopropanecarboxylate* (4).—The ester (4) was prepared by the action of 33% (w/w) ethanolic methylamine solution on compound (8) and obtained as a liquid, b.p. 58—60 °C at 0.7 mmHg (lit.,[3] 87 °C at 5 mmHg); *hydrochloride*, m.p. 141—143 °C (Found: C, 46.45; H, 7.7; Cl, 19.75; N, 7.8. $C_7H_{14}ClNO_2$ requires C, 46.8; H, 7.85; Cl, 19.75; N, 7.8%); $\nu_{max.}$ (KBr) 3 320—2 340br, 1 725, 1 575, 1 380, 1 210, 1 175, and 940 $cm^{-1}$; $\tau(D_2O)$ 5.83 (2 H, q, *J* 7 Hz, $CH_2CH_3$), 7.01 (2 H, d, *J* 7 Hz, $CH_2N$), 7.65—9.42 (4 H, m, cyclopropyl), and 8.75 (3 H, t, *J* 7 Hz, $CH_2CH_3$).

trans-2-(*Aminomethyl*)*cyclopropanecarboxylic Acid* (2b).—A mixture of the *trans*-amino-ester (4) (0.72 g, 5 mmol), ethanol (10 ml), and 1M-sodium hydroxide (5 ml, 5 mmol) was heated on a water-bath for 30 min and then the cooled solution evaporated to dryness. The residue was dissolved in water (5 ml) and deposited on an ion-exchange column (20 g resin). Elution with 1M-ammonium hydroxide and evaporation of the appropriate fractions gave the *trans*-amino-acid (2b) (0.51 g, 89%) as a crystalline monohydrate, m.p. 262—266 °C (decomp.) [lit.,[4] 270—275 °C (decomp.)] (from ethanol–water) (Found: C, 45.1; H, 8.35; N, 10.5. Calc. for $C_5H_9NO_2{\cdot}H_2O$; C, 45.1; H, 8.35; N, 10.5%); $\nu_{max.}$ (KBr) 3 320—2 300br, 2 140, 1 660, 1 560, 1 440, 1 395, 1 275, and 920 $cm^{-1}$; $\tau(D_2O)$ 6.90—7.15 (2 H, m, $CH_2N$) and 8.20—9.35 (4 H, m, cyclopropyl); *m/z* 115 ($M^+$, 1%), 98 (82), 43 (100), 42 (40), 30 (74), and 28 (41); $R_F$: I, 0.14; II, 0.39.

*Ethyl* trans-2-(*Methylaminomethyl*)*cyclopropanecarboxylate* (11).—A solution of the *trans*-bromomethyl compound (5) (2.48 g, 12 mmol) in ethanolic methylamine [5 ml; 33% (w/w)] was stirred at room temperature for 16 h and then evaporated to dryness. Water (20 ml) was added to the residue and the mixture extracted with chloroform (4 × 100 ml). The organic extract was dried and evaporated. Distillation of the residue under reduced pressure yielded the *ester* (11) (1.27 g, 67%) as a liquid, b.p. 46—47 °C at 0.2 mmHg; $\nu_{max.}$ (film) 2 970, 2 920, 1 725, 1 370, 1 180, and 1 040 $cm^{-1}$; $\tau(CDCl_3)$ 5.89 (2 H, q, *J* 7 Hz, $CH_2CH_3$), 7.49 (2 H, d, *J* 7 Hz, $CH_2N$), 7.58 (3 H, s, $NCH_3$), 8.52 (1 H, s, NH), 8.76 (3 H, t, *J* 7 Hz, $CH_2CH_3$), and 8.00—9.45 (4 H, m, cyclopropyl); *m/z* 157 ($M^+$, 12%), 127 (17), 102 (14), 57 (37), 44 (100), and 28 (18).

