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# A NOVEL ROUTE TO 3,5,5-TRISUBSTITUTED THIAZOLIDINE-4-ONES

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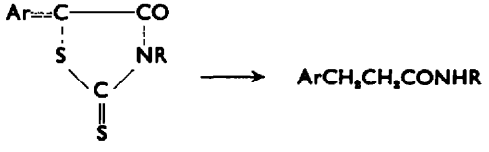
**Abstract**—New 3,5,5-trisubstituted thiazolidine-4-ones have been prepared by the reductive partial desulphurization of the corresponding 2-thiono derivatives.

THIAZOLIDINE-4-ONES are usually obtained by the cyclization of acyclic compounds.[1] However, the interconversion among substituted thiazolidine-4-ones such as the conversions of 2-substituted derivatives into compounds having other substituent groups in the 2-position has been achieved in some cases.[2,3]

In the course of an investigation on thiazolidine chemistry[4] the desulphurization of 2-thionothiazolidine-4-one (rhodanine) derivatives was undertaken as a means of preparing new thiazolidine-4-ones unsubstituted in the 2-position.

Thiazolidine-4-ones are desulphurized with Raney nickel and 2-substituted thiazolidine-4-ones are converted into amides lacking both the sulphur atom and the carbon in the 2-position;[5] the reductions are completed by refluxing the substances with Raney nickel in ethanolic solution. In some cases the thiazolidine ring is ruptured with loss of sulphur but the carbon in the 2-position is retained.[6]

When rhodanine (2-thionothiazolidine-4-one) derivatives are treated with Raney nickel in aqueous solution they are hydrolysed to α-mercapto acids from which the mercapto group is eliminated and replaced by hydrogen.[7] When 5-arylidenerhodanines are refluxed in ethanolic solution with excess Raney nickel good yields of the corresponding hydrocinnamic acid amides are obtained.[8]

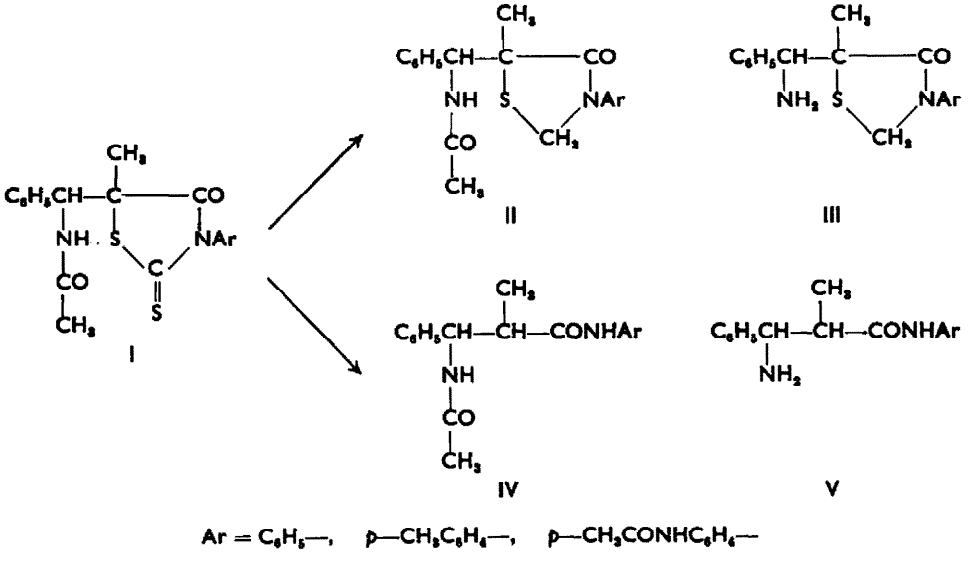



In these reactions, as in the desulphurization of the thiazole derivatives, the carbon between two hetero atoms is eliminated.

[1] F. C. Brown, *Chem. Revi* **61**, 463 (1961).
[2] H. Taniyama, K. Hagiwara, A. Okada and H. Uchida, *Yakugaku Zasshi* **77**, 1236 (1957); *Chem. Abstr.* **52**, 6322 (1958).
[3] R. Andreasch, *M.* **10**, 73 (1889); R. Tambach, *Liebigs Ann.* **280**, 233 (1894).
[4] Gj. Stefanović, M. Stefanović and A. Stojiljković, *Tetrahedron* **18**, 413 (1962).
[5] D. H. Marrian, *J. Chem. Soc.* 1797 (1949); P. N. Rylander and E. Champaigne, *J. Org. Chem.* **15**, 249 (1950).
[6] W. M. McLamore, W. D. Celmer, V. V. Boggert, F. C. Pennington, B. A. Sobin and I. A. Solomons, *J. Amer. Chem. Soc.* **75**, 105 (1953).
[7] C. K. Bradsher, F. C. Brown and R. J. Grantham, *J. Amer. Chem. Soc.* **73**, 5377 (1951); G. G. Allen, D. McLean and G. T. Newbold, *J. Chem. Soc.* 5053 (1952).
[8] H. Behringer, E. Dillinger, H. Suter and K. Kohl, *Chem. Ber.* **91**, 2773 (1958).

