DERIVATIVES OF 3-DIPHENYLACETAMIDO-THIAZOLIDIN-4-ONE

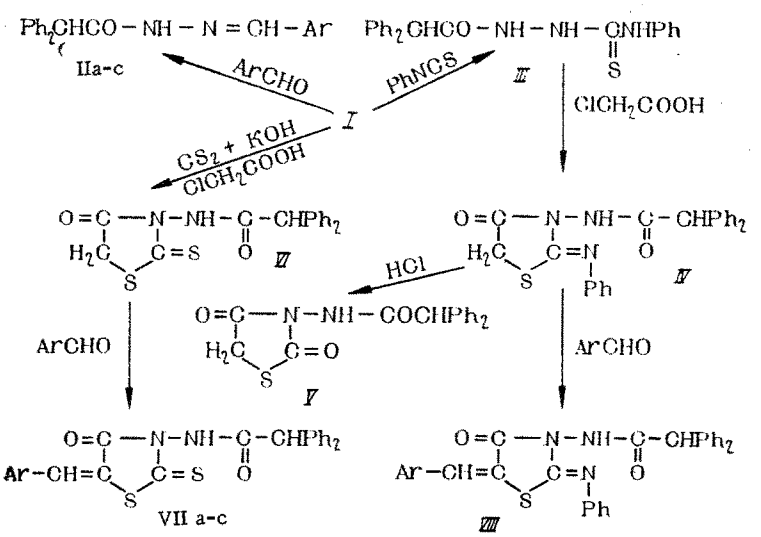
S. A. Yurzhenko

UDC 615.245.3-011.24

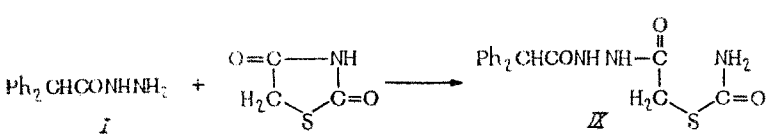
Derivatives of hydrazine, particularly hydrazides, have recently become important in modern chemotherapy [1]. However, hydrazides in the thiazolidine series have been little investigated, expecially their chemical behavior. They are certainly interesting, since the presence of a thiazolidine ring in the molecule generally leads to a decrease in toxicity. Our aim was to synthesize a series of thiazolidin-4-one derivatives containing a residue of N-diphenyl-acetylhydrazide as part of the molecule [2].

We took advantage of the ability of the primary amino group of N-diphenylacetylhydrazide (I) to undergo reactions of electrophilic substitution by which hydrazones with the corresponding aromatic aldehydes (IIa, IIb) could be formed, and so we introduced I into the reaction with phenylisothiocyanate and also with carbon disulfide in a basic medium [3]. N-Phenyl-N'-diphenylacetamido-thiourea (III) was formed and on reaction with monochloroacetic acid [4] was converted into N-(2-phenylimino-4-oxothiazolidinyl-3)-diphenylacetamide (IV). The structure of IV was confirmed by acid hydrolysis through the formation of N-(2,4-dioxothiazolidinyl-3)-diphenyl-acetamide (V). The potassium dithiocarbamate obtained in the second case was further condensed with a neutralized solution of monochloroacetic acid to give N-(2-thioxo-4-oxothiazolidinyl-3)-diphenylacetamide (VI).

Compounds IV and VI readily condense with aromatic aldehydes to yield corresponding 5-benzylidene derivatives of thiazolidin-4-one (VIIa-VIIc and VIII):



The basic properties of I also manifest themselves, although rather weakly, when the latter compound is reacted, analogously to hydrazine hydrate, with thiazolidine-2,4-dione. The thiazolidine ring is cleaved at its 3-4 bond and N-diphenyl-N'-(S-carbamyl-thioglycolyl)-hydrazine (IX) is formed:



L'vov Medical Institute. Translated from Khimiko-Farmatsevticheskii Zhurnal, No. 12, pp. 12-15, December, 1968. Original article submitted January 30, 1968.

TABLE 1. Derivatives of Diphenylacetylhydrazide and 3-diphenylacetamido-thiazolidin-4-one

Compound	Melting point (°C)	Ar	Found (%)		Empirical formula	Calculated		Yield (%)
			N	S		N	S	
IIa	210—1	*n*-$NO_2C_6H_4$[1]	11,81	—	$C_{31}H_{17}N_3O_3$	11,69	—	66,8
IIb	237—9	*n*-BrC_6H_4[2]	7,25	—	$C_{21}H_{17}Br_1N_2O_1$	7,27	—	71,8
IIc	205—6	*n*-$(CH_3)_2NC_6H_4$[3]	11,85	—	$C_{23}H_{23}N_3O_1$	11,76	—	73,8
III	176—7	—	11,85	8,96	$C_{21}H_{19}N_3O_1S_1$	11,63	8,87	65,4
IV	138—40	—	10,28	8,14	$C_{23}H_{19}N_3O_2S_1$	10,47	7,99	56,7
V	106—7	—	8,76	9,79	$C_{17}H_{14}N_2O_3S_1$	8,59	9,82	54,0
VI	175—6	—	8,29	18,78	$C_{17}H_{14}N_2O_2S_2$	8,18	18,73	63,7
VIIa	231—2 (dec.)	*n*-$NO_2C_6H_4$	9,02	13,54	$C_{24}H_{17}N_3O_4S_2$	8,84	13,49	66,3
VIIb	211—2 (dec.)	*n*-BrC_6H_4[4]	5,72	—	$C_{24}H_{17}Br_1N_3O_2S_2$	5,50	—	81,0
VIIc	252—3 (dec.)	*n*-$(CH_3)_2NC_6H_4$	8,62	13,58	$C_{26}H_{23}N_3O_2S_2$	8,87	13,54	65,4
VIII	265—6 (dec.)	*n*-$NO_2C_6H_4$	10,61	6,04	$C_{30}H_{22}N_4O_4S_1$	10,48	6,00	63,6
IX	282—5 (dec.)	—	11,98	9,10	$C_{17}H_{17}N_3O_3S_1$	12,24	9,34	67,3