trans-2-(*Methylaminomethyl*)*cyclopropanecarboxylic Acid* (13).—The *trans*-amino-ester (11) (0.785 g, 5 mmol) was hydrolysed in a similar manner to the *trans*-amino-ester (4) using ethanol (10 ml) and 1M-sodium hydroxide (5.5 ml). Work-up on an ion-exchange column (15 g resin) gave the *amino-acid* (13) (0.47 g, 73%) as a crystalline solid, m.p. 211—213 °C (decomp.) (from EtOH) (Found: C, 55.85; H, 8.55; N, 10.8. $C_6H_{11}NO_2$ requires C, 55.8; H, 8.6; N, 10.85%); $\nu_{max.}$ (KBr) 3 650—2 320br, 1 650, 1 570, 1 390, 1 430, 1 270, and 1 055 $cm^{-1}$; $\tau(D_2O)$ 7.03 (2 H, d, *J* 7 Hz, $CH_2N$), 7.30 (3 H, s, $CH_3$), and 8.20—9.32 (4 H, m, cyclopropyl); *m/z* 129 ($M^+$, 19%), 57 (56), 44 (100), 42 (44), and 30 (28).

*Ethyl* trans-2-(*Propylaminomethyl*)*cyclopropanecarboxylate* (12).—A mixture of the *trans*-bromomethyl compound

(5) (2.48 g, 12 mmol) and n-propylamine (1.60 g, 27 mmol) in dry toluene (10 ml) was refluxed for 8 h and then the cooled solution poured on to water (20 ml). The organic layer was separated off and the aqueous layer washed once with ether (20 ml); the combined organic extract was dried and evaporated. Distillation of the residue under reduced pressure yielded the *ester* (12) (1.57 g, 71%) as a liquid, b.p. 62—63 °C at 0.1 mmHg; $\nu_{max.}$ (film) 2 960, 2 870, 2800, 1 730, 1 415, 1 270, and 1 180 $cm^{-1}$; $\tau(CDCl_3)$ 5.89 (2 H, q, *J* 7 Hz, $CH_2CH_3$), 7.40 (2 H, t, *J* 7 Hz, $NCH_2CH_2$), 7.42 (2 H, d, *J* 7 Hz, $CH_2N$), 7.96 (1 H, s, NH), 8.76 (3 H, t, *J* 7 Hz, $CH_2CH_3$), and 8.05—9.45 (9 H, m, $NCH_2CH_2CH_3$ and cyclopropyl); *m/z* 185 ($M^+$, 15%), 156 (100), 110 (67), 43 (55), 30 (55), and 29 (42); *hydrochloride*, m.p.186—188 °C (Found: C, 53.9; H, 8.95; Cl, 16.05; N, 6.3. $C_{10}H_{20}ClNO_2$ requires C, 54.15; H, 9.1; Cl, 16.0; N, 6.3%); $\nu_{max.}$ (KBr) 3 300—2 360br, 3 020, 2 980, 1 730, 1 470, 1 180, and 1 015 $cm^{-1}$.

trans-2-(*Propylaminomethyl*)*cyclopropanecarboxylic Acid* (14).—This amino-acid was prepared in a manner similar to the preparation of the *trans*-amino-acid (2b) using the *trans*-amino-ester (12) (1.3 g, 7 mmol), ethanol (15 ml), and 1M-sodium hydroxide (7.7 ml, 7.7 mmol). Work-up on an ion-exchange column (15 g resin) and evaporation of the appropriate fractions gave the *amino-acid* (14) (0.95 g, 86%) as almost colourless crystals, m.p. 195—197 °C (decomp.) (from EtOH–$Et_2O$) (Found: C, 60.8; H, 9.5; N, 8.75. $C_8H_{15}NO_2$ requires C, 61.1; H, 9.6; N, 8.9%); $\nu_{max.}$ (KBr) 3 700—2 360br, 1 640, 1 570, 1 425, 1 285, and 680 $cm^{-1}$; $\tau(D_2O)$ 6.80—7.15 (4 H, m, $CH_2NHCH_2$) and 8.05—9.40 (9 H, m, $NCH_2CH_2CH_3$ and cyclopropyl); *m/z* 157 ($M^+$, 12%), 128 (100), 110 (52), 81 (28), 43 (26), and 30 (65).