The partial desulphurization of rhodanine derivatives i.e. the desulphurization of the thiono (>C=S) group in the 2-position without breaking the thiazolidine is the subject of the present investigation. 3-Aryl-5,5-disubstituted-2-thionothiazolidine-4-ones were obtained by the condensation of benzylidene-bisacetamide with 3-aryl-5-methyl-rhodanines. It has been found that the treatment of rhodanine derivatives with Raney nickel at ordinary temperatures and under thirty atmospheres pressure of hydrogen results in partial desulphurization, whereby the thiono group is replaced by a methylene group. Under similar experimental conditions but at the temperature of 100°, complete desulphurization takes place and the carbon adjoining both hetero atoms is eliminated. The complete desulphurization also occurs when an ethanolic solution of 3-aryl-5,5-disubstituted rhodanines is refluxed with Raney nickel.

The partial desulphurization of 2-thiono-3-aryl (phenyl-, *p*-tolyl-, *p*-acetylamino-phenyl-)-5-methyl-5-α-acetylaminobenzylthiazolidine-4-ones (I), results in the corresponding thiazolidine-4-ones (II) in yields of about 50%.




Acid hydrolysis of the products (II) yields the thiazolidine-4-ones (III) having an α-aminobenzyl group in the 5-position. These substances may be of biological interest since they possess, in addition to the thiozalidine ring, a free amino group in the side chain. Chemically they behave as true bases and give the corresponding salts.

The structures of the partially desulphurized products (II and III) are supported by microanalyses and IR spectra. The compounds (I) exhibit strong absorptions in the region 1250–1100 $cm^{-1}$, generally assigned to > C=S group and the derivatives (II and III) possess only weak absorption bands in this region.

The products of complete desulphurization were identified as amides of the corresponding β-amino acids (IV and V).

It has been observed that the substituents attached to the 3- and 5- positions affect the desulphurization reactions of rhodanine derivatives. Neither 5-methylrhodanine, nor 5-methyl-3-phenylrhodanine, nor 5-α-acetylaminobenzyl-3-phenylrhodanine

could be partially desulphurized under the given experimental conditions. Thus, the present work constitutes a new method of synthesizing 3,5,5-trisubstituted thiazolidine-4-ones

Further desulphurization reactions are under investigation.

## EXPERIMENTAL

M.ps are not corrected.

*5-Methyl-3-phenyl-2-thionothiazolidine-4-one* was prepared by heating a mixture of trithiolactic acid (11 g), aniline (5 g) and water (200 ml) for 3 hr. The red-yellow oil which was separated was treated with hot ethanol and a white crystalline powder (7 g) precipitated; m.p. 116–117°.[9]

*5-Methyl-3-p-tolyl-2-thionothiazolidine-4-one.* A mixture of trithiolactic acid (40 g), *p*-toluidine (18 g) and water (600 ml) was treated as above. The yellow crystals obtained melted at 100°. (Found: C, 56·0; H, 4·8; N, 6·6; $C_{11}H_{11}NOS_2$ requires: C, 55·69; H, 4·67; N, 5·91%).

*5-Methyl-3-p-actylaminobenzyl-2-thionothiazolidine-4-one.* A mixture of trithiolactic acid (11 g), *p*-aminoacetanilide (5 g) and water (200 ml) was treated as above. The resultant white crystals (4 g) were filtered off and recrystallized from ethanol and water; m.p. 228–230°. (Found: C, 52·2; H, 4·4; N, 10·0; $C_{18}H_{12}N_2O_2S_2$ requires: C, 51·43; H, 4·32; N, 9·99%).

*5-Methyl-5-α-acetylaminobenzyl-3-phenyl-2-thionothiazolidine-4-one* (I, Ar = $C_6H_5$—). 5-Methyl-3-phenyl-2-thionothiazolidine-4-one (2 g; 0·008 mole), benzylidenebisacetamide (1·6 g; 0·008 mole) and acetic acid anhydride (10 ml) were heated on an oil-bath till dissolved and the heating was continued for 2 hr at 150°. The reaction mixture was diluted with ice and water and the separated oil washed several times with ice water until a solid precipitate was obtained (1·5 g; 40%). This was recrystallized from methanol and water, m.p. 194°. (Found: C, 61·2; H, 4·8; N, 7·5; $C_{19}H_{18}N_2O_2S_2$ requires: C, 61·61; H, 4·86; N, 7·56%).

