Rearrangements in a Series of Thiazol-2-ylsemicarbazides

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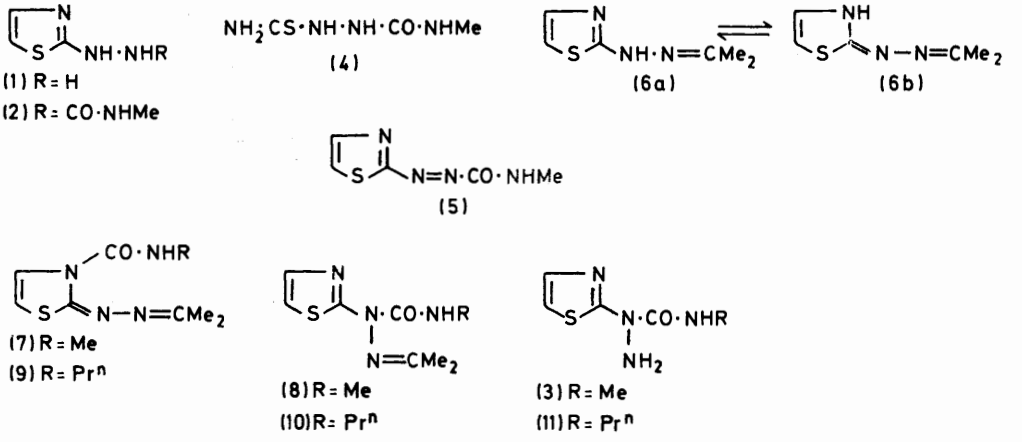
Treatment of 2-hydrazinothiazole (1) with methyl isocyanate gave 4-methyl-1-(thiazol-2-yl)semicarbazide (2), identical with the product obtained from 1-(methylcarbamoyl)thiosemicarbazide (4) and chloroacetaldehyde diethyl acetal. At room temperature 1-isopropylidene-2-(thiazol-2-yl)hydrazine (6a) and methyl isocyanate afforded 2-(isopropylidenehydrazono)-3-methylcarbamoyl-Δ^4-thiazoline (7), but in boiling methyl cyanide a 2 : 1 mixture of the thiazoline (7) and the isomeric 1-isopropylidene-4-methyl-2-(thiazol-2-yl)semicarbazide (8) was obtained. Hydrolysis of the isopropylidene derivative (8) to 4-methyl-2-(thiazol-2-yl)semicarbazide (3) occurred during column chromatography on silica gel. The thiazoline (7) rearranged to give the isomeric thiazole (8) in boiling methyl cyanide, and was converted into the semicarbazide derivative (2) in boiling dilute hydrochloric acid.

In the course of chemotherapeutic studies involving derivatives of 2-hydrazinothiazole (1) we have examined the synthesis of the isomeric thiazol-2-ylsemicarbazides (2) and (3).

Treatment of 2-hydrazinothiazole [1] (1) with methyl isocyanate in anhydrous pyridine afforded the semi-

[1] A. L. Lee, D. McKay, and E. L. Manery, *Canad. J. Chem.*, 1970, **48**, 355.

carbazide (2), identical with the product from the reaction of 1-(methylcarbamoyl)thiosemicarbazide (4) and chloroacetaldehyde dimethyl acetal. Assignment of structure (2) was based on i.r. and n.m.r. spectroscopy, and its ready oxidation to the azo-compound (5) on treatment with chromic acid.