cis-2-(*Phthalimidomethyl*)*cyclopropanecarboxylic Acid* (17).—A mixture of the cyclopropyl lactone (15) [1] (0.735 g, 7.5 mmol) and potassium phthalimide (1.39 g, 7.5 mmol) in DMF (10 ml) was heated at 140—150 °C for 3.5 h under an atmosphere of dry nitrogen. The cooled mixture was poured on to ice–water (50 ml) and the white solid that separated was filtered off. The filtrate was acidified to pH 3—4 by a dropwise addition of glacial acetic acid and the precipitated white solid filtered off and dried. Recrystallisation gave the pure *acid* (17) (0.55 g, 30%) as almost colourless crystals, m.p. 188—189 °C (from EtOAc) (Found: C, 63.55; H, 4.55; N, 5.7. $C_{13}H_{11}NO_4$ requires C, 63.65; H, 4.5; N, 5.7%); $\nu_{max.}$ (KBr) 3 320—2 330br, 1 770, 1 720, 1 710, 1 690, 1 387, 1 235, 1 050, and 715 $cm^{-1}$; $\tau(CDCl_3)$ 2.00—2.45 (4 H, m, ArH), 6.04 (2 H, d, *J* 6 Hz, $CH_2N$), 6.65 (1 H, s, $CO_2H$), and 7.95—9.18 (4 H, m, cyclopropyl); *m/z* 245 ($M^+$, 0.5%), 199 (27), 173 (100), 160 (61), 104 (58), and 76 (46).

cis-2-(*Aminomethyl*)*cyclopropanecarboxylic Acid* (2a).—A solution of the *cis*-phthalimido-acid (17) (0.5 g) in ethanolic methylamine [10 ml; 33% (w/w)] was stirred at room temperature for 16 h and then the mixture evaporated to dryness. Water (5 ml) was added to the residue and the undissolved *N*,*N*-dimethylphthalamide filtered off. The filtrate was deposited on an ion-exchange column (15 g resin) and eluted with water followed by 1M-ammonium hydroxide. Evaporation of the appropriate fractions gave the *cis*-amino-acid (2a) (0.1 g, 43%) as almost colourless crystals, m.p. 217—218 °C (lit.,[4] 225—226 °C) (from MeOH) (Found: C, 52.1; H, 7.9; N, 12.25. Calc. for $C_5H_9NO_2$: C, 52.15; H, 7.9; N, 12.15%); $\nu_{max.}$ (KBr) 3 350—2 250br, 2 160, 1 660, 1 570, 1 410, 1 290, 800, and 650 $cm^{-1}$; $\tau(D_2O)$ 6.78 (2 H, d, *J* 7 Hz, $CH_2N$) and 8.00—9.30 (4 H, m, cyclopropyl); *m/z* (15 eV) 115 ($M^+$, 0.7%), 97 [($M$ − $H_2O$), 40], 69 (15), 56 (14), 43 (100), and 30 (14); $R_F$: I, 0.17; II, 0.46.

