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Chemistry of ureido carboxylic and ureylene dicarboxylic acids

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Abstract. The review presents a comparative analysis of procedures for the synthesis of ureido carboxylic and ureylene dicarboxylic acids. Chemical transformations of these compounds are summarised. New fields of application of ureido carboxylic acids in the synthesis of chiral, diastereomeric and enantiomerically pure *N*-carboxyalkylglycolurils are considered. The bibliography includes 129 references.

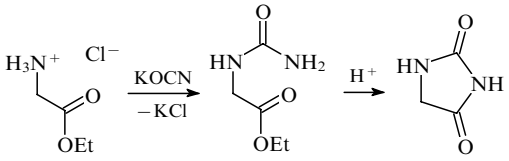
I. Introduction

Procedures for the preparation of ureido carboxylic and ureylene dicarboxylic acids (hereinafter, ureido acids and ureido diacids, respectively) and their chemical transformations are being widely discussed in the literature. These compounds deserve attention because of diverse physiological activities.[1–7] For example, the simplest representative of ureido acids, *viz*., *N*-carbamoylglycine, exerts sedative, antihypoxic and anticonvulsant effects in mice.[2] *N*-Carbamoyl-β-alanine binds to the PEPT2 protein in *Pichia pastoris* yeast cells, serves as a peptide transporter in *Xenopus laevis* oocytes and has antidiabetic properties.[3] *N*-Carbamoyl-γ-aminobutyric acid shows properties of a weak GABA antagonist (GABA is γ-aminobutyric acid).[4] N^{δ}-Methyl-N^{δ}-nitroso-(*S*)-citrulline was shown[5] to be an antitumor agent. *N*,*N*′-Carbonylbis(methionine) is used for the design of insulin analogues.[6,7] Besides, ureido (di)acids are promising building blocks in the synthesis of various biologically active heterocyclic compounds.

The aim of the present review is to systematise procedures for the synthesis of ureido (di)acids and their chemical transformations. Reactions of achiral, racemic and optically pure ureido acids with α-dicarbonyl compounds and 4,5-dihydroxyimidazolidin-2-ones in the synthesis of potential biologically active glycoluril derivatives containing *N*-carboxyalkyl groups are considered.

II. Synthesis of ureido carboxylic and ureylene dicarboxylic acids

First syntheses of ureido acids were performed by Harries[8] in the early twentieth century and were based on the reaction of glycine ethyl ester hydrochloride with potassium cyanate (by analogy with the first synthesis of urea from ammonium isocyanate[9]). The reaction product, *viz*., ethyl ester of ureidoacetic acid (*N*-carbamoylglycine), was not isolated in pure form but was subjected to cyclisation giving rise to hydantoin.



Various procedures have been developed for the synthesis of ureido acids. Let us mention the following three main methods:

(1) reactions of amino acids with KOCN (the cyanate method);

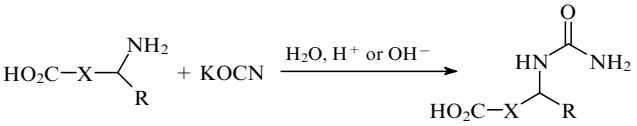
(2) reactions of amino acids with urea;

(3) cleavage of 5-substituted imidazolidine-2,4-diones (hydantoins) and related compounds.

Selected representatives of this class were synthesised according to alternative procedures. Methods for the synthesis of ureylene dicarboxylic acids are reviewed in a special section.

1. Cyanate method for the synthesis of ureido carboxylic acids

Numerous ureido acids were synthesised by the cyanate method. *N*-Carbamoylation reactions were carried out with achiral, racemic and optically active *S*- and *R*-amino acids (Table 1). The reactions of KOCN with amino acids were carried out in aqueous solutions in the absence of catalysts or in the presence of an alkali or an acid at temperatures from 20 to 100 °C; the reaction time varied from 20 min to 48 h. The yields of ureido acids **1a**–**u** are 40% – 67% (see Table 1).



1a–**u**

R = H, X = $(CH_2)_n$: *n* = 0 (**a**), 1 (**b**), 2 (**c**), 3 (**d**); R = H, X = $CH_2NHC(O)$ (**e**); X is absent: R = Me (**f**), Et (**g**), Pr^n (**h**), Pr^i (**i**), Bu^i (**j**), Bu^s (**k**), CH_2SH (**l**), $(CH_2)_2SMe$ (**m**), CH_2CO_2H (**n**), $CH_2C(O)NH_2$ (**o**), $(CH_2)_2CO_2H$ (**p**), $(CH_2)_2C(O)NH_2$ (**q**), CH(OH)Me (**r**), Bn (**s**), $CH_2C_6H_4OH$-4 (**t**), $(CH_2)_3NHC(O)NH_2$ (**u**).

The reactions of amino acid esters with alkyl isocyanates also afford ureido acid derivatives. In both cases, the reactions proceed by the mechanism[33] analogous to the mechanism of the synthesis of urea from ammonium cyanate.[9,28]

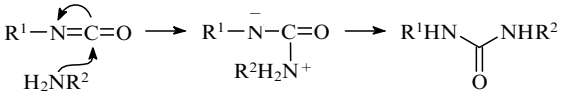
A N Kravchenko, I E Chikunov N D Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky prosp. 47, 119991 Moscow, Russian Federation. Fax (7-495) 135 53 28, tel. (7-495) 135 88 17, e-mail: kani@ioc.ac.ru

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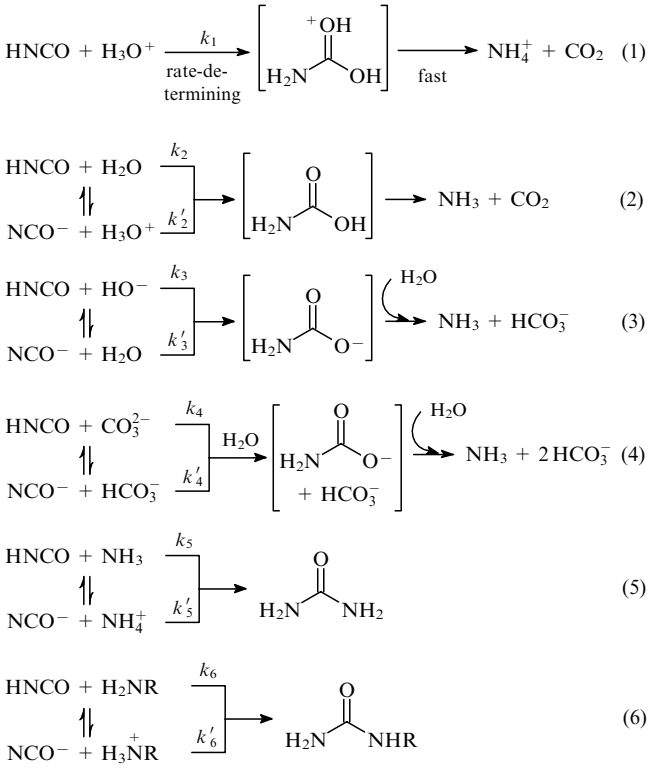
Table 1. Synthesis of ureido acids by the cyanate method.

Starting amino acid	Reaction conditions	Ureido acid **1**	Ref.
Gly	H_2O, 100 °C; HCl	**a**	10, 11
	H_2O, KOH	**a**	12
	H_2O, Δ, 20 min; HCl, pH 3	**a**	13, 14
β-Ala	H_2O, Δ, 20 min; HCl, pH 3	**b**	13–15
GABA	H_2O, 20 °C, 22 h; 6 M AcOH	**c**	16
	H_2O, Δ, 20 min; HCl, pH 2, −20 °C, 7 h	**c**	14, 17, 18
	H_2O, Δ, 4 h; HCl, pH 2	**c**	19
δ-APA	H_2O, Δ, 20 min; HCl, 7 h	**d**	10, 14, 20
Gly-Gly	H_2O, Δ, 30 min; HCl, 20 °C, 7 h	**e**	10, 14
N-MeAla	H_2O, 40 °C	**f**	21
Ala	H_2O, Δ	**f**	11, 22
	HCl, H_2O, Δ, 20 min, pH 3	**f**	13
	H_2O, 50 °C, 15 h, pH 7.5	**f**	15
Ala·HCl	H_2O, 60 °C, 4 h	**f**	23
α-ABA	H_2O, 20 °C, 60 h	**g**	19
nor-Val	H_2O, 20 °C, 48 h, pH 2	**h**	19, 24
Val	H_2O, 50 °C, 15 h, pH 7.5	**i**	15
	H_2O, 60 °C, 4 h	**i**	11
	H_2O, 20 °C, 48 h, pH 2	**i**	19
Leu	H_2O, 20 °C, 72 h, pH 2	**j**	19
Leu·HCl	H_2O, 60 °C, 4 h or 50 °C, 18 h; pH 7.5	**j**	15
Ile	H_2O	**k**	25
Cys	KOH, H_2O [a]	**l**	26
Met	H_2O, Δ, 30 min	**m**	15
Asp	1 M KOH, H_2O [b]	**n**	27, 28
	H_2O, Δ	**n**	27, 28
Asn	H_2O, Δ [c]	**o**	29, 30
Glu	KOH, H_2O	**p**	12
Gln	H_2O, 20 °C, 40 h; HCl, pH 2, 5–7 h	**q**	31
Thr	H_2O, 50 °C, pH 8	**r**	15
Phe	H_2O, Δ, 4 h; pH 2	**s**	23
Phe·HCl	H_2O, 60 °C, 4 h	**s**	23
	H_2O, 50 °C, 15 h, pH 7	**s**	15
Tyr	H_2O, Δ	**t**	30
Cit	H_2O, Δ [d]	**u**	32

Note Hereinafter, δ-APA is δ-aminopentanoic acid and α-ABA is α-aminobutyric acid, Cit is citrulline; [a] the reaction was carried out also with the use of NaOCN and NaOH; [b] fulminic acid was used instead of KOCN; [c] partial racemisation of amino acid occurs; [d] the reaction was performed with the use of HNCO.



The mechanism and kinetics of the reaction of amino acids with cyanate anions have been considered in detail.[15] In this study, a kinetic model of *N*-carbamoylation in the pH range of 2–13 at ~40–50 °C was suggested. In aqueous solutions, KOCN forms isocyanic acid, which undergoes to hydrolysis or nucleophilic addition of amines, *i.e.*, several competitive processes occur. It is assumed that the reactions of cyanate ions with water (reactions 1–3), ammonia (reaction 5) and alkylamines (reaction 6) involve the electrophilic (proton) or nucleophilic (OH^-) attack on isocyanic acid to form carbamates or urea derivatives (in the case of N-nucleophiles). In addition, the CO_3^{2-} anion efficiently catalyses hydrolysis of HNCO (reaction 4). Each slow step (the rate constants of these steps are denoted by k_1-k_4) is followed by fast cleavage of carbamates (or carbaminic acid) to give NH_3 and CO_2. It should be noted that ureas are much more stable than carbamates. Calculations and experimental data showed [15] that all reactions are first order with respect to each reagent.



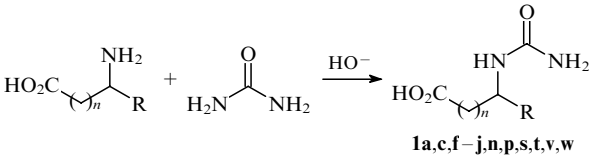
The following optimum conditions of the selective formation of ureido acids were found by studying the reactions of glycine, L-alanine, β-alanine, L-phenylalanine, L-valine, L-leucine, DL-methionine, N^{ε}-trifluoroacetyl-L-lysine and L-threonine: pH 7–8, 50 °C, a 1.5–2-fold excess of cyanate and the reaction time of 10–24 h. Under these conditions, the NH_3 and CO_2 concentrations are low, the formation of carbamates and urea is insignificant, and hydrolysis of ureido acids occurs so slowly that this process can be ignored. Consequently, ureido acids are formed as the major products. The results of kinetic studies were used to synthesise the corresponding ureido acids in preparative yields (40%–80%).

