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Aminoacids of the cyclobutane series

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Abstract. The literature data on the methods of synthesis, the reactivities, and biological activities of aminoacids of the cyclobutane series and their derivatives are described systematically and discussed. The bibliography includes 112 references.

I. Introduction

Aminoacids of the cyclobutane series (AACB) are compounds which have been relatively little investigated. Until recently AACB were almost the only type of aminoacids (AA) which have not been detected in natural sources. It was not until 1980 that Bell et al.[1] isolated for the first time 1-aminocyclobutane-1,3-dicarboxylic (2,4-methanoglutamic) and 2,4-methanopyrrolidine-2-carboxylic (2,4-methanoproline) acids from the seeds of the plant *Atelia Herbert Smithii* (*Sophoreae*, *Leguminosae*). Austin et al.[2] isolated in 1987 from the same material yet another achiral non-protein aminoacid—*cis*-1-amino-3-hydroxymethylcyclobutane-1-carboxylic acid, while Adlington et al.[3] discovered in 1983 *trans*-2-amino-1-hydrocyclobutylacetic acid in a dipeptide—an antimetabolite of the unidentified microorganism *Streptomyces species X-1092*. Since biologically active substances with antiviral, neurotropic, analgesic, depressant, antimicrobial, and other activities have been found among AACB derivatives,[4–20] these compounds have attracted the attention of investigators during the recent decades.

In the present review, an attempt is made for the first time to give a systematic account of and to survey studies in which the methods of synthesis, reactivities, and biological activities of AACB and their derivatives are considered. In order to achieve an ordered arrangement of the literature data, we subdivided all the AACB into two groups: aminocyclobutanecarboxylic acids and aminocyclobutyl-substituted carboxylic acids. All the acids and their derivatives in which the carboxy-group is linked directly to the four-membered carbocycle were included in the present review among aminocyclobutanecarboxylic acids. Compounds in which the carboxy-group is separated from the carbocycle by one or several carbon atoms were assigned to the class of aminocyclobutyl-substituted carboxylic acids. In our view, this approach facilitates a systematic treatment of these compounds and also makes it possible to compare their properties and to survey the methods of their synthesis.

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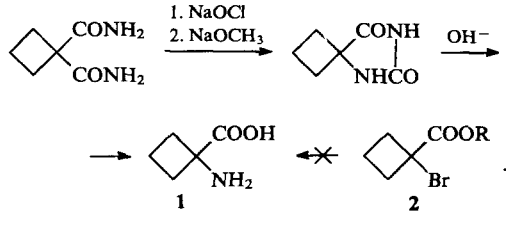
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II. Aminocyclobutanecarboxylic acids

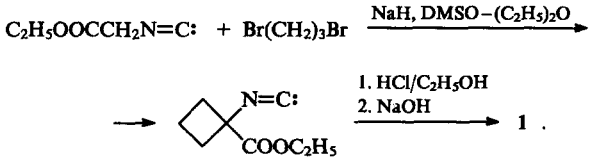
Various methods may be used for the synthesis of aminocyclobutanecarboxylic acids, including both the construction of molecules from individual units containing amino- and carboxy-groups as well as the introduction of the amino-group directly into the cyclobutanecarboxylic molecule.

1. 1-Aminocyclobutane-1-carboxylic acids

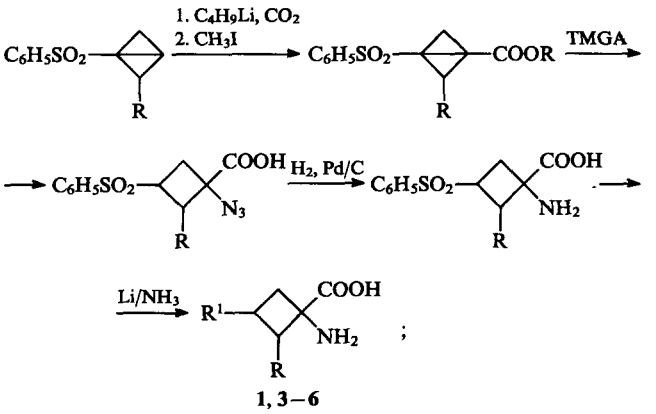
1-Aminocyclobutane-1-carboxylic acid **1** itself is of the greatest interest. Its toxicity is low and it is an inhibitor of the growth of tumours[10, 21] and a selective antagonist of *N*-methyl-D-aspartic acid in relation to the [^{2}H]-receptors of histamine and [^{3}H]-receptors of glycine,[22–25] while its 2-(3-methoxyphenyl) derivative inhibits aminooxidases in rat liver mitochondria.[6] The attempts to obtain compound **1** by the direct ammonolysis of 1-bromo-cyclobutane-1-carboxylic acid **2** (R = H) or its ester **2** (R = CH_3, C_2H_5) by ammonium hydroxide as well as by the reaction of compound **2** with potassium phthalimide (the Gabriel synthesis) or hexamethylenediamine did not yield satisfactory results. The synthesis of compound **1** by this procedure is complicated by the fact that dehydrobromination takes place in the ammonolysis stage, which, according to Connors and Ross[10] and Sudo and Ichihara,[26] leads to the formation of an unsaturated acid with the empirical formula $C_5H_{11}BrN_2O$, the structure of which has not been established. It has also not been possible to obtain compound **1** with the aid of the most often employed two-stage method of synthesis of aliphatic α-aminoacids—by the reaction of α-bromoacids or their esters with sodium azide and the subsequent reduction of the azido-group to the amino-group, since the replacement of the bromine atom in compound **2** by the azido-group was unsuccessful. A more successful preparative method of synthesis of compound **1** is the classical hydantoin synthesis of aminoacids.[10, 11, 27–31] Compound **1** was synthesised by this procedure for the first time as early as 1937,[27] and its yield reached 97%. The initial 5,5-trimethylenehydantoin was obtained by Ingold's method[32] from cyclobutane-1,1-dicarboxylic acid diamide.



The method of synthesis involving the use of ethyl isocyanoacetate and 1,3-dibromopropane has been developed recently for the preparative synthesis of compound **1** (in 95% yield). The reaction was carried out in the presence of sodium hydride in dimethyl sulfoxide/ether or acetone with subsequent stepwise hydrolysis of the intermediate cyclic α-isonitrile.[6, 33–35] Ethyl isocyanoacetate was obtained by dehydrating the ethyl ester of *N*-formylglycine with phosgene[36] or with trichloroacetic acid chloride in the presence of triethylamine.[33]



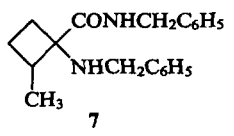
The aminoacid **1** as well as 1-aminocyclobutane-1-carboxylic acids of type **3–6** substituted in the carbocycle and their *N*-derivatives have been synthesised by the regiospecific addition of nitrogen-containing nucleophiles to 1-(arenesulfonyl)-bicyclo-[1.1.0]butane.[37] The synthesis was carried out in four stages: carboxylation of bicyclobutane, introduction of the azido-group by treatment with *N,N,N',N'*-tetramethylguanidinium azide or trimethylsilazide, reduction of the amide, and finally reductive elimination of the arenesulfo-group with lithium in liquid ammonia.



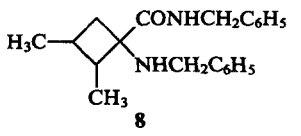
1, 3–6

R = R¹ = H (**1**); R = H, R¹ = $C_6H_5SO_2$ (**3**);
R = CH_3, R¹ = $C_6H_5SO_2$ (**4**);
R = CH_3, R¹ = H (**5**); R = R¹ = CH_3 (**6**);
TMGA = *N,N,N',N'*-tetramethylguanidinium azide.

The carboxy-group was introduced into bicyclobutane at −78 °C in solution in hexane or tetrahydrofuran (THF), while the azido-group was introduced in *N*-methyl-2-pyrrolidinone or dimethylformamide (DMF) at 80–90 °C. Although the reaction of bicyclobutane with trimethylsilazide is ten times slower than that with *N,N,N',N'*-tetramethylguanidinium azide, the methoxycarbonyl groups are not solvolysed under these conditions and the corresponding esters are obtained in 92% yield. The aminoacids **1** and **3–6** were isolated on Dowex 50 × 8 ion-exchange resin mainly in the form of the *cis*-isomers. Amides substituted in the amino-group, for example, the benzamide of *N*-benzylmethanovaline **7** and the benzamide of *N*-benzylmethanoisoleucine **8**, were also synthesised in this way.