*Methyl* trans-2-(*Phthalimidomethyl*)*cyclobutanecarboxylate* (9).—The *trans*-cyclobutyl tosylate (7) [1] (10.43 g, 35 mmol) was treated with potassium phthalimide (7.03 g, 38 mmol) in DMF (60 ml) in a manner similar to that for the *trans*-cyclopropyl derivative (5). On pouring the cooled reaction mixture on to ice (200 g), an oil separated. This was extracted with chloroform (2 × 150 ml), and the organic extract washed with 5% aqueous potassium hydroxide (100 ml) then water (100 ml), dried, and finally evaporated. The trans-*phthalimide* (9) (6.3 g, 66%) was thus obtained as a light yellow viscous liquid (Found: C, 66.0; H, 5.65; N, 5.15. $C_{15}H_{15}NO_4$ requires C, 65.95; H, 5.55; N, 5.15%); $\nu_{max.}$ (film) 2 960, 1 780, 1 735, 1 725, 1 440, 1 400, 1 250, 1 050, and 720 $cm^{-1}$; $\tau(CDCl_3)$ 2.00—2.43 (4 H, m, ArH), 6.10—6.45 (2 H, m, $CH_2N$), 6.69 (3 H, s, $CH_3$), 6.75—7.45 (2 H, m, cyclobutyl-CHCH), and 7.60—8.50 (4 H, m, cyclobutyl-$CH_2CH_2$); *m/z* 273 ($M^+$, 15%), 213 (71), 187 (37), 160 (100), 126 (34), and 67 (33).

trans-2-(*Aminomethyl*)*cyclobutanecarboxylic Acid* (2d).—The *trans*-phthalimido-ester (9) (4.1 g, 15 mmol) was dissolved in 33% (w/w) ethanolic methylamine (40 ml) and the solution stirred at room temperature for 16 h. The precipitated white solid was filtered off and 1M-sodium hydroxide (80 ml, 80 mmol) added to the filtrate which was then heated to reflux for 4 h. The cooled mixture was evaporated and the residue dissolved in water (10 ml) and deposited on an ion-exchange column (30 g resin). Elution with 1M-ammonium hydroxide and evaporation of the appropriate fractions yielded the trans-*amino-acid* (2d) (0.9 g, 47%) as almost colourless crystals, m.p. 214—216 °C (decomp.) (from EtOH) (Found: C, 55.9; H, 8.5; N, 10.8. $C_6H_{11}NO_2$ requires C, 55.8; H, 8.6; N, 10.85%); $\nu_{max.}$ (KBr) 3 320—2 360br, 2 140, 1 670, 1 640, 1 585, 1 545, 1 410, 1 300, 810, and 660 $cm^{-1}$; $\tau(D_2O)$ 6.70—7.00 (2H, m, $CH_2N$), 6.95—7.65 (2 H, m, cyclobutyl-CHCH), and 7.65—8.58 (4 H, m, cyclobutyl-$CH_2CH_2$); *m/z* 129 ($M^+$, 0.3%), 111 (0.7), 57 (40), 56 (69), 39 (13), 30 (100), and 29 (22); $R_F$: I, 0.24; II, 0.51.

cis-2-(*Phthalimidomethyl*)*cyclobutanecarboxylic Acid* (18).—A mixture of the cyclobutyl lactone (16) [1] (4.48 g, 40 mmol) and potassium phthalimide (7.40 g, 40 mmol) in DMF (40 ml) was heated at 140—150 °C for 3.5 h. The cooled mixture was poured on to ice–water (400 ml) and the solution acidified to pH 4—5 by a dropwise addition of glacial acetic acid. The precipitated solid was filtered off, washed well with water, dried, and recrystallised to give the cis-*phthalimido-acid* (18) (5.8 g, 56%), m.p. 155—157 °C (from EtOAc) (Found: C, 64.9; H, 5.1; N, 5.4. $C_{14}H_{13}NO_4$ requires C, 64.85; H, 5.05; N, 5.4%); $\nu_{max.}$ (KBr) 3 360—2 350br, 1 770, 1 720, 1 695, 1 465, 1 400, 1 305, 1 260, 1 040, and 710 $cm^{-1}$; $\tau(CDCl_3)$ 0.10—0.47br (1 H, s, $CO_2H$), 2.00—2.44 (4 H, m, ArH), 6.08 (2 H, d, *J* 7 Hz, $CH_2N$), 6.41—7.11 (2 H, m, cyclobutyl-CHCH), and 7.39—8.19 (4 H, m, cyclobutyl-$CH_2CH_2$); *m/z* 259 ($M^+$, 2%), 187 (100), 169 (50), 160 (80), 85 (53), and 83 (96).

