CROATICA CHEMICA ACTA CCACAA 57 (2) 265—269 (1984)

YU ISSN 0011—1643
CCA-1440 UDC 547.5
Original Scientific Paper

Ferrocene Compounds. XII*. Reactions of Ferrocenecarbaldehyde with Benzanilides and *n*-Butyllithium

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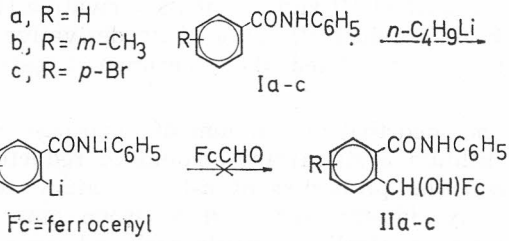
Received September 4, 1983

The reactions of ferrocenecarbaldehyde with benzanilides, and *n*-butyllithium, depending on the benzanilide used, gave mixtures of 1-hydroxypentylferrocene, 1-phenoxypentylferrocene, pentylferrocene, hydroxymethylferrocene, bis(ferrocenylmetyl) ether and ferrocene. The mixtures obtained have been separated into pure components by chromatographic methods and their structures have been assigned by spectroscopic means.

It is well known that ferrocenecarbaldehyde reacts with organolithium compounds giving the corresponding ferrocenylcarbinols in a good yield. Thus, condensation of ferrocenecarbaldehyde with ferrocenyllithium in diethyl ether /THF gave 62% of differrocenylmethanol,[1] and reaction of ferrocenecarbaldehyde with lithio *tert*-butyl acetate in liquid ammonia/diethyl ether gave the β-hydroxy ester which was dehydrated and hydrolyzed to 63% of β-ferrocenylacrylic acid.[2]

In this connection we have planned to study reactions of ferrocenecarbaldehyde with dilithio derivatives of some benzanilides (*Ia—c*) aiming to prepare intermediates *IIa—c* for syntheses of substituted ferrocene analogs of antraquinone.



* Part XI: V. Rapić and L. Korontoš, *J. Organometall. Chem* **260** (1984) 219.

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Analogous reactions of substituted anilides and benzaldehyde are presented in an U.S. patent:[3] the lithiation is performed from —60 to +10 °C for 1—3 hours whereas the second step (without separation of the dilithio intermediate) was achieved from —10 to +10 °C for additional 1—3 hours.

The reactions of stoichiometric amounts of ferrocenecarbaldehyde with benzanilides *Ia—c* and butyllithium under conditions of the experiments described,[3] did not give the desired carbinols *IIa—c;* depending on the benzanilide used, the products presented in the Table I were isolated. By changing the conditions (temperature, solvent) and the molar ratios of reactants from equimolar to 1 : 1.5 : 3.5 (the molar excess of *n*-butyllithium was used to complet the metalation reaction!) the formation of carbinols *II* could not be achieved, but the same products were isolated.

TABLE I

Reactions of Ferrocenecarbaldehyde with Benzanilides and n-*Butyllithium*

Experiment	$RC_6H_4CONHC_6H_5$	Products (% yield)
1.	R = H	*III* (16.1), *IV* (7.2), Ferrocene (23.2)
2.	R = *m*-CH_3	*III* (6.3), *V* (11.1) *VI* (12.3), Ferrocene (15.6)
3.	R = *p*-Br	*VII* (10.8), Ferrocene (18.1)

Notes: The yields given are based on reacted ferrocencarbaldehyde (10—20% of unreacted aldehyde was isolated). Structural formulas are given in Table II. In all experiments the significant amounts of decomposed material were produced. In experiment 2. 120 mg of unidentified material (base peak in the mass spectrum 508) was isolated; in the experiment 3. 200 mg of unidentified material (base peak 256) was obtained.

The failure of the desired condensation could be rationalized in terms of steric hinderance between the bulky ferrocene nucleus and both lithium atoms in molecules *Ia—c*. The structure of the compounds isolated shows that ferrocenecarbaldehyde reacted preferentially with *n*-butyllithium.

Reactions of lithium alkyls with nonenolizable carbonyl compounds yield exclusively or preferentially the addition products (*e. g.*, benzophenone gave 73% of addition and 26% of reduction product, and benzaldehyde gave 100% of addition product[4]).

Reaction of ferrocenecarbaldehyde with *n*-butyllithium gave 77% of addition product *III*. From the Table I it can be seen that the experiment 1. gave 16% of the addition product *III* and 7% of its derivative *IV;* in the experiment 2. 6% of the addition product *III*, 11% of its derivative *V*, and 12% of the reduction product *VI*[5] was isolated; the experiment 3. gave 11% of the reduction product *VII*.[5]