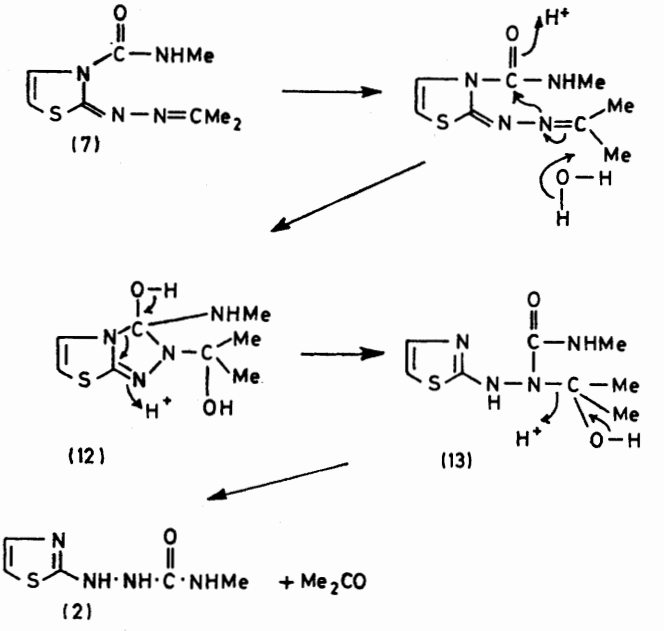


SCHEME 1

1-Isopropylidene-2-(thiazol-2-yl)hydrazine [2] can in principle be represented by two tautomeric structures (6a and b). N.m.r. studies of solutions in a number of solvents showed that at room temperature it was almost entirely present as the thiazole tautomer (6a). Its reaction with methyl isocyanate was examined in an attempt to obtain compound (8), a precursor of the required thiazol-2-ylsemicarbazide (3). At room temperature in methyl cyanide solution, carbamoylation occurred almost exclusively at the ring nitrogen atom to give the thiazoline (7).[3] When the reaction was carried out at the b.p. of the solvent, equilibrium [(7) ⇌ (8)] was reached in *ca.* 6 h, and removal of the solvent afforded a mixture of the thiazoline (7) and the required isomeric thiazole (8) in ratio *ca.* 2 : 1 (as estimated by n.m.r.). A mixture of similar composition was also obtained when a solution of the thiazoline (7) was heated under reflux in methyl cyanide for 6 h. When the thermal rearrangement was carried out in the presence of 1 molar proportion of n-propyl isocyanate, significant amounts of the thiazolines (7) and (9) were present in the reaction mixture. Thermal rearrangement of the thiazoline (7) to the isomeric thiazole (8) therefore seems to involve dissociation of the methylcarbamoyl group from the thiazoline (7), followed by a thermodynamically controlled carbamoylation step, which at the higher temperature is more favourable for the formation of the thiazole (8).

Attempts to separate the isomeric isopropylidene derivatives (7) and (8) by column chromatography (silica gel) led to the unexpected finding that whereas the thiazoline (7) was eluted unchanged, the isomeric thiazole (8) was hydrolysed on the column to the required thiazol-2-ylsemicarbazide (3).

Similarly the thiazoline (9) was obtained by reaction of the isopropylidene derivative (6a) with n-propyl isocyanate in methyl cyanide solution at room temperature. In boiling solution a 2 : 1 mixture of the isomeric thiazoline (9) and thiazole (10) was obtained. Separation by column chromatography (silica gel) gave the thiazoline (9), but the thiazole (10) appeared to be less stable than its methyl homologue (8), and an n.m.r. study of the eluates after removal of the thiazoline (9) from the column showed the main product to be 2-hydrazinothiazole. No clear evidence was obtained for the presence of the required thiazol-2-ylsemicarbazide (11).



SCHEME 2

A further rearrangement of the thiazoline (7) was observed in boiling 2N-hydrochloric acid: the thiazol-2-ylsemicarbazide (2) was obtained in 43% yield together with acetone. A reaction pathway is proposed (see Scheme 2) involving the formation of a bicyclic

[2] Y. Usui, *Ann. Rep. Takeda Res. Lab.*, 1968, **27**, 144.
[3] For review of polar addition of isocyanates to carbon–nitrogen bonds see H. Ulrich, *Accounts Chem. Res.*, 1969, **2**(6), 186.

intermediate (12), followed by ring opening to the carbinol (13), and subsequent hydrolysis to the semicarbazide (2) and acetone.

Thiazole and thiazoline structures were distinguished by comparison of the coupling constant between the 4- and 5-protons of the heterocyclic ring. In a large number of thiazoles $J_{4,5}$ was found to be 3·55 ± 0·2 Hz, whereas for thiazolines a higher value of 4·9 ± 0·3 Hz was obtained. The upfield shift of thiazoline resonances in comparison with those of the isomeric thiazole has been used previously to distinguish between isomeric structures.[4]

EXPERIMENTAL

M.p.s were determined on an Electrothermal gas-heated apparatus. T.l.c. was carried out on Camlab Machery-Nagel Polygram silica plates. Column chromatography separations were carried out on a 30 × 2·5 cm column packed with silica gel (70 g) (May and Baker laboratory chemical grade). Samples for analysis were dried at 10 mmHg at suitable temperatures between 25 and 100°.