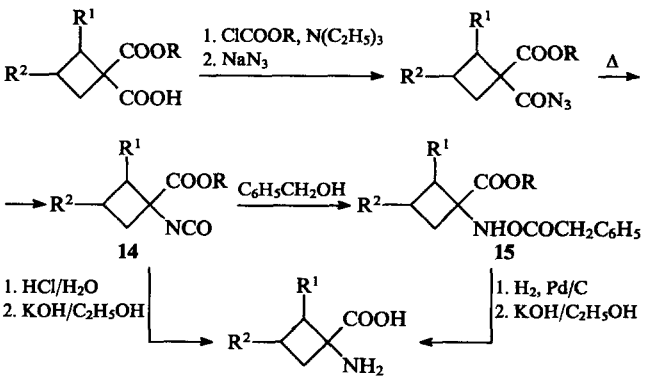


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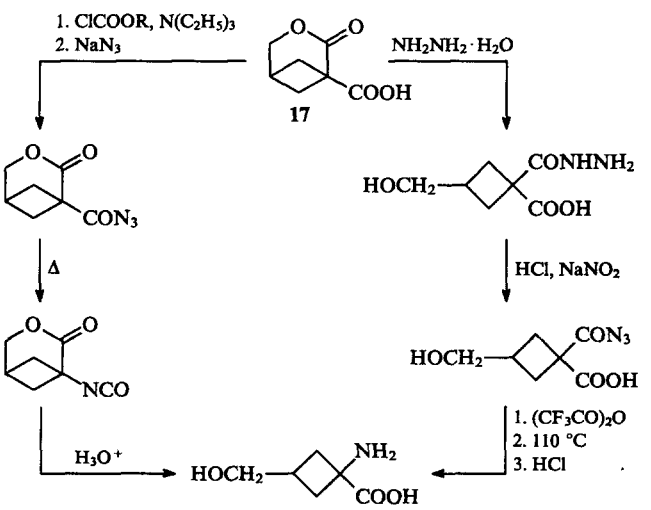
The conversion of the carboxy-group into the amino-group by the Curtius method has been used to obtain analogues of compound **1** aryl-substituted in the four-membered carbocycle.[9, 11, 38] A modified Curtius method has been proposed for the synthesis of 1-amino-2-arylcyclobutane-1-carboxylic acids **9** and **10** and 1-amino-3-arylcyclobutane-1-carboxylic acids **11–13**.[39] It is based on the conversion of 2- and 3-arylcyclobutane-1,1-dicarboxylic acids into the corresponding isocyanates of arylcyclobutane-1-carboxylic acids **14**. This was achieved by the successive treatment of the monoesters of cyclobutane-1,1-dicarboxylic acids initially with chlorocarbonic ester in the presence of triethylamine and then with sodium azide and by heating the resulting acyl azide in dry toluene.[38]



9–13

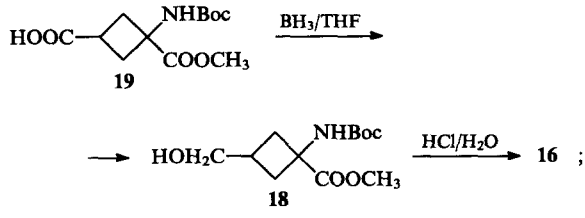
R = CH_3, C_2H_5; R² = H; R¹ = C_6H_5 (**9**), 3,4-$CH_2O_2C_6H_3$ (**10**);
R¹ = H; R² = C_6H_5 (**11**), 3,4-$(CH_3O)_2C_6H_3$ (**12**), 3,4-$CH_2O_2C_6H_3$ (**13**).

The reaction of the isocyanates **14** with benzyl alcohol made it possible to obtain the aminoacid esters **15** containing the *N*-benzyloxycarbonyl group. The catalytic elimination of the benzyloxycarbonyl group from compound **15** over Pd/C in ethyl acetate and alkaline hydrolysis of the ester group lead to the *trans*-aminoacids **9–13**. The *trans*-aminoacid **13** has been obtained[38] in this way in a yield exceeding 90%. The Curtius reaction has also been used as the key stage in the synthesis of the natural *cis*-1-amino-3-hydroxymethylcyclobutane-1-carboxylic acid(*cis*-**16**)[2] from oxabicyclo[3.1.1]-heptan-2-one-1-carboxylic acid **17**.[40, 41]



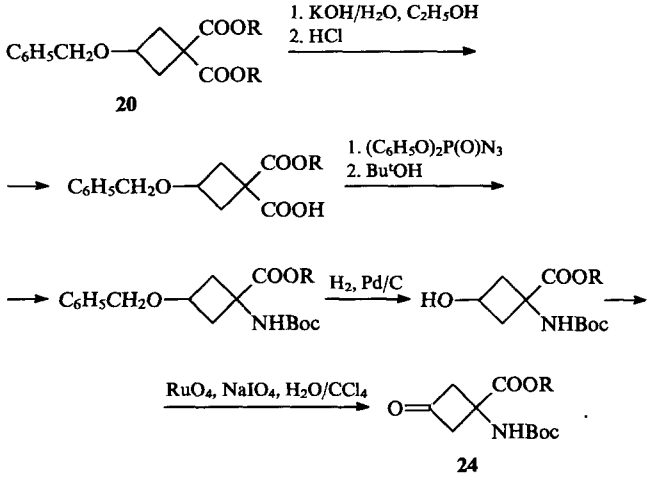
16

The lactone **17** is converted into the hydrazide, the reaction of which with nitrous acid affords the azide; the rearrangement of the latter in the presence of trifluoroacetic acid anhydride leads to compound *cis*-**16**. The rearrangement of the azide of 3-oxabicyclo[3.1.1]-heptan-2-one-1-carboxylic acid and the subsequent hydrolysis of the resulting isocyanate afforded compound *trans*-**16**, which Hughes and Clardy[42, 43] obtained by acid hydrolysis (yield ~97%) from the methyl ester of *cis*-1-[(*tert*-butoxycarbonyl)amino]-3-(hydroxymethyl)cyclobutanecarboxylic acid **18**, which was synthesised, in its turn, by the selective reduction of the methyl ester of *N*-(*tert*-butoxycarbonyl)-2,4-methanoglutamic acid **19** with borane in THF.



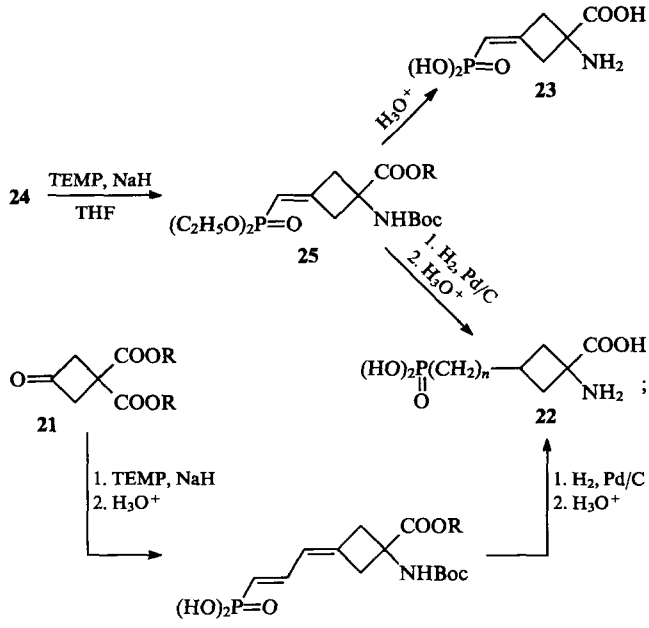
Boc = *tert*-butyloxycarbonyl.

