3-(Thiazolidin-3-yl)rhodanines. A Novel Class of Rhodanine Derivatives

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Received September 8, 1993

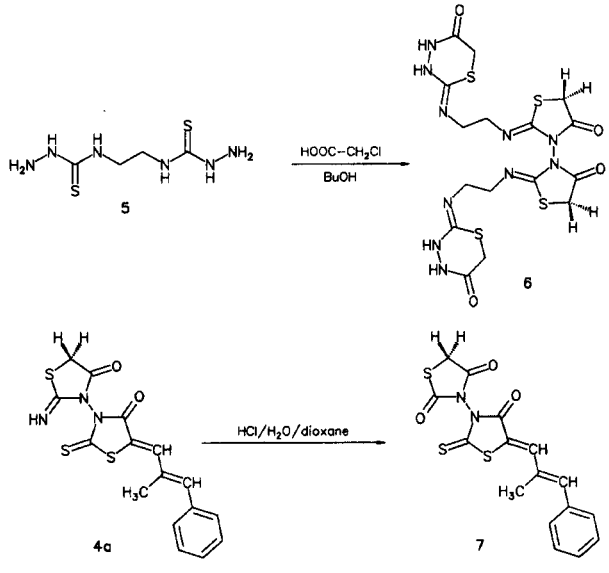
α-Bromoacetylaminorhodanines **1** were reacted with NH_4SCN yielding 3-(thiazolidin-3-yl)rhodanines **4**, a novel type of rhodanine derivatives bearing a uncommon N-N ring-connection.

J. Heterocyclic Chem., **31**, 391 (1994).

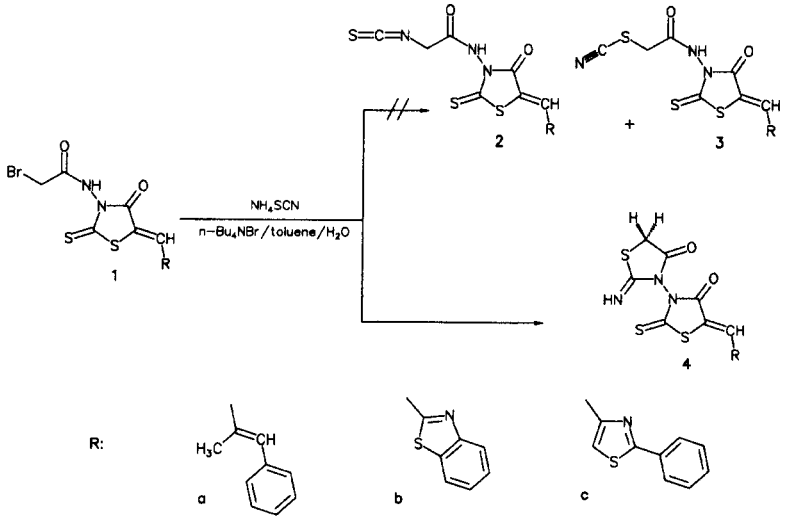
The design of inhibitors of the aldose reductase (EC 1.1.1.21) has received considerable interest because of the proposed role of this enzyme in the development of diabetic complications [1-5]. During our course of study of potential aldose reductase inhibitors [6] we intended to synthesize rhodanine derivatives bearing a functional group capable of modifing the aldose reductase *via* nucleophilic addition. Therefore we reacted the α-bromoacetylaminorhodanines **1a-c** with NH_4SCN in a toluene/water two-phase system using $(n\text{-Bu})_4NBr$ as a phase transfer catalyst. The reaction products were neither the expected isothiocyanates **2** nor their isomers **3** but the 3-(thiazolidin-3-yl)rhodanines **4a-c**. The emergence of **4a-c** can be understood as an intramolecular nucleophilic addition of the amide nitrogen to the intermediate thiocyanates **3**.

A literature survey revealed that there is only one compound described which contains a N-N-connection between two thiazolidine rings. Ucrainic authors claimed to have obtained the symmetric bisthiazolidine **6** by heating the bisthiosemicarbazide **5** with α-chloroacetic acid in butanol for 30 minutes [7]. Whereas **6** is a symmetric bisthiazolidine derivative, our compounds consist of two different heterocycles, a rhodanine ring and a thiazolidine connected in an uncommon 3-3 fashion. The 3'-imino-function of **4a** is readily hydrolyzed in dioxane/water with a trace of hydrochloric acid to the corresponding oxo group yielding **7**.