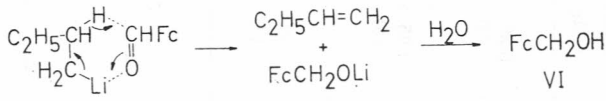
It could be concluded that in reactions of ferrocenecarbaldehyde, benzanilides and *n*-butyllithium a significant amount of reduction compounds were produced. The reduction properties of *n*-butyllithium can be interpreted in analogy with the hydride-transfer from β-carbon atom of alkylmagnesium halides to carbonyl of sterically hindered carbonyl compounds,[6a] or with the Meerwein-Pondorff-Verley reduction.[6b,7] The hydride-transfer could be rationalized in a cyclic mechanism by complexation of lithium from butyllithium with the carbonyl oxygen.[6b] On the other hand butyllithium adds to ferroce-

TABLE II

Compd.	Formula[a]	Mol. mass Calc'd. Found	M.p./°C	^{1}H-NMR spectra[d] CH	Fc	CH_2	CH_3	OH
III	$FcCH(OH)(CH_2)_3CH_3$	272.2 272	(oil)	4.29 . . . 4.01 m (10)	4.20 s,	1.70 . . . 1.11 m (6)	0.90 t (3)	2.12 s (1)
IV	$FcCH(OC_6H_5)(CH_2)_3CH_3$	348.3 347 (M-1)	83—4	4.21 . . . 3.85 m (10)	4.13 s,	1.80 . . . 1.15 m (6)	0.95 t (3)	—
V	$Fc(CH_2)_4CH_3$	256.2 255 (M-1)	73—4		4.20 s, 4.11 . . . 4.30 m (9)	2.02 . . . 1.01 m (8)	0.92 t (3)	—
VI	$FcCH_2OH$	216.1 216	70—3[b]		4.18 s, 4.36 . . . . . 4.11 m (11)		—	1.63 s (1)
VII	$(FcCH_2)_2O$	414.1 414	128—30[c]		4.17 s, 4.35	4.10 m	—	—

[a] Fc = ferrocenyl; [b] literature[5] m. p. = 74—6 °C; [c] literature[10] m. p. = 132—4 °C; [d] s = singlet, t = triplet, m = multiplet; numerals in paratheses denote a number of protons; the phenyl protons of compd. *IV* give multiplet at δ 7.13 . . . 6.67(5) p.p.m.

necarbaldehyde, giving product *III*, which could be reduced to pentylferrocene *V* in usual manner, probably because of the electron-releasing properties of the ferrocene nucleus.[6c] The phenoxy derivative *IV* could be produced by reaction (an nucleophylic substitution[8]?) of benzanilide with α-ferrocenylpenta-



nolate ion (derived from *III*). Ether *VII* was described[5] as a hydrogenation product of ferrocenecarbaldehyde in the presence of Raney nickel catalyst. In our experiments it must have been formed as one of the reduction products of ferrocenecarbaldehyde with *n*-butyllithium.

EXPERIMENTAL

The experiments were performed under an argon atmosphere. THF was destilled from $LiAlH_4$. Benzanilide, *m*-methylbenzanilide, and *p*-bromobenzanilide were prepared by modified procedure,[9] and recrystallized from ethanol. The m. p.'s and the IR spectra of the anilides prepared corresponded to those described in literature.

TABLE III

IR Spectra (cm^{-1})

Compd.	OH . . . O	Ar—H	C—H Aliph.	Monosubst. Ferrocene
III	3572 s, b 3462 s, b	3110 s (Fc)	2995 s 2950 s 2888 s	1115 s 1010 s 825 s
IV	—	3100 m (Fc) 3060 w (Ph) 3025 w (Ph)	2965 s 2930 s 2860 s	1105 s 1000 s 815 s
V	—	3100 m (Fc)	2960 s 2940 s 2865 s	1110 s 1005 s 820 s
VI	3240 s, b	3100 m (Fc)	2960 w 2934 w 2880 w	1102 s 985 s
VII	—	3105 m(Fc)	2960 m 2929 m 2850 m	1103 s 998 s 815 s

Notes: Structural formulas are given in Table II. s = strong, m = medium, w = week, b = broad

The m. p.'s were determined in a Büchi apparatus and are uncorrected. The IR spectra were recorded as KBr pellets or liquid films with a Perkin-Elmer 257 Grating Infrared Spectrophotometer. The ^{1}H-NMR spectra (δ values; in $CDCl_3$ solution) were recorded using a Varian EM 360 spectrometer with tetramethylsilane as internal standard.

Reaction of Ferrocenecarbaldehyde, Benzanilides Ia—c, and n*-Butyllithium (III—VII)*

General procedure. — 0.01 mole of the appropriate benzanilide in 20 ccm of THF was added unter mechanical strring at —10 °C to the mixture of 0.03 mole of *n*-butyllithium in hexane and 5 ccm of THF. The pale-yellow colour of the reaction mixture changed thereby in a red-orange hue. After 2 hours of stirring 2 g (0.01 mole) of ferrocenecarbaldehyde in 20 ccm of THF was added dropwise during 10 minutes. Reaction was continued in the course of 2 hours at room temperature, and an additional hour under reflux. Then, the reaction mixture was hydrolyzed by pouring onto ice and water containing some ascorbic acid, and extracted with diethyl ether. The ethereal extracts were washed with water, dried over Na_2SO_4 anhyd., and evaporated to dryness, giving red-brownish oily product, which was separated into components by column and TL chromatography (see Tables I, II and III).