cis- and *trans*-1-Amino-3-phosphonylmethylcyclobutane-1-carboxylic acids **22** (n = 1), 1-amino-3-(3-phosphonylpropyl)cyclobutane-1-carboxylic acid **22** (n = 3), 1-amino-3-phosphonylmethylenecyclobutane-1-carboxylic acid **23**, and their derivatives have been synthesised recently[44] from the esters of 3-benzyloxycyclobutane-1,1-dicarboxylic acid **20** and 3-oxocyclobutane-1,1-dicarboxylic acid **21** in order to investigate them as agonists and antagonists of neurotransmitter aminoacids, in particular *N*-methyl-D-aspartic acid (NMDA). The initial ester of 1-amino-3-oxocyclobutane-1-carboxylic acid **24** was obtained from 3-benzoyloxycyclobutane-1,1-dicarboxylic acid **20** in four stages.[44]



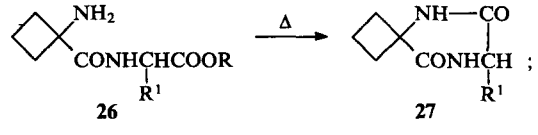
The interaction of the aminoester **24** with tetraethylmethylenebisphosphonate (TEMP) in the presence of sodium hydride leads to the ethyl ester of 1-[(*tert*-butoxycarbonyl)amino]-3-[(diethoxyphosphonyl)methylene]cyclobutane-1-carboxylic acid **25**, the acid hydrolysis of which affords the aminoacid **23** (yield 42%–74%), while the reduction and acid hydrolysis of the unsaturated intermediate ester give rise to a mixture of the *cis*- and *trans*-aminoacids **22** (n = 1) in 33% yield.

cis- and *trans*-1-Amino-3-(3-phosphonylpropyl)cyclobutane-1-carboxylic acids **22** (n = 3) were obtained by a similar procedure in an overall yield of 79% from *cis*- and *trans*-tetraethyl 2-propenylene-1,3-diphosphonate (TEPP) and diethyl 3-oxocyclobutane-1,1-dicarboxylate **21**.



R = C_2H_5; n = 1, 3 .

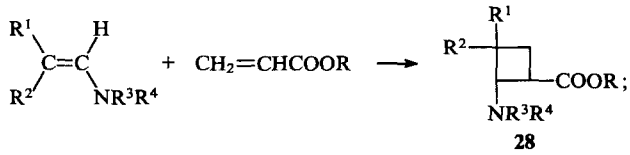
The stereoisomers were separated on Dowex AG50W ion-exchange resin.[44] L-Aspartyl and D-alanyl dipeptides[45, 46] and D-alanyl tripeptides,[45] the structure of which includes compound **1**, have been obtained. The cyclic dipeptides **27** have been synthesised by cyclising the dipeptides having the general formula **26**. They have been recommended for use in medicine and veterinary science.[46]



R = CH_3:
R^1 = H, CH_3, $CH_2CH(CH_3)_2$, $CH(CH_3)_2$, CH_2OH, $C_6H_5CH_2$.

2. 2-Aminocyclobutane-1-carboxylic acids

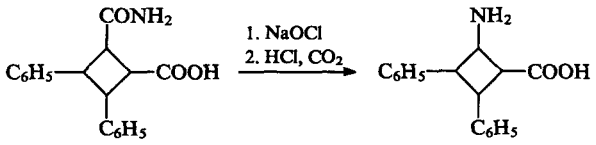
2-Aminocyclobutane-1-carboxylic acids **28** (R = H) are the most numerous among the AACB synthesised and are of interest as biologically active compounds,[7, 17–19, 46–48] antioxidants,[7, 46] and monomers for the synthesis of polyamide resins.[4] Substances with analgesic,[7, 17] anaesthetic,[18] and sedative[7] activities have been discovered among them.



R = CH_3, C_2H_5; R^1 = R^2 = CH_3, C_2H_5;
R^1+R^2 = $(CH_2)_5$; R^3 = R^4 = CH_3, C_2H_5, $CH_3(CH_2)_2CH_2$;
R^3+R^4 = $(CH_2)_5$, $CH_2CH_2OCH_2CH_2$; NR^3R^4 = CN .

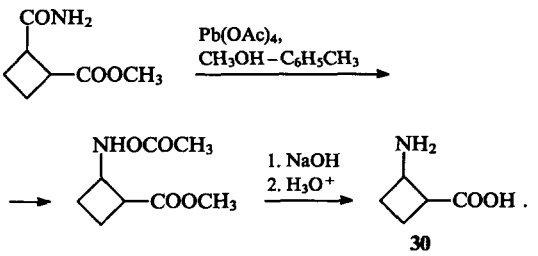
The principal method of synthesis of 2-aminocyclobutane-1-carboxylic acids is the cycloaddition of enamines to electrophilic olefins, for example acrylonitrile and acrylic acid esters.[7, 17, 18, 46, 50–56] Enamines without a hydrogen atom in the β-position, in particular enamines based on isobutenyl, have been mainly used. The reaction was carried out at ~85 °C in solution in acetonitrile (yield ~91%) or in an autoclave at 170–175 °C (yield 70%–75%). 2-(*N*,*N*-Dialkylamino)-3,3-dialkylcyclobutane-1-carboxylic acids **28** (R^1–R^4 = alkyl; R = H) and their esters

and amides have been obtained in this way. Shoemer and Schenk[57] used the Hofmann rearrangement for the synthesis of 2-amino-3,4-diphenylcyclobutane-1-carboxylic acid **29**. The target acid **29** was obtained from β-truxinic acid by treatment with sodium hypochlorite.



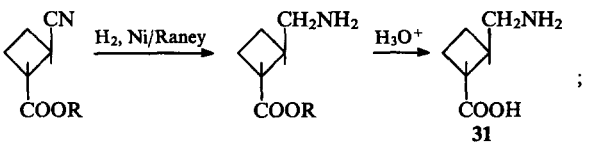
29

Unsubstituted *cis*- and *trans*-2-aminocyclobutane-1-carboxylic acids **30** have been synthesised from the esters of *cis* and *trans*-2-carbamoylcyclobutane-1-carboxylic acids. On treatment with lead tetraacetate, the ester amides were converted into the corresponding esters of *N*-(2-methoxycarbonylcyclobutyl)carbamates, the hydrolysis and decarboxylation of which led to a mixture of *cis*-**30** and *trans*-**30**.[58] The corresponding diastereoisomers were obtained in 56% and 66% yields by resolution on ion-exchange resins.[49]



30

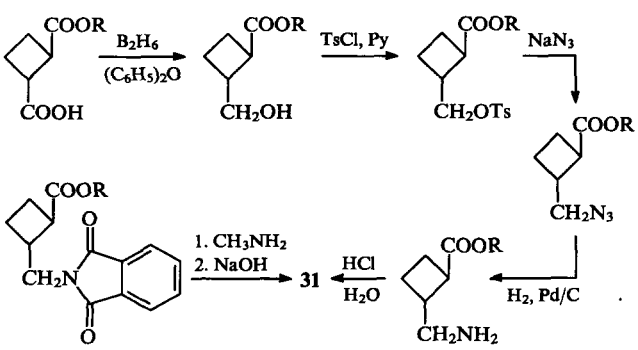
trans-2-Aminomethylcyclobutane-1-carboxylic acid **31** has been synthesised by the catalytic reduction of methyl 2-cyanocyclobutane-1-carboxylic acid and the subsequent acid hydrolysis of the ester. The reduction was carried out over Raney nickel at a pressure of ~14 MPa on heating to 130 °C.



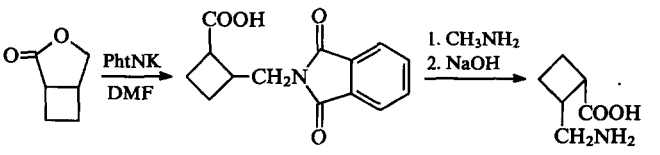
31

R = CH_3, C_2H_5, C_3H_7.