Scheme 2



Scheme 1



EXPERIMENTAL

Melting points were determined on a Leitz HM Lux apparatus. Microanalyses were obtained on a Hewlett Packard CHN-Autoanalyser (N only) and a Labormatic CH-Analyser. Mass spectra were recorded on a Vacuum Generators Spectrometer 7070H with EI (70ev). The infrared spectra were run using a Perkin Elmer PE 398 instrument. The ^1H and ^{13}C nmr spectra were recorded on a Jeol JNM-GX 400 instrument.

General Procedure for Preparation of 3-(Thiazolidin-3-yl)rhodanines (**4**).

To a boiling suspension of 3-bromoacetylaminorhodanine (**1**) [6] in toluene (150-200 ml) was added a solution of NH_4SCN (3 equivalents) and $(n\text{-}Bu)_4NBr$ (0.3 equivalents) in water (20-50 ml). The resulting mixture was vigorously stirred and refluxed. After 2 hours the organic layer was separated, washed with hot water (2 x 75 ml), dried over Na_2SO_4 and evaporated to dryness. The resulting solid was purified by column chromatography (ethyl acetate-*n*-hexane 3:2) and recrystallized from toluene/dioxane.

Z-3-(2-Imino-4-oxothiazolidin-3-yl)-5-[(2*E*)-2-methyl-3-phenylpropenylidene]-2-thioxothiazolidin-4-one (**4a**).

This compound was obtained in 82% yield as yellow-orange crystals, mp 236°; ir (potassium bromide): 3290, 1745, 1720, 1640 cm^{-1}; ^1H nmr ([D$_6$]-DMSO): 9.77 (s, 1H, =N*H*), 7.73 (s, 1H, 6-*H*), 7.50-7.44 and 7.41-7.39 (2 m, 4H, and 2H, 8-*H* and 2'-, 6'-*H*), 4.36 and 4.34 (AB-system, 2H, J = 17 Hz, 5''-*H*), 2.26 (s, 3H, H_3C-C-7); ^{13}C nmr ([D$_6$]-DMSO): 187.7 (*C*-2), 166.8 (*C*-4''), 161.8 (*C*-4), 150.5 (*C*-2''), 146.2 (*C*-8), 142.6 (*C*-6), 135.7 (*C*-1'), 133.1 (*C*-7), 129.8 (*C*-2', -6'), 128.9 (*C*-4'), 128.7 (*C*-3', -5'), 116.6 (*C*-5), 30.9 (*C*-5''), 15.9 (H_3C-C-7); ms: m/z (%) = 375 (32, M$^+$), 174 (100), 173 (40), 172 (37), 169 (35), 141 (93).

Anal. Calcd. for $C_{16}H_{13}N_3O_2S_3$ (375.48): C, 51.18; H, 3.49; N, 11.19; S, 25.62. Found: C, 51.03; H, 3.47; N, 11.12; S, 25.49.

5-(Benzothiazol-2-ylmethylene)-3-(2-imino-4-oxothiazolidin-3-yl)-2-thioxothiazolidin-4-one (**4b**).

This compound was obtained in 85% yield as yellow crystals, mp 233°; ir (potassium bromide): 3310, 1750, 1725, 1640, 1595 cm^{-1}; ^1H nmr ([D$_6$]-DMSO): 9.86 (br, =N*H*), 8.35 (s, 1H, 6-*H*), 8.25-8.22 (m, 2H, 5'-, 8'-*H*), 7.68-7.56 (m, 2H, 6'-, 7'-*H*), 4.46 (A-part of a AB-system, 1H, J = 17 Hz, 5''-*H*), 4.41 (B-part of a AB-system, 1H, J = 17 Hz, 5''-*H*); ^{13}C nmr ([D$_6$]-DMSO): 191.9 (*C*-2), 166.5 (*C*-4''), 161.3 (*C*-4), 160.5 (*C*-2'), 152.9 (*C*-9'), 150.3 (*C*-2''), 136.4 (*C*-6), 127.6 (*C*-8'), 126.9 (*C*-6'), 125.3 (*C*-5'), 124.0 (*C*-5), 123.7 (*C*-7'), 122.8 (*C*-4'), 30.7 (*C*-5''); ms: m/z 392 (11, M$^+$), 278 (36), 220 (17), 219 (19), 193 (11), 192 (22), 191 (100).

Anal. Calcd. for $C_{14}H_8N_4O_2S_4$ (392.48): C, 42.84; H, 2.05; N, 14.27; S, 32.67. Found: C, 42.62; H, 2.27; N, 14.17; S, 32.39.

3-(2-Imino-4-oxothiazolidin-3-yl)-5-[(2-phenyl-1,3-thiazol-4-yl)methylene]-2-thioxothiazolidin-4-one (**4c**).