1-Hydroxypentylferrocene (III)

A mixture of 100 mg (0.4 mmole) of ferrocenecarbaldehyde and 3.2 mmoles of *n*-butyllithium in 10 ccm of THF was gently boiled during 2 hours, giving a purple colour. The reaction mixture was worked up as described above giving after purification by TL chromatography 100 mg (77%) of *III*; its IR spectrum was identical with the spectrum of the sample *III* from the previous experiments.

Acknowledgement. — The authors are indebted to Dr. J. Jelenčić and Mrs. J. Brckvić for taking the IR spectra. Thanks are due to the Council for Scientific Research, Socialist Republic of Croatia, Zagreb, Yugoslavia, for partial support by a grant.

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SAŽETAK

Reakcije ferocenkarbaldehida, benzanilida i *n*-butil-litija

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U reakcijama ferocenkarbaldehida, benzanilidâ i *n*-butil-litija, u ovisnosti o upotrebljenom benzanilidu, nastaju smjese 1-hidroksipentilferocena, 1-fenoksipentilferocena, pentilferocena, hidroksimetilferocena, bis(ferocenilmetil)-etera i ferocena. Te su smjese razdvojene kromatografskim postupcima u čiste spojeve, čija je struktura određena na temelju spektroskopskih podataka.

CROATICA CHEMICA ACTA CCACAA 57 (2) 271—280 (1984)

CCA-1441

YU ISSN 0011—1643
UDC 547.4

Original Scientific Paper

N-4-Chlorobutyryl Aminoacids as a Common Intermediate in the Synthesis of *N*-Alkylamides of 2-Oxo-Pyrrolidine and L-Aspartyl-L-Phenylalanine Esters

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Received July 7, 1983

Different organic compounds were prepared from *N*-4-chlorobutyryl aminoacids or dipeptides (*I*), depending on the reaction medium. In methanol solution and in the presence of cation exchange resin, *I* gave methyl esters. In the presence of a strong base or anion exchange resin cyclisation of *II* occurred to yield *N*-alkylamides of 2-oxo-pyrrolidine (*III*). Heating of the dipeptide ester (*VII*), protected with 4-chlorobutyryl group, in aqueous acetone caused hydrolysis of the 4-chlorobutyryl group and dipeptide ester hydrochloride was obtained (*VIII*).

It is convenient from the technological and the economic point of view to use the same starting material for the production of different final products. The stimulus to explore the *N*-4-chlorobutyryl aminoacids as a common intermediate in the synthesis of *N*-alkylamides of 2-oxo-pyrrolidine and L-aspartyl dipeptide esters stemmed from the study of a suitable process for the production of Piracetam[1] and Aspartame.[2] Piracetam was introduced into medicine as a therapeutic agent for the improvement of brain metabolism and Aspartame may be used as a law calorie artificial sweetener in the food and drug industry. The interesting nootropical activity of Piracetam stimulated the synthesis of a number of structurally related *N*-alkylamides of 2-oxo-pyrrolidine. It is noteworthy that the glycyl homologue of Piracetam, *i. e. III* (R = H, n = 1, m = 1) exhibits similar activation of the electrocorticogram curve in experimental animals (rabbits and rats) in a state of depression.

In spite of the several different methods reported for the preparation of individual *N*-alkylamides of 2-oxo-pyrrolidine, no general method has been developed for the synthesis of *N*-alkylamidoamides of 2-oxo-pyrrolidine. Even the synthetic method claimed for the production of Piracetam, i. e. the action of the sodium salt of 2-oxo-pyrrolidine on omega-halogenoalkylamides, cannot be succesfully applied in the case of gamma-halogenobutyrylamides, since in this case the cyclisation occurred into butyrolactam.[3]

On the other hand, although aspartyldipeptides can be prepared conveniently by the coupling of *N*-protected aspartyl anhydride with other aminoacid esters, followed by deprotection, this method usually gives a mixture of alpha- and beta-aspartyl dipeptides.[4,5,6] Furthermore, the separation of the obtained isomers is generally so difficult and complicated that only a few methods have been reported for the separation, *i. e.* fraction extraction, column chromatography or the use of aromatic acids.[7,8]

The easy participation[9,10,11] of the amido carbonyl or amido nitrogen group in the internal displacement of neighbouring halogen in omega-halogenoalkylamides, makes 4-chlorobutyryl derivatives of aminoacids suitable starting material for this purpose. Namely, in basic conditions, a proton could be removed from the amide nitrogen and cyclisation occurred to give *N*-substituted 2-oxo-pyrrolidines.[12] In neutral or acid media, cyclisation occurs by displacement of the halide ion by the carbonyl oxygen of the amide group, whereupon the exocyclic imino group is formed. The resulting iminoether in most cases rapidly hydrolysed into lactone and yielded a free amino group.[13,14] This reaction can be used in the protection of the amino group.

