Synthesis of γ-Aminobutyric Acid Analogues of Restricted Conformation. Part 1. The 2-Aminocycloalkylacetic Acids †

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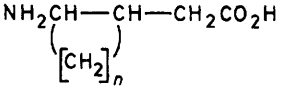
The syntheses of *cis*- and *trans*-2-aminocyclopropyl, -cyclobutyl, -cyclopentyl, and -cyclohexylacetic acids as γ-aminobutyric acid analogues of restricted conformation are described. Mass spectral evidence fully supports the stereochemical assignments of the configurational isomers.

γ-AMINOBUTYRIC ACID (GABA) (1) is generally regarded as the major inhibitory neurotransmitter [1] within the vertebrate central nervous system. Pharmacological studies have implicated disorders in the GABA-dependent inhibitory system as being involved in the development of neurological and psychiatric diseases such as Huntington's chorea,[2] Parkinson's disease,[3] and, possibly schizophrenia [4] and epilepsy [5] in man. Consequently the development of compounds capable of activating the GABA-dependent system and thus possibly alleviating some or all of these disorders has been the target of a number of studies.[6]

$NH_2CH_2CH_2CH_2CO_2H$

(1)

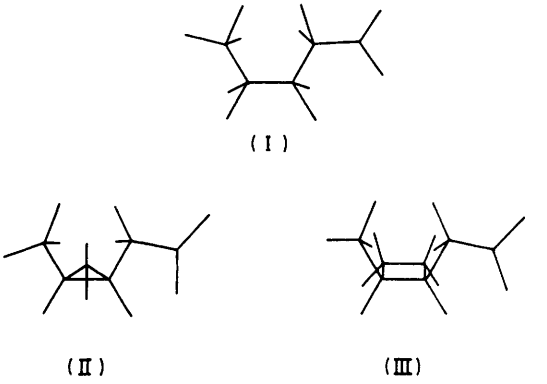


(2)

	n	isomer
a	1	*cis*
b	1	*trans*
c	2	*cis*
d	2	*trans*
e	3	*cis*
f	3	*trans*
g	4	*cis*
h	4	*trans*

The GABA molecule has a considerable degree of conformational flexibility as a result of free rotation about the single bonds and therefore could interact with its receptor(s) in one or more of a number of conformations. Several studies have been undertaken in order to elucidate the conformation(s) of GABA necessary for its biological activity. One such approach has been the preparation and pharmacological evaluation of structurally rigid analogues containing the GABA 'structure element.' Thus, for example, Allan *et al.*[7] have described the preparation of *cis*- and *trans*-3-aminocyclobutane-1-carboxylic acids as conformationally restricted analogues of GABA. Our approach has been to restrict rotation about single bonds and we report here the synthesis of the 2-aminocycloalkylacetic acids (2) which represent the GABA molecule with restricted rotation about the C(3)–C(4) atoms. Nicholson *et al.*[8] proposed that GABA adopts a planar, eclipsed [C(3) and C(4)], and partially folded conformation (I) (Figure 1) when interacting with its receptor. Such a conformation can also be simulated

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



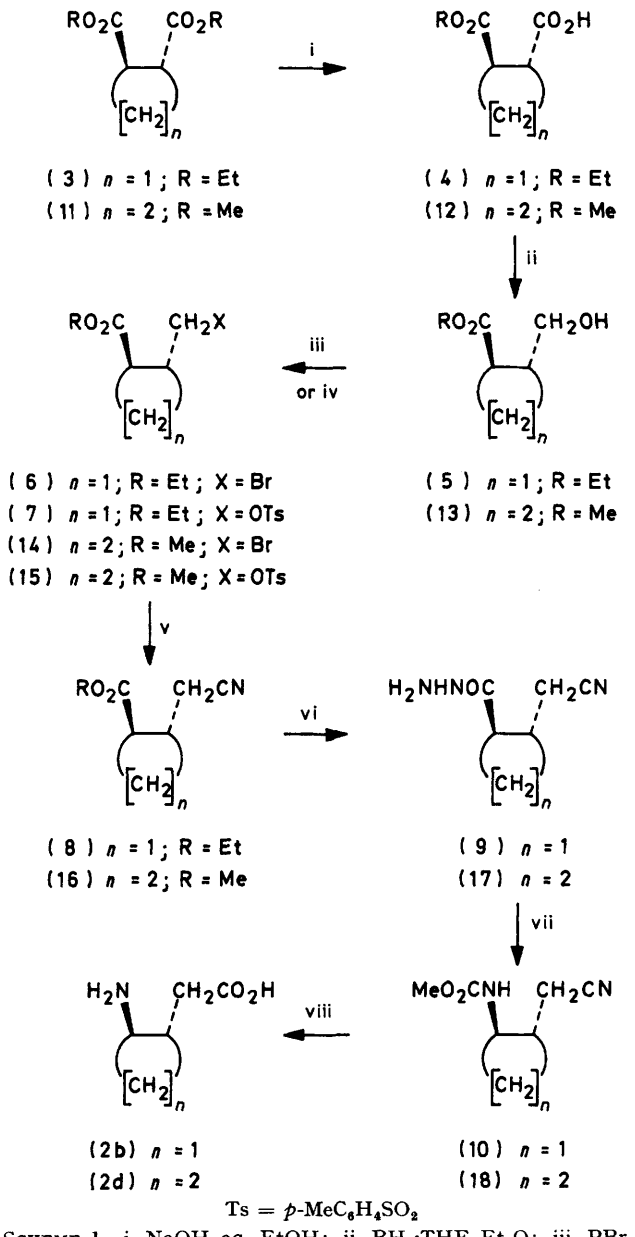
(I) (II) (III)

FIGURE 1 Dreiding stereomodel drawings of the 'active conformation' of GABA (I) as proposed by Nicholson *et al.*[8] and the simulated conformations of amino-acids (2a) (II) and (2c) (III)

by the *cis*-2-aminocycloalkylacetic acids as shown in Figure 1 for the cyclopropyl and cyclobutyl amino-acids (2a) and (2c). In the case of (2c) the cyclobutane ring is forced into a planar conformation. For the amino-acid (2 g), a high-energy boat conformation for the cyclohexyl ring is necessary for the GABA conformation (I) to be adopted. In contrast to the *cis*-isomers, the *trans*-2-aminocycloalkylacetic acids cannot exist in conformations resembling (I) (Figure 1).

RESULTS AND DISCUSSION

The synthetic routes to the *trans*-amino-acid (2b) and its homologue (2d) are outlined in Scheme 1 and involved a stereoselective approach. Commercially available *trans*-cyclobutane-1,2-dicarboxylic acid served as the starting material for the cyclobutane series and was esterified to give (11) according to the method of Schroff *et al.*,[9] whilst the synthesis in the cyclopropane series started with the preparation [10] of the *trans*-diester (3). Partial hydrolysis of (3) and (11) yielded respectively the mono-acids (4) and (12) [9,11] which could be regioselectively reduced to the alcohols (5) [12] and (13) [9] by borane–tetrahydrofuran (THF) complex.[13] Whilst the conversion of the cyclopropyl alcohol (5) into the bromide (6) [14] proceeded satisfactorily by reaction with phosphorus tribromide at −10 °C, the preparation of the cyclobutyl analogue (14) was far from satisfactory. The presence of signals in the olefinic region of the ^1H n.m.r. spectrum of the crude reaction product was indicative of

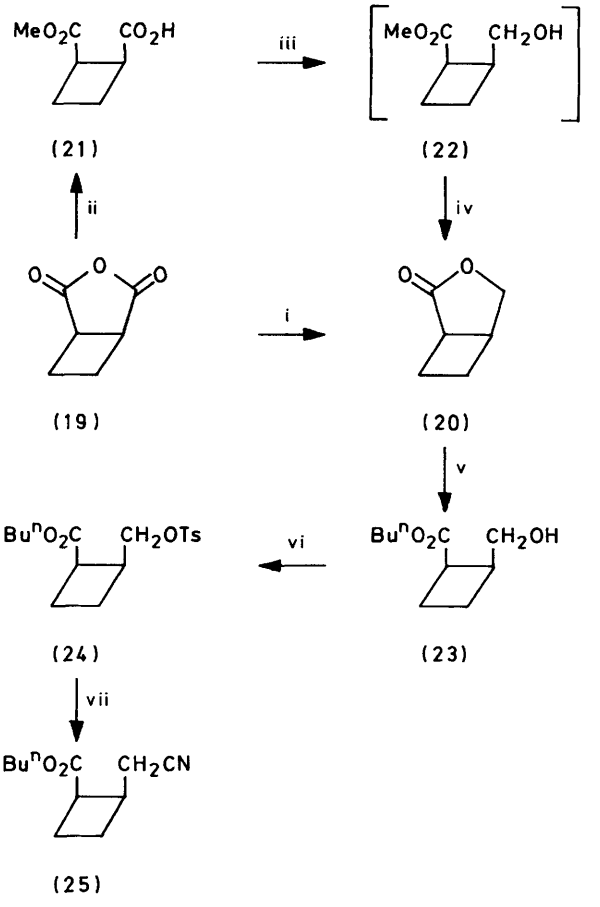


Ts = p-$MeC_6H_4SO_2$

SCHEME 1 i, NaOH–aq. EtOH; ii, BH_3·THF–Et_2O; iii, PBr_3, −10 °C; iv, p-$MeC_6H_4SO_2Cl$–pyridine; v, KCN–DMSO; vi, NH_2NH_2·H_2O–EtOH; vii, (a) $NaNO_2$–HCl, (b) heat, (c) MeOH; viii, NaOH–aq. EtOH

elimination products. Tosylation of both alcohols, however, proceeded with relative ease to give the tosylates (7) and (15). Treatment of the bromide (6) or of the tosylates (7) or (15) with potassium cyanide afforded the nitriles (8) and (16) which were converted into the acid hydrazides (9) and (17) respectively following the method of Witiak *et al.*[15] and Hart *et al.*[16] Curtius rearrangement of (9) and (17) was accomplished by established procedures [15,16] and the carbamates (10) and (18) respectively were isolated and characterised prior to hydrolysis to the amino-acids (2b) and (2d). This rearrangement, which proceeds *via* a nitrene intermediate and with retention of configuration at the migrating origin, has been widely used to introduce the amino substituent into the cyclopropane [9,17] and cyclobutane [9,15,16] ring systems.

