1 *N* aq $KHCO_3$ was added 17 g (0.16 mole) of ethyl chloroformate with vigorous stirring. When CO_2 evolution subsided the organic phase was washed with H_2O, dried ($MgSO_4$), and evapd to an oil. Vacuum distillation provided 14.5 g of pure **31**: bp 107–110° (0.1 mm); ir (film) 5.8 μ; nmr δ 5.2 (s, 2 H).

5(6*H*)-Phenanthridinecarboxylic Acid, Ethyl Ester (34).—A solution of 9.1 g (50 mmoles) of 5,6-dihydrophenanthridine (prepared according to the method of Wooten and McKee[5]) was treated with ethyl chloroformate as in the preceding experimental procedure. Pure **34** was obtained as a colorless liquid: bp 158–159° (10 μ); ir (film) 5.8 μ; nmr δ 4.8 (s, 2 H).

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Notes

Synthesis and Activity of Some 1,2,4-Triazolylthiazolidones

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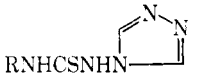
Thiazolidine derivatives exhibit sedative,[1] anesthetic,[2] anticonvulsant,[3] antituberculous,[4] amebicidal,[5] and fungicidal[6] activity. Previous publications from this laboratory[7–12] have shown that some derivatives of 5-carboxymethylthiazolidine-2,4-dione inhibit viral growth.

In continuing these investigations some new thiazolidine derivatives have been synthesized. 1,2,4-Triazolylthioureas (**1**) (Table I), obtained by condensing 4-amino-1,2,4(4*H*)-triazole with several isothiocyanates, were cyclized with maleic anhydride to the corresponding thiazolidin-4-ones (**2**) (Table II).

The 1,2,4-triazolylthioureas were also condensed with 1,2-dibromoethane to afford the corresponding thiazolidines (**3**). It can be envisaged that the reaction could take place to give two different monocyclic products, *i.e.*, **3a** or **3b**, or even a bicyclic product. To ascertain the structure of the products, some of these were hydrolyzed with HCl at 200°. The expected primary cleavage products would be **4a** and $PhNH_3^+Cl^-$ from **3a**, or 4-amino-1,2,4-triazole·HCl and **4b** from **3b**. From the hydrolysates of **3a** (R = C_6H_5) $PhNH_3^+Cl^-$ and an unidentified product were isolated. Similarly, when 2-phenylimino-3-phenylthiazolidine, as a model compound, was hydrolyzed under the same conditions, 3-phenylthiazolidin-2-one and $PhNH_3^+Cl^-$ were identi-

TABLE I



No.	R	Reaction time, hr	Mp, °C	Yield, %	Formula[a]
1	*p*-$C_2H_5OC_6H_4$	0.5	164	38	$C_{11}H_{13}N_5OS$
2	*p*-ClC_6H_4	0.5	176	70	$C_9H_5ClN_5S$
3	n-C_4H_9	2.0	134	6	$C_7H_{13}N_5S$
4	2,6-$Me_2C_6H_3$	6.0	168–170	8	$C_{11}H_{13}N_5S$
5	2,4-$Me_2C_6H_3$	1.0	182–184	57	$C_{11}H_{13}N_5S$
6	*o*-$CH_3OC_6H_4$	1.0	152–154	26	$C_{10}H_{11}N_5OS$
7	*p*-$CH_3OC_6H_4$	0.5	172–174	45	$C_{10}H_{11}N_5OS$

[a] All compds had analyses for C,H,N, and S within 0.4% of the theoretical values.