cis-2-(*Aminomethyl*)*cyclobutanecarboxylic Acid* (2c).—The *cis*-phthalimido-acid (18) (5.2 g, 20 mmol) was treated with ethanolic methylamine solution [70 ml; 33% (w/w)] in a similar manner to the cyclopropyl derivative (17). Work-up on an ion-exchange column (70 g resin) using 1M-ammonium hydroxide as the eluant gave the cis-*amino-acid* (2c) (1.73 g, 67%) as almost colourless crystals, m.p. 207—209 °C [from EtOH–water (19 : 1)] (Found: C, 55.8; H, 8.55; N,

10.85. $C_6H_{11}NO_2$ requires C, 55.8; H, 8.6; N, 10.85%); $\nu_{max.}$ (KBr) 3 320—2 360br, 2 170, 1 660, 1 630, 1 530, 1 405, 1 020, 920, 810, 790, and 695 $cm^{-1}$; $\tau(D_2O)$ 6.40—7.50 (4 H, m, $CH_2N$ and cyclobutyl-CHCH) and 7.50—8.60 (4 H, m, cyclobutyl-$CH_2CH_2$); *m/z* (15 eV) 129 ($M^+$, 0.4%), 111 [($M$ − $H_2O$), 22], 100 (8), 57 (75), 56 (88), and 30 (100); $R_F$: I, 0.18; II, 0.40.

cis-3-*Azabicyclo*[3.2.0]*heptan*-2-*one* (38).—The *cis*-amino-acid (2c) (0.15 g) was heated in an oil-bath at 220 °C for 15 min. The cooled product was dissolved in chloroform (5 ml), and the solution washed once with water (5 ml), dried, and evaporated. The bicyclic lactam (38) (0.1 g, 78%) was thus obtained as an almost colourless oil, $\nu_{max.}$ (film) 3 260, 2 980, 2 940, 1 700, 1 490, 1 505, and 750 $cm^{-1}$; $\tau(CDCl_3)$ 2.90—4.01br (1 H, s, NH), and 6.25—8.35 (8 H, m, $CH_2N$ and cyclobutyl); *m/z* 111 ($M^+$, 100%), 83 (24), 67 (50), 55 (50), and 30 (30).

trans-8-*Oxabicyclo*[4.3.0]*nonan*-7-*one* (21).—A solution of the *trans*-anhydride (19) (30.8 g, 0.2 mol) in freshly distilled THF (200 ml) was added dropwise to a stirred suspension of sodium borohydride (7.6 g, 0.2 mol) in dry THF (40 ml) The mixture was stirred at room temperature for 48 h, then decomposed with 5M-hydrochloric acid (80 ml) and concentrated under reduced pressure. The residue was diluted with water and the product extracted with ether (3 × 150 ml). The organic extract was washed once with water, dried, and evaporated. The residue was taken up in ether (50 ml) and any undissolved solid material filtered off. Evaporation of the filtrate and distillation of the residue under reduced pressure yielded the trans-*lactone* (21) (12.9 g, 46%) as a liquid, b.p. 86—87 °C at 0.9 mmHg (Found: C, 68.3; H, 8.6. $C_8H_{12}O_2$ requires C, 68.55; H, 8.65%); $\nu_{max.}$ (film) 2 940, 2 860, 1 785, 1 450, 1 375, 1 180, 1 100, and 992 $cm^{-1}$; $\tau(CDCl_3)$ 5.45—5.85 (1 H, m, $OCH_aH_b$), 5.88—6.42 (1 H, m, $OCH_aH_b$), and 7.32—9.22 (10 H, m, cyclohexyl); *m/z* 140 ($M^+$, 0.6%), 67 (100), 66 (48), 54 (48), 39 (43), and 41 (23).