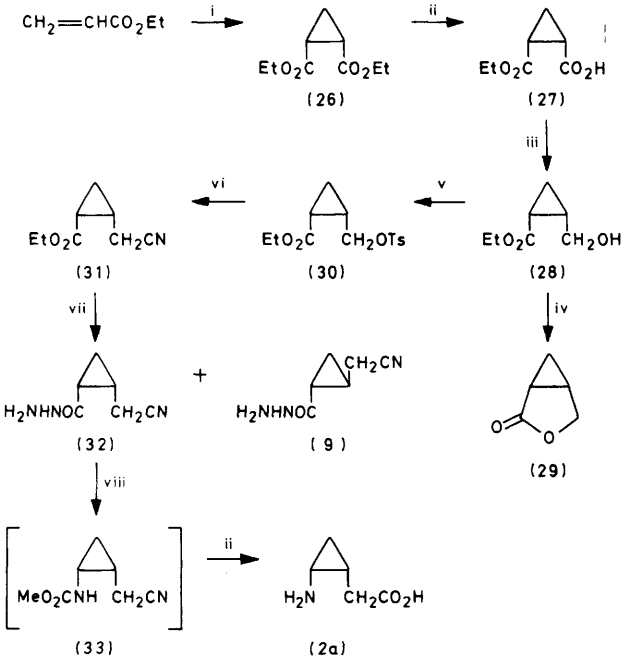
Whilst the synthesis of the *trans*-amino-acids (2b) and (2d) presented no major synthetic difficulties, the preparation of the *cis*-isomers (2a) and (2c) proved much more troublesome. Thus in the *cis*-cyclobutane series an approach analogous to that of the *trans*-series (Scheme 2)



SCHEME 2 i, $NaBH_4$–Pr^iOH; ii, MeOH; iii, BH_3·THF–Et_2O; iv, heat; v, $NaOBu^n$–Bu^nOH; vi, p-$MeC_6H_4SO_2Cl$–pyridine; vii, KCN–DMSO

failed when the major product from the condensation of the *cis*-nitrile (25) with hydrazine hydrate proved to be the *trans*-acid hydrazide (17). This type of base-induced isomerisation to give the thermodynamically more stable *trans*-isomer has previously been reported [15,18] for carbocyclic ring systems by several workers.

For the *cis*-cyclopropane series (Scheme 3), the *cis*-diester (26) [10,19] was partially hydrolysed to the mono-acid (27).[20] Reduction of (27) by a slight modification of the method of Schroff *et al.*[9] gave the *cis*-alcohol (28), attempted purification of which resulted in cyclisation to the lactone (29) [9,21] on distillation or even when kept for a long time at room temperature. The *cis*-tosylate (30) obtained from (28) by reaction with toluene-p-sulphonyl chloride was converted into the *cis*-nitrile

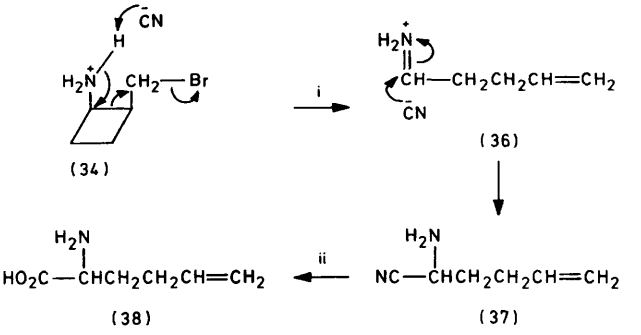


SCHEME 3 i, $ClCH_2CO_2Et$–NaH; ii, NaOH–aq. EtOH; iii, BH_3·THF–Et_2O; iv, heat; v, *p*-$MeC_6H_4SO_2Cl$–pyridine; vi, KCN–DMSO; vii, NH_2NH_2·H_2O; viii, (a) $NaNO_2$–HCl, (b) heat, (c) MeOH

(31) by treatment with potassium cyanide. Treatment of (31) with hydrazine hydrate in refluxing ethanol, however, gave predominantly the *trans*-acid hydrazide (9) together with minor amounts of the *cis*-acid hydrazide (32). Some steric control was gained by carrying out the reaction at ice-bath temperature and using this method (32) was obtained after separation from (9) by high-performance liquid chromatography (h.p.l.c.). Curtius rearrangement of (32) employing the method used for the *trans*-series then proceeded satisfactorily and, without its isolation, the *cis*-cyano-carbamate (33) was hydrolysed to the *cis*-amino-acid (2a).

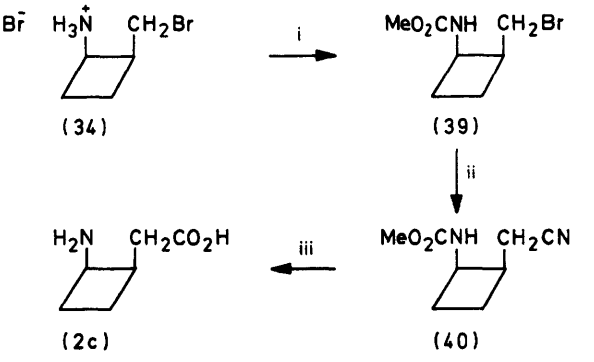
In view of these difficulties, an alternative approach was adopted which involved the introduction of the amino group at an earlier stage.

By avoiding the use of the strongly electronegative ester group directly attached to the ring, epimerisation to the thermodynamically more stable *trans*-isomer should be suppressed. Thus the readily available [9] bromomethyl derivative (34) was treated with cyanide either in dimethyl sulphoxide (DMSO) at room temperature or in refluxing ethanol in an attempt to prepare the *cis*-nitrile (35), but in both cases the ^1H n.m.r. spectrum of the crude product showed the presence of olefinic protons. Further, hydrolysis of the crude product followed by ion-exchange chromatography gave the known [22] α-amino-acid (38) (Scheme 4). Presumably



SCHEME 4 i, NaCN–DMSO or NaCN–EtOH; ii, NaOH–aq. EtOH

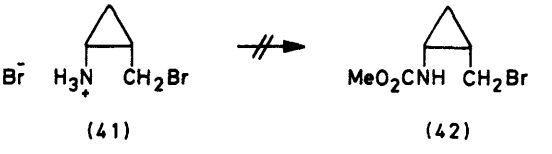
(38) is the hydrolysis product of the amino-nitrile (37) produced by cleavage of the cyclobutane ring to generate the iminium ion (36) followed by addition of the cyanide anion. However, this ring-opening reaction can be suppressed if (34) is converted into the *cis*-carbamate (39) prior to the cyanide treatment (Scheme 5). When



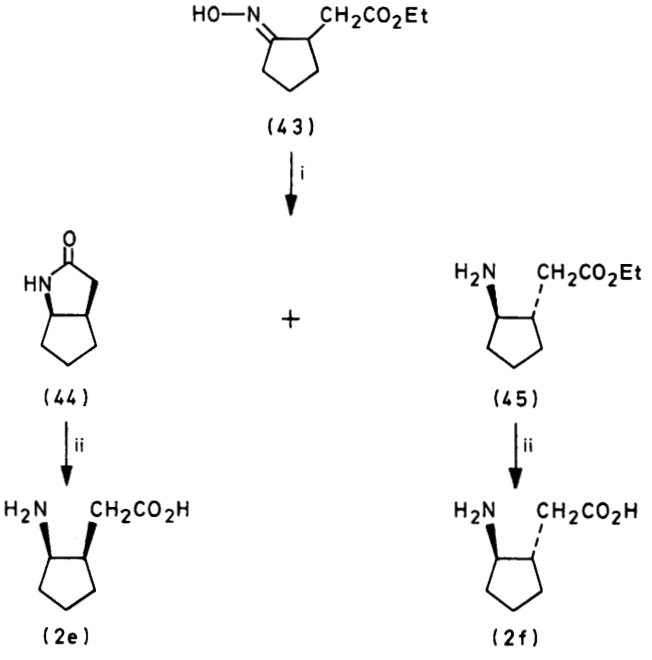
SCHEME 5 i, $ClCO_2Me$–pyridine–Et_2O; ii, KCN–DMSO; iii, NaOH–aq. EtOH

treated with potassium cyanide in DMSO at 90 °C, (39) was readily converted into the *cis*-nitrile (40), base hydrolysis of which then yielded the required *cis*-amino-acid (2c).

Unlike the cyclobutane derivative (34), the cyclopropyl ammonium salt (41),[9] when treated with methyl chloroformate under identical conditions, failed to yield the corresponding carbamate (42) and gave instead a mixture of unidentified products. This difference in the reaction of (34) and (41) with methyl chloroformate probably results from the relative stabilities of the two ring systems.