One of the authors of the present review has made an important contribution to the development of the cyanate method (see Refs 13 and 14). The conditions of the reaction of amino acids with KOCN were optimised taking into account the data [15] on the kinetics of *N*-carbamoylation. A distinguishing feature of the procedure is that KOCN is added portionwise to an amino acid solution in water or aqueous isopropyl alcohol at 80–90 °C. Then the reaction mixture is heated to boiling followed by storage of the reaction mixture for 20–30 min, which afforded ureido acids **1a**–**u** in 60%–94% yields. In the procedures used earlier, KOCN was added in one portion, and, after 48 h, the reaction products were obtained in yields of only 43%–61%.[24] In addition, *N*-carbamoylation performed under the conditions used earlier [24] was accompanied by competitive hydrolysis of cyanate ions.

In many investigations,[11–15, 17–27, 29, 31, 32] it was reported that the chiral carbon atom was not affected in transformations of optically active amino acids into ureido acids. However, partial racemisation of (*R*)- and (*S*)-aspartic acids was observed [30] in the reaction with potassium cyanate in the presence of an alkali. This fact remained unexplained.

2. Reactions of amino acids with urea

Some ureido acids were synthesised by the reactions of amino acids with urea (Table 2).



1a,**c**,**f**–**j**,**n**,**p**,**s**,**t**,**v**,**w**

n = 0: R = $(CH_2)_4NH_2$ (**v**), CH_2Ind (Ind is indol-3-yl) (**w**).

Table 2. Synthesis of ureido acids by the reaction of amino acids with urea.

Ureido acid **1**	Reaction conditions	Ref.
a	H_2O, NaOH, 110 °C, 2 h; 140 °C	34
	H_2O, $Ba(OH)_2$	21, 35
c	110–112 °C, 1 h	36
	HCl, H_2O, Δ, 15 h	19
f	H_2O, $Ba(OH)_2$	35
g	HCl, H_2O, Δ, 15 h	19
i	H_2O, $Ba(OH)_2$	35
	H_2O, Na_2CO_3	12
j	HCl, H_2O, Δ, 15 h	19, 35
n	H_2O, $Ba(OH)_2$	37
p	H_2O, $Ba(OH)_2$	35
s	HCl, H_2O, Δ, 15 h	19
	H_2O, $Ba(OH)_2$	35
t	H_2O, $Ba(OH)_2$	35
v [a]	H_2O, Na_2CO_3	12
w [b]	H_2O, $Ba(OH)_2$	38

[a] Lys was used as the staring amino acid; [b] Trp was used as the staring amino acid.

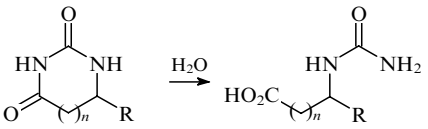
The reactions can be carried out according to two procedures: either by prolonged (up to 15 h) refluxing of an acidified aqueous solution of the reagents or by heating in the presence of an alkali at 110–140 °C (see Table 2). In both cases, it is necessary to purify ureido acids by repeated recrystallisations. The yields of the reaction products prepared according to both procedures are comparable with those attained by the cyanate method. However, the advantage of the latter is that the product precipitates from the reaction mixture, so that one recrystallisation from an appropriate solvent is sufficient to obtain pure products in individual form.

The synthesis of ureido acids **1a**,**j** by the reactions of Gly and Leu, respectively, with nitrourea was also documented.[39]

On the whole, the procedure for the synthesis of ureido acids involving urea is less popular than the cyanate method.

3. Cleavage of hydantoins and related compounds

Virtually all ureido acids can be synthesised by the cleavage of the corresponding 5-substituted hydantoins or related compounds. Both chemical and biochemical processes are suitable for this purpose (Table 3).



2a–**c**,**f**,**i**–**k**,**m**,**n**,**p**–**u** **1a**–**c**,**f**,**i**–**k**,**m**,**n**,**p**–**u**

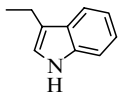
Alkaline hydrolysis is the simplest method for the cleavage of heterocycles **2**. Under these conditions, ureido acids **1a**–**c** were prepared from the corresponding achiral compounds, *viz*., hydantoin (**2a**),[40] dihydrouracil (**2b**)[42] and [1,3]diazepane-2,4-dione (**2c**),[44] and compounds **1f**,**m**,**n**,**s**–**u** were synthesised from chiral substrates, *viz*., 5-methylhydantoin (**2f**),[45] 5-[2-(methylthio)ethyl]-hydantoin (**2m**),[51] 2,6-dioxohexahydropyrimidine-4-carboxylic acid (**2n**),[25] 5-benzylhydantoin (**2s**), 5-(4-hydroxybenzyl)hydantoin (**2t**)[30] and [3-(2,5-dioxoimidazolidin-4-yl)propyl]urea (**2u**).[32] Generally, hydrolysis is performed with aqueous NaOH or $Ba(OH)_2$ on heating. This approach is suitable only for the synthesis of ureido acids in which the chiral carbon atom retains the configuration of the chiral centre of the starting hydantoin.

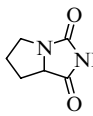
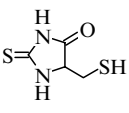
Biochemical cleavage of cyclic compounds **2** under the action of microorganisms or enzymes is the most common and preparative method.

Table 3. Synthesis of ureido acids by decomposition of hydantoins **2**.

Compounds **1** and **2**	n	R	Chemical method		Biochemical method	
			reaction conditions	ref.	reaction conditions	ref.
a	0	H	H_2O, $Ba(OH)_2$, Δ	40	*Pseudomonas sp*. AJ-11220, Tris–HCl buffer (pH 8.5), 30 °C, 2 h	41
b	1	H	H_2O, NaOH, Δ	42	the same	41
					hydantoinase (dihydropyrimidinase EC 3.5.2.2) *P. putida* DSM 84	43
c	2	H	H_2O, NaOH	44	–	
f	0	Me	0.6 N KOH, 70 °C, 8 h	45	hydantoin-hydrolysing enzyme, ATP, KCl, $MgSO_4$, 0.1 M Tris–HCl, 30 °C, 20 h	46
					anaerobic bacterium *P. anaerobius*, 50 °C	47
					immobilised cells of *Agromyces*, *Chromobacterium* or *Cellulomonas,* glucose, yeast extract, 30 °C, 20 h	18
					DL-hydantoinase from *Bacillus stearothermophilus* $NS_{1122}A$, phosphate buffer (pH 7.0), 60 °C, 30 min	48
					Pseudomonas sp. AJ-11220, Tris–HCl buffer (pH 8.5), 30 °C, 2 h	41
					D-hydantoinase 1, H_2O, 50 °C, 22.8 h, pH 8.5	49
i	0	Pr^i	–		*Pseudomonas sp*. AJ-11220, Tris–HCl buffer (pH 8.5), 30 °C, 2 h	41
					D-hydantoinase 2, H_2O, 50 °C, 43.7 h, pH 8.5	49
					Hansenula sp. Tris buffer, 32 °C, 24 h	48, 50
					hydantoin-hydrolysing enzyme, ATP, KCl, $MgSO_4$, 0.1 M Tris–HCl, 30 °C, 20 h	46
					Bacillus brevis AJ-12299, 0.1 M Tris–HCl (pH 7), 30 °C, 24 h	46

Table 3 (continued).

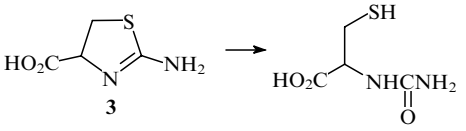
Compounds **1** and **2**	*n*	R	Chemical method		Biochemical method	
			reaction conditions	ref.	reaction conditions	ref.
j	0	Bu^{i}	–		DL-hydantoinase from *Bacillus stearothermophilus* $NS_{1122}A$, phosphate buffer (pH 7.0), 60 °C, 30 min	48
					Pseudomonas sp. AJ-11220, Tris – HCl (pH 8.5) buffer, various solvents, 30 °C, 2 h	41
					D-hydantoinase 2, H_2O, 50 °C, 18 h, pH 8.5	49
k	0	Bu^{s}	–		hydantoin-hydrolysing enzyme, ATP, KCl, $MgSO_4$, 0.1 M Tris – HCl, 30 °C, 20 h	46
					DL-hydantoinase from *Bacillus stearothermophilus* $NS_{1122}A$, phosphate buffer (pH 7.0), 60 °C, 30 min	48
					D-hydantoinase 2, H_2O, 50 °C, 41 h, pH 8.5	49
m	0	C_2H_4SMe	NaOH, H_2O, 80 – 120 °C, < 2 h	51	hydantoin-hydrolysing enzyme, ATP, KCl, $MgSO_4$, 0.1 M Tris – HCl, 30 °C, 20 h	46
					D-hydantoinase 1, H_2O, 50 °C, 12.7 h, pH 8.5	49
n	1	CO_2H	NaOH, H_2O, 25 °C, variable pH	25	–	
n[a]	0	CH_2CO_2H	–		*Pseudomonas sp*. AJ-11220, Tris – HCl buffer (pH 8.5), 30 °C, 2 h	41
p	0	$(CH_2)_2CO_2H$	–		the same	41
r	0	CH(OH)Me	–		D-hydantoinase 1, H_2O, 50 °C, 21 h, pH 8.5	49
s	0	Bn	KOH, H_2O	30	hydantoin-hydrolysing enzyme, ATP, KCl, $MgSO_4$, 0.1 M Tris – HCl, 30 °C, 20 h	46
					Pseudomonas sp. AJ-11220, Tris – HCl (pH 8.5) buffer, 30 °C, 2 h; *Flavobacterium sp*. AJ-3912, Tris – HCl (pH 8.5) buffer, 30 °C, 2 h	41
					DL-hydantoinase from *Bacillus stearothermophilus* $NS_{1122}A$, phosphate buffer (pH 7.0), 60 °C, 30 min	48
					D-hydantoinase 1, H_2O, 50 °C, 39.2 h, pH 8.5	49
t	0	$CH_2C_6H_4OH$-4	KOH, H_2O	30	hydantoin-hydrolysing enzyme, ATP, KCl, $MgSO_4$, 0.1 M Tris – HCl, 30 °C, 20 h	46
					Pseudomonas sp. AJ-11220, Tris – HCl (pH 8.5), 30 °C, 2 h	41
					Flavobacterium sp. AJ-3912, Tris – HCl (pH 8.5), 30 °C, 2 h	52
u	0	$(CH_2)_3NHC(O)NH_2$	NaOH, H_2O	32	*Agrobacterium radiobacter*, 40 °C, 24 h, 6 bar or 1 atm, 40 °C, 24 h	32
w	0		–		*Pseudomonas sp*. AJ-11220, Tris – HCl buffer (pH 8.5), 30 °C, 2 h	41
x	0	$CH_2C_6H_3(OH)_2$-3,4	–		the same	41
y[b]		–	–		*Agromyces, Chromobacterium* or *Cellulomonas*, phosphate buffer, 30 °C, 20 h	53
z[c]		–	–		*Pseudomonas sp*. AJ-11220, Tris – HCl (pH 8.5), buffer 30 °C, 2 h	41
					D-hydantoinase 1, H_2O, 50 °C, 16.6 h, pH 8.5	49

Note. Tris is tris(hydroxymethyl)aminomethane; ATP is adenosine triphosphate. [a] Ureido acid **1n** was synthesised from (2,5-dioxoimidazolidin-4-yl)acetic acid; [b] ureido acid **1y** was synthesised from  (**2y**); [c] ureido acid **1z** was synthesised from  (**2z**).

