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Preparations of N-Alkylthiomethyl and N-Amidomethyl Derivatives of Amino Acids

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As N-functionalized derivatives of amino acids ($XCH_2NHCHCO_2H$, R), N-alkylthiomethyl (X=RS) and N-amidomethyl (X=RCONH) derivatives have been furnished by the reaction among XH, formaldehyde, and amino acid.

Keywords——amino acid derivatives; formaldehyde; amide; alkanethiol; N-(alkylthiomethyl)amino acid; N-(amidomethyl)amino acid; N,N-bis(amidomethyl)-amino acid

In our attention to amino acid chemistry it seems interest to furnish N-(alkylthiomethyl)- and N-(amidomethyl)amino acids as possibly versatile N-functionalized derivatives. They are amino acid analogs of the previously reported alkylaminomethyl alkyl sulfide hydrochlorides[2] and N-(alkylaminomethyl)amide hydrochlorides.[3] Although several examples of N-(amidomethyl)amino acids have been synthesized,[4] we wish to describe, in the present paper, synthesis of both the amino acid derivatives with additional informations.

Alkylaminomethyl alkyl sulfide hydrochlorides have been previously reported[2] to be prepared by the condensation among primary amine hydrochloride, formaldehyde, and alkanethiol in ethanol. N-(Alkylthiomethyl)amino acids, a new type of sulfur-containing derivatives of amino acids, have now been synthesized generally by a similar mode of the reaction of the corresponding materials in aqueous ethanol, where in place of primary amine hydrochlorides amino acids are effective as reacting species.

$$R^1SH + CH_2O + NH_2CHCO_2H \longrightarrow R^1SCH_2NHCHCO_2H + H_2O \quad (R^2)$$

It may be emphasized that a large excess of formaldehyde (8 molar equiv.) against amino acid and alkanethiol is necessary to induce the reaction. A series of N-alkylthiomethyl derivatives of amino acids (Ia—f) prepared are listed in Table I. They are insoluble in any common solvent, and their crystals were obtained in pure state as precipitates deposited in the reaction solution. Under the same reaction condition glycine and β-alanine were inert to the reaction.

Similarly, N-amidomethyl derivatives of amino acids were synthesized by the reaction among amino acid, formaldehyde, and amide, as reported previously[4] for several examples of them.

$$R^1CONH_2 + CH_2O + NHCHCO_2H \longrightarrow R^1CONHCH_2N\text{-}CHCO_2H + H_2O \quad (R^2, R^3)$$

We obtained the compounds (IIa—i) listed in Table II by carrying out the reaction in aqueous ethanol or in water in which use of large excess of formaldehyde (4 molar equiv.)

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Table I. N-(Alkylthiomethyl)amino Acids

$R^1SCH_2NHCHCO_2H$ (R² on the CH)

Compd. No.	R^1	R^2	Yield (%)	mp (°C) (dec.)	Formula	Analysis (%) Found (Calcd.) C	H	N
Ia	$C_6H_5CH_2$	CH_3	74	210—212	$C_{11}H_{15}NO_2S$	58.85 (58.64)	6.61 (6.71)	6.14 (6.22)
Ib	$C_6H_5CH_2$	$CH(CH_3)_2$	42	163—166	$C_{13}H_{19}NO_2S$	61.33 (61.64)	7.50 (7.56)	5.46 (5.53)
Ic	$C_6H_5CH_2$	$CH_2C_6H_5$	78	181—184	$C_{17}H_{19}NO_2S$	67.29 (67.76)	6.32 (6.36)	4.68 (4.65)
Id	$C_6H_5CH_2$	$CH_2CH(CH_3)_2$	85	182—185	$C_{14}H_{21}NO_2S$	62.98 (62.90)	7.93 (7.92)	5.34 (5.24)
Ie	C_3H_7	CH_3	57	182—184	$C_7H_{15}NO_2S$	47.36 (47.43)	8.48 (8.53)	7.61 (7.90)
If		CH_3	55	189—192	$C_{10}H_{19}NO_2S$	55.01 (55.27)	8.61 (8.81)	6.14 (6.45)

Table II. N-(Amidomethyl)amino Acids

$R^1CONHCH_2N(R^2)CHCO_2H$ (R³ on the CH)

