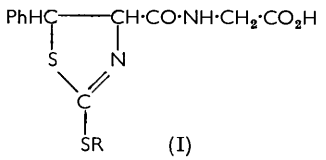
927. *Thiazolidines. Part III.*[1] *The Reaction of 2-Methylthio-5-phenylthiazoline-4-carboxylic Acid with Thionyl Chloride and Phosphorus Pentachloride.*

By D. O. Holland and P. Mamalis.

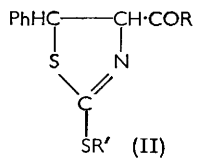
cis- or *trans*-2-Methylthio-5-phenylthiazoline-4-carboxylic acid (II; R = OH, R′ = Me) with thionyl chloride or phosphorus pentachloride gives a gum which with bases yields compounds believed to be α-(methylthio-thiocarbonylamino)cinnamic acid derivatives (VI).

A synthesis of *trans*-5-phenyl-2-thiothiazolidine-4-carbonylglycine (I; R = H) * and its *S*-methyl derivative (I; R = Me) from the 4-carboxylic acids (II; R = OH, R′ = H or Me respectively) by way of the hydrazides (II; R = NH·NH$_2$, R′ = H or Me) is described in the preceding paper, but the *cis*-peptide could not be obtained by this method. The acid chloride route to peptides was therefore explored.

trans-5-Phenyl-2-thiothiazolidine-4-carboxylic acid (II; R = OH, R′ = H) with thionyl chloride or phosphorus pentachloride in chloroform or benzene yielded dark oils which with aniline or ammonia furnished intractable gums.

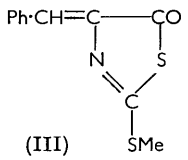


(I)

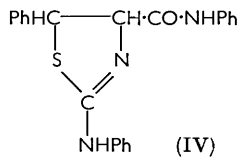


(II)

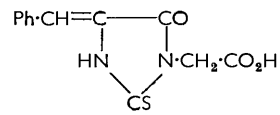
The corresponding *S*-methyl acid (II; R = OH, R′ = Me) with phosphorus pentachloride in benzene solution gave, besides a small quantity of 4-benzylidene-2-methylthiothiazolin-5-one (III), a gum which with aniline yielded a solid possessing the empirical formula for the required anilide (II; R = NHPh, R′ = Me). However, whereas the authentic anilide, prepared by the action of aniline on the azide derived from *trans*-2-methylthio-5-phenylthiazoline-4-carboxyhydrazide (II; R = NH·NH$_2$, R′ = Me),[1] on further reaction with warm aniline yielded compound (IV), the isomeric product from the phosphorus pentachloride reaction remained unchanged (cf. Cook, Elvidge, and Shaw,[2] who converted ethyl 2-ethylthio-5 : 5-dimethylthiazoline-4-carboxylate into the 2-anilino-derivative in this way). The ultraviolet absorption was also quite different.



(III)



(IV)



(V)

The phosphorus pentachloride reaction product, when treated with glycine methyl ester, gave two solids after alkaline hydrolysis. One proved to be the thiohydantoin (V),[1] probably derived from the benzylidene derivative (III), while the other, a white solid soluble in aqueous sodium hydrogen carbonate, gave correct analyses for the required glycyl-peptide (I; R = Me), but again its properties precluded this structure and its methyl ester (prepared with diazomethane) differed from *trans*-2-methylthio-5-phenylthiazoline-4-carbonylglycine methyl ester.

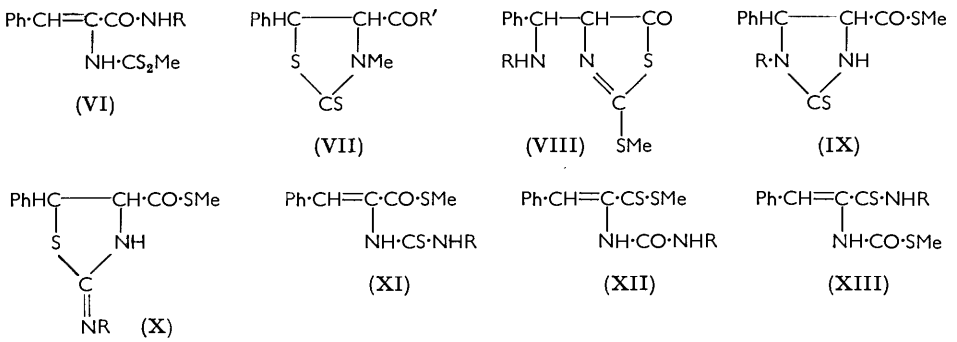
The *S*-methyl acid (II; R = OH, R′ = Me) with thionyl chloride gave similar results.

