Chromatograph at 190 °C and with a gas flow of 190 ml per min. The methyl glucosides were separated on a column (120 × 0.5 cm I.D.), the packing of which was composed of LAC-4R-886[2] (15%) polyester wax on Chromosorb W(60–80 mesh). The glucitols were separated on a similar column containing LAC-4R-886[2] (10%) polyester wax. Experimental details are given in reference (1).

[2]Chromatographic Specialities, Brockville, Ontario.

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New synthesis of *S*-alkyl-DL-homocysteines

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A simple method for the synthesis of *S*-alkyl-DL-homocysteines is described. The method involves the reaction of homocysteine thiolactone with a primary alkyl halide in sodium methoxide solution.

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Ethionine, *S*-ethyl homocysteine, has long been known to be a methionine antagonist in biological systems (1). More recently it has been found capable of lowering the level of activity of rat liver urocanase (2–4). Because we desired to learn whether the effect on liver urocanase could also be produced by other *S*-alkyl homocysteines, it was necessary to prepare these commercially unavailable compounds.[1]

Previously published methods for the synthesis of the homologous series of alkyl homocysteines require the use of liquid ammonia and/or hydrogen cyanide (5, 6). In an attempt to avoid the use of these reagents, we have developed a simple method for the synthesis of alkyl homocysteines giving yields of 75–95%. The method involves the reaction of homocysteine thiolactone[2] (**1**) with a primary alkyl halide[3] (**2**) in sodium methoxide solution. The reaction sequence is outlined in Scheme 1, using the synthesis of methionine as an example.

[1]Recent experiments conducted in our laboratory have demonstrated that the higher alkyl homologues do not affect the level of urocanase activity in rat liver.
[2]Obtained from the Aldrich Chemical Company.
[3]We found that a secondary alkyl iodide can be used, but the yield of final product was significantly reduced. Using 2-iodopropane, we synthesized *S*-isopropyl homocysteine in 20% yield.

Experimental

The purity of each compound whose synthesis is reported was assayed by: *1*) melting points; *2*) thin-layer chromatography (t.l.c.); *3*) infrared (i.r.) spectroscopy; and *4*) nuclear magnetic resonance (n.m.r.) spectroscopy.

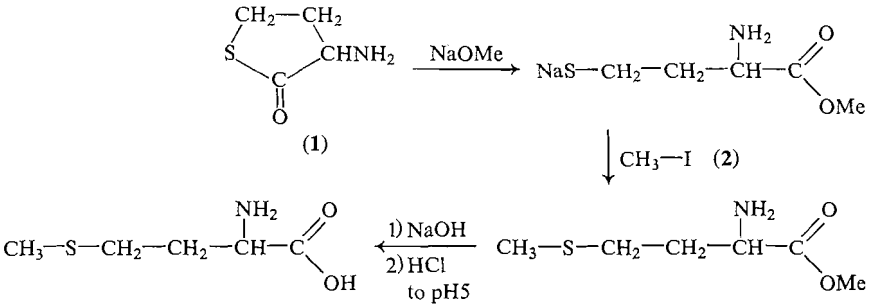
Melting points were determined using a Hoover–Thomas capillary melting point apparatus at a heating-rate setting of 7. Each compound was recrystallized until its melting point was constant.

The compounds were examined by t.l.c. on Bio-Sil A[4] using three solvent systems: *1*) $CHCl_3$/methanol/17% NH_4OH (2:2:1, v/v); *2*) *n*-propanol/water (64:36, w/w); and *3*) *n*-butanol/glacial acetic acid/water (60:20:20, w/w). Each compound was chromatographically pure in all three solvent systems. The modified ninhydrin solution described by Moffat and Lytle (7) was used to detect the presence of the amino acids on the thin-layer plates.[5]

The i.r. spectra were obtained with a Perkin–Elmer 337 spectrophotometer using KBr pellets. The spectra were very similar to one another showing strong absorption bands near 1420, 1345, 1282, 1078, 547, and 435 cm^{-1}. The spectra of the DL-methionine and of the DL-ethionine, prepared by using the method outlined below, were identical with those obtained from the respective commercial compounds. The other *S*-alkyl homocysteines are not commercially available.

The absence of absorption bands at 840 and 904 cm^{-1} in the spectra of each compound indicates that neither

[4]Silicic acid, available from Bio–Rad Laboratories.
[5]We also sprayed identical chromatograms with concentrated sulfuric acid in order to detect any non-amino acid impurities. None were found.



SCHEME 1

TABLE I

Nuclear magnetic resonance spectra of the *S*-alkyl-DL-homocysteines (τ, parts per million)*

S-Alkyl substituent	Homocysteine protons		*S*-Alkyl protons
	C-2 proton	Methylene protons	
Methyl	5.79t	7.07–8.00m	7.88s
Ethyl	5.76t	7.07–8.05m	8.79t
Propyl	5.76t	7.05–8.01m	8.17–8.75m and 8.75–9.30m
Butyl	5.78t	7.08–8.00m	8.15–8.90m and 8.90–9.33m
Pentyl	5.79t	7.06–8.00m	8.10–8.95m and 8.95–9.42m
Hexyl	5.79t	7.08–8.06m	8.06–9.00m and 9.00–9.42m
Benzyl	5.71t	7.05–7.95m	2.58s and 6.16s

*The notations m, s, and t refer to multiplets, singlets, and triplets respectively.

homocysteine nor its thiolactone are significant contaminants of any of the compounds synthesized. Furthermore, none of the spectra had absorption bands in the 1070–1030 cm^{-1} and the 1160–1120 cm^{-1} regions indicating the absence of sulfoxides and sulfones respectively.