Compd. No.	R^1	R^2	R^3	Yield (%)	mp (°C) (dec.)	Formula	Analysis (%) Found (Calcd.) C	H	N
IIa	C_6H_5	H	CH_3	91	152—159[a]	$C_{11}H_{14}N_2O_3$	59.24 (59.45)	6.34 (6.34)	12.52 (12.61)
IIb	C_6H_5	H	$CH(CH_3)_2$	65	146—148	$C_{13}H_{18}N_2O_3 \cdot H_2O$	58.77 (58.19)	7.47 (7.51)	10.46 (10.44)
IIc	C_6H_5	H	$CH_2CH(CH_3)_2$	74	164—166	$C_{14}H_{20}N_2O_3$	63.62 (63.61)	7.62 (7.63)	10.48 (10.16)
IId	C_6H_5	H	$CH_2C_6H_5$	83	157—159	$C_{17}H_{18}N_2O_3 \cdot 1/2H_2O$	66.99 (66.44)	6.08 (6.23)	9.11 (9.11)
IIe	$C_6H_5CH_2$	H	CH_3	70	180—185	$C_{12}H_{16}N_2O_3$	60.72 (61.00)	6.76 (6.83)	11.84 (11.86)
IIf	CH_3	H	CH_3	94	164—165[b]	$C_6H_{12}N_2O_3$	45.19 (44.98)	7.63 (7.55)	17.42 (17.50)
IIg	CH_3	H	$CH(CH_3)_2$	75	160—162[c]	$C_8H_{16}N_2O_3$	51.08 (51.05)	8.53 (8.57)	14.84 (14.88)
IIh	C_2H_5	H	CH_3	82	203—205	$C_7H_{14}N_2O_3$	47.76 (48.27)	7.96 (8.10)	15.55 (16.08)
IIi	C_2H_5	H	$CH(CH_3)_2$	89	152—153	$C_9H_{18}N_2O_3$	53.30 (53.45)	8.78 (8.97)	14.05 (13.85)
IIj	C_6H_5	H	C_6H_5	57	143—146	$C_{16}H_{16}N_2O_3$	67.01 (67.59)	5.74 (5.68)	9.77 (9.86)
IIk	C_6H_5	CH_3	H	64	149—151	$C_{11}H_{14}N_2O_3$	59.12 (59.45)	6.38 (6.35)	12.25 (12.60)

a) lit.[4a] mp 150—154° (dec.) b) lit.[4a] mp 176—180° (dec.) c) lit.[4b] mp 164° (dec).

was necessary. The compounds, IIa—e, obtained as precipitates deposited in the reaction solution, are insoluble in any common solvent, whereas IIf—i are soluble only in water. The case of using α-phenylglycine was an exception to the above procedure. Its N-benzamidomethyl derivative (IIj) was obtained by carrying out the reaction in HCl-containing aqueous ethanol in the use of very large excess (40 molar equiv.) of formaldehyde. On the other hand, sarcosine possessing secondary amine residue reacted easily by the use of small excess (1.5

molar equiv.) of formaldehyde. The reactions of glycine and of β-alanine with formaldehyde and benzamide were distinguished from that described above, giving N,N-bis(benzamidomethyl) derivatives (IIIa, b) which have not been described previously.

$$2C_6H_5CONH_2 + 2CH_2O + NH_2(CH_2)_nCO_2H \longrightarrow (C_6H_5CONHCH_2)_2N(CH_2)_nCO_2H + 2H_2O$$

IIIa(n=1), Yield, 52%
IIIb(n=2), Yield, 65%

Experimental

All melting points are uncorrected. All α-amino acids used are racemates except leucine which is L-isomer.

N-(Alkylthiomethyl)amino Acids (Ia—f)——General Procedure: N-(Alkylthiomethyl)amino acids listed in Table I were prepared by the following general procedure.

To a saturated aqueous solution of 0.03 mol of amino acid, 18 ml (0.24 mol) of 37% formalin and, successively, a solution of 0.03 mol of alkanethiol in 30 ml of EtOH were dropwise added with vigorous stirring at 35—40°. The mixture was stirred and warmed for further 5 hr and then allowed to stand overnight at room temperature. The deposited fine crystals were collected by filtration followed by washing with petr. ether and then water. The product obtained in every case was shown to be analytically pure without further purification. Yields, melting points, and analytical data are recorded in Table I.

N-(Amidomethyl)amino Acids (IIa—k)——Either of the following four procedures is chosen for the preparation of N-(amidomethyl)amino acids listed in Table II. Table II also shows yields, melting points, and analytical data of the products.

a) General Procedure for IIa—e: To a saturated aqueous solution of 0.5 mol of amino acid, 150 ml (2.0 mol) of 37% formalin and, successively, a solution of 0.5 mol of amide in EtOH (20 ml for benzamide, 50 ml for phenylacetamide) were dropwise added with stirring at room temperature, and the stirring was continued for further 1 hr. A small amount of crude crystals deposited at this time was removed by filtration, and the filtrate was allowed to stand for three days in a refrigerator. The deposited fine crystals were collected, washed with EtOH, and dried. The product obtained in every case was shown to be analytically pure without further purification.

b) General Procedure for IIf—i: To a saturated aqueous solution of 0.5 mol of amino acid combined with 150 ml (2.0 mol) of 37% formalin, 0.5 mol of acetamide or propionamide was added in several portions with stirring. After standing overnight at room temperature, the reaction solution was concentrated under reduced pressure below 45°. In every case, for the preparation of the pure material the obtained crystals were once reprecipitated by addition of acetone to their aqueous solution.