* See footnote on p. 4584.

[1] Parts I and II, preceding papers.
[2] Cook, Elvidge, and Shaw, *J.*, 1949, 2369.

Thionyl chloride, added to the acid in dry benzene at room temperature, yielded a deliquescent solid which appeared to be a loose complex of the thiazoline with thionyl chloride since *in vacuo* it reverted to the starting material. The hydrochloride of the thiazoline was found to be quite stable under these conditions.[1] When the reaction mixture was heated, the solid dissolved with evolution of sulphur dioxide and hydrogen chloride, and a good yield of 4-benzylidene-2-methylthiothiazolin-5-one (III) was obtained. When, however, the reaction was carried out in chloroform the gummy product contained none of the thiazolinone (III): after treatment with aniline or glycine ester it gave the same products as were obtained from the phosphorus pentachloride reaction. Similarly, when the gum was allowed to react with ammonia a product isomeric with the required amide (II; R = NH_2, R′ = Me) was obtained. The same products also arose from *cis*-2-methylthio-5-phenylthiazoline-4-carboxylic acid (II; R = OH, R′ = Me).

The ammonia reaction product was soluble in concentrated but insoluble in dilute hydrochloric acid and with acetic anhydride yielded a monoacetyl derivative. On hydrolysis with either acid or alkali it yielded an acid isomeric with the thiazoline acid (II; R = OH, R′ = Me) and affording a different methyl ester on treatment with diazomethane. This ester was also obtained directly from the gum by reaction with methanol. This product and the other derivatives of the gum described above, with the exception of that from aniline, have very similar ultraviolet absorption spectra which differ markedly from those of the isomers possessing the 2-methylthio-5-phenylthiazoline structure (no maximum).

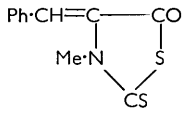


Of the possible structures (VI—XIII) for the new amino-derivatives, structures (IX—XII) appeared unlikely since methanethiol was not released on comparatively mild acid hydrolysis (cf. Doyle, Holland, and Nayler [3]): carbamic esters derived from amino-acids resist acid hydrolysis (cf. Cagnon and Boivin [4]) and hence structures (VI) and (XIII) would not be expected to lose methanethiol under these conditions. The loss of the amino-group on acid or alkaline hydrolysis to yield an acid which with diazomethane gave the same methyl ester as that obtained directly from the gum eliminated structure (VIII) and indicated the presence of an amide group which brought formulæ (VI), (VII; R′ = NHR), and (XIII) into consideration. The thioamide (XIII) appeared unlikely in comparison with the normal amide (VI) since it would have been expected to lose a sulphur atom on hydrolysis. The structure (VII) was eliminated by synthesis of the authentic acid, methyl ester, and amide whose ultraviolet spectra differed from those of the compounds obtained from the gum. The acid and the amide were prepared by the ring-turning of 4-benzylidene-3-methyl-2-thiothiazolid-5-one (XIV) with alkali and ammonia respectively,[5] and the methyl ester was made from the acid by reaction with diazomethane. The amide was also obtained from the ester by reaction with ammonia.

The methyl ester (VII; R′ = OMe), m. p. 107—108°, had an ultraviolet spectrum

[3] Doyle, Holland, and Nayler, *J.*, 1955, 2265.
[4] Cagnon and Boivin, *Canad. J. Res.*, 1948, **26**, *B*, 503.
[5] (*a*) Cook and Cox, *J.*, 1949, 2342; (*b*) Siddappa, Thesis, London, 1950.

almost identical with that of the suspected methyl 3-methyl-5-phenyl-2-thiothiazolidine-4-carboxylate, m. p. 125—125·5°, obtained by the action of diazomethane on *cis*-5-phenyl-2-thiothiazolidine-4-carboxylic acid (II; R = OH, R′ = H).[1] Evidently ring-turning of 4-benzylidene-3-methyl-2-thiothiazolid-5-one with alkali or ammonia leads to *trans*-*N*-methylated thiazolidines (VII; R′ = OH or NH_2).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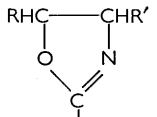
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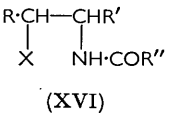
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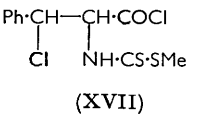
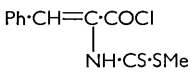

(XVII)

Attempts to synthesize compounds with the structure (VI) by alternative routes were not made.

