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Synthesis of Potentially Antineoplastic Derivatives of *N*-[*N*-(2-Chloroethyl)-*N*-nitrosocarbamoyl]amino Acids

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The synthesis of *N*-[*N*-(2-chloroethyl)-*N*-nitrosocarbamoyl]amino acids and their anilides, congeners of *N*-(2-chloroethyl)-*N*-nitrosoureas, as potential antineoplastic substances is reported. *N*-[*N*-(2-chloroethyl)-*N*-nitrosocarbamoyl]amino acids are prepared by reaction of amino acids with *N*-(2-chloroethyl)-*N*-nitrosocarbamoyl azide. Corresponding anilides and toluidides are obtained by condensation of the primary reaction products with aniline and toluidine using dicyclohexylcarbodiimide (DCC).

Synthese von potentiell antineoplastischen N-[N-(2-Chlorethyl)-N-nitroso-carbamoyl]aminosäurederivaten

Die Synthese von N-[N-(2-Chlorethyl)-N-nitrosocarbamoyl]aminosäuren und ihrer Anilide, Analogen von N-(2-Chlorethyl)-N-nitrosoharnstoffen als potentiell antineoplastischen Substanzen wird beschrieben. N-[N-(2-Chlorethyl)-N-nitrosocarbamoyl]aminosäuren werden hergestellt durch Reaktion von Aminosäuren mit N-(2-Chlorethyl)-N-nitroso-carbamoylazid. Durch Kondensation der primären Reaktionsprodukte mit Anilin oder Toluidin unter Verwendung von Dicyclohexylcarbodiimid (DDC) werden die entsprechenden Anilide und Toluidide erhalten.

N-halogenalkyl-N-nitrosoureas have attracted increasing attention as antineoplastic agents[1]. Some are in clinical use, e. g. N,N'-bis-(2-chloroethyl)-N-nitrosourea (BCNU), N-(2-chloroethyl)-N'-cyclohexyl-N-nitrosourea (CCNU) and its methyl derivative, N-(2-chloroethyl)-N-nitroso-N'-(4-methyl-cyclohexyl)-urea (MeCCNU). Sugar derivatives (e. g. chlorozotocin) have become available recently and further analogs are awaiting chemical tests; many more new compounds with various substituents have been synthesized[2–11].

In this paper, the synthesis of some N-[N'-(2-chloroethyl)-N'-nitroso-carbamoyl]-amino acids and their anilides or p-toluidides as potential antineoplastic agents is described.

Usually, a nitrosourea derivative is prepared by reacting an amino compound with an isocyanate followed by subsequent nitrosation of the resulting urea. Compounds with different substituents at the N-atoms, however, can only be prepared by this way when steric or electronic influences of the substituents direct the nitroso group into the desired position of the urea molecule. When there is no such influence of the substituents on selectivity of nitrosation, mixtures of isomers are obtained which are difficult to separate. *Eisenbrand* et al.[12,13] therefore used the aminolysis of N-(2-chloroethyl)-N-nitroso carbamoylazide (**1**) to obtain selectively nitrosated unsymmetrical urea derivatives in an one-step reaction.

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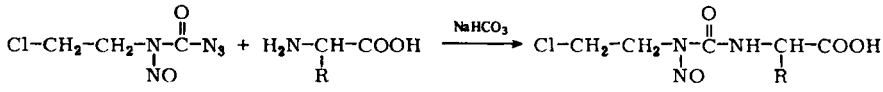
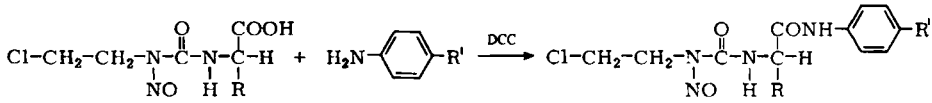
This paper describes the extension of this reaction to the synthesis of a series of amino acid derivatives (Scheme 1):



1 **2** R: see table 1 **3**

Reaction products **3** were used without further purification for the preparation of anilides **6** and p-toluidides **7**: Amino acid derivatives **3** were reacted with aniline **(4)** or p-toluidine **(5)** using dicyclohexyl-carbodiimide (DCC) as condensating agent (Scheme 2).