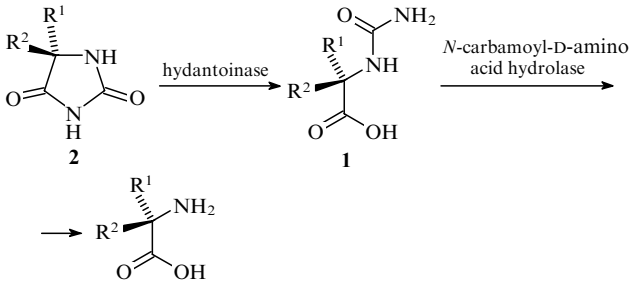
Biochemical methods for hydrolytic cleavage of hydantoin (**2a**), dihydrouracil (**2b**), 5-methylhydantoin (**2f**), 5-isopropylhydantoin (**2i**) and 5-isobutylhydantoin (**2j**) under the action of *Pseudomonas sp*. AJ-11220 in a Tris – HCl buffer were documented.[41] Hydantoins **2f** and **2i**, 5-*sec*-butylhydantoin (**2k**), 5-[2-(methylthio)ethyl]hydantoin (**2m**), 5-benzylhydantoin (**2s**) and 5-(4-hydroxybenzyl)hydantoin (**2t**) are transformed into the corresponding *N*-carbamoyl-α-amino acids **1** with different enantiomeric excesses under the action of hydantoin-hydrolysing enzymes in the presence of various inorganic salts (30 °C,

20 h).[46] Tetrahydropyrrolo[1,2-*c*]imidazole-1,3-dione (**2y**)[53] and 5-methylhydantoin (**2f**)[18] are cleaved with immobilised cells of *Agromyces*, *Chromobacterium* or *Cellulomonas* in a yeast extract in 20 h. DL-Hydantoinase from bacterium *Bacillus stearothermophilus* $NS_{1122}A$ in a phosphate buffer (pH 7.0) at 60 °C cleaves hydantoins **2f**,**j**,**k**.[48] Hydantoins **2f**–**m**,**s**, (5-mercaptomethyl)thiohydantoin (**2z**) and 5-(1-hydroxyethyl)hydantoin (**2r**) give ureido acids in high chemical and optical yields under the action of D-hydantoinase at 50 °C (pH 8.5).[49] Dihydrouracil **2b** is cleaved with dihydropyrimidinase (EC 3.5.2.2) from *P. putida* DSM 84;[43] 5-methylhydantoin (**2f**), with anaerobic bacterium *P. anaerobius* at 50 °C;[47] 5-isopropylhydantoin (**2i**), with bacterium *Hansenula sp.*;[48, 50] 5-(4-hydroxybenzyl)hydantoin (**2t**), with bacteria *Flavobacterium sp.* AJ-3912;[2] and [3-(2,5-dioxoimidazolidin-4-yl)propyl]urea (**2u**), with bacterium *Agrobacterium radiobacter*.[32]

The ring opening in (+)-2-amino-4,5-dihydrothiazole-4-carboxylic acid (**3**) occurs analogously to hydantoins. This transformation can be performed by either a biochemical method[54] or alkaline hydrolysis to give *N*-carbamoylcysteine.[55]



Hydantoin derivatives **2** are precursors of substituted α-amino acids and pyruvic acid.[56–59] Biochemical cleavage of optically active hydantoins occurs through ureido acids and is used for the synthesis of enantiomerically pure amino acids.[60–65]

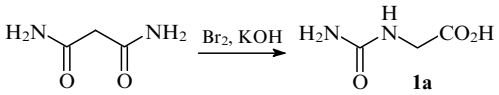


R^1, R^2 = H, Alk, Ar.

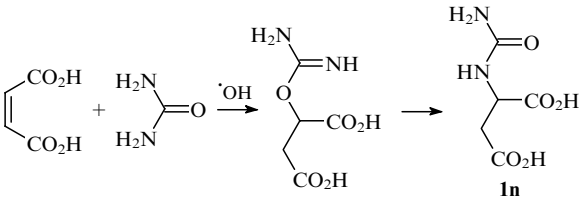
This method can be used for the synthesis of both natural and artificial amino acids having the desired absolute configuration.

4. Other methods for the synthesis of ureido carboxylic and ureido dicarboxylic acids

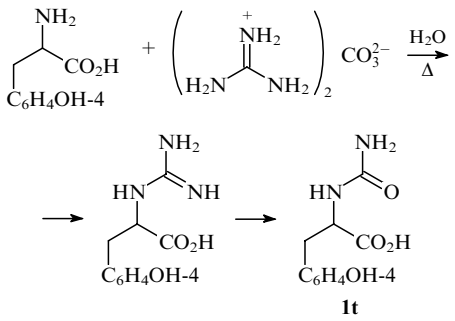
Examples of the synthesis of ureido acids by non-conventional methods are scarce. For instance, *N*-carbamoylglycine (**1a**) was synthesised[66] by heating of an aqueous solution of malonamide with bromine in an alkaline medium.



N-Carbamoylaspartic acid (**1n**) was prepared by the reaction of maleic acid with an aqueous urea solution at 60 °C or by the flame-induced radical reaction. In the latter case, compound **1n** is formed as a result of the thermal rearrangement of amidinoxysuccinic acid.[67]



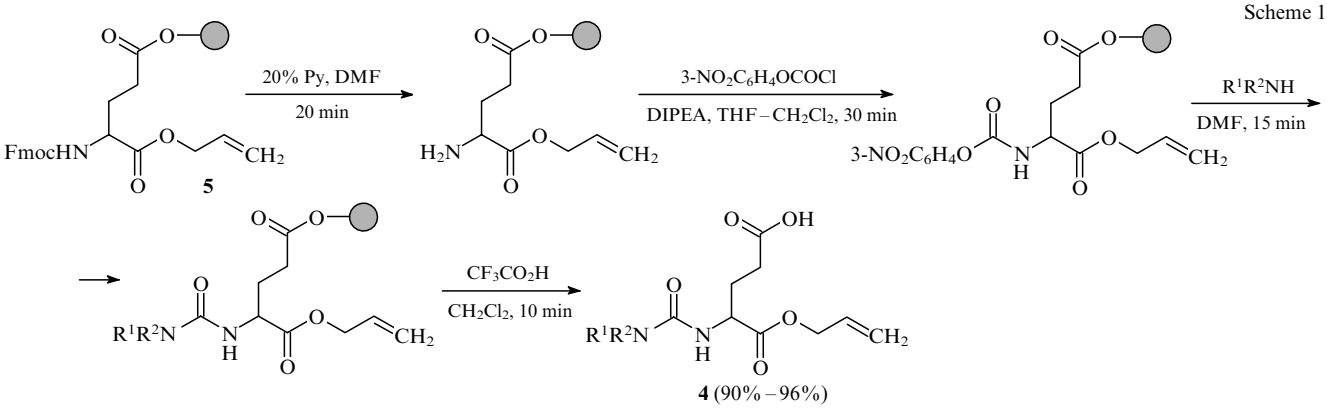
Ureido acid **1t** was synthesised from tyrosine by the reaction with guanidinium carbonate.[35] Under the reaction conditions, the guanidine moiety was transformed into the ureido fragment.



Currently, solid-phase syntheses are widely used in amino acid chemistry. In the study,[68] derivatives of ureido dicarboxylic acid monoallyl ester **4** were prepared. Protected amino acid **5** on a polystyrene support was used as the starting compound. The sequence of transformations is presented in Scheme 1.

Thus, the most convenient method for the synthesis of ureido acids is that developed in the studies.[13, 14]

Scheme 1



4 (90%–96%)

R^1, R^2 = Alk, Het; Fmoc is 9-fluorenylmethoxycarbonyl, ◯ is a polymeric support, DIPEA is *N*,*N*-diisopropylethylamine.

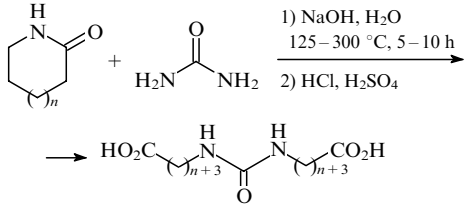
5. Synthesis of ureylene dicarboxylic acids

The simplest procedure for the synthesis of symmetric ureylene dicarboxylic acids involves thermal decomposition of ureido acid salts at 125–300 °C in a nitrogen atmosphere under elevated pressure. For example, this method was used for the synthesis of disodium 6,6′-ureylenedihexanoate (**6a**).[69]

$$H_2NC(O)NH(CH_2)_5CO_2Na \xrightarrow[N_2]{250\ ^\circ C,\ 6\ h} [NaO_2C(CH_2)_5NH]_2CO$$

6a (62%)

Another procedure for the synthesis of symmetric ureido diacids is based on the reaction of a lactam with urea. For example, compounds **6a**,**b** were prepared by heating of an alkaline solution of the reagents in an autoclave followed by acidification of the reaction mixture.[70]

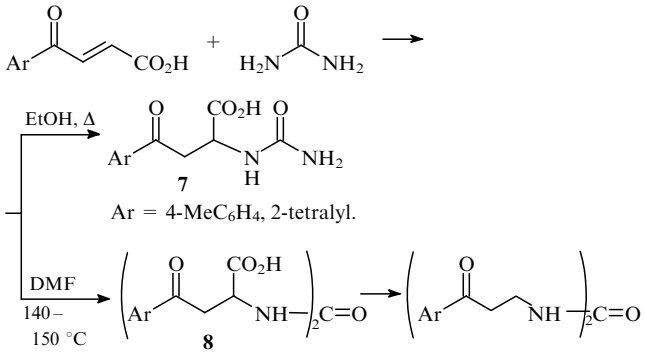


6a,**b** (52%–78%)

n = 2 (**a**), 4 (**b**).

An analogous procedure for the synthesis of ureylene dicarboxylic acids $[HO_2C(CH_2)_mNH]_2CO$ (m = 3–5 or 11) with the use of an excess of ω-amino acid instead of lactam was covered by a patent.[71] In this case, the products are purified by anion-exchange chromatography.

The reactions of β-aroylacrylic acids with urea produce different compounds depending on the reaction conditions.

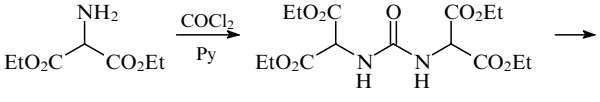


Ar = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 2-tetralyl.

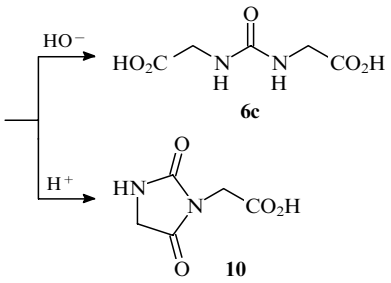
For example, the reactions in boiling ethanol give ureido acids **7**, whereas the reactions in DMF yield ureido diacids **8**, which readily undergo decarboxylation.[72]

Ureido diacids can also be synthesised by the reactions of amino acid derivatives with $COCl_2$, CS_2, 1,1′-carbonyldiimidazole, 1,1′-carbonyldi(benzotriazole), *etc*.

The reaction of $COCl_2$ with diethyl aminomalonate in the presence of pyridine gives urea derivative **9**, whose hydrolysis with an alkali or an acid affords ureido diacid **6c** or hydantoinoacetic acid **10**, respectively.[73]



9 (80%)

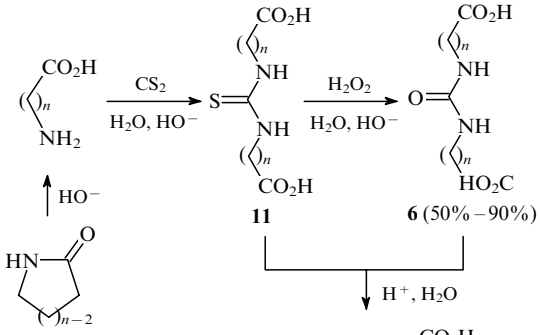


6c

10

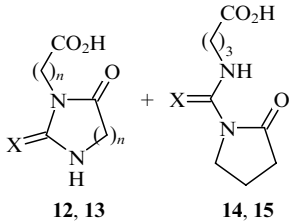
N,*N*′-Carbonyldi(phenylalanine) ester was synthesised[74] by the reaction of phenylalanine ethyl ester with carbon disulfide in benzene.