The aminoacid **31** was isolated in ~81% yield by chromatography on ion-exchange resins.[48] Methods in which *trans*-cyclobutane-1,2-dicarboxylic acid and its reaction products were used as the initial compounds have also been proposed for the preparative synthesis of compound **31**.[19, 49, 50] Thus compound **31** has been synthesised from the monoester of *trans*-cyclobutane-1,2-dicarboxylic acid by converting a carboxy-group into an alcoholic group. This was achieved by tosylation and the replacement of the tosyl group (Ts) by the azido-group. After the reduction of the azido-group, the ester of *trans*-2-methylamino-cyclobutane-1-carboxylic acid was obtained in 44% yield. Acid hydrolysis of the ester leads to compound **31** in 72% yield. The aminoacids **31** have also been synthesised by the Gabriel reaction,[50] but in this case the product was obtained in a lower yield (~47%).



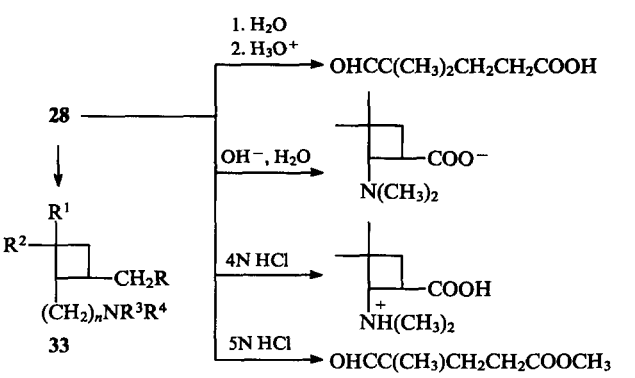
A convenient method of synthesis of *cis*-2-aminomethylcyclobutane-1-carboxylic acid **32** is based on the reaction involving the nucleophilic ring opening in *cis*-3-oxabicyclo[3.2.0]heptan-2-one with potassium phthalimide (PhtNK) and subsequent hydrolysis of the resulting phthalimide derivative with methylamine.[49]

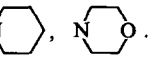


32

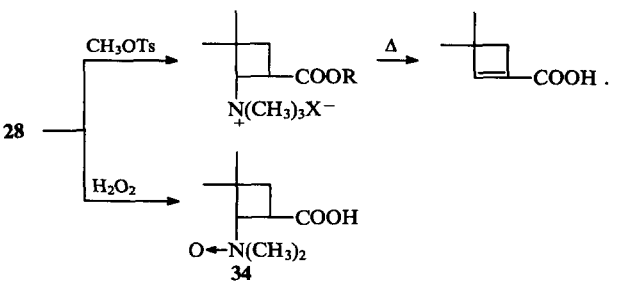
The aminoacid **32** was obtained in 67% yield.[50] Biological studies confirmed the hypothesis that the acids **31** and **32** exhibit a neurotropic activity.

The reduction of the esters **28** with metal hydrides leads to the aminoalcohols of the cyclobutane series **33**.[18, 50, 54–56] Substances with anaesthetic, analgesic, and anticholinergic activities have been discovered among the aminoalcohols **33**. They have been recommended also as intermediates for the synthesis of stabilisers of liquid fuels and for the modification of polymers.



n = 0; R = OH;
R^1 = H, CH_3, C_2H_5;
R^2 = H, C_6H_5, CH_3, C_2H_5;
R^3 = R^4 = CH_3, C_2H_5 or NR^3R^4 = .

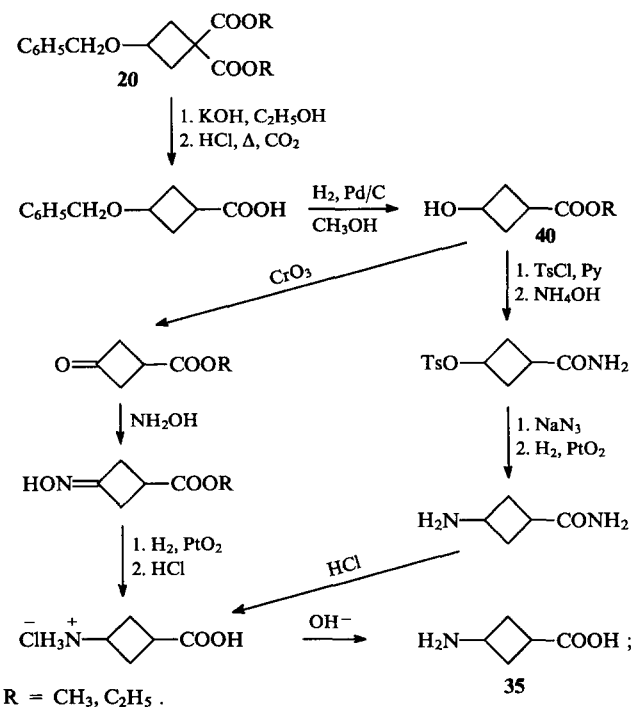
The hydrolysis of the esters **28** (R – R^4 = CH_3) in the presence of acids leads to the opening of the cyclobutane ring and the formation of dimethylglutaraldehyde and methyl dimethylglutarate.[52, 54] However, in an alkaline medium the hydrolysis involves only the ester group. The cyclobutane ring is also opened on treatment with Grignard reagents.[54] The quaternisation of the amino-group in compound **28** (R – R^4 = CH_3) by methyl tosylate and subsequent elimination of the quaternary amino-group by bases lead to 3,3-dimethylcyclobutene-1-carboxylic acid,[51, 52] whilst oxidation of compound **28** (R = H, R^1 – R^4 = CH_3) with a H_2O_2 solution affords the *N*-oxide **34**.[52]



34

3. 3-Aminocyclobutane-1-carboxylic acid

Only the *cis*- and *trans*-3-aminocyclobutane-1-carboxylic acids **35**, *cis*-3-amino-2,2-dimethylcyclobutane-1-carboxylic acid **36**, *cis*-3-(α-aminoethyl)-2,2-dimethylcyclobutane-1-carboxylic acid **37**, 3-(β-aminoethyl)-2,2-dimethylcyclobutane-1-carboxylic acid **38**, and 3-amino-2,4-diphenylcyclobutane-1-carboxylic acid **39** have been synthesised in this group of AACB and described. The *cis*- and *trans*-aminoacids **35** and **36** are of interest as cyclobutyl analogues of γ-aminobutyric acid (GABA).[61] A multistage method has been proposed for the synthesis of compound **35**, in which the diester of 3-benzyloxycyclobutane-1,1-dicarboxylic acid **20** was used as the initial compound.[63] Alkaline hydrolysis and decarboxylation of compound **20** led to 3-benzyloxycyclobutane-1-carboxylic acid, which was converted in the presence of the Adams catalyst into the ester of 3-hydroxycyclobutane-1-carboxylic acid **40**. A mixture of the diastereoisomers of compound **35** was obtained from the latter in an overall yield of 25% (relative to the intial ester **40**).

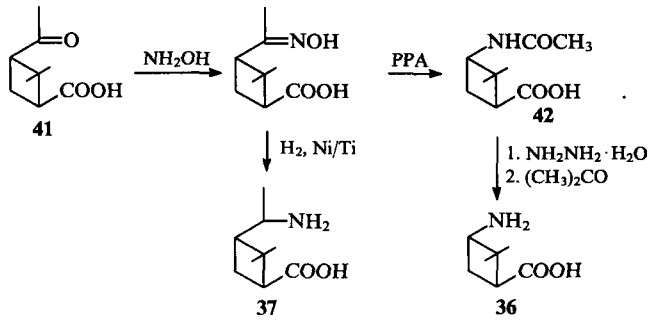


R = CH_3, C_2H_5 .

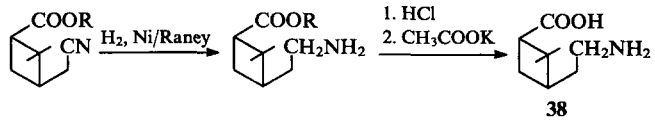
The *cis* : *trans* isomer ratio in the mixture was 1 : 1.8. The isomers were separated by crystallisation from *tert*-butyl alcohol or by chromatography on Dowex 50 × 8 ion-exchange resin. This method is distinguished by high yields at each stage of the process and by the relative availability of the initial compounds.