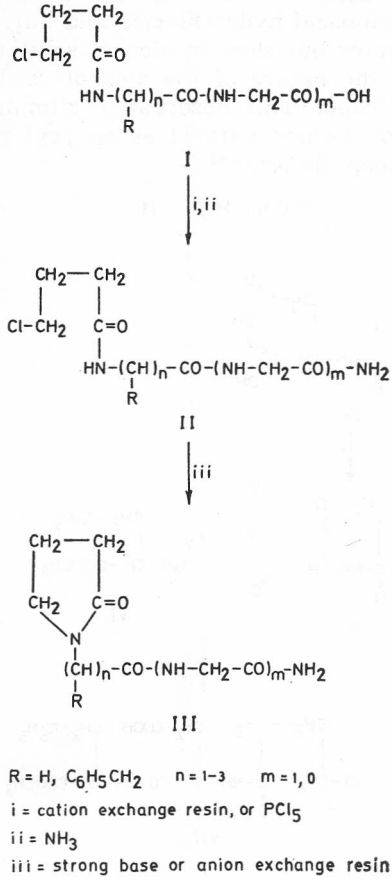
Although many preparations[15,16,17] of *N*-alkyl or *N*-aryl derivatives of 2-oxo--pyrrolidines have been reported, by made of cyclisation of a simple omega-halogenoalkylamide, no reports have been theses of *N*-alkylamides of 2-oxo-pyrrolidines by the cyclisation of omega-halogenoalkylamidoamides i. e. *N*-omega-halogenoalkylamides with an additional amide group in the molecule. At the same time, the use of the 4-chlorobutyryl group as an amino-protecting group and simultaneously as an activating group was reported by Peter.[18] For the removal of this group, silver tetrafluoroborate was used in order to form a cyclic iminoether, which was cleaved on coupling with the other aminoacid chloride to form the dipeptide.

Here we wish to report the results of a study of the cyclisation of *N*-4-chlorobutyryl derivatives of aminoacids and dipeptides in different reaction media. This enables us to synthesize *N*-alkylamides of 2-oxo-pyrrolidine by the use of basic agents; at the same time 4-chlorobutyryl was used as a protecting group in the synthesis of aspartyl dipeptide esters without using silver tetrafluoroborate but only heating in aqueous acetone to remove the 4-chlorobutyryl group.

One of the possible ways to prepare *N*-4-chlorobutyryl aminoacid amides was acylation of aminoacid amides with 4-chlorobutyryl chloride. However, the low solubility of the simple aminoacid amides in common organic solvents, except alcohols, was the main problem in this acylation. Therefore, *N*-(4-chlorobutyryl)-glycinamide was prepared by the acylation of glycinamide in dimethylacetamide.[19] Another problem in the preparation of higher aminoacid amides was the easy lactam formation during liberation from their salts, *i. e.* butyrolactam in the cases of 4-aminobutyryc acid amide or ketopiperazine of glycylglycine. Therefore, in those cases *N*-4-chlorobutyryl derivatives were prepared by another route, starting from halogenoacyl derivatives of aminoacids or dipeptides.

Halogenobutyryl derivatives of aminoacids can be prepared by the standard methods of acylation of aminoacids with 4-chlorobutyryl chloride in aqueous solution in the presence of a basic agent[20] but better results were obtained if aminoacids were first protected by the trimethylsilyl group.[21] In that case *N,O*-disilyl aminoacids were prepared by the standard method of

SCHEME I



R = H, $C_6H_5CH_2$ n = 1-3 m = 1, 0

i = cation exchange resin, or PCl_5

ii = NH_3

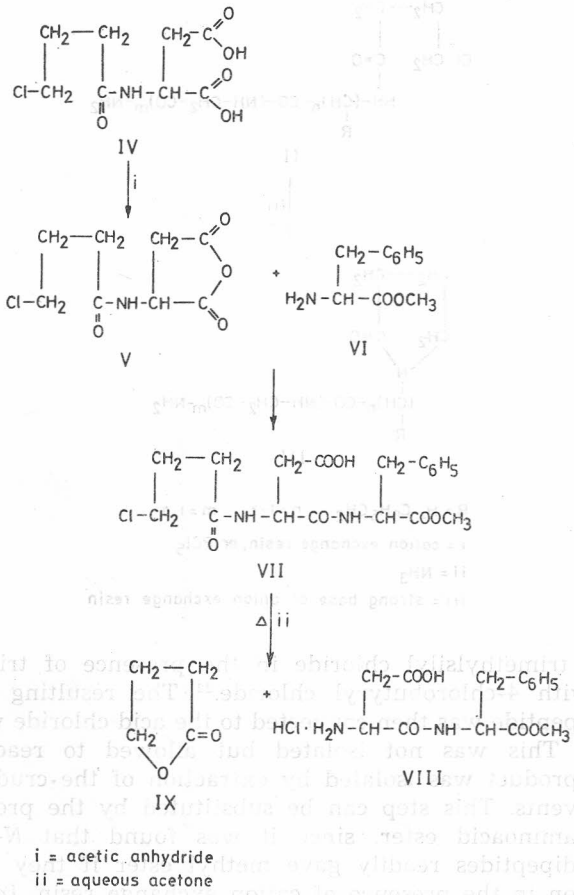
iii = strong base or anion exchange resin

