Synthesis of 1*H*,3*H*-Imidazo[1,5-*c*]thiazole-5,7-[6*H*,7a*H*]-dione and 7,8-Dihydro-5*H*-imidazo[1,5-*c*][1,3]thiazine-1,3-[2*H*,8a*H*]-dione and Derivatives

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1*H*,3*H*-Imidazo[1,5-*c*]thiazole-5,7-[6*H*,7a*H*]-dione and the corresponding 7-thione derivatives as well as 7,8-dihydro-5*H*-imidazo[1,5-*c*][1,3]thiazine-1,3-[2*H*,8a*H*]-dione and the corresponding 3-thione derivatives were synthesized starting from L-cysteine and DL-homocysteine thiolactone, respectively. The second group of bicyclic compounds represents a new heterocyclic ring system. The structures of the compounds were confirmed by spectroscopic studies and elemental analyses.

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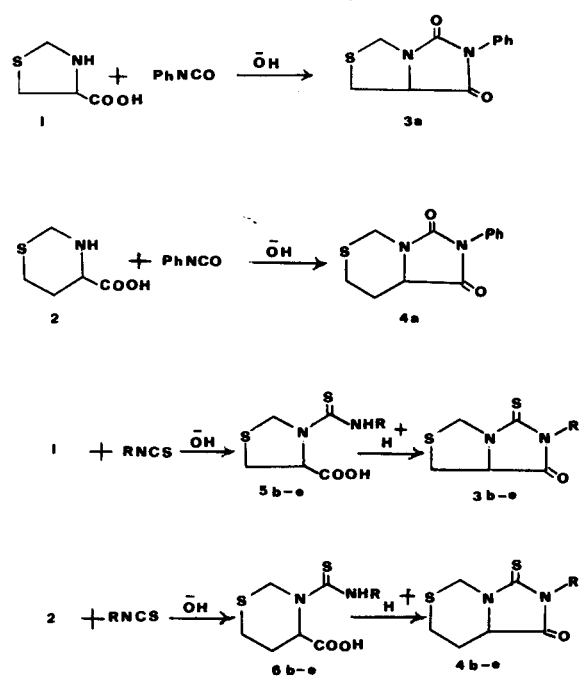
Continuing our interest in the synthesis of heterocyclic compounds based on natural products (3,4) we report the synthesis of some fused heterocyclic compounds derived from cysteine and homocysteine.

The formation of thiazolidine-4-carboxylic acids through the interaction of cysteine and carbonyl compounds was described by Schubert (5) and by Ratner and Clarke (6). Thus a number of aldehydes and ketones react with cysteine to form the corresponding thiazolidine-4-carboxylic acids (**1**). In a similar reaction, homocysteine and homocysteine thiolactone react with formaldehyde to give tetrahydro-2*H*-1,3-thiazine-4-carboxylic acid (**2**) (7). L-Thiazolidine-4-carboxylic acid (**4**) (thioproline) has been reported to inhibit uptake of L-proline by *Pseudomonas aeroginosa* (8). In the present work, thiazolidine-4-carboxylic acid and acid (**2**) were reacted with phenylisocyanate and certain alkyl or aryl isothiocyanates to give the corresponding hydantoin derivatives, **3** and **4**. Historically, Clough (9) suggested that the very large negative rotations possessed by the hydantoin derivatives of amino acids can be used for configurational considerations.

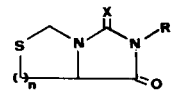
Thiazolidine-4-carboxylic acid was reacted with phenylisocyanate in aqueous potassium hydroxide solution. It was found that the addition of acetone to the warm reaction mixture was necessary to induce a vigorous reaction. In the absence of acetone, symmetrical diphenylurea was the major reaction product. Apparently the function of acetone is to form a single phase reaction mixture and thus facilitate interaction of the reagents. Recrystallization of the resulting mass gave an almost quantitative yield of 6-phenyl-1*H*,3*H*-imidazo[1,5-*c*]thiazole-5,7-[6*H*,7a*H*]-dione (**3**). compound **3a** was identical with a sample prepared according to the literature by a multistep reaction starting from cysteine ethyl ester, with an overall yield of 33 per cent (10). 2-Phenyl-7,8-dihydro-5*H*-imidazo-[1,5-*c*][1,3]thiazine-1,3-[2*H*,8a*H*]-dione (**4a**) was prepared similarly starting from **2**. The yield of the latter compound was found to be almost quantitative.