3 R: see Table 1 **4**: $R' = H$ **5**: $R' = CH_3$ **6**: $R' = H$ **7**: $R' = CH_3$

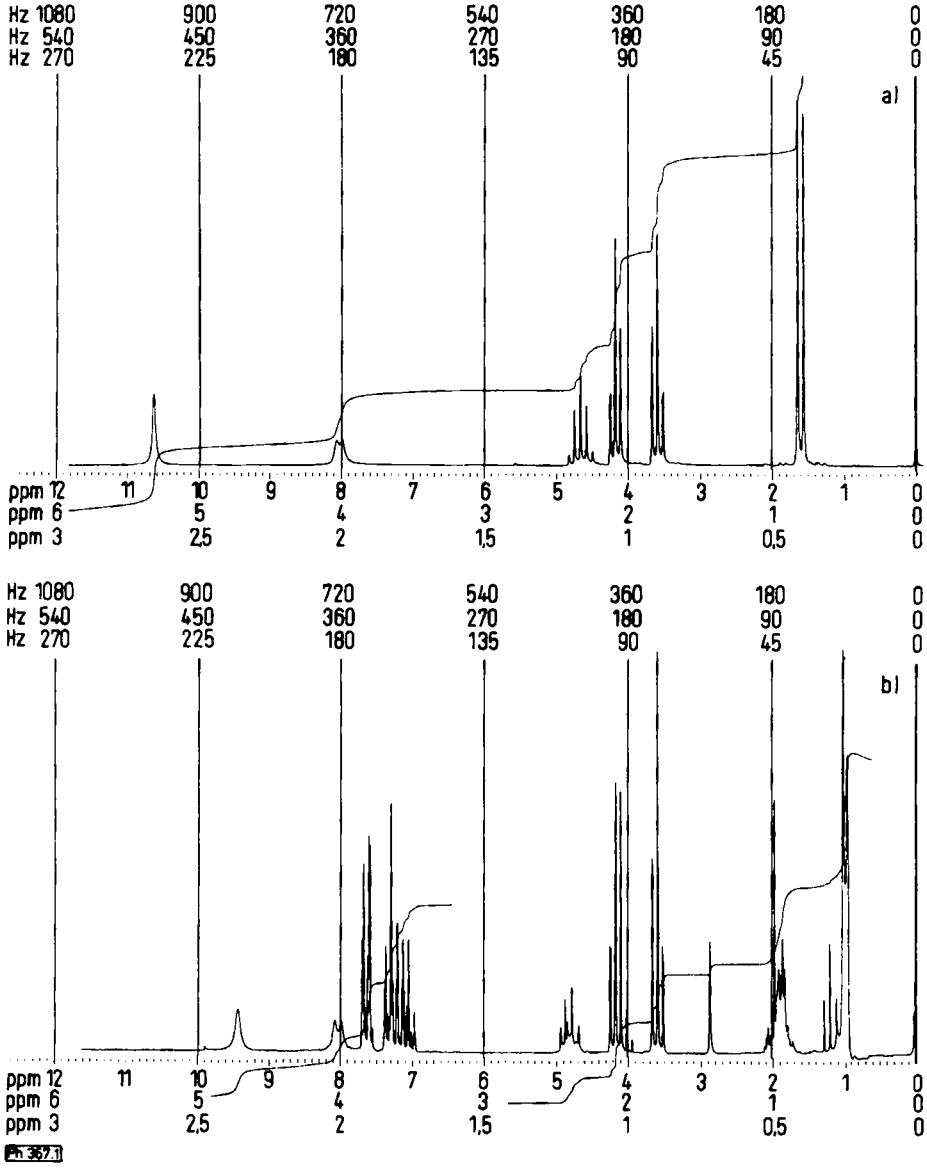
Results and Discussion

Amino acid derivatives **3** with a free carboxyl group were difficult to crystallize, except for the derivatives of glycine, alanine, methionine, glutamine and tryptophane. The derivative of tryptophane decomposed on standing, even when kept in a refrigerator. In contrast to the free acids, the corresponding anilides and toluidides **6, 7** are very stable and crystallize well. Derivatives **3** although they could not be crystallized, nevertheless showed typical NMR-spectral features, indicative of the correct structures. For these compounds (derivatives of valine, leucine, isoleucine, phenylalanine, serine, threonine, proline, 4-amino-n-butyric acid), data of elementary analysis as well as spectral data are not given in table 1, because they could not be obtained without impurities. Unequivocal proof of the assigned structures, however, in all cases was obtained by the preparation of the corresponding anilides **6** and toluidides **7**.

Spectral Data

Structural confirmation of derivatives **3, 6** and **7** can be obtained from ^{1}H-NMR-spectroscopic data. The chloroethyl group shows a characteristic pattern of two triplets, at δ (ppm) = 3.45 – 3.6 (Cl-CH_2-,) and at δ (ppm) = 4.1–4.2 (-CH_2-N-NO), which can be recognized in all spectra of nitrosated 2-chloro-ethylcarbamoyl derivatives[2]. The proton at the asymmetric center normally can be detected as a multiplet in the range between δ (ppm) = 4.5 to 4.8, depending on the nature of the substituents at this center. Signals of the protons at the N-atoms of the ureido group (dublet) and of the amide group (singulet) are located in the range between δ (ppm) = 7.5 to 9.5. Furthermore, the proton signals of other functional groups, for example, for phenyl-, methyl-, carboxyl-, hydroxy- and others are also recognizable in these spectra. Examples are given in Fig. 1a and b.

In the mass spectra, intense fragments at M-107 and M-108, which are invariably present, are of high diagnostic value, because they can be assigned to loss of $ClCH_2CH_2$-NNO or $ClCH_2CH_2$-N=NOH.