The synthesis of the hydrochlorides of the cyclopentyl amino-acids (2e) and (2f) has previously been described.[23] In the present study, the free amino-acids were prepared by a slight modification of the reported route. Thus the oxime (43) [23,24] (Scheme 6) was hydrogenated over

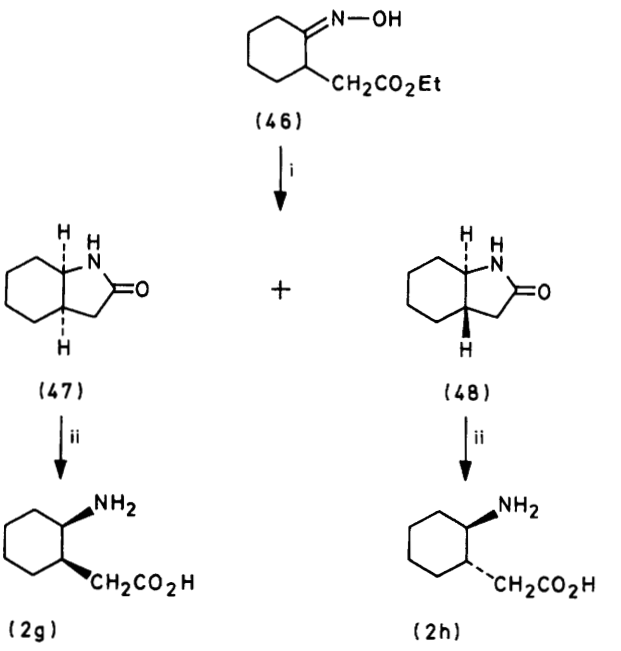


SCHEME 6 i, (a) H_2–PtO_2–HCl–EtOH, (b) heat; ii, NaOH–aq. EtOH

platinum oxide in ethanolic HCl [25] to provide a mixture of isomeric amino-esters which on distillation afforded the *cis*-lactam (44) and the *trans*-amino-ester (45). Hydrolysis of (44) and (45) then yielded the *cis*- and *trans*-amino-acids (2e) and (2f) respectively, both of which were isolated by ion-exchange chromatography.

A similar approach was adopted for the synthesis of the cyclohexyl amino-acids (2g) and (2h). Booth and King [26] have reported the reduction of the oxime (46) by catalytic hydrogenation over Raney nickel in ethanolic ammonia and they isolated only the *trans*-amino-acid (2h) after hydrolysis of the crude reaction product. Scheme 7 outlines the synthetic route to both (2h) and (2g). The oxime (46) was hydrogenated over platinum oxide in ethanolic HCl [25] and distillation of the crude product gave a mixture of the known [26] *trans*-lactam (48) and the previously unreported *cis*-lactam (47). Separation of (47) and (48) by h.p.l.c., followed by base hydrolysis of the pure isomers, afforded the amino-acids (2g) and (2h) respectively.

Although the stereochemical assignments of the amino-acids (2a—h) were based essentially on the stereoselective routes used in their preparation, several interesting observations with respect to the *cis–trans* arrangement of the amino and acetic acid substituents were made. Of the amino-acids studied, all isomers with the *cis*-configuration melted at lower temperatures than the *trans*-isomers and all configurational pairs could be sep-



SCHEME 7 i, (a) H_2–PtO_2–HCl–EtOH, (b) heat; ii, NaOH–aq. EtOH

arated by t.l.c. Further evidence to substantiate the stereochemical integrity of the *cis*- and *trans*-isomers of these amino-acids was provided by mass spectral data. The mass spectra of the *cis*-amino-acids (2a), (2e), and (2g) and the *trans*-cyclohexyl amino-acid (2h) showed a relatively abundant (M — 18) fragment while this ion was not significant in the mass spectra of the *trans*-isomers (2b) and (2f). The loss of 18 mass units in the *cis*-isomers and the *trans*-isomer (2h) is consistent with loss of water and the formation of a bicyclic lactam. Since lactam formation in the *trans*-isomers (2b) and (2f) is not expected, the very low abundance of the (M — 18) fragment in these molecules is good evidence for the *trans*-orientation of substituents. Thus in the mass spectrum of the *cis*-amino-acid (2a) (Figure 2), a prominent peak at m/z 97 corresponding to a bicyclic lactam was observed whilst this peak was not significant in the spectrum of the *trans*-amino-acid (2b). For the amino-acids (2g) and (2h) the greater flexibility of the cyclohexane ring allows both isomers to form lactams and consequently the mass spectra of both showed a significant peak at m/z 139 corresponding to the (M — 18) fragment. The proposed fragmentation pathway for the *cis*-amino-acid (2c) is shown in Figure 3. In this case the expected $(M - H_2O)^{\cdot+}$ fragment at m/z 111 is not significant as it appears to eliminate ethylene to give a relatively abundant ion corresponding to a monocyclic lactam at m/z 83. To provide evidence that the peak at m/z 83 does arise from the bicyclic lactam (49) (Figure 3), this compound was prepared by thermal cyclisation of the *cis*-amino-acid (2c) and its mass spectrum examined. This showed a low abundance of the molecular ion peak at m/z 111 and a base peak at m/z 83. Figure 4 shows the proposed mass spectral fragmentation pathway for the *trans*-amino-

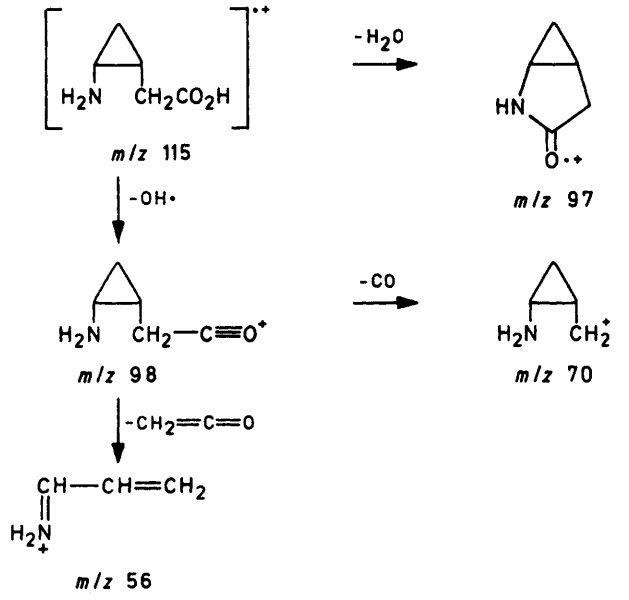


FIGURE 2 The proposed mass spectral fragmentation pathway for the amino-acid (2a)

acid (2d). As expected, the peaks arising from the fragmentation of the cyclobutane ring are common to those of the *cis*-isomer (2c); the peaks *via* lactam formation are not significant.

In biochemical receptor binding studies, only the cyclopropyl and cyclobutyl amino-acids showed any significant biological activity. The *cis*-isomers (2a) and (2c) were found to be relatively weak inhibitors of [^{3}H]-muscimol binding (IC_{50} 100 and 49 μM respectively) to whole rat brain synaptic membranes. Surprisingly, the *trans*-isomers (2b) and (2d) were both found to be potent inhibitors of [^{3}H]muscimol binding (IC_{50} 0.7 and 4.4 μM respectively). Since the 'active conformation' of GABA proposed by Nicholson *et al.*,[8] which the *cis*-isomers (2a) and (2c) can adopt, is not available to the *trans*-isomers (2b) and (2d), it may be inferred that their model may not be applicable in this case and that either these GABA analogues interact with a different class of GABA receptors or that there is an alternative 'active conformation' of GABA. It is probable that the inactivity of the cyclopentyl and cyclohexyl analogues (2e)—(2h) is a consequence of the steric bulk of the carbocyclic ring which prevents these molecules from interacting with GABA receptor sites.

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

Melting points were determined on a Kofler hot-stage apparatus (Reichert). I.r. spectra were recorded with a Pye-Unicam SP 1000 spectrophotometer. ^{1}H N.m.r. spectra were determined with a Perkin-Elmer R 12 A spectrophotometer at 60 MHz with tetramethylsilane as internal standard (all –NH and –OH peaks were removed by addition of D_2O). Mass spectra were obtained on either an A.E.I. MS 30 or a Varian MAT 311 A spectrometer at 70 eV. Elemental analyses were carried out by C.H.N. Analysis Ltd., Leicester. T.l.c. was carried out on Merck Kieselgel 60 F_{254} plates (0.25 mm) and silica gel for chromatography refers to Merck Kieselgel 60 (63—200 μm). Small-scale (<1 g sample) preparative h.p.l.c. was carried out using Jobling HPLC glass columns (15—25 × 400 mm) and on Merck Kieselgel 60 (40—63 μm) while for larger samples (>1 g) Jobin Yvon Chromatospec Prep 100 was used. Ion-exchange chromatography was performed on Bio-Rad glass barrel Econo-columns (1.5 × 30 cm) using Dowex 50W-X8 (H^+ form, 100—200 mesh) ion-exchange resin. All amino-acids were detected on t.l.c. plates by ninhydrin colouration. The R_F values quoted refer to the