silylation with trimethylsilyl chloride in the presence of triethylamine and then treated with 4-chlorobutyryl chloride.[22] The resulting 4-chlorobutyryl aminoacid or dipeptide was then converted to the acid chloride with phosphorus pentachloride.[23] This was not isolated but allowed to react further with ammonia. The product was isolated by extraction of the crude mixture with hot organic solvents. This step can be substituted by the preparation of the corresponding aminoacid ester, since it was found that *N*-4-chlorobutyryl aminoacids or dipeptides readily gave methyl ester if they were stirred in methanol solution in the presence of cation exchange resin. In that case *N*-4--chlorobutyryl aminoacid amide or dipeptide amide was obtained in the reaction with ammonia very conveniently in high yield and purity.

The cyclization[19,22] of *N*-4-chlorobutyryl aminoacid amides or peptide amides into *N*-alkylamides of 2-oxopyrrolidine (*III*) was performed in alcohol solution with different strong basic agents such as sodium alcoholates or anion exchange resins. In some cases high yield and purity of product was obtained

by the use of anion exchangers in spite of the reaction time being slightly longer. It was observed that in the absence of basic agents, *i. e.* in neutral media *N*-chlorobutyryl aminoacid undergoes cyclisation into iminoether, to give after hydrolysis aminoacid hydrochloride and butyrolactone. This reaction was faster in boiling water but slow in alcohol solution. The rate of reaction was also dependent on the nature of the alcohol used in the reaction, being very slow in tertiary alcohol. This observation stimulated us to consider the possibility of the use of 4-chlorobutyryl as an acyl protecting group in the synthesis of aspartyl-dipeptide ester.[24]

SCHEME II



N-4-chlorobutyryl aspartic acid (*IV*), prepared by acylation of *N,O*-disilyl aspartic acid with 4-chlorobutyryl chloride was transformed into the anhydride (*V*) by the use of acetic anhydride. Condensation of *V* with L-phenylalanine methyl ester (*VI*) gave a mixture of alpha- and beta- isomers of *N*-4-chlorobutyryl-aspartyl-L-phenylalanine methyl ester (*VII*). Pure alpha- isomer was obtained from this mixture by crystallisation from benzene solution. Heating

of *VII* in aqueous acetone solution gave, after neutralisation, pure alpha-L--aspartyl-L-phanylalanine methyl ester in 90% yield.

The obtained product had the same physical properties and sweetness test as a standard sample of Aspartame.

EXPERIMENTAL

Melting points are uncorrected.

The IR spectra were recorded on a Perkin-Elmer Infracord Model 257 G and are reported in wavelenghts followed by relative intensities in brackets.

TLC was conducted on original plates (Merck, Kieselgel HF_{254}) in the following solvent systems:

(A) *n*-Butanol : acetic acid : water (4 : 1 : 1)

(B) Ethyl acetate : acetic acid : water (3 : 1 : 1)

(C) Dichloromethane : acetone : methanol (5 : 5 : 1)

Spots were located by exposure of t.l.c. plates to iodine vapour or by the chlorine-starch-iodine method.

Compounds with free amino groups were detected with the sodium salt of naphthoquinone sulfonic acid (Folins reagent).

Optical rotations were measured on an Opton 372149 polarimeter at ambient temperature.

PREPARATION OF *N*-(4-CHLOROBUTYRYL) DERIVATIVES OF AMINOACIDS AND PEPTIDES (*I*)

General Procedure

To a suspension of aminoacid (0.036 mol) in dichloromethane (60 ml) was added trimethylchlorosilane (9.98 ml, 0.079 mol), the reaction mixture was cooled to 0 °C and a solution of triethylamine (11.06 ml, 0.079 mol) in dichloromethane (20 ml) was added dropwise with stirring. The solution was stirred for one hour at 25 °C, then cooled to 0 °C and stirring was continued as a further quantity of triethylamine (5.04 ml, 0.036 mol) was added. To the cooled reaction mixture, a solution of 4-chlorobutyryl chloride (4.03 ml, 0.036 mol) in dichloromethane (10 ml) was added gradually. After stirring for one hour at 25 °C, the precipitate was filtered and the filtrate washed with water (10 ml). The organic layer was dried ($MgSO_4$) and evaporated to an oil residue. Yield 75—85%.

N-(4-Chlorobutyryl)-glycine (Ia, R = H, n = 1, m = 0)

R_f = 0.70 (solvent system A)

Neutralisation equivalent: calc'd 179
found 173

Anal. $C_6H_{10}ClNO_3$ (179.5) calc'd: C 40.11; H 5.57; N 7.80%
found: C 39.80; H 5.15; N 7.40%

IR spectrum (film): 3360 (m), 3320 (w), 1740 (s), 1655 (m), 1540 (m) cm^{-1}.