The formation of the thiazolinone (III) by the action of phosphorus pentachloride or thionyl chloride on the thiazoline acid (II; R = OH, R′ = Me) must involve fission of the thiazoline ring. Fry [6] has shown that analogous oxazolines (XV) open under the influence of hydrogen halides to give β-halogeno-α-amido-compounds (XVI). It is possible that a similar reaction occurs with the thiazoline (II; R = OH, R′ = Me) to give an intermediate (XVII) which loses one molecule of hydrogen chloride to give the unsaturated acid chloride (XVIII). Under the influence of thionyl chloride or phosphorus pentachloride this may partly cyclise to the thiazolinone (III) in an analogous manner to the ring closure of ethyl carboxymethyldithiocarbamate with phosphorus tribromide described by Cook, Harris, Heilbron, and Shaw.[7] It is noteworthy that 4-ethylidene-2-phenyloxazolin-5-one (XX) has been obtained [8] by the action of thionyl chloride on *N*-benzoyl*allo*threonine (XIX).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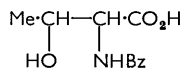
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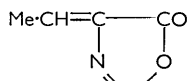
(XX)

Experimental

Reaction of trans-2-*Methylthio-5-phenylthiazoline-4-carboxylic Acid with Phosphorus Pentachloride.*—The acid (2·5 g.) and phosphorus pentachloride (2·1 g.) in dry benzene (20 ml.) were heated under reflux for 1·5 hr. The solvent was then removed *in vacuo* and the resulting partially crystalline residue crystallised from benzene–light petroleum, to yield 4-benzylidene-2-methylthiothiazolin-5-one (0·4 g.), m. p. 93—97°. On recrystallisation from the same solvents it was obtained as yellow needles, m. p. 97° alone and when mixed with an authentic specimen (see below). (Found: C, 55·9; H, 4·2; N, 6·1. Calc. for $C_{11}H_9ONS_2$: C, 56·2; H, 3·9; N, 6·0%).

To the mother-liquor from the crystallisation of the above compound aniline (1 ml.) was added. After 2 hr. the solution was extracted with dilute hydrochloric acid, washed with water, and dried ($MgSO_4$). It was then concentrated to small volume and treated with light petroleum; a solid (0·3 g.) separated, as yellow prisms, m. p. 152—153°, probably α-(*methylthio-thiocarbonylamino*)*cinnamanilide* (VI; R = Ph) (Found: C, 62·3; H, 4·8; N, 8·3; S, 19·6. $C_{17}H_{16}ON_2S_2$ requires C, 62·3; H, 4·9; N, 8·5; S, 19·5%), $\lambda_{max.}$ (in EtOH) 287 mμ (ε 18,235).

The mother-liquors from a similar reaction were treated with glycine methyl ester (prepared from 1·65 g. of the ester hydrochloride) and triethylamine (2·1 ml.) in chloroform (10 ml.) and kept for 2 hr. The solution was then extracted with dilute hydrochloric acid, washed with water, dried, and evaporated. The sticky residue was treated with N-sodium hydroxide (20 ml.) for 2 hr. at room temperature. The resulting sticky yellow-brown solid was removed and crystallised from alcohol, to give 4-benzylidene-2-methylthiothiazolin-5-one, m. p. 96—97°.

[6] Fry, *J. Org. Chem.*, 1949, **14**, 887; 1950, **15**, 438.
[7] Cook, Harris, Heilbron, and Shaw, *J.*, 1948, 1056.
[8] Pfister, Robinson, Shabica, and Tishler, *J. Amer. Chem. Soc.*, 1948, **70**, 2297; 1949, **71**, 1101.

The remaining alkaline solution was extracted with chloroform and acidified with dilute hydrochloric acid. On addition of chloroform to this acid solution a solid separated (0·18 g.). It was crystallised by dissolving it in N-sodium hydroxide and acidifying the solution carefully at 85°, 4-benzylidene-4 : 5-dihydro-2-mercapto-5-oxoglyoxalin-1-ylacetic acid separating as pale yellow needles, m. p. 255°, alone and when mixed with an authentic specimen [1] (Found: C, 55·2; H, 4·0; N, 10·7. Calc. for $C_{12}H_{10}O_3N_2S$: C, 55·1; H, 3·9; N, 10·7%).