In the reactions of amino acids and their derivatives with CS_2, the initially formed thioureas **11** are oxidised with hydrogen peroxide (or sodium hypochlorite) to form the corresponding ureido diacids **6**.[75] In an acidic medium, the former undergo cyclisation to give carboxyalkylthiohydantoins **12**, whereas the latter form oxygen-containing analogues **13**. In some cases (n = 3), the reactions afford *N*-substituted lactams **14** and **15** as by-products. These syntheses can be performed starting from lactams.[76] Substantial drawbacks of this method consists of the use of toxic flammable CS_2 and long reaction times (up to 12 h). The use of COS instead of carbon disulfide makes it possible to exclude oxidation of thiourea, the yields of diacids **6** being ~90%.[77]



11

6 (50%–90%)

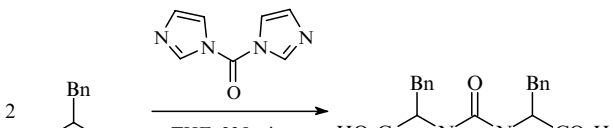


12, **13**

14, **15**

n = 3–5; X = S (**12**, **14**), O (**13**, **15**).

The reaction of phenylalanine with 1,1′-carbonyldiimidazole proceeds smoothly to afford ureido diacid **6d**.[78]

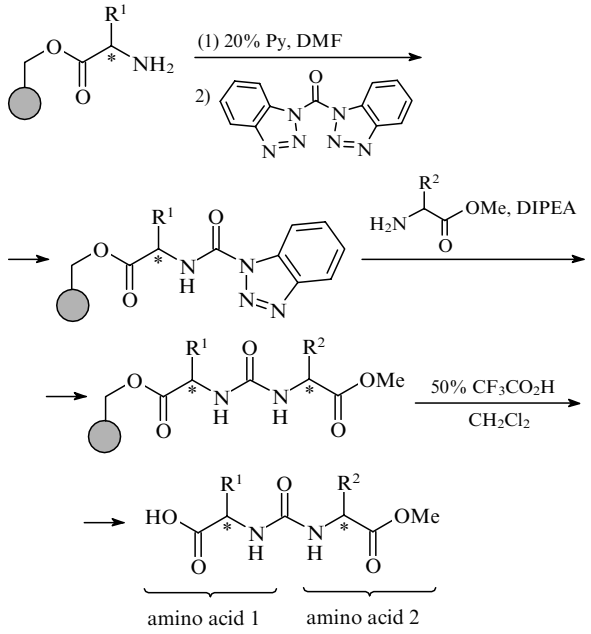


6d

The solid-phase synthesis, which allows one to prepare both symmetric and non-symmetric derivatives, is most promising for the synthesis of ureido diacids. The maiority of procedures were developed for the preparation of 1,3,3-trisubstituted ureas on a polystyrene support (see, for example, Refs 79 and 80).

Recently, 1,1′-carbonyldi(benzotriazole) has been successfully used[81] in the solid-phase synthesis of non-symmetric ureido diacids **16a**–**g** containing two different amino acid residues (Table 4). The products can be purified from a benzotriazole impurity by extraction with a borate buffer (pH 9.2). This method

affords ureido diacids **16a**–**g** in good yields and with high optical purity (see Table 4).



16a–**g** (70%–100%)

R^1 = Bn, R^2 = CH_2OBu^t (**a**); R^1 = Pr^i, R^2 = CH_2OBu^t (**b**); R^1 = $(CH_2)_2SMe$, R^2 = Bu^i (**c**); R^1 = $(CH_2)_2C(O)NH_2$, R^2 = $(CH_2)_3NHC(=NH)NHNO_2$ (**d**); R^1 = H, R^2 = CH_2Ind (**e**); R^1 = CH_2Ind, R^2 = CH_2Im (**f**); R^1 = CH_2Im, R^2 = $(CH_2)_2CO_2Me$ (**g**); Im = 3-tritylimidazol-5-yl.

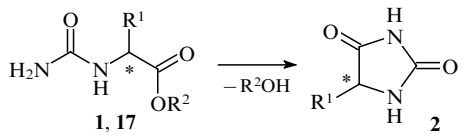
Table 4. Non-symmetric ureido diacids **16a**–**g**.[81]

Compound **16**	Amino acid 1	Amino acid 2	*ee* (%)
a	Phe	Ser(Bu^t)	95
b	Val	Ser(Bu^t)	74
c	Met	Leu	80
d	Gln	Arg(NO_2)	97
e	Gly	Trp	71
f	Trp	His(Trt)	79
g	His(Trt)	Glu(OMe)	91

III. Chemical transformations of ureido carboxylic acids

1. Mechanism of cyclisation of ureido carboxylic acids to hydantoins

In spite of low reactivity of ureido acids, many chemical transformations involving the amino group of these compounds were documented. Cyclisation of ureido acids **1** and their esters **17** to hydantoins **2** has been the subject of the most studies.[11,28,60,61,82–91]

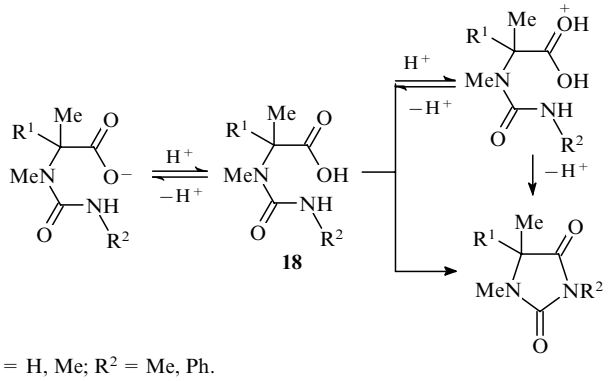


1, **17** **2**

R^1 = Alk, Ar, Het, ArAlk; R^2 = H (**1**), Alk (**17**).

These reactions are generally performed in an acidic medium; more rarely, in an alkaline medium. In most cases, the reactions are not accompanied by racemisation.

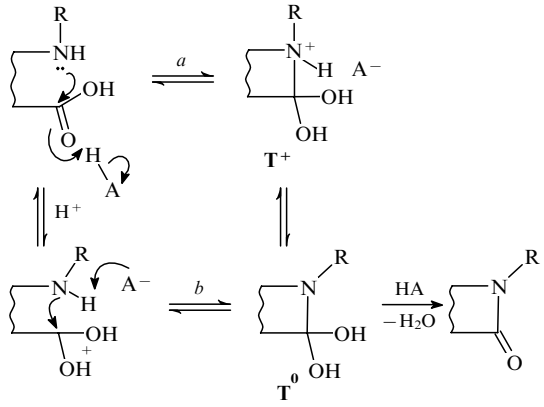
The kinetics and mechanism of cyclisation of ureido carboxylic acids giving rise to hydantoins were studied in-depth for *N*-substituted ureido acids **18**.[11,84]



R^1 = H, Me; R^2 = Me, Ph.

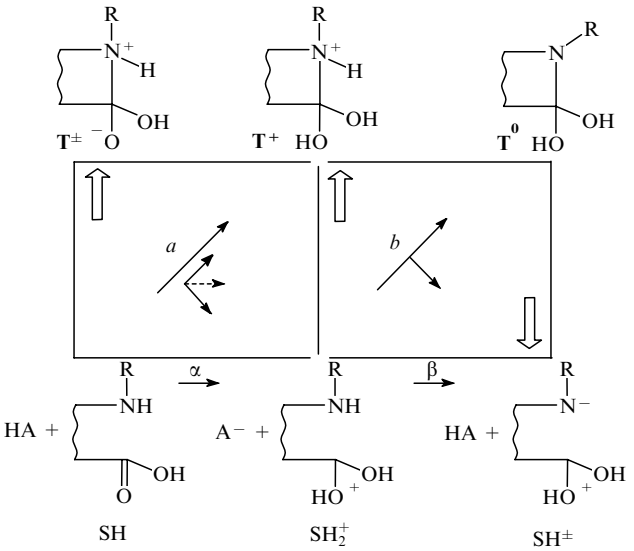
The reaction proceeds under conditions of general acid-base catalysis and involves the attack of the urea nitrogen atom on the carboxyl carbon atom.[84]

Based on a detailed analysis of the mechanism of condensation under acidic conditions, it cannot be conclusively established whether general acid catalysis (pathway *a*) or kinetically equivalent specific catalysis (pathway *b*) occurs.[84]



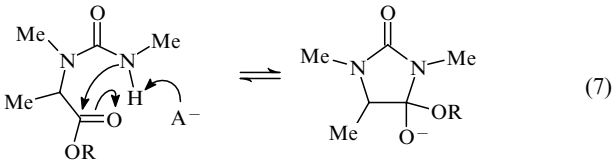
HA is acid; R = Me, Ph.

Since the cyclisation rate of ureido acids under conditions of general acid catalysis is too high to be determined precisely, the measurements were carried out for the corresponding esters, whose reactions are approximately 30 times slower due apparently to larger steric hindrance caused by the OEt group upon the formation of tetrahedral intermediates $\mathbf{T}^+$ and $\mathbf{T}^0$. The substitution of the *N*-phenyl group in the ureido fragment for the *N*-methyl group would be expected to change the structure of the transition state in the ring closure reaction performed under conditions of general acid catalysis, which can be represented in the diagram using the More O'Ferrall–Jencks reaction coordinates.[92] Blagoeva *et al.*[84] represented the alternative pathways *a* and *b* as a pair diagram, which shows that the formation of the tetrahedral intermediate $\mathbf{T}^+$ is the rate-determining step in these reactions.



R = Ph.

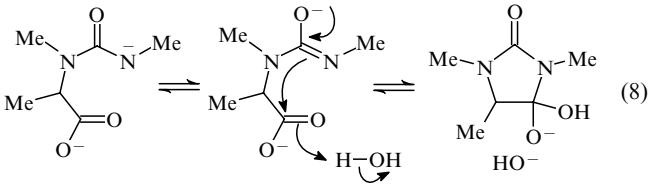
It is assumed that the initial formation of the imidazolidine ring by the reaction (7) is the rate-determining step under conditions of general base catalysis.



(7)

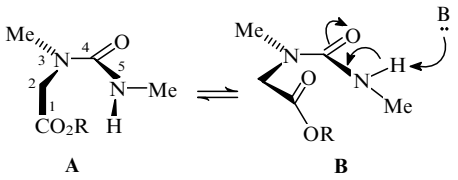
R = H, Et.

Therefore, the assumed mechanisms of cyclisation in the case of general base or acid catalysis involve the nucleophilic attack of the sp^2-hybridised NH group giving rise to a C–N bond and deprotonation as either a concerted reaction [reaction (7)] or an individual step (pathway *a*). In the base-catalysed reaction, deprotonation of the urea cannot be an individual rate-determining step because this requires that reprotonation of the ureido anion be more slow than the nucleophilic addition of N^- to the CO_2R group. Although the latter reaction is very fast, reprotonation of the ureido anion should occur at a rate of at least 100 times higher. The mechanisms involving the formation of the iminol tautomer of urea [reaction (8)] can also be ruled out.