I.r. spectra were recorded for KBr discs on Unicam SP 200 and Perkin-Elmer 21 spectrometers, and for solutions in $CHCl_3$ on a Unicam SP 700 spectrometer. ^1H N.m.r. spectra were recorded on a Varian A 60 D spectrometer.

1-(*Methylcarbamoyl*)*semicarbazide* (4).—Methyl isocyanate (62·7 g) was added dropwise to a stirred suspension of finely ground thiosemicarbazide (100 g) in anhydrous pyridine (370 ml), with the temperature kept below 40° by cooling in ice. The mixture was then stirred for a further 2 h, and set aside overnight at room temperature. The solid was filtered off, washed with pyridine, and crystallised from water (1·8 l) to give white *crystals* (126 g, 78%), m.p. 222° (decomp.) (Found: C, 24·5; H, 5·5; N, 38·0. $C_3H_8N_4OS$ requires C, 24·3; H, 5·45; N, 37·8%).

4-*Methyl*-1-(*thiazol*-2-*yl*)*semicarbazide* (2).—(*a*) Methyl isocyanate (3·42 g) was added dropwise to a stirred solution of 2-hydrazinothiazole [1] (6·9 g) in anhydrous pyridine (40 ml) at such a rate that the temperature did not exceed 40°. The mixture was stirred for a further 8 h and then set aside overnight at room temperature. The solid was filtered off, washed with ice-cold pyridine, and crystallised from ethanol to give white *crystals* (5·2 g, 51%), m.p. 181—182° (decomp.), t.l.c. ($CHCl_3$) R_F 0·13, δ [$(CD_3)_2SO$] 7·11 (d, ring 4-H), 6·76 (d, ring 5-H, $J_{4,5}$ 3·5 Hz), 9·0br (NH, probably that next to the ring), 8·25br (NH), 6·49 (q, NHMe), and 2·57 (d, MeNH, J 4·8 Hz) (Found: C, 34·9; H, 4·7; N, 32·5; S, 18·6. $C_5H_8N_4OS$ requires C, 34·85; H, 4·65; N, 32·55; S, 18·6%).

(*b*) 1-(Methylcarbamoyl)thiosemicarbazide (10 g) and chloroacetaldehyde diethyl acetal (10·5 g) in acetic acid (25 ml) were heated for 2 h on a steam-bath, and the solution was set aside overnight at room temperature. The crystals which separated were filtered off, washed with ether, and recrystallised from ethanol giving 4-*methyl*-1-(*thiazol*-2-*yl*)-*semicarbazide hydrochloride* (9·2 g, 65%), m.p. 202—203° (decomp.) (Found: C, 28·9; H, 4·4; N, 26·9; S, 15·3. $C_5H_8N_4OS$,HCl requires C, 28·75; H, 4·35; N, 26·85; S, 15·35%). Addition of fused sodium acetate (4 g) to a solution of the hydrochloride (9 g) in water (20 ml) precipitated the base (6·3 g), m.p. 181° (decomp.), identical with the product obtained in (*a*).

2-*Methylcarbamoylazothiazole* (5).—Potassium dichromate (5 g) was added in portions to a stirred solution of 4-methyl-1-(thiazol-2-yl)semicarbazide (10 g) in water (50 ml) and concentrated hydrochloric acid (15 ml). The reaction was mildly exothermic and a brown solid was precipitated. The solid was filtered off, washed with water, and crystallised from ethanol giving brown *crystals* (5·5 g, 55%), m.p. 160° (decomp.) (Found: C, 35·3; H, 3·5; N, 33·1. $C_5H_6N_4OS$ requires C, 35·3; H, 3·55; N, 32·95%).

1-*Isopropylidene*-2-(*thiazol*-2-*yl*)*hydrazine* (6a *or* b).—A solution of 2-hydrazinothiazole (10 g) in acetone (100 ml) was refluxed for 0·5 h. The solvent was evaporated off and the residue crystallised from ethanol as buff needles (9·4 g, 70%), m.p. 139—141°, t.l.c. ($CHCl_3$) R_F 0·14, δ ($CDCl_3$) 7·16 (d, ring 4-H), 6·55 (d, ring 5-H) ($J_{4,5}$ 3·7 Hz), 10·2br (NH), 2·03 (s, Me), and 1·91 (s, Me) (Found: C, 46·8; H, 5·9; N, 27·2. Calc. for $C_6H_9N_3S$: C, 46·45; H, 5·85; N, 27·1%). The compound has been reported previously,[2] but no preparative details or physical data were given.