c) N-Benzamidomethyl-α-phenylglycine (IIj): To a solution of 30 g (0.2 mol) of α-phenylglycine dissolved in 300 ml of 1 N HCl combined with 600 ml (8.0 mol) of 37% formalin, 24 g (0.2 mol) of benzamide in 200 ml of EtOH was dropwise added with stirring at room temperature. After standing overnight, the reaction solution was neutralized with 300 ml of 1N NaOH on cool and the deposited fine crystals were collected, washed with water, and dried.

d) N-(Benzamidomethyl)sarcosine (IIk): The reaction was carried out by a similar manner as described in a) except that 56.3 ml (0.75 mol) of 37% formalin was used. After standing overnight at room temperature, the reaction solution was concentrated under reduced pressure below 45°. The residual material crystallized in a refrigerator was collected, washed with a small amount of acetone, and dried. NMR[5] (in DMSO-d_6) δ: 2.42 (3H, singlet, CH_3), 3.42 (2H, singlet, $>NCH_2CO-$), 4.43 (2H, doublet, J=6 Hz, $>NCH_2$-$N<$), *ca.* 6.00 (1H, broad singlet, OH), 7.65—8.21 (5H, multiplet, aromatic protons), 9.05 (1H, triplet, J= 6 Hz, -CONH-).

N,N-Bis(benzamidomethyl)glycine (IIIa) and N,N-Bis(benzamidomethyl)-β-alanine (IIIb)——To a solution of 0.03 mol of glycine or β-alanine in 30 ml of H_2O, 3.0 g (0.036 mol) of 37% formalin and, successively, 3.6 g (0.03 mol) of benzamide in 30 ml of EtOH were dropwise added with stirring at room temperature, and the stirring was continued for further 1 hr. A small amount of crude crystals deposited at this time was removed by filtration, and the filtrate was allowed to stand for several days at room temperature. The deposited fine crystals were collected, washed with water and then EtOH, and dried. The material was shown to be analytically pure without purification.

IIIa: prisms, mp 164—165° (dec.). Yield, 52%. IR ν_{max}^{KBr} cm^{-1}: 3294 (NH), 2770 (NH^+), 1679, 1545 (CONH), 1648, 1411 (COO^-). *Anal.* Calcd. for $C_{18}H_{19}N_3O_4$: C, 63.33; H, 5.61; N, 12.31. Found: C, 62.93; H, 5.65; N, 12.74.

5) Determined at 60 MHz using TMS as an internal standard.

IIIb: prisms, mp 142—143° (dec.). Yield, 65%. IR ν_{max}^{KBr} cm^{-1}: 3284 (NH), 1674, 1528 (CONH), 1612, 1400 (COO$^-$). *Anal.* Calcd. for $C_{19}H_{21}N_3O_4$: C, 64.21; H, 5.96; N, 11.83. Found: C, 64.37; H, 6.05; N, 11.83.

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Studies on Constituents of Medicinal Plants. XIX.[1] Constituents of *Schizandra nigra* Max. (3)

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(+)-Catechin-7β-D-glucopyranoside was isolated from the wooden part of *Schizandra nigra* Max.

Keywords——(+)-catechin-7β-D-glucopyranoside; *Schizandra nigra* Max.; NMR; MS; magnoliaceae

The authors have previously isolated schizandronic acid,[3] schizandrolic acid,[4] schizandronol[4] and oplodiol[4] from the methanol-soluble fraction of the wooden part of *Schizandra nigra* Max. and elucidated the structures of the former three. This paper concerns with the isolation and the structural elucidation of a new (+)-catechin glucoside. As the (+)-catechin type glycoside, (+)-catechin-7-L-arabinoside,[5] (+)-catechin 5β-D-xylopyranoside,[6] (+)-catechin-7 β-D-xylopyranoside[7] and (+)-catechin-7 α-L-rhamnopyranoside[8] have been reported.

The methanol-soluble fraction afforded a compound (I), $C_{21}H_{24}O_{11}\cdot 1\frac{1}{2}H_2O$, colorless needles of mp 215—216°, $[\alpha]_D^{32}=-33.4$ (c=1.0, MeOH). Compound I gave green coloration with $FeCl_3$ and shows the ultra-violet (UV) absorption maximum at 281.5 nm (log ε 3.56) and the infra-red (IR) absorption bands (cm^{-1}) at 3500—3000 (OH), 1620, 1600 (benzene ring), 1170—1030 (-C-O-). Compound I afforded octaacetyl derivative $C_{37}H_{40}O_{19}$ (II), colorless needles of mp 130° on acetylation with acetic anhydride and pyridine, and trimethyl derivative $C_{24}H_{30}O_{11}\cdot H_2O$ (III), colorless needles of mp 171—174° on methylation with diazomethane, but I did not afford tetramethyl derivative on methylation with diazomethane.

On enzymatic hydrolysis with β-glycosidase (emulsin), III afforded D-glucose and a compound $C_{18}H_{20}O_6$ (IV), colorless plates of mp 261—264° and IV afforded a compound $C_{19}H_{22}O_6$ (V), colorless needles of mp 145—147° by methylation with diazomethane. The compounds

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