6-Substituted 1*H*,3*H*-imidazo[1,5-*c*]thiazole[6*H*,7a*H*]-5-one-7-thiones (**3b-e**) and 2-substituted 7,8-dihydro-5*H*-imidazo[1,5-*c*][1,3]thiazine[2*H*,8a*H*]-1-one-3-thiones (**4b-e**) were synthesized by reactions involving two steps. Their ir and nmr spectra suggest that the gummy reaction products of **1** and **2** with alkyl or aryl isothiocyanates in basic aqueous acetone solutions were the corresponding open ring *N*-thiocarbamoyl derivatives (**5b-e** and **6b-e**) rather than the expected bicyclic compounds **3** and **4**. To promote ring closure to obtain the desired compounds **3** and **4**, the reaction mixtures were acidified strongly with concentrated hydrochloric acid and heated for a brief time. The overall yields ranged from 60 to 85 per cent (See Scheme I).



The structure of compounds **3** and **4** were supported by appropriate analytical and spectral data. In the ^{1}H nmr

Table I



Compound No.	n	X	R	Mp °C	Yield %	Formula	C % Calcd.	C % Found	H % Calcd.	H % Found	N % Calcd.	N % Found
3a	1	0	Ph	131-132 (a)	97	$C_{11}H_{10}N_2O_2S$	56.41	56.20	4.27	4.33	11.96	12.24
3b	1	S	Me	98-99	61	$C_6H_8N_2OS_2$	38.29	38.26	4.25	4.10	14.89	15.01
3d	1	S	Ph	195-197	86	$C_{11}H_{10}N_2OS_2$	52.80	52.73	4.00	4.09	11.20	11.11
3c	1	S	Et	55-56	66	$C_7H_{10}N_2OS_2$	41.58	41.58	4.95	4.83	13.86	13.67
3e	1	S	α-naphthyl	138-140	72	$C_{15}H_{12}N_2OS_2$	60.00	59.83	4.00	3.88	9.33	9.42
4a	2	O	Ph	208-209	98	$C_{12}H_{12}N_2O_2S$	58.06	57.88	4.83	4.82	11.29	11.33
4b	2	S	Me	130-132	68	$C_7H_{10}N_2OS_2$	41.58	41.42	4.95	5.02	13.86	14.00
4c	2	S	Et	92-94	59	$C_8H_{12}N_2OS_2$	44.44	44.32	5.55	5.60	12.96	13.01
4d	2	S	Ph	190-193	78	$C_{12}H_{12}N_2OS_2$	54.54	54.22	4.54	4.55	10.60	10.62
4e	2	S	α-naphthyl	178-190	80	$C_{16}H_{14}N_2OS_2$	61.14	61.26	4.45	4.30	8.01	7.93

(a) Ref (10) mp 149-150°.