cis-8-*Oxabicyclo*[4.3.0]*nonan*-7-*one* (22).—This compound was prepared by the reduction of the *cis*-anhydride (20) and obtained as a colourless liquid, b.p. 80—82 °C at 0.7 mmHg (lit.,[13] 123—125 °C at 13 mmHg).

trans-2-(*Phthalimidomethyl*)*cyclohexanecarboxylic Acid* (23).—This compound was prepared in a similar manner to the cyclobutyl derivative (18) using the *trans*-cyclohexyl lactone (21) (5.25 g, 37.5 mmol), potassium phthalimide (6.94 g, 37.5 mmol), and DMF (40 ml) except that the reaction took 5 h to reach completion. The crude product on recrystallisation gave the pure trans-*acid* (23) (4.90 g, 46%) as almost colourless crystals, m.p. 164—165 °C (from $Et_2O$) (Found: C, 66.95; H, 6.0; N, 4.85. $C_{16}H_{17}NO_4$ requires C, 66.9; H, 5.95; N, 4.85%); $\nu_{max.}$ (KBr) 2 940, 1 780, 1 720, 1 700, 1 405, 1 360, 1 195, 945, 870, and 720 $cm^{-1}$; $\tau(CDCl_3)$ 2.02—2.50 (4 H, m, ArH), 4.03—4.42br (1 H, s, $CO_2H$), 6.21 (2 H, d, *J* 7 Hz, $CH_2N$), and 7.12—9.00 (10 H, m, cyclohexyl); *m/z* 287 ($M^+$, 6%), 269 (24), 241 (35), 160 (100), 148 (26), and 94 (26).

Similar treatment of the *cis*-lactone (22) (5.25 g, 37.5 mmol) with potassium phthalimide (6.94 g, 37.5 mmol) in DMF (40 ml) yielded almost colourless crystals (5.13 g, 48%) (from ether), identical by m.p., mixed m.p., t.l.c. and i.r., $^1H$ n.m.r., and mass spectra to the *trans*-acid (23).

trans-2-(*Aminomethyl*)*cyclohexanecarboxylic Acid* (2f).—A solution of the *trans*-phthalimido-acid (23) (4.31 g, 15 mmol) in ethanolic methylamine solution [60 ml; 33% (w/w)] was stirred at room temperature for 72 h, and the white precipitate was filtered off. The filtrate was evaporated and the residue, dissolved in water (20 ml), deposited on an ion-exchange column (50 g resin). Elution with water followed by 1M-ammonium hydroxide and evaporation of the appropriate fractions gave the *amino-acid* (2f) (0.9 g, 38%) as a crystalline solid, m.p. 190—193 °C (from EtOH–$H_2O$) (Found: C, 61.05; H, 9.7; N, 8.85. $C_8H_{15}NO_2$ requires C, 61.1; H, 9.6; N, 8.9%); $\nu_{max.}$ (KBr) 3 350—2 360br, 2 200, 1 655, 1 625, 1 560, 1 405, 1 275, 930, 805, and 685 $cm^{-1}$; $\tau(D_2O)$ 6.96 (2 H, d, *J* 7 Hz, $CH_2N$) and 7.20—8.90 (10 H, m, cyclohexyl); *m/z* 157 ($M^+$, 4%), 139 [($M$ − $H_2O$), 7], 84 (5), 67 (6), 56 (8), and 30 (100); $R_F$: I, 0.27; II, 0.79.

trans-8-*Azabicyclo*[4.3.0]*nonan*-7-*one* (39).—The *trans*-amino-acid (2f) (0.1 g) was heated in an oil-bath at 200 °C for 15 min. On cooling, the product solidified and was triturated with light petroleum, filtered, and dried, thus yielding the bicyclic lactam (39) (0.06 g, 68%) as a solid, m.p. 95—97 °C, $\nu_{max.}$ (KBr) 3 220, 2 930, 2 840, 1 690, 1 480, 1 260, 1 057, and 700 $cm^{-1}$; *m/z* 139 ($M^+$, 90%), 84 (89), 67 (79), 54 (22), and 30 (100).