An alternative approach, involving the oxidation of the ester **40** with chromic acid, the conversion of the carbonyl group of 3-oxocyclobutane-1-carboxylic acid into an oxime group, and subsequent catalytic reduction of the oxime group, also affords a mixture of the diastereoisomers of compound **35** (yield ⩽20%), but the isomer ratio has not been established.[63] The aminoacid **35** exhibits a neurochemical activity, the *cis*-isomer proving to be much more active.[61]

cis-3-Amino-2,2-dimethylcyclobutane-1-carboxylic acid **36** has been synthesised from *cis*-3-acetyl-2,2-dimethylcyclobutane-1-carboxylic (pinononic) acid **41**.[64] 3-Acetamido-2,2-dimethylcyclobutane-1-carboxylic acid **42** was obtained from the ketoacid **41** in accordance with the usual scheme for the Beckmann reaction in polyphosphoric acid (PPA). Its hydrazinolysis with hydrazine hydrate leads to the aminoacid **36**. The catalytic hydrogenation of pinononic acid oxime in the presence of the Ni/Ti catalyst (Lyubarskii's catalyst) at atmospheric pressure afforded *cis*-3-(α-amino-ethyl)-2,2-dimethylcyclobutane-1-carboxylic acid **37** in 87.4% yield.[64]

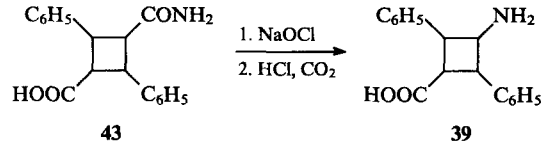


cis-3-(β-Aminoethyl)-2,2-dimethylcyclobutane-1-carboxylic acid **38** has been synthesised under similar conditions form *cis*-(3-ethoxycarbonyl-2,2-dimethyl-1-cyclobutyl)acetonitrile by reduction with hydrogen in the presence of Raney nickel.[65]



R = CH_3, C_2H_5 .

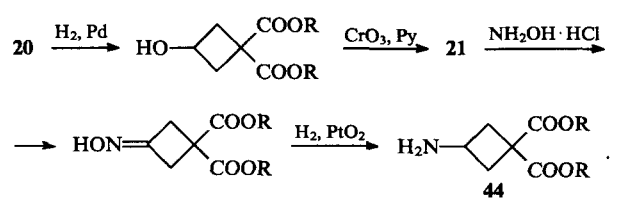
The monoamides of α-, β-, and ε-truxillic acids can be used as the key compounds in the synthesis of 3-amino-2,4-diphenylcyclobutane-1-carboxylic acid **39** by the Hofmann reaction. This was demonstrated in relation to the rearrangement of the monoamide of γ-truxillic acid **43**.[57] The rearrangement was carried out at 30–40 °C in an aqueous solution of sodium hypochlorite. The aminoacid was isolated by neutralising the reaction mixture with HCl and CO_2; the yield of compound **39** was 68% – 80%.



Biological tests showed that aminoacid **37** exerts a weak effect on the vesicular stomatitis virus and inhibits the multiplication of the group A_2 virus in chicken embryos. Among the hydrochlorides of its amides, substances were found with antistaphylococcal and antiviral activities.[64] The aminoacid **36** also exhibits a psychotropic activity, but there is no information concerning more detailed studies of this compound.

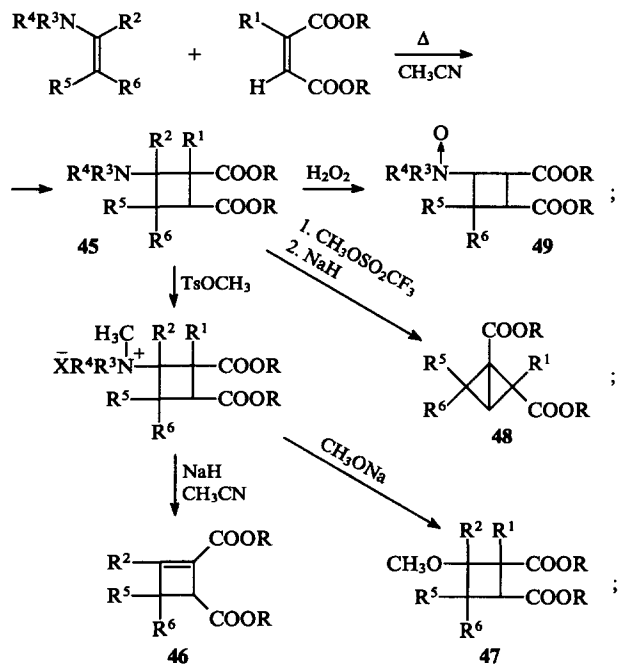
4. Aminocyclobutane-1,1-dicarboxylic and aminocyclobutane-1,2-dicarboxylic acids

Among aminocyclobutane-1,1-dicarboxylic acids, only 3-aminocyclobutane-1,1-dicarboxylic acid **44**, obtained solely as its diethyl ester, is known.[62] Compound **44** has been synthesised from diethyl 3-benzyloxycyclobutane-1,1-dicarboxylate **20** by a procedure similar to that used in the synthesis of compound **35**.[63]



The only examples of aminocyclobutane-1,2-dicarboxylic acids are 3-aminocyclobutane-1,2-dicarboxylic acids **45**, which, like the aminoacid **28**, have been obtained by the cycloaddition of

enamines to electrophilic olefins, in particular to the esters of maleic or fumaric acid.[17, 47, 51, 52, 55, 66] The reaction was carried out at 110–170 °C in solution in acetonitrile. The yields of compounds **45** are 70%–78%. It is noteworthy that the majority of the aminoacids **45** obtained were characterised as the methyl and ethyl esters. Systematic studies of their properties have not been carried out.



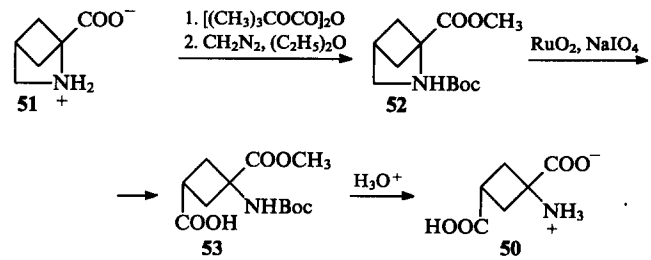
R = R^2 = H, CH_3; R^1 = H, CN, COOMe; R^3 = R^4 = CH_3, C_2H_5; R^5 = R^6 = H, CH_3, C_2H_5; R^6 = H, C_2H_5, $CH_2N(CH_3)_2$;

NR^3R^4 =  .

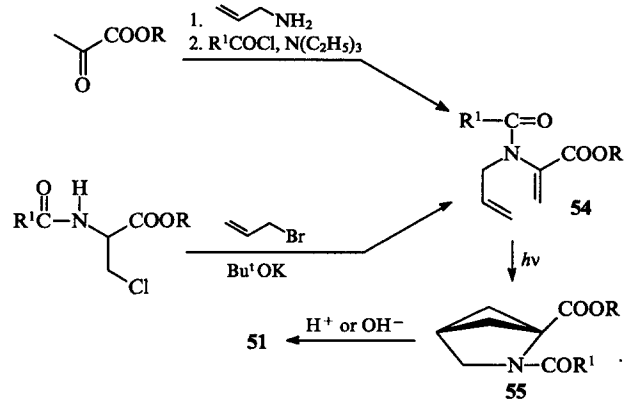
The reduction of the esters **45** (R = CH_3, C_2H_5) with $LiAlH_4$ or $NaBH_3$[55] leads to the corresponding 3-aminocyclobutane-1,2-glycols, which are of interest as intermediates for organic synthesis. As in compound **28**, the amino-group in the aminoacid **45** is quaternised with methyl iodide, methyl tosylate, and methyl trifluoromethane-sulfonate. However, in contrast to compound **28**, the elimination of the quaternary amino-group with sodium hydride, leading to the formation of cyclobutene-1,2-dicarboxylic acids **46**, proceeds only in aprotic solvents (for example, in CH_3CN).[51, 52] On the other hand, on treatment with sodium methoxide in methanol, the quaternary amino-group is replaced by the methoxy-group with formation of the corresponding 3-methoxycyclobutane-1,2-dicarboxylic acid **47**.[66] On quaternisation of 2-methoxycarbonyl-3-(*N*,*N*-dimethylamino)-4,4-dimethylcyclobutane-1,2-dicarboxylic acid **45** (R = CH_3, R^1 = $COOCH_3$, R^2 = H, R^3–R^6 = CH_3) with methyl trifluoromethanesulfonate and the elimination of the quaternary amino-group with sodium hydride, the methyl ester of 4,4-dimethylbicyclo[1.1.0]butane-1,2,2-tricarboxylic acid **48** (R = R^5 = R^6 = CH_3, R^1 = $COOCH_3$, R^2 = H) was obtained.[66] Oxidation of compound **45** with H_2O_2 solution is accompanied by partial hydrolysis and leads to the relatively stable *N*-oxides **49** (R = CH_3; R^1 = R^2 = H; R^3–R^6 = CH_3).