(8)

Cyclisation performed under conditions of both general base and acid catalysis is characterised by the strong influence of stereoelectronic factors. In the conformation **A** of the ground state, only the C(1) atom can deviate from the plane of the ureido group so that the formation of the bond between the C(1) and N(5) atoms is virtually impossible. For the bond between these atoms to be formed, rotation about the C(2)–N(3) bond and about one of the C–N bonds of the urea fragment must occur. Evidently, rotation about the C(4)–N(5) bond (transition **A** ⇆ **B**) is most efficient, because it is accompanied by violation of π-conjugation and makes accessible the partially localised lone pair of the nitrogen atom, which should act as a nucleophile.



A **B**

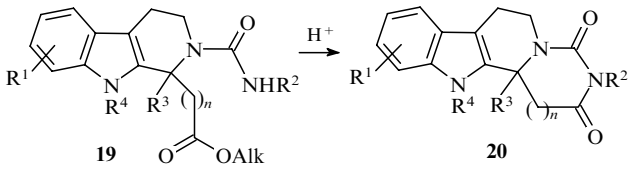
Apparently, both mechanisms considered above give rise to the conformation **B**. General base catalysis partially restores the lost delocalisation in the transition state for the subsequent addition to the CO_2R group. In the acid-catalysed reactions, the partially protonated CO_2R group is electrophilic and can react without additional activation.

It was demonstrated [11] that the kinetics of the process is first order with respect to ureido acid, and the reaction is substantially accelerated as pH decreases. Cyclisation of ureido acids occurs more easily as the size of the substituent in the amino acid fragment and its hydrophobicity increase.

2. Reactions of ureido carboxylic acid derivatives

Cyclisation of ureido acids has attracted attention of researchers as a procedure for the preparation of various heterocyclic compounds containing the urea fragment. Hydantoins can also be used for the synthesis of acyclic ureido derivatives.

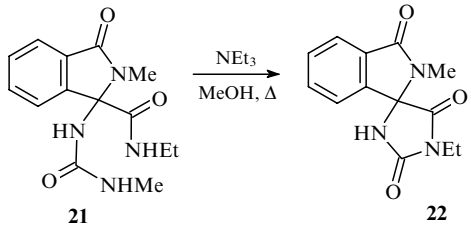
Intramolecular cyclisation of 3-carbamoyltetrahydro-β-carbolines **19** in an acidic medium at high temperatures affords tetracyclic derivatives **20**, which are used as antihypoxic and psychotropic agents.[85]



19 **20**

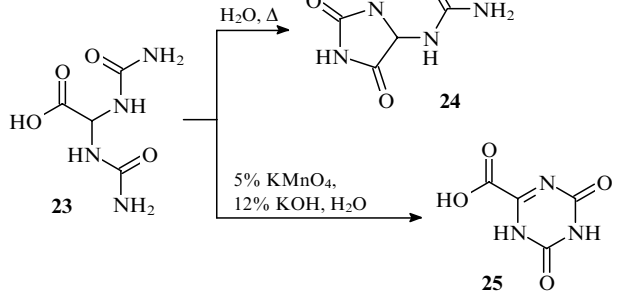
R^1 = H, Hal, Alk; R^2 = H, Alk, Ph; R^3 = H, Alk;
R^4 = H, Alk; n = 0, 1.

Heating of ureido acid amide **21** in methanol in the presence of triethylamine affords spirohydantoin **22**.[86]



21 **22**

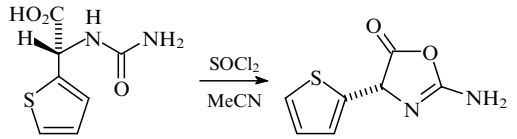
The cyclisation of diureidoacetic acid **23** gave allantoin (**24**),[87] which accelerates wound healing. Oxidation of compound **23** affords 1,4,5,6-tetrahydro-4,6-dioxo-1,3,5-triazine-2-carboxylic acid (**25**).[88]



23 **24** **25**

It should be noted that (*S*)-(2-thienyl)ureidoacetic acid (**26**) undergoes cyclisation under the action of thionyl chloride to form

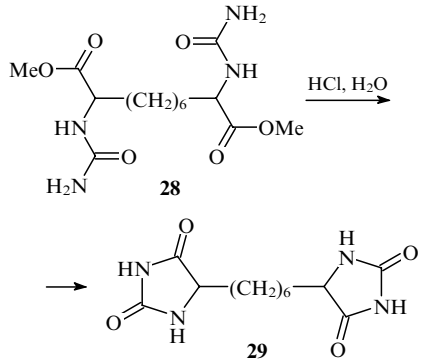
(*S*)-2-amino-4-(2-thienyl)-4*H*-oxazol-5-one (**27**) rather than the corresponding hydantoin.[89]



26 **27**

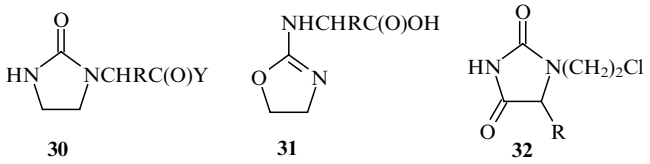
Acid-catalysed cyclisation of *N*-carbamoyl-2,2-diphenylaminoacetic acid in aqueous methanol gives 5,5-diphenylhydantoin.[11] The latter is known under the name difenin as an anticonvulsant and anti-arhythmic drug.[93–97]

The reaction of dimethyl 2,9-diureidodecanedioate (**28**) in the presence of HCl produced the corresponding 4,4′-hexamethylenedihydantoin (**29**).[90]



28 **29**

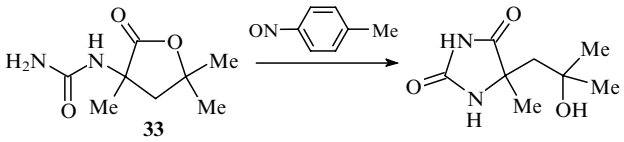
Intramolecular cyclisation of *N*-(2-chloroethylcarbamoyl) derivatives of glycine, valine and phenylalanine $Cl(CH_2)_2NHC(O)NHCHRC(O)X$ (R = H, Pr^i, Bn; X = OH, OAlk, NH_2) affords imidazolidones **30**, oxazolines **31** or hydantoins **32** depending on the nature of the substituent R and the reaction conditions.[98]



30 **31** **32**

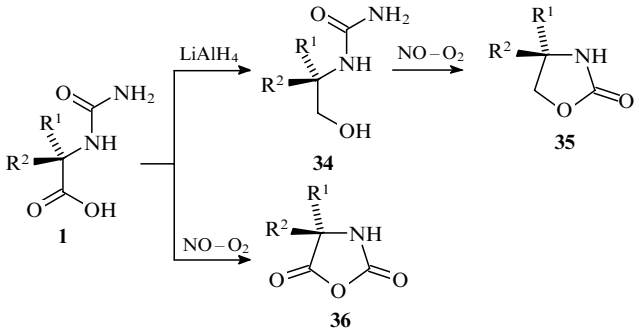
Y = OH, NH_2.

Like ureido acids, ureido lactone **33** was rearranged into hydantoin under the action of nitroso compounds.[91]



33

Ureido acids **1** can be used as the starting compounds in the synthesis of other heterocyclic compounds. For example, reduction of ureido acids to form ureido alcohols **34** followed by the reaction with a $NO-O_2$ mixture either in solution or in the solid phase affords oxazolidinones **35**.[99]

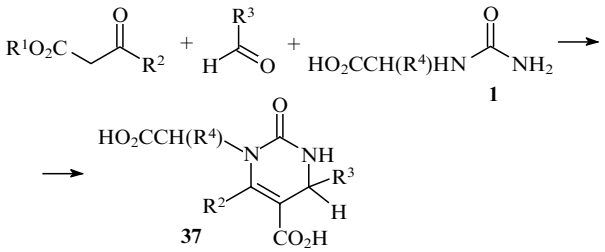


1 **34** **35** **36**

R^1, R^2 = H, Alk.

Direct nitrosation of substituted ureido acids **1** (R^1 and $R^2 \neq H$) yields α-amino acid *N*-carboxyanhydrides (oxazolidine-2,5-diones) **36**, which can be used in the peptide synthesis.[100] The reaction is not accompanied by racemisation and gives products in quantitative yields both in solution and on a support.

Three-component one-pot condensation of ureido acids **1**, β-keto esters and aldehydes is a very promising synthetic procedure because it affords Biginelli dihydropyrimidinones **37**.[101] Derivatives **37** have antiviral [102] and antihypertensive [103] activities and block calcium channels in cell membranes.[104]

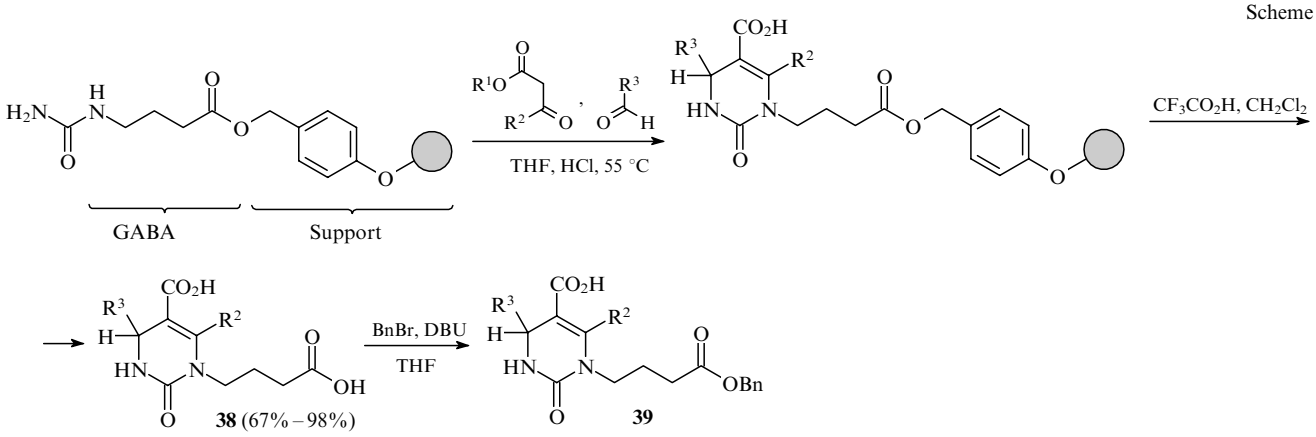


1 **37**

R^1, R^2, R^3, R^4 = Alk, Ar.

The solid-phase reaction is a preferred modification, for example, in the case of GABA derivatives (Scheme 2). Products

Scheme 2

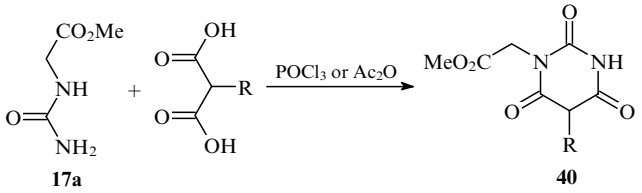


38 (67%–98%) **39**

R^1, R^2, R^3 = Alk, Ar; DBU is diazabicyclo[4.5.0]undec-4-ene.

38 are formed in good yields and readily undergo benzylation at the peripheral carboxy group to give protected derivatives **39**.

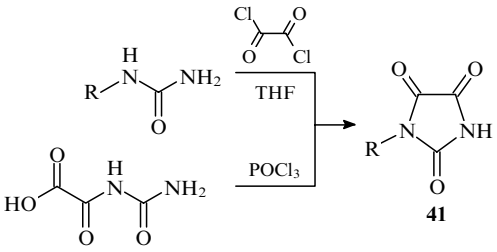
The reaction of *N*-carbamoylglycine methyl ester **17a** with malonic acid derivatives in $POCl_3$ (or in Ac_2O) afforded 5-substituted derivatives of barbituric acid **40**,[105] which have a pronounced sedative effect.[106] On the whole, the reactions are similar to the conventional synthesis of barbituric acid [107] and its *N*- (see Ref. 108) and *C*(5)-substituted analogues (for example, of cyclobarbital [109]).