*5-Methyl-5-α-acetylaminobenzyl-3-p-tolyl-2-thionothiazolidine-4-one* (I, Ar = *p*-$CH_3C_6H_4$—). A mixture of 5-methyl-3-*p*-tolyl-2-thionothiazolidine-4-one (4 g; 0·016 mole), benzylidenebisacetamide 3.2 g; 0·016 mole) and acetic acid anhydride (10 ml) yielded a solid product (2 g; 32%) which recrystallized from ethanol and water; m.p. 200–202°. (Found: C, 62·7; H, 5·4; N, 7·3; $C_{20}H_{20}N_2O_2S_2$ requires: C, 62·49; H, 5·20; N, 7·29%).

*5-Methyl-5-α-acetylaminophenyl-3-p-acetylaminophenyl-2-thionothiazolidine-4-one* (I, Ar = *p*-$CH_3CONHC_6H_4$—). A mixture of 5-methyl-3-*p*-acetylaminophenyl-2-thionothiazolidine-4-one (2 g; 0 007 mole), benzylidenebisacetamide (1·5 g; 0·007 mole) and acetic acid anhydride (20 ml) yielded a solid product (0·9 g) which recrystallized from ethanol; m.p. 210°. (Found: C, 58·8; H, 5·1, N, 9·2; $C_{21}H_{21}N_3O_3S_2$ requires: C, 59·01; H, 4·91; N, 9·83%).

*5-Methyl-5-α-acetylaminobenzyl-3-phenylthiazolidine-4-one* (II, Ar = $C_6H_5$—). To a solution of the product (I, Ar = $C_6H_5$—; 2 g) in ethanol (100 ml) Raney N: (5 g) was added and the mixture shaken in an autoclave under 30 atm. $H_2$ for 4 hr. The Raney Ni was filtered off and the filtrate concentrated to 20 ml. On standing and cooling a white crystalline product was deposited (1 g; 55%); m.p. 198°. (Found: C, 66·7; H, 5·9; N, 8·5; $C_{19}H_{20}N_2O_2S$ requires C, 67·04; H, 5·92; N, 8·23%).

*5-Methyl-5-α-acetylaminobenzyl-3-p-tolylthiazolidine-4-one* (II, Ar = *p*-$CH_3C_6H_4$—). An ethanolic solution of the product (I, Ar = *p*-$CH_3C_6H_4$—; 2 g) was shaken in an autoclave under 30 atm. $H_2$ for 4 hr. After separation of Raney Ni and evaporation of ethanol a white crystalline product (1·1 g; 60%) was obtained and recrystallized from ethanol and water; m.p. 178–180°. (Found: C, 67·4; H, 6·2; N, 7·9; $C_{20}H_{22}N_2O_2S$ requires: C, 67·78; H, 6·21; N, 7·90%).

*5-Methyl-5-α-aminobenzyl-3-phenylthiazolidine-4-one* (III, Ar = $C_6H_5$—). The product (II; Ar = $C_6H_5$—; 1 g) was heated with conc. HCl (50 ml) for 4 hr. The cooled reaction mixture was diluted with ice water and NaOHaq added until the reaction was alkaline. The product (0·65 g; 74%) was recrystallized from ethanol and water; m.p. 100°. (Found: C, 68·6; H, 6·1; N, 9·2; $C_{17}H_{16}N_2OS$ requires: C, 68·45; H, 6·04; N, 9·39%).

*5-Methyl-5-α-aminobenzyl-3-p-tolylthiazolidine-4-one* (III, Ar = *p*-$CH_3C_6H_4$—). A mixture of the product (II; Ar = *p*-$CH_3C_6H_4$—; 1 g) and conc. HCl (50 ml) was heated until a solution was obtained (4 hr). The cooled mixture was diluted with ice water and made alkaline with NaOHaq.

[9] R. Andreasch and A. Zipser, **M.25**, 179 (1904).

The product (0·6 g; 70%) were filtered off and recrystallized; m.p. 145°. (Found: C, 69·3; H, 6·6; N, 8·82; $C_{18}H_{20}N_2OS$ requires: C, 69·23; H, 6·41; N, 8·94%).

*β-N-acetylamino-β-phenyl-α-methylpropionic acid* N-p-*tolyl amide* (IV, Ar = *p*-$CH_3C_6H_4$). The product (I; Ar = *p*-$CH_3C_6H_4$—; 1 g) was dissolved in ethanol (100 ml) and heated on a water bath with Raney Ni (5 g) for 4 hr. Raney Ni was filtered off and after the removal of the solvent a white crystalline product (0·6 g; 75%) m.p. 250° was obtained. (Found: C, 73·3; H, 7·7; N, 8·4; $C_{19}H_{22}N_2O_2$ requires: C, 73·54; H, 7·14; N, 9·03%).