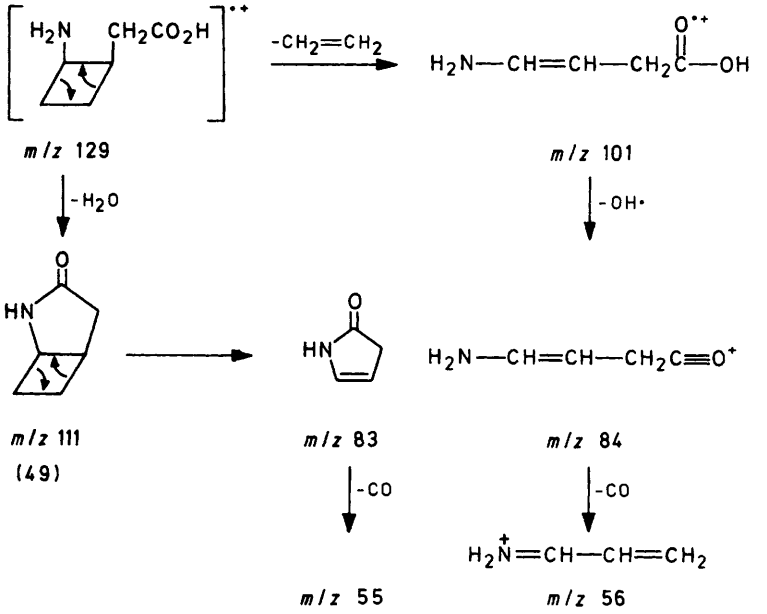


FIGURE 3 The proposed mass spectral fragmentation pathway for the amino-acid (2c)

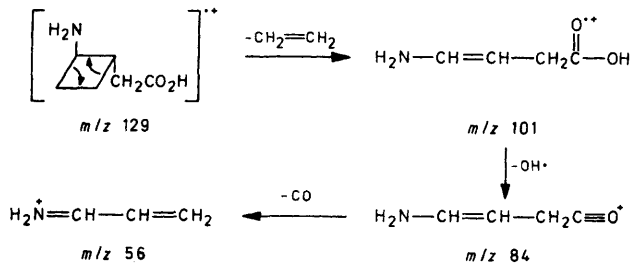


FIGURE 4 The proposed mass spectral fragmentation pathway for the amino-acid (2d)

following solvent systems: I, methanol; II, chloroform–methanol–water–acetic acid (30 : 20 : 6 : 4); III, propan-2-ol–water (7 : 3); IV, t-butyl alcohol–water (3 : 1). Light petroleum refers to the fraction of b.p. 40—60 °C. All organic extracts were dried over anhydrous magnesium sulphate. Evaporations were carried out (< 50 °C) under reduced pressure using a rotary evaporator. Pure products were colourless unless otherwise stated.

The following compounds were prepared essentially by the literature methods indicated: ethyl *trans*-2-(hydroxymethyl)cyclopropanecarboxylate (5), b.p. 85—88 °C at 0.8 mmHg (lit.,[12] 113—119 °C at 7 mmHg); ethyl *trans*-2-(bromomethyl)cyclopropanecarboxylate (6), b.p. 63—65 °C at 0.7 mmHg (lit.,[14] 102 °C at 11 mmHg); ethyl *cis*-2-(hydroxymethyl)cyclopropanecarboxylate (28);[9] *cis*-3-oxabicyclo[3.1.0]hexan-2-one (29);[9] methyl *trans*-2-(hydroxymethyl)cyclobutanecarboxylate (13), b.p. 91—94 °C at 1.75 mmHg (lit.,[9] 81—82 °C at 1.0 mmHg); butyl *cis*-2-(hydroxymethyl)cyclobutanecarboxylate (23), b.p. 97—102 °C at 0.6 mmHg (lit.,[27] 92 °C at 0.2 mmHg); butyl *cis*-2-(tosyloxymethyl)cyclobutanecarboxylate (24);[27] *cis*-2-azabicyclo[3.3.0]octan-3-one (44), m.p. 50—51 °C (lit.,[23] 51—53 °C); ethyl *trans*-2-aminocyclopentylacetate (45) b.p. 63—67 °C at 0.5 mmHg (lit.,[23] 60—65 °C at 0.5 mmHg)

Ethyl trans-2-(*Tosyloxymethyl*)*cyclopropanecarboxylate* (7).—The *ester* (7) was prepared by tosylation of the *trans*-alcohol–ester (5) under standard conditions as a viscous oil in 54% yield (Found: C, 56.25; H, 6.05; S, 10.7. $C_{14}H_{18}O_5S$ requires C, 56.35; H, 6.1; S, 10.75%); $\nu_{max.}$ (film) 2 980, 1 730, 1 370, 1 180, 950, and 665 cm^{-1}; τ($CDCl_3$) 2.53 (4 H, q, *J* 8 Hz, ArH), 6.02 (2 H, q, *J* 7 Hz, CH_2Me), 5.75—6.35 (2 H, m, CH_2OTs), 7.68 (3 H, s, ArCH_3), 8.88 (3 H, t, *J* 7 Hz, CH_2CH_3), and 8.25—9.48 (4 H, m, cyclopropyl).

Ethyl trans-2-(*Cyanomethyl*)*cyclopropanecarboxylate* (8).—A stirred mixture of the *trans*-bromomethyl-ester (6) (5.6 g, 27 mmol) and potassium cyanide (2.3 g, 35 mmol) in dry dimethyl sulphoxide (DMSO) (50 ml) was heated at 90 °C under an atmosphere of dry nitrogen for 3 h and then the cooled mixture poured on to water (200 ml). The mixture was extracted with ether (2 × 100 ml), and the ethereal extract washed once with water (100 ml), dried, and finally evaporated. The residual liquid on distillation under reduced pressure yielded the trans-*cyano-ester* (8) (3.1 g, 75%) as a liquid, b.p. 87—88 °C at 0.8 mmHg. A sample (0.1 g) for elemental analysis was further purified by h.p.l.c. using n-pentane–ethyl acetate (85 : 15) as eluant (Found: C, 62.65; H, 7.25; N, 8.9. $C_8H_{11}NO_2$ requires C, 62.75; H, 7.25; N, 9.15%); $\nu_{max.}$ (film) 2 980, 2 230, 1 730, 1 410, 1 210, 1 185, and 1 040 cm^{-1}; τ($CDCl_3$) 5.86 (2 H, q, *J* 7 Hz, CH_2Me), 7.30—7.60 (2 H, m, CH_2CN), 8.00—9.45 (4 H, m, cyclopropyl), and 8.73 (3 H, t, *J* 7 Hz, CH_3); *m/z* 153 (M^+, 20%), 108 (100), 80 (34), 53 (68), 29 (73), and 27 (83).

Similarly, treatment of the *trans*-tosylate (7) (0.745 g, 2.5 mmol) with potassium cyanide (0.175 g, 2.7 mmol) in dry DMSO (5 ml), in the manner just described for the *trans*-bromo-compound (6), yielded the *trans*-cyano-ester (8) (0.28 g, 73%), identical (i.r. and ^{1}H n.m.r.) with the sample prepared from (6).

trans-2-(*Cyanomethyl*)*cyclopropanecarbohydrazide* (9).—A stirred mixture of the *trans*-cyano-ester (8) (3.06 g, 20 mmol), 100% hydrazine hydrate (3.0 g, 60 mmol), and ethanol (5 ml) was heated in an oil-bath at 130—135 °C for 1 h. The cooled mixture was evaporated and the residual red oil crystallised when kept in the cold. The product was triturated with ether, filtered, and dried. Purification on silica gel (150 g) using chloroform–methanol (9 : 1) as eluant gave the trans-*hydrazide* (9) (1.6 g, 58%) as almost colourless crystals, m.p. 102—103 °C (from EtOAc) (Found: C, 51.7; H, 6.45; N, 30.15. $C_6H_9N_3O$ requires C, 51.8; H, 6.5; N, 30.2%); $\nu_{max.}$ (KBr) 3 330, 3 300, 3 200, 3 040, 2 230, 1 630, 1 540, 1 415, 1 265, 1 040, and 655 cm^{-1}; τ($CDCl_3$) 7.08 br (3 H, s, $NHNH_2$), 7.30—7.55 (2 H, m, CH_2CN), and 8.00—9.40 (4 H, m, cyclopropyl); *m/z* 139 (M^+, 6%), 108 (100), 80 (26), 53 (60), 32 (23), and 27 (18).

Methyl trans-2-(*Cyanomethyl*)*cyclopropylcarbamate* (10).—A mixture of the *trans*-hydrazide (9) (1.53 g, 11 mmol), sodium nitrite (0.9 g, 13 mmol), water (25 ml), and ether (50 ml) was stirred and cooled to 0 °C. With the temperature kept between 0 and 5 °C throughout, 6M-hydrochloric acid (2.17 ml, 13 mmol) was added dropwise and then the mixture stirred at 0—5 °C for 30 min. The ether layer was separated off and the aqueous layer extracted with ether (2 × 50 ml). The combined ethereal extract was dried, dry toluene (25 ml) added to the solution, and the ether evaporated off under reduced pressure. The i.r. spectrum (toluene solution) showed the characteristic absorption band for the azide group at 2 130 cm^{-1}. The toluene solution was refluxed for 1 h and then cooled. The i.r. spectrum (toluene solution) showed the characteristic isocyanate absorption band at 2 260 cm^{-1}. Dry methanol (25 ml) was added to the solution which was refluxed for 16 h and then evaporated. The residual yellow oil on distillation under reduced pressure yielded the trans-*cyano-carbamate* (10) (1.32 g, 78%) as a light yellow viscous oil, b.p. 120—121 °C at 0.15 mmHg. A sample (0.1 g) for elemental analysis was further purified by h.p.l.c. using dichloromethane–methanol (98 : 2) as eluant (Found: C, 54.2; H, 6.6; N, 18.1. $C_7H_{10}N_2O_2$ requires C, 54.55; H, 6.55; N, 18.15%); $\nu_{max.}$ (film) 3 340, 3 000, 2 960, 2 240, 1 730, 1 530, 1 265, 1 095, and 775 cm^{-1}; τ($CDCl_3$) 4.45—5.15 br (1 H, s, NH), 6.32 (3 H, s, CH_3), 7.30—7.80 (3 H, m, CH_2CN and cyclopropyl-CHN), and 8.45—9.30 (3 H, m, cyclopropyl); *m/z* 154 (M^+, 4%), 127 (16), 114 (100), 59 (28), 41 (23), and 28 (36).