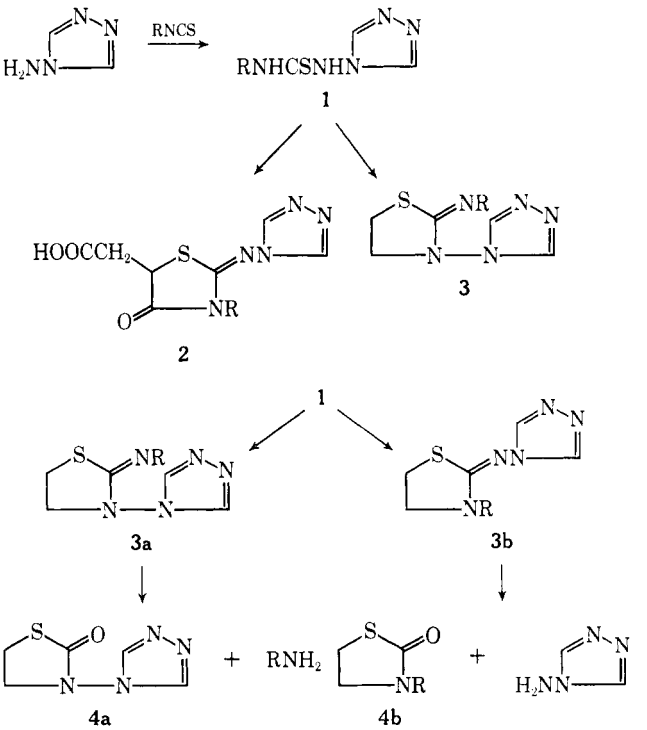


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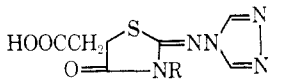
TABLE II



No.	R	Reaction time, hr	Mp, °C	Yield, %	Formula[a]
1	p-$C_2H_5OC_6H_4$	15	263–265	17	$C_{15}H_{15}N_5O_3S$
2	p-ClC_6H_4	10	260–263	20	$C_{13}H_{10}ClN_5O_3S$
3	2,4-$Me_2C_6H_3$	17	262–264	4	$C_{15}H_{15}N_5O_3S$
4	o-$CH_3OC_6H_4$	10	239–241	2	$C_{14}H_{13}N_5O_4S$

[a] See Table I, footnote *a*.

fied as degradation products. These results favor structure **3a** and such hydrolytic cleavages are known to have synthetic importance for the synthesis of thiazolidinediones.[13]

The antiviral activity was tested with Herpes simplex virus as described earlier.[14] At 3.10^{-3}–5.10^{-4} M the test compounds were found to be either toxic or inactive (**2**, R = C_6H_5; and **3**, R = p-$C_2H_5OC_6H_4$).

Experimental Section[15]

1-(1,2,4-Triazolyl-4)-3-phenylthiourea (1, R = C_6H_5).—A mixture of 4-amino-1,2,4(4*H*)-triazole[16] (8.4 g, 0.1 mole), phenyl isothiocyanate (13.5 g, 0.1 mole), and EtOH (30 ml) was heated on a water bath for 15 min. The product which sepd upon cooling was collected, washed with EtOH, and recrystd from the same solvent: yield 15.0 g (68%); mp 175° (lit.[17] mp 105°). *Anal.* ($C_9H_9N_5S$), C, H, N.

By the same procedure other substituted triazolylthioureas were obtained (Table I). In all cases EtOH was used as solvent for recrystn. If the product did not sep or if only a little of the product sepd, the solvent was evapd *in vacuo* to dryness and the residue was then purified by crystn.

2-[(1,2,4-Triazolyl-4)imino]-3-phenyl-5-carboxymethylthiazolidin-4-one (2, R = C_6H_5).—A mixture of **1** (R = C_6H_5; 4.38 g, 0.02 mole), finely powdered maleic anhydride (1.96 g, 0.02 mole), anhyd C_6H_6 (50 ml), and anhyd Me_2CO (50 ml) was heated under reflux on a water bath for 24 hr. Some Me_2CO was added and the mixture heated to boiling to give an almost clear soln. Upon filtration the filtrate was evapd to dryness *in vacuo* and the residue recrystd from Me_2CO to give 0.45 g (7%) of the pure compound, mp 251–253°. *Anal.* ($C_{13}H_{11}N_5O_3S$), C, H, N, S.