cis-2-*Aminocyclobutanecarboxylic Acid* (24).—To a solution of the carbamate (26) [15] (4.68 g, 25 mmol) in ethanol (35 ml) was added a solution of sodium hydroxide (4.0 g, 0.1 mol) in water (35 ml) and the mixture heated to reflux for 3 h. The cooled mixture was evaporated and the solid residue dissolved in water (20 ml). The solution was acidified to pH 3 with concentrated hydrochloric acid and then deposited on an ion-exchange column (50 g resin). The usual elution with 1M-ammonium hydroxide and evaporation of the appropriate fractions yielded the cis-*amino-acid* (24) (1.6 g, 56%) as a crystalline solid that was triturated with cold ethanol, filtered, and dried, m.p. 129—132 °C (decomp.) (Found: C, 52.2; H, 7.7; N, 11.95. $C_5H_9NO_2$ requires C, 52.15; H, 7.9; N, 12.15%); $\nu_{max.}$ (KBr) 3 350—2 360br, 2 170, 1 655, 1 610, 1 565, 1 550, 1 410, 1 210, 850, and 780 $cm^{-1}$; $\tau(D_2O)$ 5.70—6.35 (1 H, m, cyclobutyl-CHN), 6.50—7.05 (1 H, m, cyclobutyl $CHCO_2H$), and 7.35—8.20 (4 H, m, cyclobutyl-$CH_2CH_2$). This compound decomposed when kept for a long time at room temperature and on attempted recrystallisation from ethanol.

trans-2-*Aminocyclobutanecarboxylic Acid* (25).—This amino-acid was prepared in a similar manner to the *cis*-isomer (24) by hydrolysis of the carbamate (27) and isolation by ion-exchange chromatography to give the *acid* (25) as a crystalline solid in 66% yield, m.p. 156—159 °C (from EtOH) (Found: C, 51.9; H, 7.7; N, 12.15. $C_5H_9NO_2$ requires C, 52.15; H, 7.9; N, 12.15%); $\nu_{max.}$ (KBr) 3 350—2 360br, 2 190, 1 650, 1 625, 1 570, 1 420, 1 245, 820, and 790 $cm^{-1}$; $\tau(D_2O)$ 5.85—6.40 (1 H, m, cyclobutyl-CHN), 6.65—7.23 (1 H, m, cyclobutyl $CHCO_2H$), and 7.52—8.45 (4 H, m, cyclobutyl-$CH_2CH_2$); *m/z* 115 ($M^+$).

cis-2-*Carbamoylcyclobutanecarboxylic Acid* (30).—A mixture of the amido-ester (28) [15] (1.96 g, 12.5 mmol), ethanol (12.5 ml), and 1M-sodium hydroxide (12.5 ml, 12.5 mmol) was heated on a water-bath for 1 h after which the solvent was removed under reduced pressure. The residue was dissolved in water (20 ml) and ' Dowex ' 50W-X8 ($H^+$ form) ion-exchange resin (20 g) added to the solution. The mixture was stirred for a short period, and the resin was filtered off and washed with water (50 ml). The combined filtrate was evaporated and the residual oil triturated with ethanol–ether to give the cis-*amido-acid* (30) (1.25 g, 70%) as a crystalline solid, m.p. 153—155 °C (from EtOH–$H_2O$) (Found: C, 50.3; H, 6.35; N, 9.85. $C_6H_9NO_3$ requires C, 50.35; H, 6.35; N, 9.8%); $\nu_{max.}$ (KBr) 3 440, 3 600—