trans-2-*Aminocyclopropylacetic Acid* (2b).—To a solution of the *trans*-cyano-carbamate (10) (1.23 g, 8 mmol) in ethanol (30 ml) was added 1M-sodium hydroxide (32 ml, 32 mmol) and the mixture refluxed for 16 h. It was then cooled and evaporated, and the residue dissolved in water (10 ml). The solution was acidified to pH 3 by a dropwise addition of concentrated hydrochloric acid and then deposited on an ion-exchange column (30 g resin). Elution with 1M-ammonium hydroxide yielded the trans-*amino-acid* (2b) (0.6 g, 65%) as a crystalline solid, m.p. 182—184 °C (decomp.) (from MeOH) (Found: C, 51.9; H, 7.9; N, 12.2. $C_5H_9NO_2$ requires C, 52.15; H, 7.9; N, 12.15%); $\nu_{max.}$ (KBr) 3 440, 3 320—2 360br, 2 160, 1 640, 1 580, 1 520,

1 410, and 1 270 cm^{-1}; τ(D_2O) 7.30—7.70 (1 H, m, cyclopropyl-CHN), 7.65—8.00 (2 H, m, CH_2CO_2H), and 8.25—9.40 (3 H, m, cyclopropyl); *m/z* 115 (M^+, 0.6%), 70 (26), 56 (100), 43 (16), 41 (12), and 30 (17); R_F: I, 0.24; II, 0.27.

Ethyl cis-2-(*Tosyloxymethyl*)*cyclopropanecarboxylate* (30).—The *ester* (30) was prepared in the usual manner from the *cis*-alcohol (28) in 36% yield as a viscous oil (Found: C, 56.35; H, 6.15; S, 10.75. $C_{14}H_{18}O_5S$ requires C, 56.35; H, 6.1; S, 10.75%); $\nu_{max.}$ (film) 2 990, 1 730, 1 600, 1 360, 1 190, 1 180, 945, and 665 cm^{-1}; τ($CDCl_3$) 2.43 (4 H, q, *J* 8 Hz, ArH), 5.35—6.15 (2 H, m, CH_2OTs), 5.92 (2 H, q, *J* 7 Hz, CH_2Me), 7.56 (3 H, s, $ArCH_3$), 8.05—9.11 (4 H, m, cyclopropyl), and 8.77 (3 H, t, *J* 7 Hz, CH_2CH_3).

Ethyl cis-2-(*Cyanomethyl*)*cyclopropanecarboxylate* (31).—The *ester* (31) was prepared in a similar manner to the *trans*-cyano-ester (8) in 76% yield as a liquid, b.p. 83—85 °C at 1.25 mmHg (Found: C, 62.75; H, 7.3; N, 8.9. $C_8H_{11}NO_2$ requires C, 62.75; H, 7.25; N, 9.15%); $\nu_{max.}$ (film) 2 990, 2 240, 1 730, 1 410, 1 388, and 1 190 cm^{-1}; τ($CDCl_3$) 5.82 (2 H, q, *J* 7 Hz, CH_2CH_3), 7.28 (2 H, d, *J* 6 Hz, CH_2CN), 7.89—9.10 (4 H, m, cyclopropyl), and 8.71 (3 H, t, *J* 7 Hz, CH_2CH_3); *m/z* 153 (M^+, 9%); 108 (100), 80 (57), 53 (54), 39 (52), and 28 (82).

cis-2-(*Cyanomethyl*)*cyclopropanecarbohydrazide* (32).—A mixture of the *cis*-cyano-ester (31) (0.46 g, 3 mmol) and 100% hydrazine hydrate (0.15 g, 3 mmol), was stirred at 0 °C for 2 h and the mixture then set aside at 5 °C for 18 h. T.l.c. indicated the presence of a mixture of two major products. This was separated by h.p.l.c. using dichloromethane–methanol (19 : 1) as eluant. Evaporation of the fractions containing the less-polar component gave the cis-*hydrazide* (32) (0.12 g, 29%) as a viscous oil (Found: C, 51.75; H, 6.45; N, 29.55. $C_6H_9N_3O$ requires C, 51.8; H, 6.5; N, 30.2%); $\nu_{max.}$ (film) 3 650—3 110br, 3 320, 3 020, 2 240, 1 670, 1 540, 1 415, 1 270, 1 020, and 750 cm^{-1}; τ($CDCl_3$) 7.07—7.50 (2 H, m, CH_2CN) and 8.10—9.40 (4 H, m, cyclopropyl); *m/z* 139 (M^+, 14%), 108(98), 80 (56), 53 (100), 32 (80), and 27 (75).

Evaporation of the fractions containing the more-polar component gave an oil that crystallised when kept in the cold. The crystalline solid (0.04 g) was triturated with ether, filtered, and dried. It was found to be identical to the *trans*-hydrazide (9) (m.p.; i.r. and ^1H n.m.r.).

cis-2-*Aminocyclopropylacetic Acid* (2a).—A mixture of the *cis*-hydrazide (32) (0.07 g, 0.5 mmol), sodium nitrite (0.036 g, 0.52 mmol), water (3 ml), and ether (5 ml) was stirred and cooled to 0 °C. With the reaction temperature kept below 5 °C, 6M-hydrochloric acid (0.085 ml, 0.52 mmol) was added, and the mixture then stirred at 0 °C for 30 min. The ether layer was separated off and the aqueous layer extracted with ether (2 × 10 ml). The combined ethereal solution was dried, dry toluene (5 ml) added, and the ether removed under reduced pressure. The i.r. spectrum of the residual toluene solution showed a characteristic absorption band at 2 130 cm^{-1} for the azide group. The toluene solution was refluxed for 1 h and then cooled. The i.r. spectrum (toluene solution) showed the characteristic isocyanate absorption band at 2 260 cm^{-1}. Dry methanol (3 ml) was added to the toluene solution and the mixture refluxed for 3 h when t.l.c. indicated formation of the *cis*-cyano-carbamate (33) on comparison with the *trans*-cyano-carbamate (10). The cooled mixture was evaporated, the residual yellow oil (0.051 g) dissolved in ethanol (4 ml), and 1M-sodium hydroxide (1.3 ml) added. The mixture was refluxed for 16 h, then cooled and evaporated, and the residue dissolved in water (2 ml). The solution was acidified to pH 3 with 10% hydrochloric acid and deposited on an ion-exchange column (10 g resin). Elution with 1M-ammonium hydroxide and evaporation of the appropriate fractions yielded the cis-*amino-acid* (2a) [0.0125 g, 22% from (32)] as a crystalline solid after trituration with methanol–ether, m.p. 163—165 °C (Found: C, 52.05; H, 7.85; N, 12.0. $C_5H_9NO_2$ requires C, 52.15; H, 7.9; N, 12.15%); $\nu_{max.}$ (KBr) 3 350—2 310 br, 2 140, 1 640, 1 590, 1 515, 1 405, and 1 270 cm^{-1}; τ(D_2O) 7.08—7.92 (3 H, m, CH_2CO_2H and cyclopropyl-CHN), and 8.43—9.45 (3 H, m, cyclopropyl); *m/z* 115 (M^+, 1%), 97 [(M − H_2O), 4], 70 (27), 56 (100), 43 (10), and 28 (18); R_F: I, 0.27; II, 0.30.

Methyl trans-2-(*Tosyloxymethyl*)*cyclobutanecarboxylate* (15).—The *ester* (15) was prepared by a standard procedure in 88% yield as a liquid (Found: C, 56.2; H, 6.1; S, 10.8. $C_{14}H_{18}O_5S$ requires C, 56.35; H, 6.1; S, 10.75%); $\nu_{max.}$ (film) 2 990, 2 950, 1 735, 1 600, 1 365, 1 190, 1 178, 960, and 665 cm^{-1}; τ($CDCl_3$) 2.44 (4 H, q, *J* 8 Hz, ArH), 5.98 (2 H, d, *J* 5 Hz, CH_2OTs), 6.37 (3 H, s, CO_2CH_3), 6.81—7.45 (2 H, m, cyclobutyl-CHCH), 7.58 (3 H, s, $ArCH_3$), and 7.62—8.47 (4 H, m, cyclobutyl-CH_2CH_2); *m/z* 298 (M^+, 2%), 173 (36), 155 (52), 91 (100), 67 (42), and 56 (33).