Table II

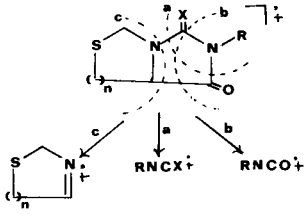
	Mass Spectral Data (a) m/e (Relative Intensity)	NMR δ ppm
3a	M^+ 234 (100), C_6H_5NCO 119 (100), C_3H_5NS (a) 87 (100), C_6H_5 77 (96), C_5H_5 65 (67)	3.18-3.85 (m, 2H, H_3), 4.45-4.78 (m, 2H, H_1), 5.46 (d, 1H, H_{7a}, J 1, 7a, 4.3 Hz), 7.35 (m, 5H, aromatics)
3b	M^+ 188 (100), C_3H_5NS 87 (75), CH_3NCS 73 (70), CH_3NCO 57 (79)	3.10-3.15 (m, 2H, H_3), 3.30 (s, 3H, CH_3), 4.41-4.60 (m, 2H, H_1), 5.50 (d, 1H, H_{7a}, J 1, 7a, 4 Hz)
3c	M^+ 202 (100), C_2H_5NCS and C_3H_5NS 87 (100), C_2H_5NCO 71 (51)	1.85 (t, 3H, CH_3), 3.49 (q, 2H, CH_2), 4.45-4.65 (m, 2H, H_1), 5.39 (d, 1H, H_{7a}, J 1, 7a, 4.2 Hz)
3d	M^+ 250 (100), C_6H_5NCS 135 (92), C_6H_5NCO 119 (55), C_6H_5 77 (98), C_5H_5 65 (49)	3.15-3.52 (m, 2H, H_3), 4.40-4.80 (m, 2H, H_1), 5.42 (d, 1H, H_{7a}, J 1, 7a, 4.7 Hz)
3e	M^+ 300 (100), $C_{10}H_7NCS$ 185 (100), $C_{10}H_7NCO$ 169 (50), $C_{10}H_7$ 127 (60), C_3H_5NS 87 (100)	3.14-3.25 (m, 2H, H_3), 4.42-4.91 (m, 2H, H_1), 5.38 (d, 1H, H_{7a}, J 1, 7a, 4.60 Hz), 7.15-8.38 (m, 7H, aromatics)
4a	M^+ 248 (100), C_6H_5NCO 119 (100), C_4H_7NS (a) 101 (96), C_6H_5 77 (93), C_5H_5 57 (44)	2.26-3.46 (m, 4H, $H_{5,7}$), 4.11-4.62 (m, 2H, H_8), 5.73 (d, 1H, H_{8a}, J 8, 8a, 6.12 Hz)
4b	M^+ 202 (100), C_4H_7NS 101 (90), CH_3NCS 73 (71), CH_3NCO 57 (10)	3.3 (s, 3H, CH_3), 2.45-3.10 (m, 4H, $H_{5,7}$), 2.95-4.50 (m, 2H, H_8), 5.75 (d, 1H, H_{8a}, J 8, 8a, 6.5 Hz)
4c	M^+ 216 (100), C_4H_7NS 101 (93), C_2H_5NCS 87 (88), C_2H_5NCO 71 (43)	1.88 (t, 3H, CH_3), 2.49-3.21 (m, 4H, $H_{5,7}$), 3.42 (q, 2H, CH_2), 3.88-4.32 (m, 2H, H_8), 5.78 (d, 1H, H_{8a}, J 8, 8a, 6.3 Hz)
4d	M^+ 264 (100), C_6H_5NCS 135 (85), C_6H_5NCO 119 (35), C_4H_7NS 101 (90)	2.2-3.5 (m, 4H, $H_{5,7}$), 4.01-4.56 (m, 2H, H_8), 5.82 (d, 1H, H_{8a}, J 8, 8a, 6 Hz)
4e	M^+ 314 (100), $C_{10}H_7NCS$ 185 (95), $C_{10}H_7NCO$ 169 (25), $C_{10}H_7$ 127 (100), C_4H_7NS 101 (100)	2.0-3.1 (m, 4H, $H_{5,7}$), 4.1 (m, 2H, H_8), 5.7 (d, 1H, H_{8a}, J 8, 8a, 6.1 Hz)

(a) See Figure I pathway c.

spectra of compounds **3** and **4**, the chemical shifts of protons 7a and 8a are of particular interest. In the compounds **3** protons 7a appear as a doublet at 4.5-5.5 with a coupling constant of 4-4.7 Hz. In compounds **4**, the doublets corresponding to the protons 8a appear at 5.75-5.88 with a coupling constant ranging between 6-6.5 Hz. These are consistent with the presence of a fused 5-membered ring in compounds **3** and a 6-membered ring in compounds **4**.

The nmr data of compounds **3** and **4** are reported in Table II.