In practically the same way other 3-substituted derivatives (**2**) were prepd (Table II). All compds were purified by recrystn from EtOH.

2-Phenylimino-3-(1,2,4-triazol-4-yl)thiazolidine (3, R = C_6H_5).—To a soln of **1** (R = C_6H_5; 2.19 g, 0.01 mole) in DMF (10 ml) anhyd K_2CO_3 (1.39 g, 0.01 mole) and 1,2-dibromoethane (1.88 g, 0.01 mole) were added and the reaction mixture was stirred at room temp for 13 hr. The product was filtered off and recrystd from EtOH: yield 0.6 g (24%); mp 190–192°. *Anal.* ($C_{11}H_{11}N_5S$), C, H, N. The same compound could be obtained in 49% yield if instead of K_2CO_3 20 ml of DMF was used altogether.

In an analogous way the following 3-(1,2,4-triazol-4-yl)-thiazolidines were synthesized and crystd from EtOH.

2-(p-Chlorophenylimino) (**3**, R = p-ClC_6H_4) was obtained in 6% yield, mp 223–225°. *Anal.* ($C_{11}H_{10}ClN_5S$), C, H, N, S.

2-(p-Ethoxyphenylimino) (**3**, R = p-$C_2H_5OC_6H_4$) was obtained in 9% yield, mp 198–200°. *Anal.* ($C_{13}H_{15}N_5OS$), C, H, N, S.

2(p-Methoxyphenylimino) (**3**, R = p-$CH_3OC_6H_4$) was obtained in 6% yield, mp 231–233°. *Anal.* ($C_{12}H_{13}N_5OS$), C, H, N.

Hydrolysis of 2-Phenylimino-3(1,2,4-triazol-4-yl)thiazolidine.—Compd **3** (R = C_6H_5; 0.5 g) was heated with 10 ml of HCl (1:2) at 200° in a sealed tube for 1 hr. After evapn *in vacuo* to dryness the residue was sublimed *in vacuo* and afforded a colorless compd, mp 196°, which by mmp and ir spectra was identified with an authentic specimen of $PhNH_3^+Cl^-$.

Hydrolysis of 2-phenylimino-3-phenylthiazolidine[18] was done in essentially the same manner and upon evaporating the reaction mixture *in vacuo* the known 3-phenylthiazolidin-2-one[18] was isolated.

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cis-1-[(2-Piperidinocyclohexyl)carbonyl]-piperidine and Related Compounds. Oral Hypoglycemic Agents

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Screening for antidiabetic agents revealed that *cis*-1-[(2-piperidinocyclohexyl)carbonyl]piperidine hydrochloride (**7a**, Table I), possessed good hypoglycemic activity in the glucose-primed, fasted, intact rat. This compound is a representative of a class of compounds not previously associated with hypoglycemic activity. As a result, a study aimed at obtaining insight into the various structural features necessary for hypoglycemic activity in this class of compounds was made.

Chemistry—Compounds **1**—**17** were prepared according to the synthetic sequence outlined in Scheme I. The desired synthetic intermediates (I) were obtained by refluxing a mixture of equiv amounts of the appropriate mixture of Et and Me 2-oxocycloalkanonecarboxylate and secondary amine for 17.5 hr–14 days. Treatment of these keto amides with primary or secondary amines in benzene, according to the method of Stork and coworkers,[1] afforded the enamines which were hydrogenated (PtO_2) to afford compounds II.

Compounds **18** and **19** were prepared according to the sequence outlined in Scheme II. Treatment of 1-(1-cyclohexen-1-yl)piperidine with phenyl and cyclohexyl isocyanate, according to the method of Hunig and coworkers,[2] afforded the enamine intermediates which were catalytically reduced to compounds II (NR_3R_4 = piperidino).

Biological Testing.—Glucose-primed, fasted (18–24 hr), Upjohn Sprague–Dawley, pathogen-free, male rats were the test animals. The test compound was administered orally at various dosages in 0.5 ml of sterile vehicle (6 rats/group). Immediately following admin-

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