Methyl trans-2-(*Cyanomethyl*)*cyclobutanecarboxylate* (16).—A mixture of the *trans*-tosylate (15) (14.9 g, 50 mmol) and potassium cyanide (3.6 g, 55 mmol) in dry DMSO (70 ml) was stirred and heated at 90 °C under an atmosphere of dry nitrogen. A work-up similar to that for the *trans*-cyclopropyl derivative (8) gave a light yellow liquid on evaporation of the dried ethereal extract. Distillation under reduced pressure yielded the trans-*cyano-ester* (16) (6.2 g, 81%) as a liquid, b.p. 98—100 °C at 1.75 mmHg. A sample (1 g) for elemental analysis was further purified by h.p.l.c. using n-pentane–ethyl acetate (4 : 1) as eluant (Found: C, 62.55; H, 7.3; N, 9.05. $C_8H_{11}NO_2$ requires C, 62.75; H, 7.25; N, 9.15%) $\nu_{max.}$ (film) 2 990, 2 950, 2 235, 1 740, 1 440, 1 210, and 1 035 cm^{-1}; τ($CDCl_3$) 6.32 (3 H, s, CH_3), 6.75—7.37 (2 H, m, cyclobutyl-CHCH), 7.38—7.60 (2 H, m, CH_2CN), and 7.62—8.40 (4 H, m, cyclobutyl-CH_2CH_2); *m/z* 153 (M^+, 1%), 94 (89), 87 (62), 67 (53), 55 (74), and 28 (100).

trans-2-(*Cyanomethyl*)*cyclobutanecarbohydrazide* (17).—A stirred mixture of the *trans*-cyano-ester (16) (4.6 g, 30 mmol) and 100% hydrazine hydrate (4.5 g, 90 mmol) was heated in an oil-bath at 130—135 °C for 30 min. The cooled mixture was evaporated to dryness and the residual oil crystallised when kept in the cold. The product was triturated with light petroleum, filtered, and dried. The trans-*hydrazide* (17) (3.3 g, 72%) was thus obtained as almost colourless crystals, m.p. 89—90 °C (from EtOAc) (Found: C, 54.9; H, 7.15; N, 27.4. $C_7H_{11}N_3O$ requires C, 54.9; H, 7.25; N, 27.45%); $\nu_{max.}$ (KBr) 3 320, 3 270, 3 040, 2 980, 2 240, 1 640, 1 540, 1 400, 1 037, 950, and 670 cm^{-1}; τ($CDCl_3$) 2.75—3.15br (1 H, s, NH), 5.75—6.65br (2 H, s, NH_2), 6.80—7.40 (2 H, m, cyclobutyl-CHCH), 7.38—7.60 (2 H, m, CH_2CN), and 7.70—8.30 (4 H, m, cyclobutyl-CH_2CH_2); *m/z* 153 (M^+, 14%), 122 (29), 94 (96), 67 (93), 41 (50), and 32 (100).

Methyl trans-2-(*Cyanomethyl*)*cyclobutylcarbamate* (18).—A mixture of the *trans*-hydrazide (17) (2.45 g, 16 mmol), sodium nitrite (1.21 g, 17.5 mmol), water (25 ml), and ether (50 ml) was stirred and cooled to 0 °C. With the temperature maintained at 0—5 °C throughout, 6M-hydrochloric acid (2.92 ml, 17.5 mmol) was added dropwise and then the mixture stirred at 0—5 °C for 30 min. Treatment of the ethereal layer in a manner similar to that used in the prep-

aration of the *trans*-cyclopropyl carbamate (10) and sub sequent reaction with methanol gave a red oil. Distillation under reduced pressure yielded the trans-*cyano-carbamate* (18) (1.5 g, 56%) as a light yellow viscous liquid, b.p. 130—132 °C at 0.8 mmHg (Found: C, 57.25; H, 7.2; N, 16.65. $C_8H_{12}N_2O_2$ requires C, 57.15; H, 7.2; N, 16.65%); $\nu_{max.}$ (film) 3 340, 2 990, 2 960, 2 240, 1 720, 1 540, 1 275, 1 045, and 775 cm^{-1}; $\tau(CDCl_3)$ 4.60—5.15 br (1 H, s, NH), 5.85—6.35 (1 H, m, cyclobutyl-CHN), 6.37 (3 H, s, CH_3), 7.30—8.85 (7 H, m, CH_2CN and cyclobutyl); *m/z* 168 (M^+, 0.2%), 108 (19), 101 (100), 81 (14), 59 (26), and 56 (29).

trans-2-*Aminocyclobutylacetic Acid* (2d).—The *trans*-cyano-carbamate (18) (1.0 g, 6 mmol) dissolved in ethanol (25 ml) was hydrolysed in a manner similar to that for the *trans*-cyclopropyl derivative (10) using 1M-sodium hydroxide (24 ml, 24 mmol). Work-up on an ion-exchange column (30 g resin) with elution by 1M-ammonium hydroxide gave the *amino-acid* (2d) (0.4 g, 52%) as a crystalline solid, m.p. 210—212 °C (decomp.) (from EtOH) (Found: C, 55.7; H, 8.75; N, 10.7. $C_6H_{11}NO_2$ requires C, 55.8; H, 8.6; N, 10.85%); $\nu_{max.}$ (KBr) 3 650—2 350br, 2 100, 1 640, 1 550, 1 400, 1 250, 1 055, 910, and 640 cm^{-1}; $\tau(D_2O)$ 6.25—6.75 (1 H, m, cyclobutyl-CHN), and 7.05—8.68 (7 H, m, CH_2CO_2H and cyclobutyl); *m/z* 129 (M^+, 0.5%), 111 (0.2), 101 (36), 56 (89), 43 (100), 42 (53), and 28 (43), R_F: I, 0.24; II, 0.40.

cis-3-*Oxabicyclo*[3.2.0]*heptan-2-one* (20).—A solution of the *cis*-mono-acid (21) [9] (55.3 g, 0.35 mol) in dry ether (350 ml) was treated with 1M-borane–tetrahydrofuran (THF) complex in THF (450 ml, 0.45 mol) during 3 h. The mixture was stirred at room temperature for 40 h and hydrolysed with methanol (100 ml), and then the solvent removed under reduced pressure. The residue was dissolved in ether (250 ml) and the solution washed with water (2 × 200 ml), dried, and evaporated giving the intermediate *cis*-alcohol-ester (22) as a liquid. The crude product was heated on a water-bath for 3 h when t.l.c. indicated complete conversion into a non-polar compound. The cooled mixture was dissolved in chloroform (250 ml) and the solution washed with saturated aqueous sodium chloride (2 × 100 ml), dried, and evaporated. Distillation of the residue under reduced pressure yielded the lactone (20) (23.4 g, 60%) as a liquid, b.p. 85—86 °C at 3.5 mmHg (lit.,[9] 63—64 °C at 1.0 mmHg); $\nu_{max.}$ (film) 3 500, 2 970, 1 770, 1 370, 1 160, 1 060, and 980 cm^{-1}; $\tau(CDCl_3)$ 5.45—5.95 (2 H, m, CH_2O), 6.57—7.15 (2 H, m, cyclobutyl-CHCH), and 7.20—8.20 (4 H, m, cyclobutyl-CH_2CH_2).

The lactone (20) was also prepared by reduction of the anhydride (19) (50.4 g, 0.4 mol scale) with sodium borohydride in propan-2-ol according to a previously reported [9] procedure. The yield of (20) by this method varied from 18 to 33%.

Butyl cis-2-(*Cyanomethyl*)*cyclobutanecarboxylate* (25).—The ester (25) was prepared in a similar manner to the *trans*-cyclopropyl nitrile (8) using the *cis*-tosylate (24) (7.14 g, 21 mmol) and potassium cyanide (1.56 g, 24 mmol) in dry DMSO (50 ml) at 90 °C. Distillation of the crude product under reduced pressure gave the cis-*cyano-ester* (25) (3.4 g, 83%) as a liquid, b.p. 102—104 °C at 0.8 mmHg. A sample (0.2 g) for elemental analysis was further purified by h.p.l.c. using n-pentane–ethyl acetate (4 : 1) as eluant (Found: C, 67.45; H, 8.85; N, 7.15. $C_{11}H_{17}NO_2$ requires C, 67.65; H, 8.8; N, 7.2%); $\nu_{max.}$ (film) 2 960, 2 870, 2 240, 1 730, 1 470, 1 195, and 1 025 cm^{-1}; $\tau(CDCl_3)$ 5.93 (2 H, t, *J* 6 Hz, CO_2CH_2), 7.30—7.65 (2 H, m, CH_2CN), and 6.80—9.30 (13 H, m, $CH_2CH_2CH_3$ and cyclobutyl); *m/z* 195 (M^+, 0.1%), 122 (100), 94 (62), 56 (55), 41 (54), and 27 (50).

Reaction of Butyl cis-2-(*Cyanomethyl*)*cyclobutanecarboxylate* (25) *with Hydrazine Hydrate*.—A mixture of the *cis*-cyano-ester (25) (3.32 g, 17 mmol), 100% hydrazine hydrate (2.55 g, 51 mmol), and ethanol (5 ml) was stirred and heated in an oil-bath at 130—135 °C for 1 h when t.l.c. indicated absence of starting material. The cooled mixture on evaporation gave an oil that crystallised when kept in the cold. The product was triturated with ethyl acetate, filtered, and dried. Recrystallisation from ethyl acetate gave a crystalline solid (1.7 g) that was shown to be identical to the *trans*-hydrazide (17) by m.p., mixed m.p., and i.r. and ^1H n.m.r. spectra.

Reaction of cis-2-(*Bromomethyl*)*cyclobutylamine Hydrobromide* (34) *with Sodium Cyanide*.—A mixture of the *cis*-amine salt (34) [9] (2.45 g, 0.01 mol) and sodium cyanide (1.5 g, 0.03 mol) in dry DMSO (50 ml) was stirred at room temperature for 16 h and then the mixture poured on to 5% aqueous sodium hydrogen carbonate (100 ml). The product was extracted with ether (2 × 200 ml) and the ethereal extract washed once with water, dried, and evaporated. The residual yellow oil (0.89 g) was shown by t.l.c. to be a mixture of products. The i.r. spectrum (film) showed a characteristic absorption band at 2 220 cm^{-1} for a nitrile group whilst the ^1H n.m.r. spectrum ($CDCl_3$) indicated the presence of olefinic protons in the τ 3.80—5.15 region.