2 360br, 1 695, 1 630, 1 590, 1 430, 1 345, 1 255, 1 000, 760, and 725 $cm^{-1}$; τ($D_2O$) 6.35—6.70 (2 H, m, cyclobutyl-CHCH) and 7.60—7.95 (4 H, m, cyclobutyl-$CH_2CH_2$); *m/z* 143 ($M^+$, 3%), 98 (100), 55 (74), 54 (54), 44 (85), and 27 (91).

trans-2-*Carbamoylcyclobutanecarboxylic Acid* (31).—A solution of the amido-ester (29) [15] (1.96 g, 12.5 mmol) in ethanol (12.5 ml) was treated with 1M-sodium hydroxide (12.5 ml, 12.5 mmol) in a manner similar to the *cis*-isomer (28). An analogous work-up gave the crystalline trans-*amido-acid* (31) (1.37 g, 77%), m.p. 129—130 °C (from EtOAc) (Found: C, 50.35; H, 6.3; N, 9.75. $C_6H_9NO_3$ requires C, 50.35; H, 6.35; N, 9.8%); $\nu_{max.}$ (KBr) 3 360, 3 600—2 360br, 1 710, 1 665, 1 605, 1 420, 1 265, 910, and 720 $cm^{-1}$; τ($D_2O$) 6.31—6.90 (2 H, m, cyclobutyl-CHCH) and 7.60—8.08 (4 H, m, cyclobutyl-$CH_2CH_2$); *m/z* 143 ($M^+$, 10%), 99 (50), 98 (100), 97 (70), 55 (85), and 44 (93).

*Ethyl* trans-2-*Carbamoylcyclopropanecarboxylate* (34).—A solution of acid chloride (36) [9] (5.3 g, 30 mmol) in dry toluene (150 ml) was stirred and ammonia gas bubbled through it for 45 min. After evaporation of the solvent, acetone (200 ml) was added to the residue and the mixture heated on a water-bath. The hot mixture was filtered and evaporation of the cooled filtrate yielded the trans-*amido-ester* (34) (4.13 g, 88%) as almost colourless needles, m.p. 112—113 °C (from EtOAc–light petroleum) (Found: C, 53.5; H, 6.9; N, 8.95. $C_7H_{11}NO_3$ requires C, 53.5; H, 7.05; N, 8.9%); $\nu_{max.}$ (KBr) 3 390, 3 220, 2 980, 1 710, 1 660, 1 620, 1 375, 1 180, 975, and 935 $cm^{-1}$; τ($CDCl_3$) 3.70—4.40br (2 H, s, $NH_2$), 5.89 (2 H, q, *J* 7 Hz, $CH_2CH_3$), 7.68—8.20 (2 H, m, cyclopropyl-CHCH), 8.40—8.85 (2 H, m, cyclopropyl-$CH_2$), and 8.75 (3 H, t, *J* 7 Hz, $CH_2CH_3$).

trans-2-*Carbamoylcyclopropanecarboxylic Acid* (35).—The *trans*-amido-ester (34) (2.5 g, 16 mmol) dissolved in ethanol (20 ml) was hydrolysed in a similar manner to the *cis*-cyclobutyl amido-ester (28) using 1M-sodium hydroxide (18 ml, 18 mmol). A similar work-up using ion-exchange, resin (20 g) to regenerate the amido-acid, yielded the *acid* (35) (1.4 g, 68%) as a crystalline solid, m.p. 196—197 °C (from EtOH) (Found: C, 46.55; H, 5.5; N, 10.7. $C_5H_7NO_3$ requires C, 46.5; H, 5.45; N, 10.85%); $\nu_{max.}$ (KBr) 3 430, 3 340, 3 160—2 200br, 1 700, 1 635, 1 610, 1 350, 1 220, and 965 $cm^{-1}$; τ($D_2O$) 7.60—8.08 (2 H, m, cyclopropyl-CHCH) and 8.40—8.82 (2 H, m, cyclopropyl-$CH_2$); *m/z* 129 ($M^+$, 1%), 84 (76), 83 (90), 60 (39), 44 (100), and 39 (78).

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