N-(4-Chlorobutyryl)-beta-alanine (Ib, R = H, n = 2, m = 0)

R_f = 0.70 (solvent system A)

Neutralisation equivalent: calc'd 193
found 190

Anal. $C_7H_{12}ClNO_3$ (193.5) calc'd: C 43.41; H 6.20; N 7.24%
found: C 43.05; H 6.40; N 6.90%

IR spectrum (film): 3400 (s), 3100 (w), 1725 (m), 1635 (m), 1550 (s) cm^{-1}.

N-(4-Chlorobutyryl)-gamma-aminobutyric acid (Ic, R = H, n = 3, m = 0)

$R_f = 0.77$ (solvent system A)

Neutralisation equivalent: calc'd 207
found 211

Anal. $C_8H_{14}ClNO_3$ (207.5) calc'd: C 46.26; H 6.75; N 6.75%
found: C 45.60; H 6.30; N 6.50%

IR spectrum (film): 3400—3180 (b), 1710 (vs), 1630 (vs), 1540 (s) cm^{-1}.

N-(4-Chlorobutyryl)-phenylalanine (Id, R = $PhCH_2$, n = 1, m = 0)

$R_f = 0.60$ (solvent system C)

Neutralisation equivalent: calc'd 269.73
found 268

IR spectrum (film): 3270—3060 (b), 1725 (vs), 1640 (vs), 1535 (s), 735 (s), 700 (s) cm^{-1}.

N-(4-Chlorobutyryl)-glycylglycine (Ie, R = H, n = 1, m = 1)

Instead of oil in this case solid was formed.

M. p. 134—136 °C (ethylacetate), $R_f = 0.57$ (solvent system B)

Neutralisation equivalent: calc'd 237
found 243

Anal. $C_{18}H_{13}ClN_2O_4$ (236.65) calc'd: C 40.58; H 5.54; N 11.84%
found: C 40.77; H 5.54; N 12.05%

IR spectrum: 3320 (vs), 3060 (w), 1710 (m), 1640 (s), 1540 (s) cm^{-1}.

PREPARATION OF AMIDES OF *N*-(4-CHLOROBUTYRYL) AMINOACIDS AND PEPTIDES (*II*)

General Procedure

a) *N*-(4-Chlorobutyryl) aminoacid (0.048 mol) was dissolved in dichloromethane (30 ml), cooled to 0 °C and then phosphorus pentachloride (10 g, 0.048 mol) was added gradually with stirring. The stirring was continued for one hour whereafter the sample of the reaction solution showed the presence of an absorption band in the IR spectrum at 1800 cm^{-1}. The reaction solution was then gradually added to a mixture of benzene and dichloromethane (1 : 1), cooled to 0 °C and a stream of ammonia was introduced for one hour. The formed precipitate was filtered and triturated with hot ethylacetate or acetonitrile. Evaporation of solvent gave the product in 65—74% yield.

N-(4-Chlorobutyryl)-glycinamide (IIa, R = H, n = 1, m = 0)

M. p. 128—130 °C (ethylacetate), $R_f = 0.66$ (solvent system B).

Anal. $C_6H_{12}N_2O_2Cl$ (178.62) calc'd: C 40.34; H 6.21; N 15.68%
found: C 40.46; H 5.97; N 15.54%

IR spectrum: 3400 (vs), 3310 (vs), 3200 (vs), 1680—1620 (vs), 1550—1530 (s), 1315 (s) cm^{-1}.

N-(4-Chlorobutyryl)-beta-aminopropionamide (IIb, R = H, n = 2 m = 0)

M. p. 124—126 °C (dioxane), $R_f = 0.76$ (solvent system B).

Anal. $C_7H_{13}ClN_2O_2$ (192.6) calc'd: C 43.64; H 6.80; N 14.54%
found: C 43.86; H 6.66; N 14.61%

IR spectrum: 3380 (s), 3310 (s), 3190 (s), 1660—1630 (vs), 1540 (s), 1430 (s) cm^{-1}.

N-(4-Chlorobutyryl)-gamma-aminobutyramide (IIc, R = H, n = 3 m = 0)

M. p. 110—112 °C (ethylacetate), $R_f = 0.60$ (solvent system A).

Anal. $C_8H_{15}ClN_2O_2$ (206.7) calc'd: C 46.49; H 7.32; N 13.56%
found: C 46.48; H 7.39; N 13.34%

IR spectrum: 3380 (s), 3310 (vs), 3180 (s), 1630 (vs), 1530 (vs), 1450 (s) cm^{-1}.

N-(4-Chlorobutyryl)-phenylalaninamide (IId, R = $PhCH_2$, n = 1, m = 0)

M. p. 178—179 °C (ethylacetate), $R_f = 0.72$ (solvent system C).

Anal. $C_{13}H_{17}ClN_2O_2$ (268.74) calc'd: C 58.09; H 6.38; N 10.43%
found: C 58.32; H 6.62; N 10.43%

IR spectrum: 3375 (vs), 3300 (vs), 3180 (vs), 1660 (vs), 1640 (vs), 1530 (s), 1430 (s) cm^{-1}.