The chloroform layer from the acidified solution was washed with water, dried, and concentrated to small volume. On addition of light petroleum a small quantity of a white solid slowly separated, being obtained as needles, m. p. 184—185°, on recrystallisation from chloroform–light petroleum. It was probably N-[α-(*methylthio-thiocarbonylamino*)*cinnamoyl*]*glycine* (VI; R = $CH_2 \cdot CO_2H$) (Found: C, 50·6; H, 4·3; N, 9·2; S, 20·5. $C_{13}H_{14}O_3N_2S_2$ requires C, 50·4; H, 4·6; N, 9·0; S, 20·6%), $\lambda_{max.}$ (in EtOH) 304 mμ (ε 12,620).

Esterification of this compound with diazomethane in ether gave the *methyl ester*, needles, m. p. 86—87° (from ether–light petroleum) (Found: C, 51·7; H, 4·7; N, 9·5. $C_{14}H_{16}O_3N_2S_2$ requires C, 51·9; H, 5·0; N, 8·7%). It depressed the m. p. of *trans*-2-methylthio-5-phenylthiazoline-4-carbonylglycine methyl ester [1] (m. p. 80—81°) by 20°.

4-Benzylidene-2-methylthiothiazolin-5-one.—4-Benzylidene-2-thiothiazolid-5-one (2·5 g.) was shaken for 10 min. with methyl iodide (1·1 ml.) in N-sodium hydroxide (11·5 ml.). The product was removed and recrystallised from methyl alcohol as yellow prismatic needles, m. p. 96—97° (1·6 g.). The same product was obtained when methyl sulphate was used instead of methyl iodide (Cook and Cox [5a] gave m. p. 99—100° for this compound, using methyl iodide for its preparation; Cook and Pollock [9] used methyl sulphate and gave m. p. 124°).

trans-2-*Methylthio-5-phenylthiazoline-4-carboxyanilide.*—A solution of *trans*-2-methylthio-5-phenylthiazoline-4-carboxyhydrazide [1] (1·35 g.) in N-hydrochloric acid (7·5 ml.) and water (12·5 ml.) was stirred at 0° in the presence of chloroform (10 ml.) while sodium nitrite (0·4 g.) in a little water was added during 5 min. The chloroform layer was separated, washed with a little ice-water, dried ($MgSO_4$), and treated with aniline (0·5 ml.). Next day the solvent was removed to leave an oil which was passed in benzene down a short alumina column; the *anilide* (0·3 g.) slowly separated from the benzene eluate on addition of a little ethyl acetate and light petroleum. It was obtained as needles, m. p. 83—84°, from the latter pair of solvents (Found: C, 62·2; H, 5·0; N, 8·9%), and had $\lambda_{max.}$ (in EtOH) 237 mμ (ε 24,750).

2-Anilino-5-phenylthiazoline-4-carboxyanilide (0·88 g.) was obtained when the above reaction was repeated and the chloroform solution containing aniline was heated on a steam-bath for 20 min. On concentration of the solution the product separated as cream-coloured prisms, m. p. 171—173°. It was obtained as colourless needles, m. p. 178°, from methanol (Found: C, 70·7; H, 5·2; N, 11·3. $C_{22}H_{19}ON_3S$ requires C, 70·8; H, 5·1; N, 11·3%).

Reaction of trans-2-*Methylthio-5-phenylthiazoline-4-carboxylic Acid with Thionyl Chloride.*—(a) *In benzene.* A solution of the acid (2·5 g.) in dry benzene (100 ml.) was concentrated to 50 ml. to remove last traces of moisture and then treated at room temperature with thionyl chloride (distilled over quinoline and linseed oil) (3·0 ml.). The precipitated *solid* was removed after 3 hr. at 10° and washed with benzene; it had m. p. 116° (decomp.) after softening from 101° (2·35 g.) and when kept in a desiccator developed an odour of thionyl chloride; the solid then gave the same analysis as the starting material (Found: C, 52·4; H, 4·4; N, 5·3. Calc. for $C_{11}H_{11}O_2NS_2$: C, 52·3; H, 4·4; N, 5·5%). Use of 6 ml. of thionyl chloride and heating under reflux for 1 hr. gave a clear solution; removal of the solvent left a syrup which solidified on the addition of a little methyl alcohol; the solid (1·8 g.) on recrystallisation from methyl alcohol gave needles, m. p. 98—99°, not depressed when mixed with 4-benzylidene-2-methylthiothiazolin-5-one.