2-(*Isopropylidenehydrazono*)-3-*methylcarbamoyl*-Δ⁴-*thiazoline* (7).—Methyl isocyanate (2 g) was added in one portion to a suspension of 1-isopropylidene-2-(thiazol-2-yl)hydrazine (4 g) in anhydrous methyl cyanide (40 ml). The reaction was mildly exothermic giving a solution which was set aside overnight at room temperature. The solvent was distilled off under reduced pressure from a water bath at 20—25°, and the residue (5·4 g), m.p. 98—101°, was crystallised from cyclohexane giving white *crystals* (3·85 g, 71%), m.p. 101—103°, t.l.c. ($CHCl_3$) R_F 0·38, δ ($CDCl_3$) 7·41 (d, ring 4-H), 6·03 (d, ring 5-H) ($J_{4,5}$ 5·0 Hz), 9·5br (NH), 2·96 (d, MeNH, J 4·7 Hz), 2·0 (s, Me), and 2·06 (s, Me) (Found: C, 45·5; H, 5·8; N, 26·7. $C_8H_{12}N_4OS$ requires C, 45·25; H, 5·7; N, 26·4%).

Reaction of 1-*Isopropylidene*-2-(*thiazol*-2-*yl*)*hydrazine* (6a) *with Methyl Isocyanate in Boiling Methyl Cyanide*. A mixture of 1-isopropylidene-2-(thiazol-2-yl)hydrazine (4 g) and methyl isocyanate (2 g) in anhydrous methyl cyanide (40 ml) was heated under reflux for 6 h. The solution was evaporated under reduced pressure, and the residual gum (5·4 g) was dried over silica gel. T.l.c. ($CHCl_3$) showed two major components, R_F 0·11 and 0·38, the latter being identical (t.l.c.) with 2-(isopropylidenehydrazono)-3-methylcarbamoyl-Δ⁴-thiazoline (7). N.m.r. ($CDCl_3$) showed the mixture to contain *ca.* 65% of compound (7), and *ca.* 30% of the isomeric 1-isopropylidene-4-methyl-2-(thiazol-2-yl)-semicarbazide (8), δ ($CDCl_3$) 7·26 (d, ring 4-H), 6·77 (d, ring 5-H), ($J_{4,5}$ 3·5 Hz), 2·88 (d, MeNH, J 4·5 Hz), 2·22 (s, Me), and 1·89 (s, Me). The mixture was dissolved in benzene (50 ml) and separated by column chromatography (silica gel). Elution with benzene (1·5 l) gave 2-(isopropylidenehydrazono)-3-methylcarbamoyl-Δ⁴-thiazoline (7) (3·0 g), m.p. 100—102°, homogeneous by t.l.c. ($CHCl_3$), and identical with an authentic sample. The column was washed with chloroform and eluted with methanol (150 ml) to give a pink solid (1·2 g), m.p. 137—140°, homogeneous by t.l.c. ($CHCl_3$; R_F 0·11) and containing a primary NH_2 group (i.r.). Crystallisation from ethanol gave 4-*methyl*-2-(*thiazol*-2-*yl*)*semicarbazide* (3) as white needles (0·6 g), m.p. 140°, δ ($CDCl_3$) 7·29 (d, ring 4-H), 6·83 (d, ring 5-H) ($J_{4,5}$ 3·8 Hz), 4·74br (NH_2), 7·7br (NH), and 2·86 (d, MeNH, J 4·6 Hz) (Found: C, 34·9; H, 4·7; N, 32·3. $C_5H_8N_4OS$ requires C, 34·85; H, 4·7; N, 32·55%).

2-(*Isopropylidenehydrazono*)-3-*propylcarbamoyl*-Δ⁴-*thiazoline* (9).—(*a*) n-Propyl isocyanate (2 g) was added dropwise to a stirred suspension of 1-isopropylidene-2-(thiazol-2-yl)-

L. M. Werbel, *Chemy. Ind.*, 1966, 1634.

hydrazine (3·4 g) in methyl cyanide (20 ml). The temperature rose to 40°, and the solution was set aside overnight at room temperature, then evaporated under reduced pressure from a bath at 20—25°. The residue (4·9 g) was crystallised from petroleum (b.p. 80—100°) to give white *crystals* (3·6 g, 68%), m.p. 76—77°, t.l.c. ($CHCl_3$) R_F 0·48, δ ($CDCl_3$) 7·44 (d, ring 4-H), 6·04 (d, ring 5-H) ($J_{4,5}$ 5·0 Hz), 9·6br (NH), 3·38 (d × t, CH_2 next to NH), 1·65 (m, CH_2), 0·99 (t, terminal Me), 2·0 (s, Me), and 2·07 (s, Me) (Found: C, 50·0; H, 7·0; N, 23·3. $C_{10}H_{16}N_4OS$ requires C, 50·0; H, 6·7; N, 23·3%).