5. Aminocyclobutane-1,3-dicarboxylic acids

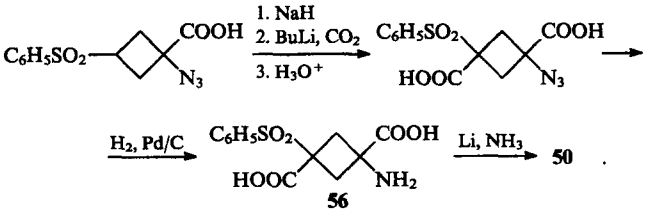
The only known aminocyclobutane-1,3-dicarboxylic acid is *trans*-1-aminocyclobutane-1,3-dicarboxylic(2,4-methanoglutamic) acid **50**, which was isolated form the seeds of *Atelia Herbert Smithii* (*Leguminosae*) together with 2,4-methanopyrrolidine-2-carboxylic acid (2,4-methanoproline) **51**.[1] The stereoisomers of compound **50** are of interest as potential antagonists of the NMDA [*N*-methyl-D-aspartic acid (Translator)] receptors,[44] as therapeutic agents for the treatment of the consequences of ischemia, and as anticonvulsants. They were synthesised by several methods. Hughes and Clardy[41, 42] obtained the achiral aminoacids **50** by oxidising the methyl ester of *N*-(*tert*-butoxycarbonyl)-2,4-methanoproline **52** with sodium metaperiodate and RuO_2 dihydrate in a solvent mixture (H_2O–CH_3CN–CCl_4). The removal of the protecting group by the acid hydrolysis of the intermediate ester of *N*-(*tert*-butoxycarbonyl)-2,4-methanoglutamic acid **53** leads to the aminoacid **50** in ~51% yield (relative to the initial compound **51**).



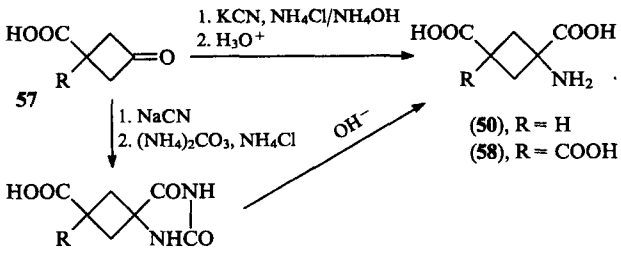
Pirrung[67] synthesised the initial aminoacid **51** from pyruvic acid and allylamine, but the yield of compound **51** proved unsatisfactory for preparative synthesis (~8.5% relative to the initial ester), since the ester of *N*-alkyl-2-acetamidopropenoic acid **54** (R = C_2H_5, R^1 = CH_3) is formed in a low yield and its photocyclisation is complicated by a side reaction and compound **55** was obtained in a yield of only 17%.



A method of synthesis of compound **51** from serine has been proposed.[42, 43] Serine was converted into 2-benzamido-3-chloropropionate, the condensation of which with allyl bromide under an inert atmosphere in the presence of potassium *tert*-butoxide at −78 °C in THF afforded the ester **54** (R = CH_3, R^1 = C_6H_5) and the photochemical cyclisation of the latter led to the ester of *N*-benzoyl-2-azabicyclo[2.1.1]hexane-1-carboxylic acid **55** in a higher yield (87%). Hydrolysis of compound **55** (R = CH_3, R^1 = C_6H_5) afforded compound **51** in 66.5% yield relative to the initial serine. Gaony[37] proposed a synthesis of a mixture of the stereoisomeric aminoacids **50** from 1-(arenesulfonyl)bicyclo[1.1.0]butane similar to the synthesis of the α-aminoacids **1** and **3**–**6**. 1-(Arenesulfonyl)bicyclo[1.1.0]-butane was converted by a standard method (see above) into the azide and then into 3-arenesulfonyl-1-azidocyclobutane-1,3-dicarboxylic acid. The reduction of the azido-group led to 1-amino-3-arenesulfonylcyclobutane-1,3-dicarboxylic acid **56**, from which the benzenesulfonyl group was removed by reductive elimination and a mixture of the stereoisomeric aminoacids **50** was obtained in 25%–30% yield.



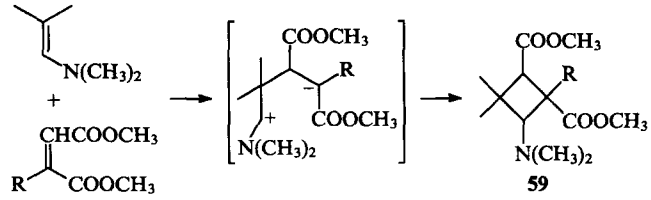
Allan et al.[44] proposed that the stereoisomeric aminoacids **50** be synthesised from 3-oxocyclobutane-1-carboxylic acid by the Strecker reaction. The yield of the aminoacids **50** was ~48% and the ratio of the *cis*- and *trans*-acids in the mixture was 3:2. An alternative synthesis of the aminoacid **50** was achieved by the Bucherer–Bergs reaction.[44] This method gives rise to a better result (overall yield 62%–66%) than the Strecker reaction, but the *cis*:*trans* isomer ratio is in this case 5:1. Pure *cis*- and *trans*-isomers of compound **50** were isolated by chromatography on Dowex AG50W resin in the H^+-form.



Biological tests showed that *trans*-**50** is 20 times more active as an agonist than NMDA; the *cis*-isomer of compound **50** is a third less active as an agonist, but it proved to be more selective.[44, 68]

6. Aminocyclobutanepolycarboxylic acids

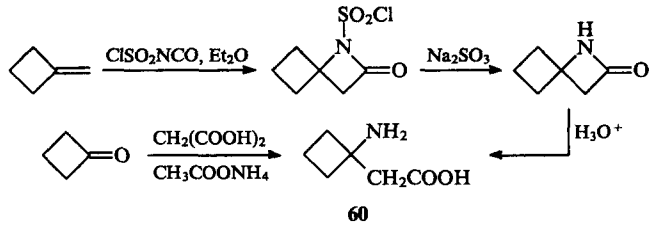
Aminocyclobutanepolycarboxylic acids are little known. 3-Aminocyclobutane-1,1,3-tricarboxylic acid **58** (R = COOH) has been obtained by the Bucherer–Bergs reaction from 3-oxocyclo-butane-1,1-dicarboxylic acid **57** (R = COOH) in solution in methanol.[44] By the cycloaddition of enamines to electron-accepting olefins, in particular by the addition of *N,N*-dimethylisobutenylamine to methyl ethylenetricarboxylate, Hall and Ykman[69] synthesised the trimethyl ester of 4-(*N,N*-dimethylamino)-3,3-dimethylcyclobutane-1,1,2-tricarboxylic acid **59** (R = $COOCH_3$), which was used for the synthesis of bicyclobutane derivatives.