^{1}H-NMR-spectra of some N[N′(2-chloroethyl)N′-nitrosocarbamoyl]acids and anilides
1a: N-[N′-(2-chloroethyl)-N′-nitroso-carbamoyl]L-alanine
1b: N-[N′-(2-chloroethyl)-N′-nitroso-carbamoyl]L-leucineanilide

These fragments arise either by cleavage of the N-C bond or by a *McLafferty* type rearrangement of the N-chloroethyl nitrosoureido group.
The amido group yields fragements at m/e 119, 120 for anilides ($(OCN\text{-}C_6H_5)^+$, $(OCNH\text{-}C_6H_5)^+$) and, correspondingly, at m/e 133, 134 for toluidides. Fragments at m/e 176 for anilides and m/e 190 for toluidides can be explained by subsequent loss of $ClCH_2CH_2\text{-}NNO$ and of the amino acid side-chain (e.g. $OCNH\text{-}CHCONH\text{-}C_6H_5)^+$.
In the IR spectra, the following peaks are prominent: amide I (1660–1670 cm^{-1}), amide II (1530–1560 cm^{-1}), NNO (1490 cm^{-1} and 1315 cm^{-1}), monosubstituted benzene (750–760 cm^{-1}), and p-disubstituted benzene (810–820 cm^{-1}).

Experimental Section

I. *General procedure*

1. *N-[N'-(2-Chloroethyl)-N'-nitroso-carbamoyl]amino acids*

10 mmol amino acid and 10 mmol sodium hydrogen carbonate were dissolved in a minimum quantity of water. This solution was added to a stirred solution of 10 mmol N-(2-chloroethyl)-N-nitrosocarbamoylazide in isopropanol under cooling in an ice-bath. The reaction mixture was further stirred for 2–6 h under ice cooling, sometimes also at room temp. After standing at 4 °C overnight, the reaction mixture was acidified with 10 mmol tartaric acid and extracted with ethyl formate. The reaction product was reextracted from the organic phase with an aqueous solution of sodium hydrogen carbonate. The aqueous phase was acidified and the N-nitroso compound transferred into ether. The etheral solution was then dried with anhydrous sodium sulfate and the solvent evaporated.
In most cases an oily residue was obtained, which was homogenous by thin layer chromatography (DC-Alufoils, Kieselgel 60 F 254 Merck). The crude product tended to decompose gradually on standing, even at 4 °C. However, further purification by column chromatography on silica gel gave pure and stable products, some of which could be crystallized (table 1).