The mass spectral fragmentation pattern of compounds **3** and **4** also exhibit some similarity. In addition to the molecular ions as major peaks, compounds **3a** and **4a** have base peaks at m/e 119 assigned to phenyl isocyanate fragment. All other compounds **3** and **4** (thiohydantoins) have alkyl (or aryl) isothiocyanate fragments as a major peak (pathway a) along with a relatively less aboundant positive ion related to their corresponding alkyl (or aryl) isocyanate portion of the compound (pathway b). All compounds **3** and **4** exhibit another series of aboundant positive fragments (pathway c) characteristic of series **3** and **4**. These are peaks at m/e 87 present in the mass spectra of all compounds **3** and attributed to thiazoline ion at m/e 101 in compounds **4** assigned to 2*H*-5,6-dihydro[1,3]thiazine ion. (See Figure I).



EXPERIMENTAL

Melting points were determined with a Thermo-line hot stage microscope and are uncorrected. The nmr spectra were recorded on a Varian M-360 instrument. Chemical shifts are reported on δ scale relative to TMS In deuteriochloroform. The mass spectra were obtained on a Varian CH5 model spectrometer at 70 eV.

6-Phenyl-1*H*,3*H*-imidazo[1,5-*c*]**thiazole-5,7-[6***H*,7a*H*]-dione (**3a**).

To a solution of 0.665 g (5 mmoles) of thiazolidine-4-carboxylic acid and 0.3 g of potassium hydroxide in 20 ml of water kept at 50°, 1 ml (10 mmoles) of phenylisocyanate was slowly added. To the stirring reaction mixture, 10 ml of acetone was added. After the exothermic reaction subsided, the stirring was continued for 15 minutes, during which time a heavy prcipitate formed. The *p*H was adjusted to 5 by addition of hydrochloric acid. The solution was filtered, washed with water and dried. The crude compound contained some 1,3-diphenylurea. It was extracted with 25 ml of dichloromethane at room temperature. After evaporation of the solvent, the residue was recrystallized from aqueous ethanol to give 1.14 g of white needles. For physical properties see Tables I and II.

2-Phenyl-7,8-dihydro-5*H*-imidazo[1,5-*c*][1,3]thiazine-1,3-[2*H*,8a*H*]-dione (**4a**).

To a warm (50°) and stirring solution of 0.735 g (5 mmoles) of acid **2** in 20 ml of water containing 0.3 g of potassium hydroxide, 1 ml (10 mmoles) of phenylisocyanate was added followed by 10 ml of acetone. After the vigorous reaction subsided, stirring was continued for 15 minutes. A heavy precipitate formed; this was filtered after adjusting the *p*H to 5 by addition of hydrochloric acid. The compound was recrystallized from dimethylformamide containing 10 per cent water to give 1.21 g of shining plates. For the physical data see Tables I and II.

6-Methyl-1*H*,3*H*-imidazo[1,5-*c*]thiazole[6*H*7a*H*]-5-one-7-thione (**3b**).

A stirring solution of 1.33 g (0.01 mole) thiazolidine-4-carboxylic acid in 25 ml water containing 0.6 g of potassium hydroxide, was preheated to 60°. To this was added 0.693 g (0.011 mole) methyl isothiocyanate and 10 ml acetone. After 15 minutes, 10 ml of concentrated hydrochloric acid was carefully added and the reaction mixture heated on a steam bath for 0.5 hour. Upon cooling, a solid was obtained. This was recrystallized from aqueous ethanol to give 1.15 g of pale yellow crystals (see Tables I and II). All other compounds **3** were prepared similarly and recrystallized using the same solvent system.

2-α-Naphthyl-7,8-dihydro-5*H*-imidazo[1,5-*c*][1,3]thiazine-[2*H*,8a*H*]-1-one-3-thione (**4e**).

A solution of 0.734 g (5 mmoles) of **2** in 20 ml of water containing 0.3 g of potassium hydroxide was prepared and warmed at 60°. To this solution, 1.01 g (5.5 mmoles) of α-naphthylisothiocyanate and 10 ml of acetone were added and stirred for 15 minutes. To that warm solution, 5 ml of concentrated hydrochloric acid was cautiously added, and the reaction mixture was heated on a steam bath for 15 minutes. Upon cooling a powder was obtained. It was recrystallized from dimethylformamide containing 10 per cent water to give 1.69 g of light yellow crystalline compound (see Tables I and II). All other compounds **4** were prepared similarly and recrystallized using the same solvent system.

REFERENCES AND NOTES

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