III. Aminocyclobutyl-substituted carboxylic acids

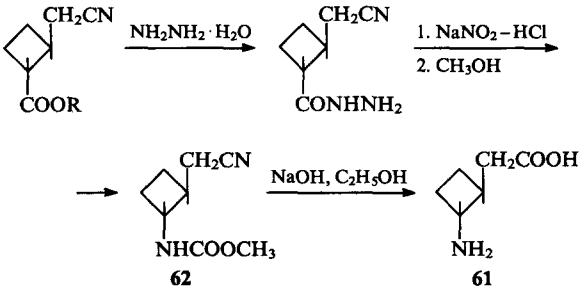
Aminocyclobutyl-substituted carboxylic acids are few in number and have been inadequately studied. Virtually all the known aminoacids of this group have been obtained by the reactions of carboxylic acids, amines, and carbonyl compounds of the cyclobutane series. The classical methods of synthesis of aminoacids have been mainly used to convert the initial compound into aminoacids.

The ability of olefins to form *N*-chlorosulfonyl-β-lactams in their reactions with chlorosulfonyl isocyanate has been used to synthesise the only known compound of this series — 1-amino-cyclobutylacetic acid **60**.[70, 75] The interaction of methylene-cyclobutane with chlorosulfonyl isocyanate led to the synthesis of *N*-chlorosulfonyl-1-azaspiro[3.3]heptan-2-one, the reduction of which with an aqueous solution of sodium sulfite[75] afforded 1-azaspiro[3.3]heptan-2-one.

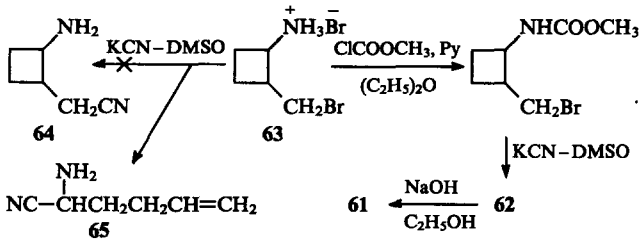


The opening of the β-lactam ring with the aid of hydrochloric acid leads to the aminoacid **60**. An alternative method of synthesis of compound **60**, from cyclobutanone, under the conditions of the Rodionov reaction has been proposed.[70] It was established that higher yields (60%–70%) of the aminoacid **60** were obtained when the monoammonium salt of malonic acid was used and on heating the reactants in solution in dimethyl sulfoxide (DMSO) or DMF. The acid **60** itself was isolated in the form of the neutral zwitter-ion on Dowex AG50W/H^+ and was used to obtain derivatives of 6-aminopenicillanic acid, which exhibit bactericidal activity.[70]

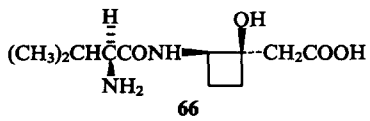
In order to investigate neurotropic activity, *cis*- and *trans*-2-aminocyclobutylacetic acids **61** were synthesised as analogues of GABA with a conformationally limited mobility.[49] *trans* **61** was obtained by a 7-stage synthesis from the diester of *trans*-cyclobutane-1,2-dicarboxylic acid.[19, 49] Using a scheme analogous to the synthesis of compound **31**,[50] the diester was converted into the ester of 2-cyano-methylcyclobutane-1-carboxylic acid.[49] The ester group was replaced by the hydrazide and further by the carbamide group, affording compound **62**. Alkaline hydrolysis of the cyanocarbamate **62** leads to *trans*-**61**.



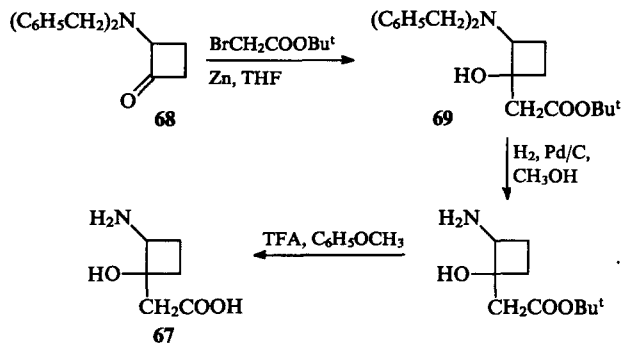
Compound *cis*-**61** was obtained by a similar procedure from the diester of *cis*-cyclobutane-1,2-dicarboxylic acid. The anhydride of *cis*-cyclobutane-1,2-dicarboxylic acid has also been used to synthesise *cis*-**61**.[49] An alternative method of synthesis of *cis*-**61** from the hydrobromide of 2-amino-1-bromomethyl-cyclobutane **63** has been proposed.[49] The conversion of the amino-group of compound **63** into the carbamide group and replacement of bromine by the cyano-group afforded the cyanocarbamate **62**, the hydrolysis of which gives rise to *cis*-**61**. It is noteworthy that the attempts to obtain the aminonitrile **64** by the direct replacement of bromine in compound **63** by the CN group as a result of treatment with potassium cyanide in DMSO at room temperature or on refluxing with sodium cyanide in ethanol led to the opening of the cyclobutane ring and the formation of the nitrile **65**. In the study of the possibility of the binding of *cis*- and *trans*-**61** to the GABA receptor, it was established that *cis*-**61** is a weak inhibitor and *trans*-**61** is a powerful inhibitor of the binding of [^{3}H]muscimol. On the other hand, *cis*- and *trans*-**61** proved to be ineffective as inhibitors of the absorption of [^{3}H]GABA.[49]



The antibiotic X-1092 was isolated from the culture medium of the unidentified microorganisms *Streptomyces species X-1092* under aerobic conditions. It proved to be a dipeptide—(1*S*, 2*S*)-1-hydroxy-2-[(*S*)-valylamino]cyclobutane-1-acetic acid **66**,[3, 72, 73] exhibiting antimicrobial activity on gram-positive and gram-negative microorganisms.



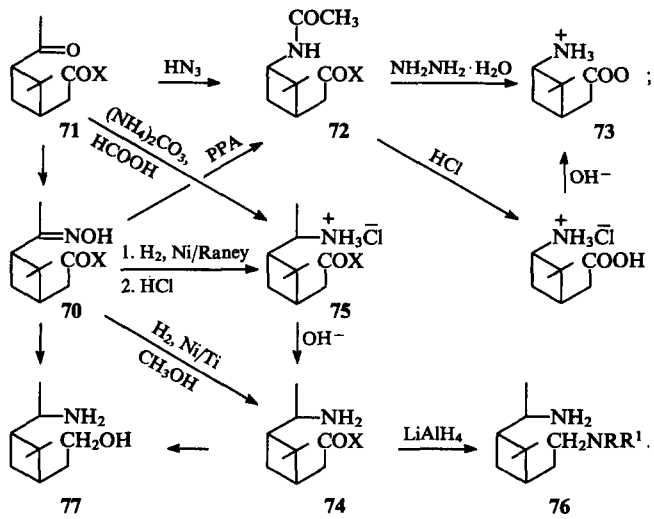
Acid hydrolysis of the dipeptide **66** yielded (1*S*, 2*S*)-2-amino-1-hydroxycyclobutylacetic acid **67**,[3, 72] which also possesses antibacterial activity against gram-positive bacteria. The aminoacid **67** and the dipeptide **66** were synthesised by Baldwin et al.[74], the initial 2-dibenzylaminocyclobutanone **68** being obtained in two stages from diethyl succinate.[76]



The *tert*-butyl acetate group was introduced into the cyclobutanone **68** by the Reformatskii reaction and the resulting mixture of racemic diastereoisomers of the dibenzylamino-alcohols (with a *cis*:*trans* isomer ratio of 8:1) was separated chromatographically on SiO_2, debenzylated, hydrolysed with trifluoroacetic acid (TFA) in anisole, and *cis*- and *trans*-**67** were obtained in 75% and 78% yields respectively (relative to *cis*- and *trans*-**69**) after purification on ion-exchange resins and subsequent high pressure liquid chromatography.