The crude product (0.5 g) was dissolved in ethanol (20 ml), 1M-sodium hydroxide (20 ml) added, and the mixture heated on a water bath for 1 h, then cooled and evaporated. The residue, dissolved in water (2 ml), was deposited on an ion-exchange column (15 g resin) and the product eluted with 1M-ammonium hydroxide. Evaporation of the appropriate fractions yielded the α-amino-acid (38) (0.077 g) as a crystalline solid, m.p. 252—255 °C (lit.,[22] 250—255 °C) (Found: C, 55.9; H, 8.6; N, 10.8. Calc. for $C_6H_{11}NO_2$: C, 55.8; H, 8.6; N, 10.85%); $\nu_{max.}$ (KBr) 3 320—2 370br, 2 090, 1 665, 1 635, 1 590, 1 520, 1 415, 1 130, and 910 cm^{-1}; $\tau(D_2O)$ 3.70—4.40 (1 H, m, =CH), 4.57—5.05 (2 H, m, $=CH_2$), 4.27 (1 H, t, *J* 6 Hz, CHN), and 7.56—8.30 (4 H, m, CH_2CH_2); *m/z* 129 (M^+); R_F (Kieselgel 60 F_{254}, n-butyl alcohol–acetic acid–water, 3 : 1 : 1) 0.44 (lit.,[22] 0.46).

Methyl cis-2-(*Bromomethyl*)*cyclobutylcarbamate* (39).—To a vigorously stirred suspension of the *cis*-amine hydrobromide (34) (3.92 g, 16 mmol) in dry ether (100 ml) was added dry pyridine (2.53 g, 32 mmol) followed by dropwise addition of methyl chloroformate (3.02 g, 32 mmol). The mixture was stirred at room temperature for 18 h, then filtered and the residue washed with ether. The combined ethereal filtrate was washed successively with water (50 ml), 5% hydrochloric acid (50 ml), and water (50 ml); the solution was then dried and evaporated giving an oil which crystallised when kept in the cold. The almost colourless needles of the *carbamate* (39) (2.38 g, 67%) were washed with light petroleum and dried, m.p. 75—76 °C (from light petroleum) (Found: C, 38.0; H, 5.45; Br, 35.85; N, 6.35. $C_7H_{12}BrNO_2$ requires C, 37.85; H, 5.45; Br, 36.0; N, 6.3%); $\nu_{max.}$ (KBr) 3 300, 2 995, 2 950, 1 720, 1 690, 1 550, 1 280, 1 050, and 780 cm^{-1}; $\tau(CDCl_3)$ 4.50—5.13br (1 H, s, NH), 5.20—5.84 (1 H, m, cyclobutyl-CHN), 6.36 (3 H, s, CH_3), 6.24—6.54 (2 H, m, CH_2Br), 6.58—7.30 (1 H, m, cyclobutyl-CH), and 7.35—8.40 (4 H, m, cyclobutyl-CH_2CH_2); *m/z* 223 (M^+, 0.1%), 221 (M^+, 0.1), 142 (94), 114 (99), 76 (100), 67 (90), and 59 (93).

Methyl cis-2-(*Cyanomethyl*)*cyclobutylcarbamate* (40).—A

mixture of the *cis*-bromomethyl compound (39) (2.0 g, 9 mmol) and potassium cyanide (0.65 g, 10 mmol) in dry DMSO (100 ml) was heated at 90 °C under an atmosphere of dry nitrogen for 1 h. The cooled mixture was carefully poured on to saturated aqueous sodium chloride solution (200 ml) and then the aqueous solution extracted with ether (3 × 100 ml). The ethereal extract was dried and evaporated giving the product as a light yellow oil (1.5 g). A sample (0.5 g) was purified by h.p.l.c. using dichloromethane–methanol (99 : 1) as eluant. Evaporation gave an oil that crystallised when kept in the cold. The crystals of the cis-*cyano-carbamate* (40) were washed with light petroleum, filtered, and dried, m.p. 60—61 °C (from light petroleum) (Found: C, 57.2; H, 7.15; N, 16.6. $C_8H_{12}N_2O_2$ requires C, 57.15; H, 7.2; N, 16.65%); ν_{max} (KBr) 3 300, 2 940, 2 240, 1 720, 1 700, 1 560, 1 275, 1 065, 1 030, and 780 cm^{-1}; $\tau(CDCl_3)$ 4.45—5.25br (1 H, s, NH), 5.35—6.00 (1 H, m, cyclobutyl-CHN), 6.35 (3 H, s, CH_3), 6.85—8.50 (7 H, m, CH_2CN and cyclobutyl); *m/z* 168 (M^+, 0.5%), 101 (100), 59 (54), 56 (67), 42 (26), and 28 (38).

cis-2-*Aminocyclobutylacetic Acid* (2c).—The crude *cis*-cyano-carbamate (40) (0.84 g, 5 mmol) dissolved in ethanol (20 ml) was hydrolysed in a manner similar to that for the *trans*-cyclopropyl derivative (10) using 1M-sodium hydroxide (20 ml, 20 mmol). A similar work-up on an ion-exchange column (30 g resin) using 1M-ammonium hydroxide as eluant gave the *amino-acid* (2c) (0.13 g, 20%) as a crystalline solid, m.p. 178—180 °C (from EtOH) (Found: C, 55.65; H, 8.65; N, 10.75. $C_6H_{11}NO_2$ requires C, 55.8; H, 8.6; N, 10.85%); $\nu_{max.}$ (KBr) 3 350—2 360br, 2 140, 1 650, 1 560, 1 425, 1 400, 1 280, and 695 cm^{-1}; $\tau(D_2O)$ 5.82—6.32 (1 H, m, cyclobutyl-CHN), and 6.73—8.43 (7 H, m, CH_2CO_2H and cyclobutyl); *m/z* 129 (M^+, 0.1%), 111 [($M - H_2O$), 0.1] 101 (10), 83 (8), 56 (43), 43 (100), and 28 (10); R_F: I, 0.30; II, 0.38.

cis-2-*Azabicyclo*[3.2.0]*heptan*-3-*one* (49).—The *cis*-cyclobutyl amino-acid (2c) (0.01 g) was heated in an oil-bath at 200 °C for 15 min when the lactam (49) was obtained as a brown oil. The crude product was dried, $\nu_{max.}$ (film) 3 280, 2 980, 2 940, 1 690, 1 420, 1 310, 1 290, and 1 240 cm^{-1}; *m/z* 111 (M^+, 0.6%), 83 (100), 55 (57), 41 (11), 28 (14), and 18 (27).

cis-2-*Aminocyclopentylacetic Acid* (2e).—A mixture of the cyclopentyl-lactam (44) (1.56 g, 12.5 mmol), ethanol (20 ml), and 1M-sodium hydroxide (15 ml, 15 mmol) was heated to reflux for 24 h and then a further quantity (15 ml) of 1M-sodium hydroxide added and the heating continued for another 24 h. The cooled mixture was evaporated, and the residue dissolved in water (5 ml) and deposited on an ion-exchange column (100 g resin). Elution with 1M-ammonium hydroxide and evaporation of the appropriate fractions gave the cis-*amino-acid* (2e) (1.0 g, 56%) as a crystalline solid, m.p. 167—170 °C (from EtOH) (Found: C, 58.55; H, 9.1; N, 9.7. $C_7H_{13}NO_2$ requires C, 58.7; H, 9.15; N, 9.8%); $\nu_{max.}$ (KBr) 3 250—2 360br, 2 200, 1 670, 1 630, 1 555, 1 415, 1 385, 1 260, and 710 cm^{-1}; $\tau(D_2O)$ 6.10—6.50 (1 H, m, cyclopentyl-CHN), and 7.40—8.90 (9 H, m, CH_2CO_2H and cyclopentyl); *m/z* 143 (M^+, 2%), 125 [($M - H_2O$), 19], 96 (48), 83 (20), 57 (17), and 56 (100); R_F: I, 0.32; II, 0.53.

trans-2-*Aminocyclopentylacetic Acid* (2f).—A mixture of the *trans*-amino-ester (45) (1.71 g, 10 mmol), ethanol (20 ml) and 1M-sodium hydroxide (11 ml, 11 mmol) was heated on a water-bath for 1 h. The cooled mixture was evaporated and the residue, dissolved in water (5 ml), deposited on an ion-exchange column (25 g resin). Elution with 1M-ammonium hydroxide and evaporation of the appropriate fractions yielded the trans-*amino-acid* (2f) (1.15 g, 80%) as a crystalline solid, m.p. 232—236 °C (decomp.) (from EtOH) (Found: C, 58.7; H, 8.95; N, 9.75. $C_7H_{13}NO_2$ requires C, 58.7; H, 9.15; N, 9.8%); $\nu_{max.}$ (KBr) 3 300—2 360br, 2 220, 1 670, 1 575, 1 450, 1 390, and 1 110 cm^{-1}; $\tau(D_2O)$ 6.50—6.95 (1 H, m, cyclopentyl-CHN), and 7.45—8.95 (9 H, CH_2CO_2H and cyclopentyl); *m/z* 143 (M^+, 0.4%), 125 (0.4), 83 (25), 57 (23), 56 (100), 43 (9), and 30 (15); R_F: I, 0.31; II, 0.55.

Conversion of Ethyl 2-*Hydroxyiminocyclohexylacetate* (46) *into* cis- *and* trans-7-*Azabicyclo*[4.3.0]*nonan*-8-*one* (47) *and* (48).—The cyclohexyl oxime (46) [26] (15 g) in ethanolic hydrogen chloride (150 ml) was reduced by catalytic hydrogenation over platinum oxide (3 g) in a similar manner to the cyclopentyl oxime (43). A similar work-up using chloroform (5 × 100 ml) to extract the final product gave, after evaporation of the dried solution, a red liquid. The crude product was heated at 170 °C for 2 h to affect conversion into the lactams (47) and (48) and then the mixture distilled under reduced pressure giving a mixture of (47) and (48) (4.4 g) as a viscous oil, b.p. 107—108 °C at 0.25 mmHg.