2. *N-[N'-(2-Chloroethyl)-N'-nitroso-carbamoyl]amino acid anilides and p-toluidides*

1 mmol of N-[N'-(2-Chloroethyl)-N'-nitrosocarbamoyl]amino acid and 1 mmol aniline or p-toluidine were dissolved in 10 mmol dichloromethane. Under ice-cooling and continued stirring, 1.1 mmol DCC in 10 ml dichloromethane was added dropwise. The reaction was complete after 1 h. The precipitated N,N'-dicyclohexyl-urea was filtered off and the solvent evaporated. Crude products were purified by column chromatography on silica gel. Yields invariably were around 80 %.

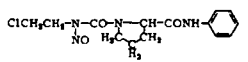
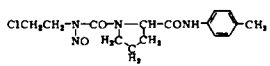
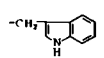
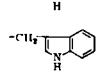
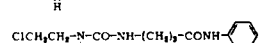
II. *Specific Compounds*

1. *N-[N'-(2-Chloroethyl)-N'-nitroso-carbamoyl]glycine* **(3a)**

10 mmol (0.75 g) of glycine and 10 mmol (0.84 g) of sodium hydrogen carbonate were dissolved in 20 ml of water. This solution was added under stirring and cooling in an ice-bath to a solution of 10 mmol N-(2-chloroethyl)-N-nitroso-carbamoylazide in 20 ml isopropanol. After addition of the amino acid solution, the reaction mixture was stirred for 2 h and then kept in an ice-box for 2 d. It then was acidified and extracted with ethyl formate. N-[N-(2-chloroethyl)-N'-nitroso-carbamoyl] glycine was extracted from the organic phase with sodium hydrogen carbonate solution, and then reextracted from the acidified aqueous phase with ethyl ether. The extract was dried over sodium sulfate. After evaporation a viscous material was obtained, which solidified after standing in an ice-box. Yield: 0.8 g

Table 1: *Data of N-[N'-(2-Chloroethyl)-N'-nitroso-carbamoyl]amino acids and the corresponding anilides and p-toluidides* $Cl\text{-}CH_2\text{-}CH_2\text{-}\underset{\underset{NO}{|}}{N}\text{-}CO\text{-}NH\text{-}\underset{\underset{R}{|}}{CH}\text{-}CO\text{-}R'$