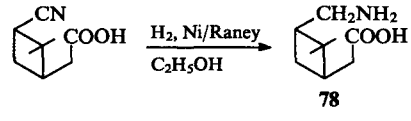
Certain aminocyclobutylacetic acids of the 2,2-dimethylcyclobutane series have been obtained from derivatives of the readily available 3-acetyl- and 3-hydroxycarbonyl-2,2-dimethylcyclobutylacetic (pinonic and pinic) acids.[8, 15, 65, 77–93] The Beckmann rearrangement of the pinonic acid oxime **70** (X = OH)[83, 84] or the interaction of pinonic acid and its esters **71** (X = OH, OR^2) with hydrogen azide (the Schmidt reaction)[15, 78, 81, 82] leads to 3-acetamido-2,2-dimethylcyclobutylacetic acid **72** (X = OH). Hydrazinolysis with hydrazine hydrate or acid hydrolysis of compound **72** affords 3-amino-2,2-dimethylcyclobutylacetic acid **73**.[15, 78, 81, 82, 84] It has been established that the best reagent for the Beckmann rearrangement of the oximes **70** (X = OH, OR^2) is polyphosphoric acid, where the optimum temperature of the rearrangement is 80 to 90 °C, and that the optimum deacylating agent is hydrazine hydrate.[84] The yield of the aminoacid **73** reaches 75.7%.

The amides of 3-acetamido-2,2-dimethylcyclobutylacetic acid **72** (X = NRR^1) have been synthesised under similar conditions from the oximes of pinonic acid amides **70** (X = NRR^1).[84] The amides **75** have been obtained by the reaction of the chloride of 3-amino-2,2-dimethylcyclobutylacetic acid with primary and secondary amines.[84] The aminoacid **73** has been recommended for the synthesis of polymeric materials forming transparent solid coatings.[5] Its esters and ureides are surfactants.[82] The reduction of compound **70** (X = OH) with sodium in isopentyl alcohol[77, 79] or catalytically over platinised nickel, Vavon platinum, Raney nickel,[79, 80, 86–89] and Lyubarskii's catalyst[90, 92, 94–98] leads to 3-(α-aminoethyl)-2,2-dimethylcyclobutylacetic (ε-aminopinanic) acid **74** (X = OH). An alternative method of synthesis of compound **74**—by the rearrangement of compound **71** (X = OH) and its esters **71** (X = OR) in the Leuckart reaction[91]—is less suitable for preparative purposes, since it requires relatively high temperatures (175–190 °C) and the yield of compound **74** (X = OH) does not exceed 33%–45%.

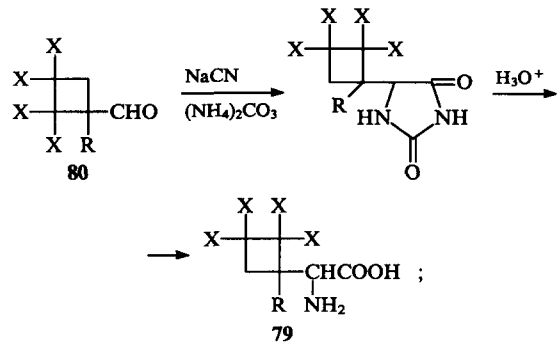


ε-Aminopinanic acid **74** and its esters[99] are of interest as starting materials for the synthesis of biologically active compounds[86–89] and polyamides[90, 91, 93, 100] The aminoacid **74** (X = OH) itself exhibits an antifibrinolytic activity.[8, 16] The hydrochlorides of the amides of ε-aminopinanic acid **75** (X = NRR^1)[95, 97] exhibit an antiviral activity.[101–103] The catalytic reduction or reduction with $LiAlH_4$ of the amides of ε-aminopinanic acid leads to the diamines **76**,[100, 104] while the reduction of the esters **74** (X = OR) leads to the aminoalcohols **77**, which are of interest as biologically active substances[12–14, 18] and as monomers for the synthesis of polymers.[104, 105]

3-Aminomethyl-2,2-dimethylcyclobutylacetic acid **78** has been obtained by the catalytic reduction of 3-cyano-2,2-dimethylcyclobutylacetic acid.[65, 85] The initial nitrile was synthesised in three stages from the monoester of pinanic acid.[65]



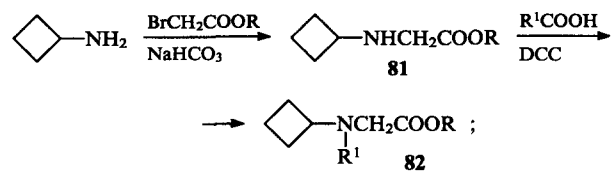
The Bucherer–Bergs method of synthesis of aminoacids has been employed to obtain the cyclobutyl analogue of glycine—α-aminocyclobutylacetic acid **79** (R = X = H) and its derivatives.[20, 106, 107] The unusual aminoacid **79** (R = CH_3, X = F) with the tetrafluorocyclobutyl substituent has also been obtained by this procedure from 2,2,3,3-tetrafluoro-1-methylcyclobutylaldehyde **80** (R = CH_3, X = F).[106]



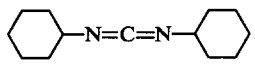
X = H, F;
R = H, CH_3 .

The amide **79** (R = X = H) exhibits a bactericidal activity[20] and certain esters of *N*-aryl-α-cyclobutylglycine exhibit an insecticidal activity.[108] α-Cyclobutylglycine **79** can be used successfully as an alternative substrate for valyl transport RNA-synthetase.[106]

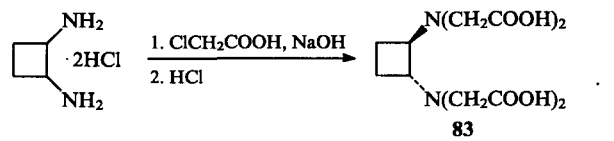
The esters of *N*-cyclobutylaminoacetic acid (*N*-cyclobutylglycine) **81** and the amido-derivatives of the esters **82**, which exhibit a hypotensive activity [antihypertensive (Translator)], have been synthesised by condensing cyclobutylamine with bromoacetic acid esters in the presence of alkaline agents.[109]



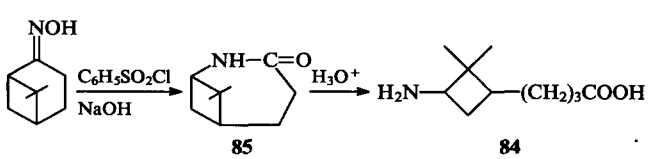
R = H, $C(CH_3)_3$;
R^1 = $COCH(CH_3)CH_2SH$, $COCH(CH_3)CH_2SCOCH_3$;

DCC =  .

trans-1,2-Diaminocyclobutane-*N,N,N',N'*-tetraacetic acid **83** has been obtained in the same way from the dihydrochloride of *trans*-1,2-diaminocyclobutane and monochloroacetic acid.[110] The dihydrochloride of *trans*-1,2-diaminocyclobutane was synthesised by the Curtius reaction from the dihydrazide of *trans*-cyclobutane-1,2-dicarboxylic acid.[111] The aminoacid **83** tends to form chelates with metal ions.



Of the higher AACB, only 3-amino-2,2-dimethylcyclobutylpropionic acid **84** has been described in the literature. It was obtained by the acid hydrolysis of 7,7-dimethyl-2-azabicyclo[4.1.1]octan-3-one **85**.[112] The lactam **85** was synthesised by the Beckmann rearrangement of nopinone oxime with benzenesulfonyl chloride.[112] The aminoacid **84** is also used for the synthesis of polyamides.



As can be seen from the literature data examined in this review, many AACB and their derivatives possess biological activity. They are of independent interest and are also of interest as intermediates in the synthesis of physiologically active and other compounds. On the other hand, their reactivity has been investigated relatively little. The majority of AACB can be obtained by the known methods of synthesis of aliphatic aminoacids. However, not all the methods quoted in this review are of preparative value. Therefore AACB still remain compounds which are difficult to obtain, particularly in the form of pure diastereoisomers and enantiomers. One may therefore expect that further studies on the synthesis of AACB will be directed towards the creation of new preparative methods of synthesis of these compounds from available starting materials and to a more detailed investigation of their reactivity, in particular the investigation of their C- and N-substituted analogues.

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