(b) *In chloroform.* A mixture of the acid (1·25 g.) and pure thionyl chloride (3 ml.) in dry chloroform (5 ml.) was heated under reflux for 1 hr. A solid separated initially but this dissolved after about 15 min. Removal of the solvent left a gum which was dissolved in chloroform (5 ml.) and treated with aniline (2 ml.). Next day the mixture was extracted with dilute hydrochloric acid, and the solvent layer washed with water, dried, and concentrated. On the addition of light petroleum α-(methylthio-thiocarbonylamino)cinnamanilide separated as yellow prisms (0·90 g.), m. p. 150—151°, not depressed on admixture with the product from the phosphorus pentachloride reaction.

[9] Cook and Pollock, *J.*, 1950, 1898.

A solution of the gum from a similar experiment (using 1·5 g. of acid) in chloroform (10 ml.) was treated with glycine methyl ester hydrochloride (1·26 g.) and triethylamine (7 ml.) in chloroform (15 ml.). After 3 hr. the solution was extracted with dilute hydrochloric acid, washed with water, and dried. Removing the solvent *in vacuo* gave a gum which was stirred with N-sodium hydroxide (15 ml.) at room temperature for 1 hr. Next day the resulting solution was extracted with chloroform and acidified with N-hydrochloric acid (18 ml.). On the addition of a little chloroform *N*-[α-(methylthio-thiocarbonylamino)cinnamoylglycine (1·1 g.) separated as a cream-coloured solid, soluble in aqueous sodium hydrogen carbonate solution. When recrystallised from water containing a little alcohol it was obtained as needles, m. p. 191°, not depressed on admixture with the product from the phosphorus pentachloride reaction.

α-(*Methylthio-thiocarbonylamino*)*cinnamamide*.—When the gum from the reaction of *trans*-2-methylthio-5-phenylthiazoline-4-carboxylic acid (1·25 g.) with thionyl chloride in chloroform solution was treated with ammonia (*d* 0·88; 5 ml.) for 16 hr. and a little methyl alcohol then added, a solid was obtained which on recrystallisation from aqueous methanol yielded needles, m. p. 122—124° (0·55 g.), probably α-(*methylthio-thiocarbonylamino*)*cinnamamide* (Found: C, 52·5; H, 4·1; N, 10·8; S, 24·9. $C_{11}H_{12}ON_2S_2$ requires C, 52·4; H, 4·8; N, 11·1; S, 25·4%), $\lambda_{max.}$ (in EtOH) 304 mμ (ε 11,485).

When this amide (0·5 g.) was heated under reflux for 15 min. with acetic anhydride (4 ml.) in the presence of 1 drop of concentrated sulphuric acid, then further on a steam-bath for 45 min. a brown solution was obtained from which the addition of water afforded a *monoacetyl derivative*, cream-coloured needles (0·34 g.) (from aqueous methanol), m. p. 97—98° (Found: C, 53·5; H, 4·4; N, 9·5; S, 21·6. $C_{13}H_{14}O_2N_2S_2$ requires C, 53·1; H, 4·8; N, 9·5; S, 21·8%).

trans-2-*Methylthio-5-phenylthiazoline-4-carboxyamide*.—A mixture of *trans*-5-phenyl-2-thiothiazolidine-4-carboxyamide (0·5 g.) and methyl iodide (0·5 ml.) in N-sodium hydroxide (2·5 ml.) was kept at 0° for 16 hr. and extracted with chloroform. After being washed and dried the chloroform extract was concentrated to small volume and treated with light petroleum; *trans*-2-methylthio-5-phenylthiazoline-4-carboxyamide separated as needles, m. p. 92—93°, not raised on recrystallisation from the same solvent mixture (Found: C, 52·2; H, 5·0; N, 11·6%). This corresponds to Cook, Hunter, and Pollock's α-form [10]

α-(*Methylthio-thiocarbonylamino*)*cinnamic Acid*.—The corresponding amide (1·0 g.) was heated under reflux for 5 hr. with concentrated hydrochloric acid (5·0 ml.), acetic acid (5·0 ml.), and water (5·0 ml.). The resulting mixture was cooled and diluted with water; on scratching, the required *acid* (0·75 g.) separated, having m. p. 140—141°, unchanged on recrystallisation from aqueous methanol whence it was obtained as pale yellow prisms (Found: C, 52·2; H, 3·8; N, 5·6; S, 24·9. $C_{11}H_{11}O_2NS_2$ requires C, 52·3; H, 4·4; N, 5·5; S, 25·3%), $\lambda_{max.}$ (in EtOH) 303 mμ (ε 10,900).