17a **40**

R = Alk, Ar.

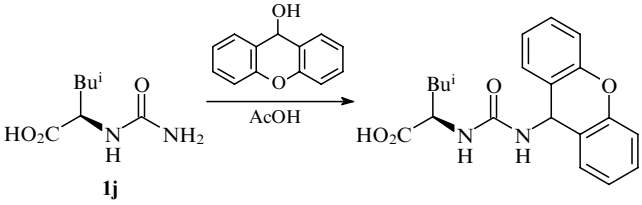
N-Carbamoylglycine esters **17**, like urea,[110] react with oxalyl chloride to form the corresponding parabanic acids **41**.[111,112] In $POCl_3$, oxalourea also undergoes cyclisation to parabanic acid.[113]



41

R = H, CH_2CO_2Alk.

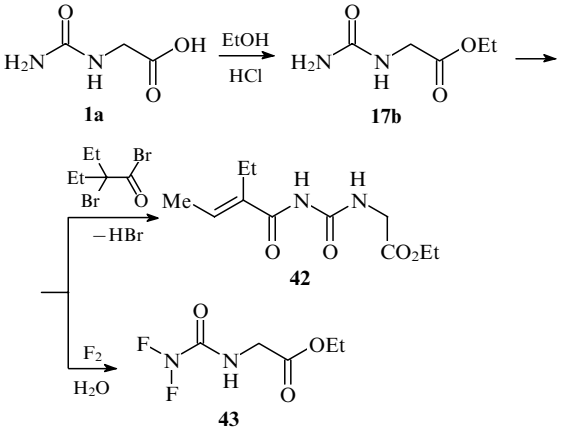
Ureido acids **1** are alkylated at the NH_2 group with certain alcohols. For example, *N*-carbamoylleucine (**1j**) reacts with xanthen-9-ol in acetic acid.[114]



1j

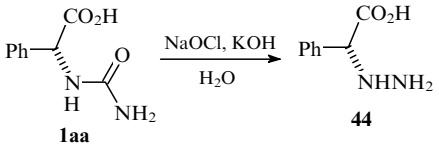
In the study,[115] *N*-carbamoylglycine ethyl ester **17b** (Ref. 116) was acylated with substituted carboxylic acid bromides (the synthesis of derivative **42** presented below is accompanied also by elimination of HBr).[115]

Compound **17b** gives *N*,*N*-difluoro derivative **43** under the action of fluorine.[117]



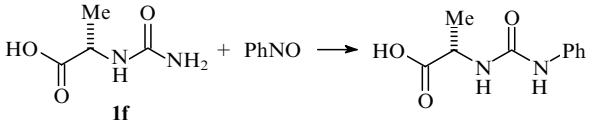
1a **17b** **42** **43**

Oxidation of ureido acid **1aa** with sodium hypochlorite affords the corresponding hydrazine **44** in which the configuration of the chiral centre is retained.[118]



1aa **44**

Like monomethylurea (see Ref. 107), ureido acids are nitrosated at the NH group with sodium nitrite in formic acid.[13] The reactions of nitrosoarenes with ureido acids **1** make it possible to introduce aryl substituents into the primary amino group.[119]



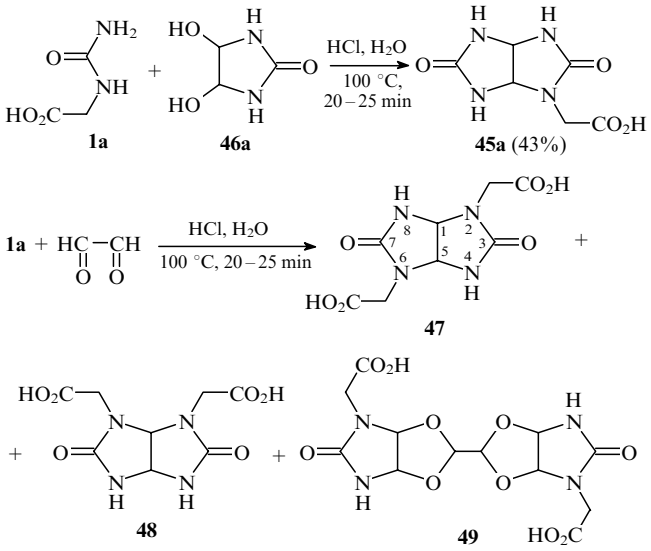
1f

Electrochemical oxidation of ureido diacids and their thio analogues $[HO_2C(CH_2)_nNH]CX$ (X = O or S; *n* = 3 or 5) using a lead cathode and a PbO_2 anode in sulfuric acid affords urea and succinic (*n* = 3) or adipic (*n* = 5) acid.[120]

3. Ureido carboxylic acids in the synthesis of *N*-carboxyalkylglycolurils

The first synthesis of 2-mono- and 2,6-dicarboxyalkylglycolurils was described in 1962.[121] 2-(Carboxymethyl)glycoluril (**45a**) was synthesised by the reaction of *N*-carbamoylglycine (**1a**) with 4,5-dihydroxyimidazolidin-2-one (DHI) (**46a**). Condensation of *N*-carbamoylglycine (**1a**) with glyoxal afforded regioisomers, *viz*., 2,6-bis(carboxymethyl)glycoluril (**47**) and 2,8-bis(carboxymethyl)glycoluril (**48**). However, only the 2,8 isomer was isolated from the reaction mixture (14% yield).

Recently, we have demonstrated [122] that the reaction of *N*-carbamoylglycine (**1a**) with glyoxal gave not only bis(carboxyalkyl)glycolurils **47** and **48** but also bis-product **49**. Bis-product **49** (20% yield) and a mixture of regioisomers **47** and **48** in a ratio of 1 : 1 (12% yield) were successively isolated from the reaction mixture by fractional crystallisation.



1a **46a** **45a** (43%) **47** **48** **49**

The reactions of ureido acids **1** with 4,5-dihydroxyimidazolidin-2-one **46** and its alkyl derivatives were studied in detail with the aim of extending the range of *N*-carboxyalkylglycolurils **45** and searching for the optimal reaction conditions.[123] The influence of the reaction time, the presence of substituents at the

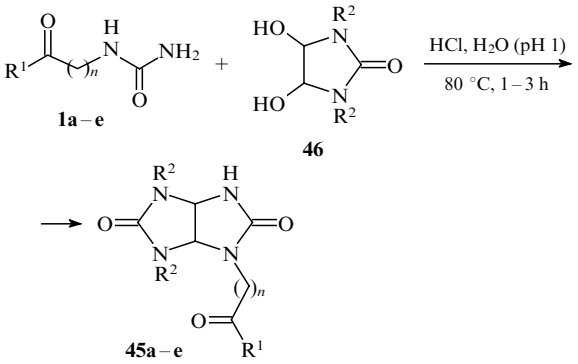
Table 5. Synthesis of *N*-carboxyglycolurils **45a**–**e**.[123]

Compounds **1** and **45**	*n*	R^2	Reaction time /h	Yield (%)	Symmetry group
a	1	H	3	68	$C2/c$, $Z = 8$
		Me	3	55	–
		Et	3	15	–
b	2	H	1	58	$P2_1/c$, $Z = 4$ ($0.5\,H_2O$)
		Me	2	45	$Pna2_1$, $Z = 4$ (H_2O)
		Et	3	5	–
c	3	H	3	63	$P2_1/c$, $Z = 8$
		Me	3	39	$P2_1$, $Z = 2$
		Et	2	40	$Pbca$, $Z = 8$
d	4	H	1	52	–
e[a]	1	H	1	40	–

[a] $R^1 = NHCH_2CO_2H$; for other compounds, $R^1 = OH$.

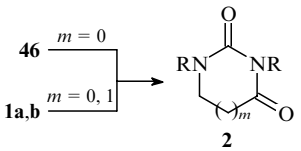
nitrogen atoms of DHI derivatives and the length of the alkyl fragment in ureido acids **1a**–**e** on the yields of the reaction products was examined (Table 5).[123]

Glycolurils **45a**–**e** were synthesised in aqueous HCl (pH 1–2) at 80 °C (see Table 5).



Glycolurils **45a**–**e** were obtained in lower yields where the reactions were performed with dialkyl derivatives of DHI instead of unsubstituted DHI as well as where the length of the carboxyalkyl chain in starting ureido acids **1a**–**d** increased. Because of long reaction times, glycolurils **45d**,**e** were synthesised only from unsubstituted DHI. The optimum reaction times for the synthesis of glycolurils **45a**–**e** are given in Table 5.

The reactions under consideration are accompanied by the following two side processes: the rearrangement of compounds **46** and cyclisation of ureido acids **1a**,**b** giving rise to the corresponding hydantoins and their analogues.



$m = 0$: R = H, Me, Et; $m = 1$, R = H.

These processes are responsible for a decrease in the yields of the target glycolurils **45**. *N*-Carbamoyl-β-alanine (**1b**) appeared to be the least reactive in reactions with alkyl-substituted DHI **46** (R^2 = Me or Et). Under these conditions, compound **1b** undergoes virtually complete cyclisation to give dihydropyrimidine-2,4(1*H*,3*H*)-dione (**2b**).

The ability of glycolurils **45** to form conglomerates was investigated.[123,124] For this purpose, glycolurils **45a**–**e**, which were prepared by crystallisation from H_2O, 30% aqueous MeOH and pure MeOH, were studied. Crystals suitable for X-ray diffraction study were obtained from H_2O. Compounds **45b** (R^2 = H, Me), **45c** (R^2 = H, Et) and **45d** (R^2 = H) crystallise as racemates in centrosymmetric space groups. 2-(Carboxypropyl)-6,8-dimethylglycoluril **45c** (R^2 = Me) exists as a mixture of homochiral crystals, which differ only in the optical rotation $[\alpha]_D = +21.92°$ ($c = 1.31$, H_2O) and $[\alpha]_D = -18.68°$ ($c = 0.38$, H_2O). Other physicochemical characteristics of the crystals are identical. The fact that crystallisation of glycoluril **45c** (R^2 = Me) gives rise to conglomerates was confirmed by X-ray diffraction (space group $P2_1$) (Fig. 1).[124]

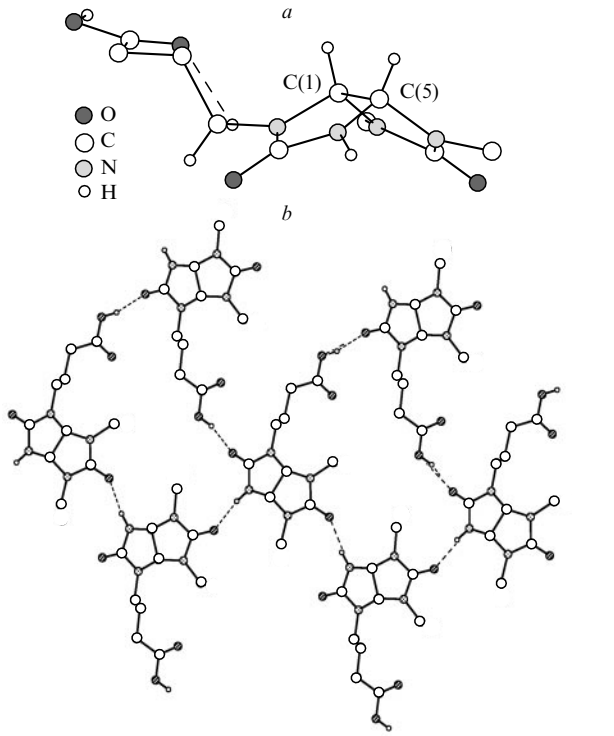
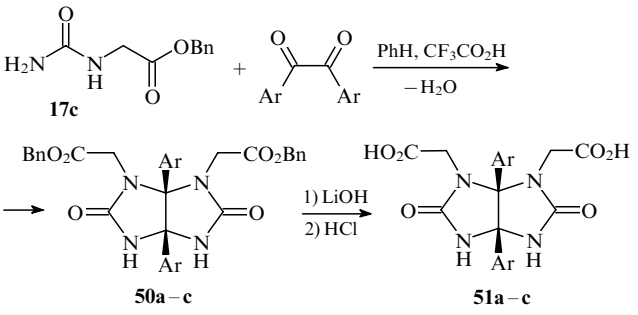