The n.m.r. spectra were obtained using a Varian A-60 spectrometer and were entirely consistent with the assigned structures. The spectra of commercial DL-methionine and DL-ethionine could be superimposed exactly on those of the corresponding compounds obtained using the synthetic method described below. Analysis of the integration data indicated that deviations from the expected number of hydrogens relative to the C-2 proton were within ±3%. The data obtained from the n.m.r. spectra are presented in Table I.

Synthesis of DL-*Methionine*

DL-Homocysteine thiolactone hydrochloride (50 mmoles, 7.65 g) was added to a cold solution, 0°, of sodium methoxide in methanol (2.7 g of sodium metal in 210 ml of methanol). After stirring at room temperature for 0.5 h, 50 mmoles (3.11 ml) of iodomethane were added dropwise during 5 min and the stirring continued for 1.25 h. The reaction mixture was then filtered and the filtrate concentrated to 20 ml under reduced pressure. The concentrate was taken up in 300 ml of 1 *N* sodium hydroxide and the resulting solution was heated under reflux for 1.5 h. Following concentration to 40 ml under reduced pressure, the reaction mixture was cooled to 0° and brought to pH 5 by the dropwise addition of concentrated hydrochloric acid with vigorous stirring. The resulting thick suspension was stirred at 0° for 15–20 min and filtered. The precipitate was dissolved in a minimum volume of boiling water and filtered. Four volumes of absolute ethanol were added to the filtrate which was cooled to 0° for 2 h to give 7.05 g of crystals, m.p. 268–270° with decomposition.

Synthesis of Other S-Alkyl-DL-*homocysteines*

The ethyl, propyl, butyl, pentyl, and hexyl homocysteines were synthesized by similar procedures. *S*-Benzyl-DL-homocysteine was synthesized by the same procedure except that benzyl chloride was used as the alkylating agent rather than benzyl iodide.

The melting points and other data pertaining to the preparation of DL-methionine and the other *S*-alkyl-DL-homocysteines are recorded in Table II.

Acknowledgments

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TABLE II

Data concerning the purification of the *S*-alkyl-DL-homocysteines

S-Alkyl substituent	Melting point observed* °C	Recrystallization solvent	% yield after recrystallization
Methyl	268–270	Ethanol:water†	95
Ethyl	267–268	Ethanol:water†	96
Propyl	258–260	Water	75
Butyl	250–252	Water	82
Pentyl	247–248	1.5 *N* HCl‡	80
Hexyl	246–248	1.5 *N* HCl‡	85
Benzyl	252–253	1.5 *N* HCl‡	86

*All melting points were accompanied by decomposition.
†See text for details.
‡The compounds were precipitated from this solvent by the addition of concentrated ammonium hydroxide.

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Partition coefficients of some *N*-alkyl-and *N,N*-dialkyl-derivatives of some cinnamamides and benzalcyanoacetamides in the system cyclohexane–water

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Substituent constants, π, and substituent interaction constants, π interaction, for the groups —CONHR and —CONRR[1] have been derived which allow the calculation of the partition coefficients of the title compounds.

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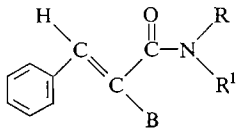
A series of *N*-alkyl and *N,N*-dialkyl derivatives of cinnamamide and α-cyanocinnamamide and their 4-chloro-, 4-methoxy-, and 3,4-methylenedioxy-derivatives, **1**, have been synthesized and



1 *a*) B = H
b) B = CN

their partition coefficients, *K*, determined in the system cyclohexane–water. From these values and eq. [1] (1,2) substituent constants, π, and substituent interaction constants, π interaction, have been determined for the functional groups —CONHR and —CONRR[1]. For —CONHR, π = −4.65 and π interaction = +2.00[2] while for −CONRR[1], π = −4.00 and π interaction = +0.95.

[1] $\log K = \Sigma\pi + \Sigma\pi \text{ interaction} - 1.30$

For cinnamamides and α-cyanocinnamamides with large alkyl groups (e.g. *N*-cyclohexyl, *N,N*-pentamethylene, *N,N*-dipentyl, and *N,N*-dicyclohexyl) the calculated partition coefficients are more positive than those observed. These lower observed values probably result from intramolecular solvation. In contrast to this, the partition coefficients calculated for the *N,t*-butyl derivatives are less positive than those measured indicating that solvation of the nitrogen atom is sterically hindered by the *t*-butyl group.

After excluding these few anomalies, the following correlations were obtained. For 41 *N*-alkyl- and *N,N*-dialkyl-cinnamamides log *K* observed =

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[2]These values replace those reported (1) for NHCOR.