(*b*) The reaction was repeated on the same scale, but the solution was heated under reflux for 6 h. The solvent was distilled off under reduced pressure, and the residual gum (5·5 g) was dried over silica gel. N.m.r. ($CDCl_3$) showed compound (9) and the isomeric 1-isopropylidene-4-n-propyl-2-(thiazol-2-yl)semicarbazide (10) to be present in a 2 : 1 ratio; δ ($CDCl_3$) 7·4 (d, ring 4-H), 6·88 (d, ring 5-H) ($J_{4,5}$ 3·5 Hz), 7·75br (NH), 3·32 (d × t, CH_2 next to NH), 1·65 (m, CH_2), 0·96 (t, Me), 1·93 (s, Me), and 2·28 (s, Me). The mixture was dissolved in benzene (50 ml) and separated by column chromatography (silica gel). Elution with benzene (1·5 l) gave compound (9) (3·1 g), m.p. 76—77°, identical with the product from (*a*). Successive elutions of the column with benzene–chloroform, chloroform, chloroform–methanol, and methanol removed only traces of compound (6a) and 2-hydrazinothiazole (1), δ [$(CD_3)_2SO$] 7·04 (d, 4-H), 6·64 (d, ring 5-H, $J_{4,5}$ 3·6 Hz), 8·3br (NH), and 4·7br (NH_2). No clear evidence for the presence of 4-n-propyl-2-(thiazol-2-yl)semicarbazide (11) was obtained in the n.m.r. spectrum.

Reaction of 2-(*Isopropylidenehydrazono*)-3-*methylcarbamoyl*-Δ⁴-*thiazoline* (7) *with n-Propyl Isocyanate.*—n-Propyl isocyanate (1 g) was added to a solution of compound (7) (2·2 g) in anhydrous methyl cyanide (20 ml). After being heated under reflux for 6 h, the solution was evaporated under reduced pressure, and the residue was dried over silica gel. The semi-solid product (2·4 g) was dissolved in benzene (50 ml) and chromatographed on silica gel. The column was eluted with benzene (7 × 50 ml), and the eluates were monitored by t.l.c. ($CHCl_3$) and n.m.r. ($CDCl_3$). Fraction (*a*) contained *ca.* 93% of 2-isopropylidenehydrazono-3-n-propylcarbamoyl-Δ⁴-thiazoline (9) and *ca.* 7% of compound (7). By fraction (*e*), the ratio of compound (7) to (9) had changed to 3 : 1. The last fraction was almost pure compound (7). The column was washed with chloroform, and eluted with methanol (3 × 50 ml) to give 4-methyl-2-(thiazol-2-yl)semicarbazide (3). The ratio of the combined yields of compounds (7) and (9) to that of compound (3) was *ca.* 4 : 1.

Rearrangement of 2-(*Isopropylidenehydrazono*)-3-*methylcarbamoyl*-Δ⁴-*thiazoline* (7).—(A) *In boiling methyl cyanide.* A solution of compound (7) (1 g) in anhydrous methyl cyanide (10 ml) was heated under reflux for 6 h. The solvent was distilled off under reduced pressure, and the residual gum (1 g) was dried over silica gel. N.m.r. ($CDCl_3$) showed the product to contain compound (7) and the isomeric thiazole (8) in the ratio *ca.* 3 : 2.

(B) *In boiling* 2N-*hydrochloric acid.* Compound (7) (1 g) was added to refluxing 2N-hydrochloric acid (40 ml), and after 5 min the solution was concentrated under reduced pressure to 5 ml, and diluted with water (25 ml). Addition of fused sodium acetate (4 g), and crystallisation of the precipitate from ethanol gave 4-methyl-1-(thiazol-2-yl)-semicarbazide (2) as white crystals (0·35 g, 43%), m.p. 181° (decomp.), identical with an authentic sample.

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