Figure 1. Molecular structure of compound **45c** (R^2 = Me) (*a*) and the scheme of formation of homochiral corrugated layers in the crystal through hydrogen bonds (*b*) (X-ray diffraction data, selected hydrogen atoms are shown).[124]

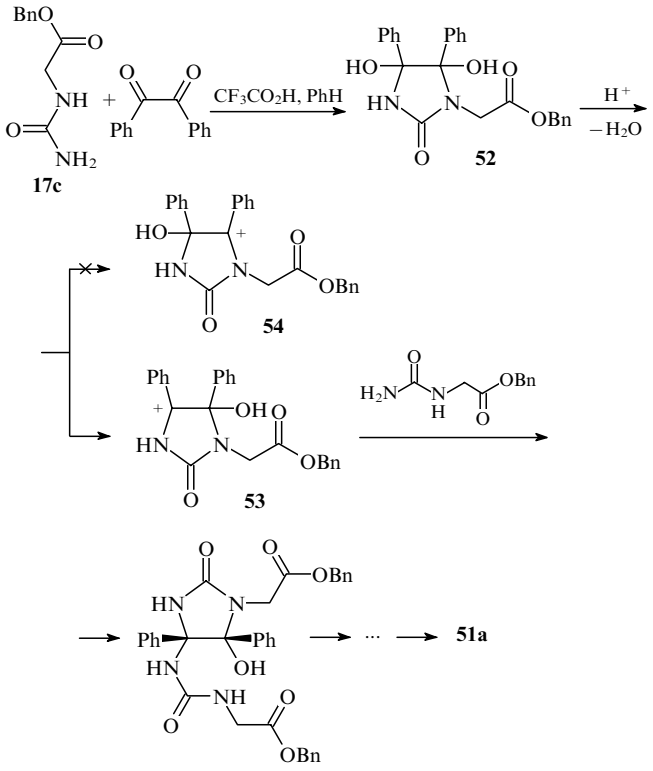
Racemic *N*-carboxyalkylglycolurils **45** that do not form conglomerates were separated by chiral-phase HPLC. This method was used to resolve racemates of compounds **45a** (R^2 = H or Me) and **45b** (R^2 = H). It should be noted that the presence of the methyl substituents [compound **45a** (R^2 = Me)] results in an increase in the selectivity of enantiomer separation compared to **45a** (R^2 = H), whereas the presence of one more methylene unit between the carboxy group and the heterocycle [compound **45b** (R^2 = H)] decreases the selectivity of separation.[123]

The synthesis of functionalised 1,5-diaryl-substituted glycolurils based on *N*-carbamoylglycine benzyl ester (**17c**) and diarylethanediones was documented.[125] α-Diketones were subjected to condensation with ester **17c** in benzene with azeotropic distillation of water. Subsequent saponification of the ester groups in compounds **50** afforded substituted glycolurils **51**.



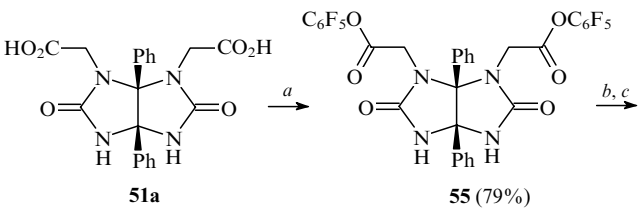
Ar = Ph (**a**), $C_6H_4OCH_2CO_2Bn$-4 (**b**), $C_6H_4OCH_2CO_2Et$-4 (**c**).

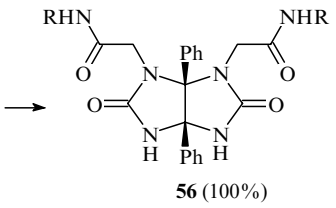
The above reactions give the 2,8-isomer of glycoluril **51** (for simplicity, the 2,6-isomer is ignored in the scheme) as the major product. If Ar = Ph, the 2,8 : 2,6 regioisomer ratio is 8 : 1. This fact can be accounted for by the following reaction mechanism:



The first step of the reaction affords 4,5-dihydroxyimidazolidin-2-one derivative **52**. After protonation, the latter can generate carbocations **53** or **54**. It was assumed [125] that it is the more electrophilic cation **53** that reacts with the more nucleophilic nitrogen atom of the urea fragment to form the 2,8-isomer of glycoluril **51a**.

In the latter study, compound **51a** (R = Ph) was subjected to esterification with pentafluorophenol to prepare bis(pentafluorophenyl) ester **55**. The reactions of the latter with amines (including amino acids and anilines) afforded derivatives **56**.





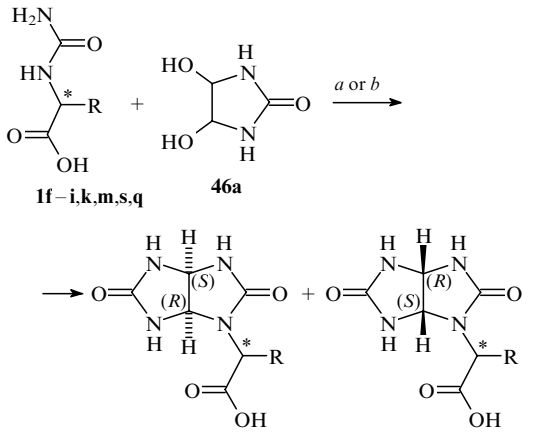
R = $CH(CO_2H)Bu^s$, $CH(CO_2Bu^t)Bu^s$;
(*a*) C_6F_5OH, EDC·MeI, DMAP; EDC is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide; DMAP is 4-(dimethylamino)pyridine;
(*b*) (H–Leu–OBu^t)·HCl; Et_3N, CH_2Cl_2, DMF; (*c*) TFA.

Thus, *N*-carboxyalkylglycolurils can be prepared by condensation of *N*-carbamoylamino acids and their esters with both DHI and α-dicarbonyl compounds.

4. Stereoselective syntheses of *N*-carboxyalkylglycolurils

The diastereoselectivity of the reaction of DHI with (*S*)-*N*-carbamoyl-α-alanine (**1f**) was described for the first time in 2001.[13] The diastereomeric (1*R*,5*S*)- and (1*S*,5*R*)-2-(3,7-dioxo-2,4,6,8-tetraazabicyclo[3.3.0]oct-2-yl)propionic acids (**45f**) were obtained (^{1}H NMR spectroscopic data) in a ratio of 5 : 2.

More recently, the diastereoselective reactions of DHI with optically active *N*-carbamoyl derivatives of amino acids, *viz*., (*S*)-norvaline (**1h**), (*S*)-α-aminobutyric acid (**1g**), (*S*)- and (*R*)-methionines (**1m**) and (*S*)-glutamine (**1q**), and with racemic compounds **1f**,**h**,**m** were studied.[126] Cyclocondensation was carried out at pH 1–2 in water or aqueous isopropyl alcohol (depending on the solubility of the starting compounds) with heating (conditions *a*). In all cases, glycolurils **45** were obtained in 33%–40% yields (Table 6).



(1*R*,5*S*)-**45f**–**i**,**k**,**m**,**s**,**q** (1*S*,5*R*)-**45f**–**i**,**k**,**m**,**s**,**q**

(*a*) H^+, H_2O–Pr^iOH, 80–90 °C, 1–3 h; (*b*) H_3O^+, 80 °C, 2 h.

The diastereomeric composition of the products was determined by ^{1}H NMR spectroscopy. It was found that glycolurils **45** were obtained as two diastereomers (major and minor), which is indicative of high diastereoselectivity of the reactions. This is evidenced by doubling of the signals for all protons, the signals for the CH protons of the major diastereomers being observed at lower field compared to the corresponding signals of the minor diastereomers. To determine the precise chemical shifts and coupling constants of the protons at the C(1) and C(5) atoms in compounds **45**, calculations were carried out by the NUMMRIT method implemented in the Xsim program (Linux OS).

Individual stereoisomers (1*R*,5*S*)-**45m** and (1*S*,5*R*)-**45m** prepared from (*S*)-*N*-carbamoylmethionine (**1m**) were separated by crystallisation from water.

The isolation of the major product obtained in the reaction of DHI with (*S*)-ureido acid **1q** (methanol, traces of HCl) was

Table 6. Diastereoselective and diastereospecific syntheses of diastereomeric and enantiomerically pure glycolurils **45**.[126, 127]

Ureido acid **1**	R	Diastereomer ratio (1*R*,5*S*)-**45** : (1*S*,5*R*)-**45**	
		conditions (*a*)	conditions (*b*) [yield (%)]
(*S*)-**1f**	Me	5 : 2	–
(*S*)-**1g**	Et	5 : 1	–
(*S*)-**1h**	Pr^n	3 : 1	–
(*S*)-**1i**	Pr^i	–	100 : 0 [30]
(*R*)-**1i**	Pr^i	–	0 : 100 [30]
(*S*)-**1k**	Bu^s	–	100 : 0 [35]
(*S*)-**1m**	$(CH_2)_2SMe$	15 : 1	100 : 0 [37]
(*R*)-**1m**	$(CH_2)_2SMe$	1 : 15	0 : 100 [37]
(*S*)-**1s**	Bn	–	100 : 0 [35]
(*S*)-**1q**[a]	$(CH_2)_2C(O)NH_2$	15 : 1	–
(*R*,*S*)-**1f**	Me	5 : 2	–
(*R*,*S*)-**1h**	Pr^n	3 : 1	[33]
(*R*,*S*)-**1m**	$(CH_2)_2SMe$	15 : 1	[37]

[a] Product **57** was formed in the course of isolation.

accompanied by hydrolysis of the amido group to form the carboxy group followed by esterification giving rise to glycoluril methyl ester **57**. The configurations of the chiral C(1) and C(5) atoms of the major diastereomers (1*R*,5*S*)-**45m** and (1*R*,5*S*)-**57q** and the minor diastereomer (1*S*,5*R*)-**45m** (Figs 2 and 3) were established by X-ray diffraction.

The reaction of DHI with (*R*)-*N*-carbamoylmethionine [(*R*)-**1m**] also proceeded with high diastereoselectivity (the diastereomer ratio was 15 : 1), but the reaction gave (1*S*,5*R*)-**45m** as the major diastereomer, which was also isolated by crystallisation from water.

Difficulties in the separation of stereoisomers is the major problems in the diastereoselective synthesis.

With the aim of searching for the conditions of the diastereospecific reaction of DHI with (*S*)- and (*R*)-*N*-carbamoylmethionines (**1m**), the influence of pH (from 0 to 5), temperature (40–90 °C) and the reaction time (0.5–4 h) on the reaction pathway was examined. It was found [127] that the highest diastereospecificity can be achieved with the use of 2 equiv. of HCl at 80 °C for 2.5 h (conditions *b*). Under these conditions, individual isomers of glycoluril **45m** were obtained (see Table 6).