No.	amino acids	R	R'	mp.(°C)[1]	formula	elemental analyses calc. / found C	H	N	^{1}H-NMR (ppm) = spectral data[2],[3] ir (cm^{-1})	MS (m/e)
3a	Glycine	-H	-OH	49–50	$C_5H_8N_3O_4Cl$	28.7 28.8	3.85 3.76	20.1 19.8	n.c.	1498	209(M^+),101/102
6a	Glycine	-H	-NH-⬡	149	$C_{11}H_{13}N_4O_3Cl$	46.4 46.3	4.60 4.39	19.7 19.5	3.6, 4.15, 4.3, 7.1–7.5, 7.55, 7.7	1695, 1680, 1545, 1495, 1315, 755	284(M^+),176/177, 119/120, 93, 77
3b	L-Alanine	$-CH_3$	-OH	60–62	$C_6H_{10}N_3O_4Cl$	32.2 32.2	4.51 4.49	18.8 18.9	3.6, 4.15, 4.65, 8.05, 10.65	1498	116
6b	L-Alanine	$-CH_3$	-NH-⬡	122–3	$C_{12}H_{15}N_4O_3Cl$	48.3 48.1	5.06 5.17	18.8 18.7	1.65, 3.5, 4.15, 4.8, 7.0–7.6, 7.6, 8.15	1700, 1665, 1530, 1490, 1315, 760	298(M^+),190/191, 119/120, 93, 77
7b	L-Alanine	$-CH_3$	-NH-⬡-CH_3	133	$C_{13}H_{17}N_4O_3Cl$	49.9 50.0	5.48 5.73	17.9 17.7	1.6, 2.3, 3.5, 4.2, 4.7, 7.0–7.45, 7.5, 7.8	1710, 1670, 1530, 1495, 1315, 820	312(M^+),204/205, 133/134, 107,91
6c	L-Valine	$-CH(CH_3)_2$	-NH-⬡	135	$C_{14}H_{19}N_4O_3Cl$	51.5 51.4	5.86 5.76	17.1 16.9	1.05–1.15, 2.35, 3.45, 4.15, 4.5, 7.0–7.55, 7.6, 8.1	1700, 1665, 1530, 1490, 1315, 760	326(M^+),218/219, 176, 119/120, 93,77
7c	L-Valine	$-CH(CH_3)_2$	-NH-⬡-CH_3	145	$C_{15}H_{21}N_4O_3Cl$	52.9 52.9	6.21 6.49	16.4 16.3	1.05–1.15, 2.3, 3.45, 4.15, 4.5, 7.0–7.45, 7.6, 8.0	1700, 1660, 1535, 1495, 1315, 820	340(M^+)232/233, 190, 133/134, 107, 91
6d	L- Leucine	$-CH_2-CH(CH_3)_2$	-NH-⬡	149	$C_{15}H_{21}N_4O_3Cl$	52.9 53.1	6.21 6.32	16.4 16.3	1.0, 1.9, 3.6, 4.15, 4.8, 7.0–7.7, 8.05, 9.45	1700, 1670, 1530, 1495, 1320, 760	340(M^+),232/233, 176, 119/120, 93, 77, 43
6e	L-Isoleucine	$-CH(CH_3)C_2H_5$	-NH-⬡	140	$C_{15}H_{21}N_4O_3Cl$	52.9 52.8	6.21 6.32	16.4 16.4	0.9–2.2, 3.45, 4.15, 4.55, 7.0–7.55, 7.65, 8.3	1700, 1665, 1530, 1500, 1315, 760	340(M^+),232/233, 176, 119/120, 93, 77, 57
6f	L-Phenylalanine	$-CH_2$-⬡	-NH-⬡	119	$C_{18}H_{19}N_4O_3Cl$	57.7 57.5	5.11 5.11	15.0 15.0	3.25, 3.45, 4.1, 4.9, 7.3, 7.65, 7.75	1700, 1670, 1530, 1495, 1320, 760	374(M^+),266/267, 119/120 93, 91, 77
7f	L-Phenylalanine	$-CH_2$-⬡	-NH-⬡-CH_3	130	$C_{19}H_{21}N_4O_3Cl$	58.7 58.5	5.44 5.30	14.4 14.3	2.3, 3.25, 3.4, 4.1, 4.85, 7.0–7.3, 7.4, 7.7	1710, 1665, 1535, 1500, 1315, 820	388(M^+),280/281, 133/134, 107, 91
6g	L-Serin	$-CH_2OH$	-NH-⬡	129	$C_{12}H_{15}N_4O_4Cl$	45.8 45.7	4.80 4.95	17.8 17.6	2.9, 3.5, 4.15, 4.3, 4.7, 7.2–7.6, 7.95, 8.5	1700, 1660, 1530, 1490, 1315, 745	314(M^+),206/207, 176, 119/120, 93, 77