This compound was obtained in 87% yield as yellow crystals, mp >255°; uv/vis (MeOH): (log ε) 392 (4.32), 267 (4.37); ir (potassium bromide): 3300, 1750, 1725, 1640, 1595 cm^{-1}; ^1H nmr ([D$_6$]-DMSO): 9.78 (s, 1H, =N*H*), 8.54 (s, 1H, 5'-*H*), 8.06, 8.04 (m, 3H, 2''-, 6''-*H* and 6-*H*), 7.62-7.56 (m, 3H, 3''-, 4''-, 5''-*H*), 4.43 (A-part of a AB-system, 1H, J = 18 Hz, 5'''a-*H*), 4.39 (B-part of a AB-system, 1H, J = 18 Hz, 5'''b-*H*); ^{13}C nmr ([D$_6$]-DMSO): 191.6 (*C*-2), 168.6 (*C*-2'), 166.6 (*C*-4''), 161.8 (*C*-4), 150.3 (*C*-2'''), 149.8 (*C*-4'), 131.7 (*C*-6), 131.1 (*C*-1'), 130.0 (*C*-4'''), 129.4 (*C*-2'', -6''), 126.7 (*C*-5'), 126.4 (*C*-3'', -5''), 120.0 (*C*-5), 30.7 (*C*-5'''); ms: m/z = 418 (24, M$^+$), 219 (11), 218 (29), 217 (100).

Anal. Calcd. for $C_{16}H_{10}N_4O_2S_4$ (418.53): C, 45.92; H, 2.41; N, 13.39; S, 30.65. Found: C, 45.88; H, 2.70; N, 13.33; S, 30.32.

Z-3-(2,4-Dioxothiazolidin-3-yl)-5-[(2*E*)-2-methyl-3-phenylpropenylidene]-2-thioxothiazolidin-4-one (**7**).

To a solution of **4a** (70 mg, 0.19 mmole) in dioxane (20 ml) was added water (0.5 ml) and concentrated hydrochloric acid (5 drops). The mixture was heated to reflux for 1 hour. Evaporation to dryness resulted in an oil, which slowly solidified. This solid was chromatographically purified (ethyl acetate-*n*-hexane) and recrystallized from dioxane/methanol, yield 55 mg (77%) as orange crystals, mp 188°; ir (potassium bromide): 1775, 1720, 1550, 1560 cm^{-1}; ^1H nmr ([D$_6$]-DMSO): 7.82 (s, 1H, 6-*H*), 7.55-7.43 (m, 5H, 2'- to 6'-*H*), 7.30 (s, 1H, 8-*H*), 4.77-4.73 (m, 2H, 5''-*H*), 2.19 (s, 3H, H_3C-C-7); ^{13}C nmr ([D$_6$]-DMSO): 187.2 (*C*-2), 166.6 (*C*-4''), 165.7 (*C*-2''), 161.4 (*C*-4), 147.0 (*C*-8), 143.6 (*C*-6), 135.5 (*C*-1'), 133.0 (*C*-7), 129.7 (*C*-2', -6'), 129.1 (*C*-4'), 128.6 (*C*-3', -5'), 115.7 (*C*-5), 32.0 (*C*-5''), 15.6 (H_3C-C-7); ms: m/z 376 (77, M$^+$), 202 (17), 174 (87), 173 (37), 172 (16), 142 (27), 141 (100).

Anal. Calcd. for $C_{16}H_{12}N_2O_3S_3$ (376.64): C, 51.05; H, 3.21; N, 7.44; S, 25.55. Found: C, 50.97; H, 3.31; N, 7.51; S, 25.18.

Acknowledgement.

We thank the Fonds der Chemischen Industrie for financial support.

REFERENCES AND NOTES

[1] P. F. Kador, J. H. Kinoshita and N. E. Sharpless, *J. Med. Chem.*, **28**, 841 (1985).

[2] P. F. Kador, W. G. Robinson, Jr. and J. H. Kinoshita, *Ann. Rev. Pharmacol. Toxicol.*, **25**, 691 (1985).

[3] P. F. Kador, *Med. Res. Rev.*, **8**, 325 (1988).

[4] D. R. Tomlinson, G. B. Willars and A. L. Carrington, *Pharmacol. Therap.*, **54**, 151 (1992).

[5] R. Sarges, *Adv. Drug Res.*, **18**, 139 (1989).

[6] Manuscript in preparation.

[7] N. M. Turkevich and D. P. Boikov, *Dopov. Akad. Nauk Ukr. RSR, Ser. B*, **33**, 1016 (1971); *Chem. Abstr.*, **76**, 153713d (1972).