N-(4-Chlorobutyryl)-glycylglycinamide (IIe, R = H, n = 1, m = 1)

M. p. 178—180 °C (dioxane), $R_f = 0.19$ (solvent system C).

Anal. $C_8H_{14}ClN_3O_3$ (235.67) calc'd: C 40.77; H 5.99; N 17.83%
found: C 40.96; H 5.99; N 18.00%

IR spectrum: 3390 (s), 3300 (vs), 3200 (s), 1660 (vs), 1640 (vs), 1540 (vs), 1430 (s) cm^{-1}.

b) *N*-(4-Chlorobutyryl aminoacid (0.195 mol) was dissolved in methanol (680 ml) and dry cation exchange resin (Dowex 50W × 8, 103 ml) was added. The reaction mixture was stirred at 25 °C for 6 hours. It was then warmed to 50 °C and the exchange resin removed by filtration. Upon cooling a precipitate was again formed but during the introduction of a stream of ammonia it again dissolved. The stream of ammonia was introduced untill amide was formed and this was followed by TLC (4—8 hours). The obtained precipitate was filtered and the filtrate evaporated nearly to a dry residue. Acetone was added to the dry residue and an additional crop product was obtained. Yield 75—80%.

The obtained amides of *N*-(4-chlorobutyryl) aminoacids and peptides are indentical to those prepared by the procedure described under a.

c) Aminoacid amide (0.15 mol) was dissolved in *N,N*-dimethylacetamide (50 ml) with heating, the solution was cooled to 0 °C and 4-chlorobutyryl chloride (10.55 g, 0.075 mol) in dioxane (10 ml) added dropwise. The solution was stirred at 25 °C for 10 minutes and the precipitate was filtered. After evaporation the product was obtained by addition of diethylether. Yield 72—80%.

The obtained amides of *N*-(4-chlorobutyryl) aminoacids and peptides are identical to those prepared by the procedures described under a and b.

CYCLISATION OF AMIDES OF *N*-(4-CHLOROBUTYRYL) AMINOACIDS AND PEPTIDES INTO 2-OXO-PYRROLIDINE-*N*-ALKYLAMIDES (*III*)

General Procedure

The amide of *N*-(4-chlorobutyryl) aminoacid or peptide (8.5 mmoles) was suspended in alcohol (absolute ethanol, isopropanol or tert. butanol; 50 ml). Into this suspension an anion exchange resin (Dowex-1, 20 ml, OH form), or an inorganic base (NaOH), or an alkali metal alkoxide (sodium ethoxide, sodium isopropoxide, sodium tert. butoxide) (8.5 mmoles) was added. The mixture was stirred at 25 °C for 3—5 hours. The ionic exchange resin was then decantde, washed with alcohol and the solvent removed by evaporation. The resulting oil residue was crystallised from the solvent. Yield 63—85%.

2-Oxo-pyrrolidine-1-acetamide (IIIa, R = H n = 1, m = 0)

M. p. 145—147 °C, $R_f = 0.39$ (solvent system B). Recrystallisation from isopropanol gave a product with m. p. 148—150 °C (Lit.[15] 151.5—152.5 °C).

2-Oxo-pyrrolidine-1-propionamide (IIIb, R = H, n = 2, m = 0)

M. p. 141—142 °C (lit. 15 142—143 °C), $R_f = 0.53$ (solvent system A).

2-Oxo-pyrrolidine-1-butyramide (IIIc, R = H, n = 3, m = 0)

M. p. 93—97 °C, $R_f = 0.66$ (solvent system C). Recrystallisation from isopropanol--ether mixture gave a product with m. p. 98—100 °C (Lit. 17 99.8—100.5 °C).

2-Oxo-pyrrolidine-1-acetylglycinamide (IIId, R = H, n = 1, m = 1)

M. p. 134—136 °C, $R_f = 0.30$ (solvent system B). Recrystallisation from ethanol gave an analytical sample with m. p. 138—139 °C.

Anal. $C_8H_{13}N_3O_3$ (199.29) calc'd: C 48.23; H 6.58; N 21.1%
found: C 48.02; H 6.58; N 20.98%

IR spectrum: 3300 (s), 3160 (s), 1680 (vs), 1665 (vs), 755 (m), 700 (s) cm^{-1}.

2-Oxo-pyrrolidine-1-(α-benzyl)-acetamide (IIIf, R = CH_2Ph, n = 1, m = 0)

M. p. 133—8 °C, $R_f = 0.53$ (solvent system C). A sample for analysis was recrystallised from ethyl acetate; m. p. 138—40 °C.

Anal. $C_{13}H_{16}N_2O_2$ (234.27) calc'd: C 67.22; H 6.94; N 12.06%
found: C 67.47; H 6.95; N 12.07%

IR spectrum: 3300 (s), 3160 (s), 1680 (vs), 1665 (vs), 755 (m), 700 (s) cm^{-1}.