6h	L-Threonine	$-CH(OH)-CH_3$	$-NH-C_6H_5$	125	$C_{13}H_{17}N_4O_4Cl$	47.5 47.3	5.21 5.04	17.0 17.0	1.3, 3.5, 3.6, 4.2, 4.6–4.7, 7.2–7.7, 7.95, 8.6	1670, 1535, 1500, 1315, 760	328(M^+),220/221, 176, 119/120, 93, 77
7h	L-Threonine	$-CH(OH)-CH_3$	$-NH-C_6H_4-CH_3$	143	$C_{14}H_{19}N_4O_4Cl$	49.1 48.9	5.59 5.54	16.4 16.2	1.3, 3.6, 4.2, 4.5, 4.6, 7.1–7.5, 7.95, 9.3	1690, 1665, 1535, 1500, 1315, 825	342(M^+),234/235, 190, 133/134, 107, 91
3f	L-Methionine	$-CH_2-CH_2-SCH_3$	$-OH$	89–90	$C_8H_{14}N_3O_4SCl$	33.9 33.8	4.97 4.93	14.8 14.5	2.1, 2.2–2.8, 3.6, 4.2, 4.8, 8.1, 9.2	1495	283(M^+), 175/176
6i	L-Methionine	$-CH_2-CH_2-SCH_3$	$-NH-C_6H_5$	130–1	$C_{14}H_{19}N_4O_3SCl$	46.9 47.0	5.34 5.51	15.6 15.4	n.c.	1680, 1530, 1495, 760	n.c.
3j	L-Glutamine	$-CH_2-CH_2-CONH_2$	$-OH$	83–5	$C_8H_{13}N_4O_5Cl$	34.2 34.0	4.67 4.66	20.0 19.7	n.c.	1640, 1530, 1500	280(M^+), 172/173
6k	L-Proline			130–1	$C_{14}H_{17}N_4O_3Cl$	51.8 51.8	5.28 5.51	17.3 17.0	2.0–2.4, 3.55, 3.85, 4.15, 4.8, 7.0–7.5, 8.3	1705, 1675, 1540, 1475, 1315, 750	324(M^+),216/217, 119/120, 93, 77, 70
7k	L-Proline			146	$C_{15}H_{19}N_4O_3Cl$	53.2 53.2	5.65 5.90	16.5 16.6	2.0–2.4, 3.55, 3.85, 4.15, 4.8, 7.0–7.4, 8.15	1705, 1670, 1535, 1480, 1310, 820	338(M^+),230/231, 133/134, 107, 91, 70
3l	L-Tryptophane		$-OH$	63–5	$C_{14}H_{15}N_4O_4Cl$	49.6 49.9	4.46 4.65	16.5 16.4	n.c.	n.c.	n.c.
7l	L-Tryptophane		$-NH-C_6H_4-CH_3$	94	$C_{21}H_{22}N_5O_3Cl$	59.0 58.8	5.18 5.12	16.4 16.2	2.3, 3.3, 3.5, 4.15, 4.95, 7.0–7.4, 7.8, 8.1	1705, 1670, 1530, 1495, 1315, 820, 745	427(M^+), 319/320, 133
6m	4-Aminobutyric acid			89–90	$C_{13}H_{17}N_4O_3Cl$	49.9 50.1	5.48 5.70	17.9 17.8	2.1, 2.45, 3.4–3.7, 4.15, 7.0–7.6, 7.85	1715, 1665, 1550, 1490, 1310, 760	312(M^+), 204/205, 119/120, 93, 77

n.c. = Not carried out

1): All melting points are not corrected

2): ^{1}H-NMR: Bruker HX 90 with Puls-Fourier; ir: Perkin Elmer 580 B; MS: Varian-MAT 811A, ionisation energy = 80 e.V.

3): We thank Mrs. *Koehler* for her help in spectral analyses

(38 %). The product was chromatographed on a silica gel column with ethyl formate/dichloromethane (1:1). The solid material obtained after evaporation of the solvent was crystallized from dichloromethane/n-pentane. Light yellow crystals, mp. 49–50 °C (dec.).

2.*[[2-Chloroethyl)-nitroso-carbamoyl]glycine anilide* **(6a)**

1 mmol (210 mg) of N-[N-(2-chloroethyl)-N'-nitroso-carbamoyl] glycine and 1 mmol (93 mg) aniline were dissolved in 10 ml dichloromethane. Under ice cooling and stirring, a solution of 1.1 mmol (230 ng) DCC in 10 ml dichloromethane was added dropwise and the reaction mixture stirred for 1 h. After filtration, the solution was evaporated. The solid matter obtained was purified by column chromatography on silica gel with ether/dichloromethane and was crystallized in dichloromethane. Yellow plates, mp. 149°.