The mixture (1.3 g) was separated by h.p.l.c. on Kieselgel 60 (40—63 μm) (1 kg) using dichloromethane–methanol (97 : 3) as eluant. Evaporation of the fractions containing the less-polar component gave the *trans*-lactam (48) as a viscous oil that crystallised when kept in the cold. The crystals of (48) (0.2 g) were washed with light petroleum and dried, m.p. 80—81 °C (lit.,[26] 82—83.5 °C) (Found: C, 68.9; H, 9.35; N, 10.1. Calc. for $C_8H_{13}NO$: C, 69.05; H, 9.4; N, 10.05%); $\nu_{max.}$ (KBr) 3 200, 3 090, 2 940, 2 860, 1 700, 1 455, 1 390, 1 335, 1 280, and 885 cm^{-1}; $\tau(CDCl_3)$ 3.25—4.12br (1 H, s, NH), 6.66—7.25 (1 H, m, CHN), and 7.39—8.95 (11 H, CH_2CO and cyclohexyl); *m/z* 139 (M^+, 52%), 96 (100), 68 (22), 67 (47), and 54 (22).

Evaporation of the fractions containing the more-polar component gave the cis-*lactam* (47) (0.87 g) as a viscous liquid (Found: C, 69.05; H, 9.4; N, 10.0. $C_8H_{13}NO$ requires C, 69.05; H, 9.4; N, 10.05%); $\nu_{max.}$ (film) 3 240, 2 950, 2 850, 1 700, 1 450, 1 428, 1 300, 1 275, and 1 015 cm^{-1}; $\tau(CDCl_3)$ 2.90—3.70br (1 H, s, NH), 6.25—6.53 (1 H, m, CHN), 7.40—8.03 (3 H, m, CH_2CO and cyclohexyl-CH), and 8.08—8.92 (8 H, m, cyclohexyl); *m/z* 139 (M^+, 64%), 96 (100), 55 (19), 41 (21), and 39 (21).

cis-2-*Aminocyclohexylacetic Acid* (2g).—A mixture of the *cis*-cyclohexyl lactam (47) (0.556 g, 4 mmol), ethanol (10 ml), and 1M-sodium hydroxide (6 ml, 6 mmol) was heated to reflux for 18 h and then a further quantity (6 ml) of 1M-sodium hydroxide added and the mixture refluxed for another 24 h. The cooled mixture was evaporated, the residue dissolved in water (5 ml), and the resulting solution deposited on an ion-exchange column (15 g resin). Elution with 1M-ammonium hydroxide and evaporation of the appropriate fractions gave the cis-*amino-acid* (2g) (0.26 g, 41%) as a crystalline solid, m.p. 185—187 °C (from MeOH) (Found: C, 60.8; H, 9.6; N, 8.8. $C_8H_{15}NO_2$ requires C, 61.1; H, 9.6; N, 8.9%); $\nu_{max.}$ (KBr) 3 300—2 360br, 2 170, 1 660, 1 630, 1 570, 1 405, 1 055, 865, and 725 cm^{-1}; $\tau(D_2O)$ 6.22—6.73 (1 H, m, cyclohexyl-CHN), and 7.50—8.79 (11 H, m, CH_2CO_2H and cyclohexyl); *m/z* 157 (M^+, 13%), 139 [($M - 18$), 40], 114 (14), 96 (86), 56 (100), and 43 (32), R_F: I, 0.26; II, 0.74; III, 0.33; IV, 0.19.

trans-2-*Aminocyclohexylacetic Acid* (2h).—The *trans*-

cyclohexyl lactam (48) (0.139 g, 1 mmol) was hydrolysed in a similar manner to the *cis*-lactam (47) using 1M-sodium hydroxide (1.5 ml, 1.5 mmol) and ethanol (5 ml). Work-up on an ion-exchange column (10 g) as before yielded the *trans*-amino-acid (2h) (0.05 g, 32%) as a crystalline solid, m.p. 236—237 °C [lit.,[26] 221 °C (decomp.) for the monohydrate] (from MeOH) (Found: C, 60.9; H, 9.6; N, 8.75. Calc. for $C_8H_{15}NO_2$: C, 61.1; H, 9.6; N, 8.9%); $\nu_{max.}$ (KBr) 3 600—2 360br, 2 140, 1 670, 1 555, 1 405, and 1 155 cm^{-1}; $\tau(D_2O)$ 6.80—7.35 (1 H, m, cyclohexyl-CHN), and 7.50—9.01 (11 H, m, CH_2CO_2H and cyclohexyl); *m/z* (M^+, 12%), 139 [($M - H_2O$), 14], 114 (31), 96 (36), 56 (100), 43 (42), and 29 (31); R_F: I, 0.29; II, 0.75; III, 0.37; IV, 0.22.

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REFERENCES

[1] T. N. Chase and D. B. Towers, eds., 'GABA in Nervous System Function,' Raven Press, New York, 1976.
[2] S. J. Enna, L. Z. Stern, G. J. Wastek, and H. I. Yamamura, *Life Sciences*, 1977, **20**, 205; P. L. McGeer and E. G. McGeer, in ref. 1, p. 487.
[3] O. Hornykiewicz, K. G. Lloyd, and L. Davidson, in ref. 1, p. 479; J. R. Walters and T. N. Chase, in 'Neurotransmitter Function, Basic and Clinical Aspects,' ed. W. S. Fields, Stratton, New York, 1977, p. 193.
[4] R. Roberts, in ref. 1, p. 515; D. P. Van Kammen, *Am. J. Psychiat.*, 1977, **134**, 138.
[5] D. B. Towers, in ref. 1, p. 461; B. S. Meldrum, *Int. Rev. Neurobiol.*, 1975, **17**, 1.
[6] P. Krogsgaard-Larsen, J. Scheel-Krüger, and H. Kofod, eds., 'GABA-Neurotransmitters; Pharmacochemical, Biochemical, and Pharmacological Aspects,' Munksgaard, Copenhagen, 1979.
[7] R. D. Allan, D. R. Curtis, P. M. Headley, G. A. R. Johnston, S. M. E. Kennedy, D. Lodge, and B. Twitchin, *Neurochem. Res.*, 1980, **5**, 393.
[8] S. H. Nicholson, C. J. Suckling, and L. L. Iversen, *J. Neurochem.*, 1979, **32**, 249.
[9] C. C. Schroff, W. S. Stewart, S. J. Uhm, and J. W. Wheeler, *J. Org. Chem.*, 1971, **36**, 3356.
[10] G. B. Payne, *J. Org. Chem.*, 1967, **32**, 3351.
[11] K. B. Wiberg, R. K. Barnes, and J. Albin, *J. Am. Chem. Soc.*, 1957, **79**, 4994.
[12] I. A. D'yakonov and N. D. Pirogova, *Zh. Obsch. Khim.*, 1951, **21**, 1979.
[13] N. M. Yoon, C. S. Pak, H. C. Brown, S. Krishnamurthy, and T. P. Stocky, *J. Org. Chem.*, 1973, **38**, 2786.
[14] I. A. D'yakonov and O. V. Guseva, *Sb. Stat. Obsch. Khim., Akad. Nauk S.S.S.R.*, 1953, **1**, 425.
[15] D. T. Witiak, B. K. Sinha, O. S. Lee, and D. R. Feller, *J. Med. Chem.*, 1972, **15**, 803.
[16] R. W. Hart, R. E. Gibson, J. D. Chapman, A. R. Reuvers, B. K. Sinha, R. K. Griffiths, and D. T. Witiak, *J. Med. Chem.*, 1975, **18**, 323.
[17] J. G. Cannon, A. B. Rege, and T. L. Gruen, *J. Med. Chem.*, 1972, **15**, 71; P. W. Erhardt, R. J. Gorczynski, and W. G. Anderson, *ibid.*, 1979, **22**, 907; D. T. Witiak, H. J. Lee, H. D. Goldman, and B. S. Zwilling, *ibid.*, 1978, **21**, 1194; P. W. Erhardt, *J. Org. Chem.*, 1979, **44**, 883.
[18] G. J. Fonken and S. Shiengthong, *J. Org. Chem.*, 1963, **28**, 3435; S. Isoda, *Chem. Pharm. Bull.*, 1979, **27**, 3039.
[19] L. L. McCoy, *J. Am. Chem. Soc.*, 1958, **80**, 6568.
[20] Y. Kusuyama, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 1944.
[21] I. A. D'yakonov and O. V. Guseva, *Zh. Obsch. Khim.*, 1952, **22**, 1355.
[22] D. J. Drinkwater and P. W. G. Smith, *J. Chem. Soc. C*, 1971, 1305.
[23] H. Booth, F. E. King, K. G. Mason, J. Parrick, and R. L. St. D. Whitehead, *J. Chem. Soc.*, 1959, 1050. I. Murakoshi, Y. Shikakura, and J. Haginiwa, *Yakugaku Zasshi*, 1964, **84**, 674.
[24] R. P. Linstead and E. M. Meade, *J. Chem. Soc.*, 1934, 935,.
[25] M. Freifelder, in 'Practical Catalytic Hydrogenation,' Wiley-Interscience, New York, 1971, p. 264.
[26] H. Booth and F. E. King, *J. Chem. Soc.*, 1958, 2688.
[27] P. G. Gassman and K. T. Mansfield, *J. Org. Chem.*, 1967, **32**, 915.