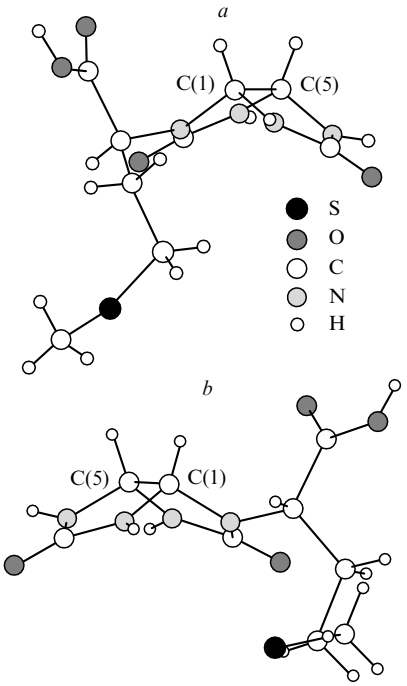


Figure 2. Overall view of the molecule (1*R*,5*S*)-**45m** (*a*) and its stereoisomer (1*S*,5*R*)-**45m** (*b*) (X-ray diffraction data).[127]

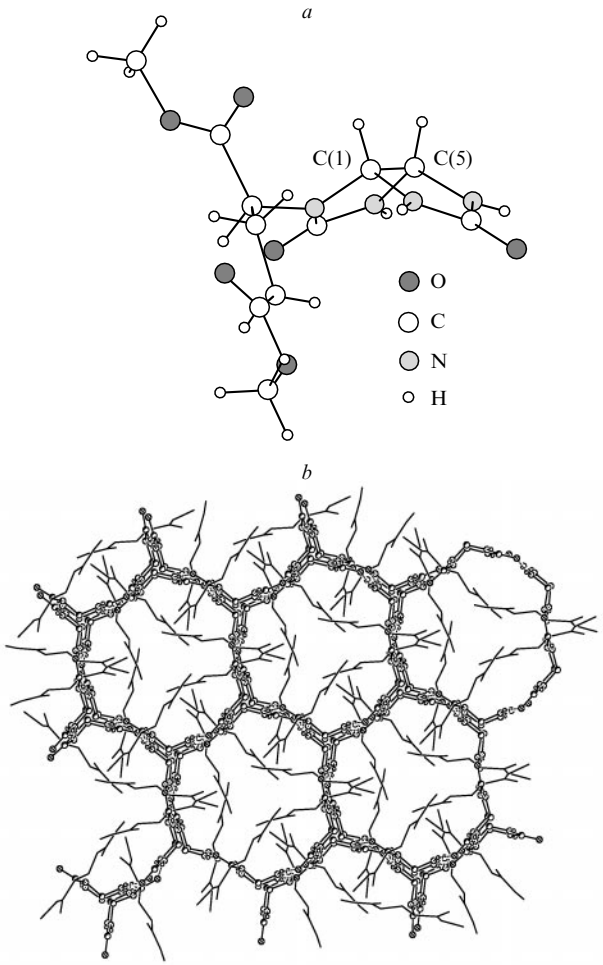


Figure 3. Overall view of the molecule (1*R*,5*S*)-**45q** (*a*) and the formation of an N–H···O-bonded honeycomb-like structure in the crystals of this compound (*b*).[127]

These conditions were used in the reactions of DHI **46a** with other (*S*)- or (*R*)-*N*-carbamoyl-α-amino acids, *viz*., compounds **1i**,**k**,**s**. In all cases, individual isomers of the corresponding glycolurils were synthesised.

The diastereospecific reactions of compounds **46a** with (*S*)- and (*R*)-*N*-carbamoylmethionines (**1m**) and (*S*)- and (*R*)-*N*-carbamoylvalines (**1i**) afforded enantiomers characterised by identical physicochemical parameters, including the optical rotation, which is equal in magnitude but opposite in sign. Ureidoalkylation of (*S*)-*N*-carbamoylisoleucine (**1k**) and (*S*)-*N*-carbamoylphenylalanine (**1s**) also occurs diastereospecifically to give enantiomerically pure glycolurils (1*R*,5*S*)-**45k**,**s** (see Table 6).

The reactions of DHI with racemic (*R,S*)-*N*-carbamoyl-α-amino acids, *viz*., (*R,S*)-*N*-carbamoylnorvaline (**1h**) and (*R,S*)-*N*-carbamoylmethionine (**1m**), under conditions of the diastereospecific synthesis affords racemates (*R*,*S*)-**45h**,**m**, respectively.

It should be noted that all known reactions yield the corresponding hydantoins as by-products.

With the aim of confirming the absolute configurations of the chiral C(1) and C(5) atoms in glycolurils derived from (*R*)-*N*-carbamoyl-α-amino acids, the coordination compound $Ni(H_2O)_6L_2(H_2O)_4$ (**58**), where L is deprotonated glycoluril, was synthesised by the reaction of glycoluril (1*S*,5*R*)-**45m** with nickel

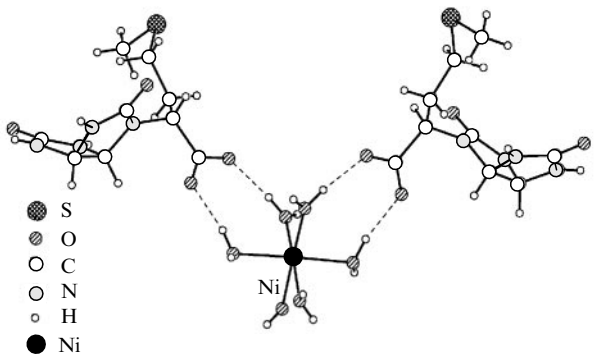


Figure 4. Solvated nickel cation and two anions of deprotonated glycoluril (1*S*,5*R*)-**45m** in the crystals of coordinated compound **58** (X-ray diffraction data).[127]

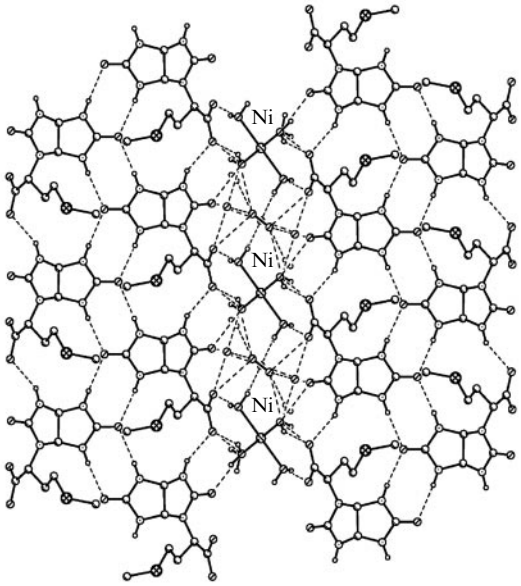
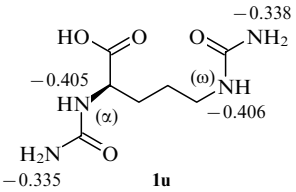


Figure 5. Projection of the molecular packing of **58** in the crystal structure illustrating alternation of the cationic layers and the anionic chains.[127]

acetate in an aqueous solution. Single crystals of **58** grown from water were studied by X-ray diffraction (Figs 4 and 5). It should be noted that the metal atom in complex **58** is not involved in direct coordination to the functional groups of the ligand (see Fig. 4). In the crystal structure, the nickel cation lies on the C_2 axis and is surrounded by six water molecules. In addition, the unit cell contains four water molecules of solvation. The presence of a large number of donors and acceptors in compound **58** results in a rather complicated supramolecular structure. The crystal structure consists of alternating inorganic (cation) and organic (anion) fragments (see Fig. 5).

5. Reactions of α,ω-diureido carboxylic acids with 4,5-dihydroxyimidazolidin-2-ones

Cyclocondensation of α,ω-diureido acids with DHI derivatives **46** was studied as an access to alkylenedi(glycolurils). The starting compounds **1u** and **59** were prepared by the reaction of (*S*)-citrulline (**60**) and (*S*)-lysine (**61**), respectively, with KOCN.[128] To estimate the reactivities of the α- and ω-ureido fragments in α,ω-diureido acids, the charges on the nitrogen atoms in N^{α}-carbamoylcitrulline (**1u**) were calculated by the MNDO method. The calculations demonstrated that the charges on the α- and ω-nitrogen atoms of the ureido fragments in diureido acid **1u** are virtually identical, and a preference cannot be given to a particular reaction centre.

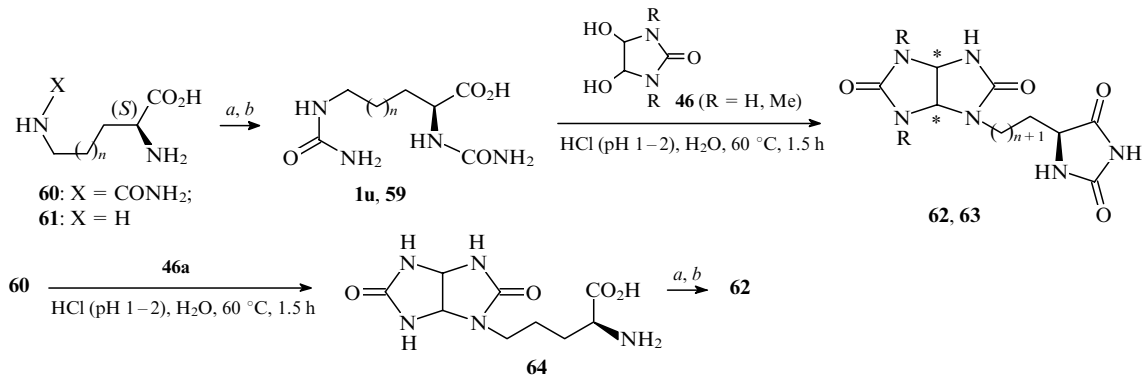


The reaction of compound **1u** was carried out with an equimolar amount of unsubstituted 4,5-dihydroxyimidazolidin-2-one **46a**, and the reaction of diureido acid **59** was performed with dimethyl-substituted DHI **46** (R = Me).[128] The structures of the resulting hydantoinoalkyleneglycolurils **62** and **63** were established by the independent synthesis of compound **62**. Initially, the reaction of (*S*)-citrulline (**60**) with DHI **46a** under the conditions of the diastereospecific synthesis afforded glycoluril **64**, which was used in the reaction with KOCN to form the α-ureido fragment. However, this reaction gave compound **62** instead of the expected glycolurilureido acid (Scheme 3).

The chiral centre in the starting diureido acids is remote from the ureido fragments involved in cyclocondensation due to which the reactions give mixtures of diastereomers. The structures of the reaction products were established by ^{1}H and ^{13}C NMR spectroscopy with the use of the highly sensitive inversion HNMQC (Heteronuclear Multiple-Quantum Correlation) and HMBC (Heteronuclear Multiple-Bond Correlation) methods.

It was demonstrated [128] that the α- and ω-ureido fragments of diureido acids differ substantially in reactivity with respect to DHI. Cyclisation of the α-ureido fragment to hydantoin is more favourable, whereas the ω-fragment is more reactive with respect to DHI, which gives rise to the glycoluril fragment of compounds **62** and **63**.

Scheme 3



(*a*) KOCN, H_2O, 100 °C, 20 min; (*b*) HCl, 5 °C; *n* = 1 (**1u**, **60**, **62**), 2 (**59**, **61**, **63**); R = H (**62**), Me (**63**).

The stereochemical aspects of diastereoselective and diastereospecific reactions of *N*-α-carbamoylamino acids open up new possibilities for the synthesis of enantiomerically pure glycolurils.

* * *

As is evident from the above-presented data, the chemistry of ureido acids and ureido diacids continues to be developed. Apparently, the use of modern solid-phase syntheses of both the starting *N*-carbamoylamino acids and various related heterocyclic compounds is most promising in this area of chemistry. The use of optically pure ureido acids provides approaches to the diastereoselective and diastereospecific syntheses of *N*-(*N*-α-carbamoyl)-substituted glycolurils, which are potential neurotropic compounds.[129]

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