3. *N-[N'-(2-Chloroethyl)-N'-nitroso-carbamoyl]L-threonine* **(3h)**

10 mmol (1.2 g) L-threonine and 10 mmol sodium hydrogen carbonate were dissolved in 20 ml water. This solution was reacted with 10 mmol N-(2-chloroethyl)-N-nitroso-carbamoylazide as described. A yellow oily liquid was obtained, which was used without further purification for the preparation of the corresponding anilide. Yield: 0.85 g (34 %).

4. *N-[N'-(2-Chloroethyl)-N'-nitroso-carbamoyl]L-threonine anilide* **(6h)**

1 mmol (250 mg) N-[N'-(2-chloroethyl)-N'-nitroso-carbamoyl] L-threonine and 1 mmol aniline were dissolved in 10 ml dichloromethane; 1.1 mmol DCC in 10 ml dichloromethane was added. After working up as described, a yellow solid was obtained. It was purified by chromatography on silica gel with ether/dichloromethane (1:3), and then crystallized from dichloromethane/n-pentane; yellowish needles, mp. 125° (dec.).

5. *N-[N'-(2-Chloroethyl)-N'-nitroso-carbamoyl]L-methionine* **(3i)**

10 mmol (1.5 g) L-methionine and 10 mmol sodium hydrogen carbonate were dissolved in 100 ml water and reacted with 10 mmol N-(2-chloroethyl)-N-nitroso-carbamoylazide as described. A waxy substance was obtained as crude product, which was purified by column chromatography on silica gel with methanol/chloroform (1:10), and was then recrystallized from dichloromethane/n-pentane; yellow crystals, mp. 89–90° (dec.). Yield: 0.9 g (32 %).

6. *N-[N'-(2-Chloroethyl)-N'-nitroso-carbamoyl]L-glutamine* **(3j)**

10 mmol (1.5 g) L-glutamine and 10 mmol sodium hydrogen carbonate were dissolved in 100 ml water and reacted with 10 mmol N-(2-chloroethyl)-N-nitroso-carbamoylazide as described. After 2 d, the reaction mixture was acidified with tartaric acid and extracted with ethyl formate. The crude product was chromatographed on silica gel with methanol/chloroform (1:2), and then crystallized from methanol/dichloromethane. Bright-yellow crystals, mp. 83–85° (dec.), yield: 0.65 g (23 %).

7. *N-[N'-(2-Chloroethyl)-N'-nitroso-carbamoyl]L-tryptophane* **(3l)**

10 mmol (2 g) L-tryptophane, dissolved under addition of 10 mmol sodium hydrogen carbonate in 200 ml water, was added dropwise under ice-cooling and stirring to a solution of 10 mmol N-(2-chloroethyl)-N-nitroso-carbamoylazide in 100 ml isopropanol. The reaction mixture was kept for 24 h at room temp. The product was extracted as described in the general procedure, purified by chromatography on silica gel with ethyl formate/dichloromethane (1:1) and crystallized from ethyl

formate/n-pentane; yellow needles, mp. 63–65° (dec.). The substance tends to decompose on standing at room temp. Yield: 1 g (30 %).

8. *N-[N'2-(2-Chloroethyl)-N'-nitroso-carbamoyl]L-tryptophane p-toluidid* (**7l**)

1 mmol (340 mg) N-[N'2-chloroethyl)-N'-nitroso]-carbamoyl L-tryptophane and 1 mmol p-toluidine were dissolved in 10 ml dichloromethane and 1.1 mmol DCC was added. After working up as described, the product was purified by chromatography on silica gel, with ether/chloroform and crystallized from dichloromethane/n-pentane. Golden-yellow needles, mp. 94°.

References

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