PREPARATION OF α-L-ASPARTYL-L-PHENYLALANINE METHYL ESTER (ASPARTAME)

N-(4-Chlorobutyryl)-L-aspartic acid (IV)

To a suspension of L-aspartic acid (5.32 g, 0.04 moles) and trimethylchlorosilane (16.6 g, 0.132 moles) in dichloromethane (100 ml) a solution of triethylamine (18.4 g, 0.132 moles) in dichloromethane (20 ml) was added dropwise under stirring. The reaction mixture was refluxed for one hour and then after cooling to —10 °C, 4-chlorobutyryl chloride (4.4 ml, 0.04 moles) in dichloromethane (40 ml) was added dropwise over 40 minutes. The mixture was stirred for another 2 hours at —10 °C and then for one hour at 25 °C. After the removal of the triethylamine hydrochloride by filtration, the mother liquor was evaporated to dryness, acetone (30 ml) was added, the solid separated by filtration and the mother liquor concentrated to an oil residue; yield 7.6 g (80%) of a light yellow oil, $R_f = 0.61$ (solvent system A), $[\alpha]_D^{23} = -3.37°$ (c = 1, acetone).

IR spectrum (CH_2Cl_2): 3400 (w), 1725 (vs), 1675 (s), 1500 (m), 1435 (m) cm^{-1}.

N-(4-Chlorobutyryl)-L-aspartic Anhydride (V)

To a solution of *N*-(4-chlorobutyryl-L-aspartic acid (7.95 g, 0.0335 moles) in dichloromethane (50 ml) was added acetic anhydride (4.7 ml, 0.503 moles). The suspension was stirred for 3 hours at 50 °C. The reaction solution was evaporated to 1/3 of its volume under reduced pressure. The residue was triturated with ether (150 ml) and the resulting crystalline solid was filtered and washed with ether. Yield 4.02 g (55%). A sample for analysis was recrystalised from dichloromethane; m. p. 123—7 °C, $[\alpha]_D^{23} = -66.2°$ (c = 1, acetone), $R_f = 0.88$ (solvent system A).

Anal. $C_8H_{10}ClO_4$ (219.63) calc'd: C 43.74; H 4.59; N 6.38%
found: C 43.72; H 4.61; N 6.55%

IR spectrum (nujol): 3225 (m), 1855 (w), 1780 (vs), 1625 (s), 1545 (s), 1445 (s) cm^{-1}

N-(4-Chlorobutyryl)-α-L-aspartyl-L-phenylalanine Methyl Ester (VII)

A solution of L-phenylalanine methyl ester (11.95 g, 0.066 moles) in dichloromethane (100 ml) was cooled to —10 °C and *N*-(4-chlorobutyryl)-L-aspartic anhydride (14.5 g, 0.066 moles) was added. The reaction mixture was stirred for two hours at —10 °C and then evaporated to dryness under reduced pressure. The crude product was recrystallised from benzene, yield 16.5 g (67%); m. p. 133—134 °C, $[\alpha]_D^{23} = -21.3°$ (c = 1, acetone), $R_f = 0.85$ (solvent system A).

Anal. $C_{18}H_{23}ClN_2O_6$ (398.84) calc'd: C 54.20; H 5.81; N 7.03%
found: C 54.43; H 5.66; N 6.83%

IR spectrum: 3290 (vs), 1725 (s), 1640 (vs), 1527 (s), 1425 (m) cm^{-1}.

α-L-Aspartyl-L-phenylalanine Methyl Ester (VIII)

The solution of *N*-(4-chlorobutyryl)-α-L-aspartyl-L-phenylalanine methyl ester (16.7 g, 0.042 moles) in acetone and water mixture (100 ml, 1 : 1) was refluxed for 6 hours. After the evaporation of solvent the residual aqueous solution was adjusted to 5.2 by addition of a saturated solution of sodium bicarbonate. The aqueous solution was washed with dichloromethane and concentrated to 1/3 of its volume by evaporation under reduced pressure. The separated crystals were filtered and washed with acetone; yield 11.2 g (90%), m. p. 239—241 °C, $[\alpha]_D^{23} = +14.01°$ (c = 1, 15 M HCOOH).

Standard sample of Aspartame (»EQUA-200«, Searle): $[\alpha]_D^{23} = +14.5°$ (c = 1, 15 M HCOOH), $R_f = 0.51$ (solvent system A).

Acknowledgement. — The authors thank the members of the Organic Chemistry Department of Research Institute Pliva, for recording the IR spectra, for microanalyses and for the neutralisation equivalent.

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SAŽETAK

N-4-klorbutiril aminokiseline kao intermedijeri u sintezi *N*-alkilamida 2-oxo-pirolidina i estera-L-aspartil-L-fenilalanina

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Priređeni su različiti spojevi iz *N*-4-klorbutiril aminokiselina ili peptida (*I*) ovisno o reakcijskom mediju. Metilni esteri nastaju iz *I* u metanolu u prisutnosti kationskog izmjenjivača. U prisutnosti jake baze ili anionskog izmjenjivača dolazi do ciklizacije *II* u *N*-alkilamide 2-oksopirolidina (*III*). Zagrijavanjem estera dipeptida (*VII*), zaštićenog s 4-klorbutiril grupom, u vodenom acetonu dolazi do hidrolize 4-klorbutiril grupe i nastaje hidroklorid estera dipeptida (*VIII*).