After the amide (1·0 g.) had been hydrolysed with sodium hydroxide (1·5 g.) under reflux for 4 hr. in 50% methanol (20 ml.) the *sodium salt* of the acid slowly separated as plates, m. p. > 290° when the product was kept at room temperature (Found: C, 47·6; H, 3·3; N, 5·2. $C_{11}H_{10}O_2NS_2Na$ requires C, 48·0; H, 3·7; N, 5·1%). When a solution of the sodium salt in warm water was acidified the free acid separated, having m. p. and mixed m. p. 139—140°.

Methyl α-(*Methylthio-thiocarbonylamino*)*cinnamate*.—The gum from reaction of *trans*-2-methylthio-5-phenylthiazoline-4-carboxylic acid (2·5 g.) with thionyl chloride in chloroform solution was dissolved in dry methyl alcohol (15 ml.). When next day water was added to the solution, the *methyl ester* separated (1·4 g.); from aqueous methanol it formed cream-coloured needles, m. p. 64—66° (Found: C, 54·4; H, 5·2; N, 5·2; S, 24·3. $C_{12}H_{13}O_2NS_2$ requires C 54·0; H, 4·9; N, 5·3; S, 24·0%).

The same ester was obtained from the acid by esterification with diazomethane in ethyl acetate, as needles (from ether–light petroleum), m. p. and mixed m. p. 66—67° (Found: C, 54·2; H, 4·7; N, 5·6%).

Reaction of cis-2-*Methylthio-5-phenylthiazoline-4-carboxylic Acid with Thionyl Chloride*.—The *cis*-acid (2·5 g.) and pure thionyl chloride (6 ml.) were heated under reflux in chloroform (10 ml.) for 30 min., then evaporated to a gum. To a solution of this in chloroform (10 ml.), glycine ethyl ester hydrochloride (1·35 g.) was added followed by triethylamine (7 ml.) in chloroform (15 ml.). After 3 days the mixture was extracted with dilute hydrochloric acid. The chloroform layer was then washed with water, dried, and concentrated *in vacuo* to leave a gum which

[10] Cook, Hunter, and Pollock, *J.*, 1950, 1892

was hydrolysed by stirring it with N-sodium hydroxide (15 ml.) for 1 hr. After extraction of a small residue with chloroform the solution was acidified, a gum separating which solidified. It recrystallised from aqueous alcohol as buff needles, m. p. 181—182° (0·6 g.), not depressed on admixture with *N*-[α-methylthio-thiocarbonylamino)cinnamoyl]glycine.

When the gum from 1·25 g. of the *cis*-acid was allowed to react with ammonia a product (0·7 g.) was obtained, having m. p. 123°, alone and when mixed with α-(methylthio-thiocarbonylamino)cinnamamide.

Similar reaction of the gum with aniline yielded the anilide, m. p. 148—152°, not depressed on admixture with the product obtained from *trans*-2-methylthio-5-phenylthiazoline-4-carboxylic acid.

Methyl trans-3-*Methyl*-5-*phenyl*-2-*thiothiazolidine*-4-*carboxylate* was obtained from the corresponding acid (Cook and Cox [5a]) by reaction with diazomethane in ether, as needles (from methyl alcohol), m. p. 107—108° (Found: C, 53·7; H, 4·8; N, 5·5%), $\lambda_{max.}$ (in EtOH) 276 mμ (ε 16,400), or by the action of refluxing methyl alcohol in the presence of a little sulphuric acid.

trans-3-*Methyl*-5-*phenyl*-2-*thiothiazolidine*-4-*carboxyamide*.—4-Benzylidene-3-methyl-2-thiothiazolidin-5-one (2·0 g.) and ammonia (*d* 0·88; 7 ml.) were heated on a steam-bath for 2 hr. To the yellow oil that was formed methyl alcohol was added. On cooling, the required amide separated (1·5 g). It was obtained as needles, m. p. 131—132°, from methanol (cf. Siddappa [5b]) (Found: C, 52·5; H, 4·3; N, 11·3%), $\lambda_{max.}$ (in EtOH) 277 mμ (ε 17,000.) The amide was also obtained by heating a solution of the methyl ester (1·0 g.) described above in methyl alcohol (15 ml.) with ammonia (*d* 0·88; 6 ml.) for several hours.

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