[1]Found (%): C 70.02; H 4.95. Calculated (%): C 70.18; H 4.77.
[2]Found (%): C 63.97; H 4.41. Calculated (%): C 64.15; H 4.36.
[3]Found (%): C 77.43; H 6.61. Calculated (%): C 77.28; H 6.49.
[4]Found (%): Br 12.64, Calculated (%): Br 12.59.

EXPERIMENTAL

Diphenylacetylhydrazide (I). Hydrazine hydrate (15 ml) was added to a solution of 22.6 g of ethyl diphenylacetate in 50 ml of ethanol, and the mixture was boiled for 3 h. The solution was filtered, and the filtrate poured into water. The yield was 21.9 g of a white, fine-crystalline power, mp 140-142° (from 60% methanol).

p-Nitrobenzaldehyde N-Diphenylacetylhydrazone (IIa). A mixture of 0.68 g (0.003 mole) of I, 0.58 g (0.005 mole) of anhydrous sodium acetate, 0.75 g (0.0045 mole) of p-nitrobenzaldehyde, and 10 ml of glacial acetic acid was boiled for half an hour. Light-yellow crystals separated out even from the hot solution. The precipitate was filtered and washed with a small amount of acetic acid and ether. The product was IIa; IIb and IIc were obtained analogously (see Table 1).

N-Phenyl-N'-diphenylacetamido-thiourea (III). Phenylisothiocyanate (8.1 g, 0.06 mole) was added to a solution of 11.3 g (0.05 mole) of I in 30 ml of ethanol. The mixture was heated for 5-10 min, and a bulky white precipitate separated out. This was filtered and washed with alcohol and ether. The yield was 12.1 g of III (see Table 1).

N-(2-Phenylimino-4-oxothiazolidinyl-3)-diphenylacetamide (IV). Monochloroacetic acid (4.72 g, 0.005 mole) and 4.1 g of anhydrous sodium acetate were added to a solution of 10.83 g (0.003 mole) of III in 45 ml of glacial acetic acid. The mixture was boiled for 4 h, and then filtered. The filtrate was cooled and poured into water. The white, amorphous precipitate was filtered, washed with water, and dried in the air. The yield was 6.81 g of IV (from a mixture of acetic acid and water) (see Table 1).

N-(2,4-dioxothiazolidinyl-3)-diphenylacetamide (V). Concentrated hydrochloric acid (10 ml) was added to a solution of 1.2 g of IV in 10 ml of ethanol. The mixture was boiled for 1 h, mixed with activated charcoal, and filtered. The filtrate was well cooled and poured into water. The white amorphous precipitate was washed with water. The yield was 0.54 g of V, which was recrystallized from dilute alcohol (see Table 1).

N-(2-Thioxo-4-oxothiazolidinyl-3)-diphenylacetamide (VI). Compound I (11.3 g) was added to a mixture of 5.6 g of potassium hydroxide, 4.56 g of carbon disulfide, and 30 ml of water. The resulting mixture was stirred for 1 h at room temperature. A solution of 4.7 g (0.05 mole) of monochloroacetic acid in 10 ml of water was neutralized with 3.5 g (0.025 mole) of potassium carbonate and added to the above mixture, which was then left to stand for 1 h. The solution was neutralized with concentrated hydrochloric acid using litmus as indicator, and another 20 ml of boiling hydrochloric acid was introduced. The mixture was then heated for 20-30 min at 90°. An oily substance separated out from the solution and eventually solidified. The product was isolated and recrystallized from dilute alcohol. The yield was 0.9 g of VI, obtained as a light-yellow powder (see Table 1).

N-(5-p-Nitrobenzylidene-2-thioxo-4-oxothiazolidinyl-3)-diphenylacetamide (VIIa). A mixture of 0.68 g (0.002 mole) of VI, 0.5 g (0.003 mole) of p-nitrobenzaldehyde, and 10 ml of acetic acid was refluxed for 1 h. The mixture was cooled and the precipitate filtered. The yield was 0.63 g of VIIa, which was recrystallized from acetic acid. Compounds VIIb, VIIc, and VIII were obtained analogously (see Table 1).

N-Diphenylacetyl-N'(S-carbamylthioglycolyl)-hydrazine (IX). Thiazolidine-2,4-dione (1.5 g) was added to a solution of 2.26 g of I in 15 ml of water. The mixture was boiled for 50 h. The solution was mixed with activated charcoal and filtered. The filtrate was cooled and poured into water. The precipitate that separated out after some time was washed with water, dried, and crystallized from butanol. The yield was 2.3 of IX (see Table 1).

LITERATURE CITED

1. N. A. Preobrazhenskii and E. I. Genkin, Chemistry of Organic Medicinal Compounds [in Russian], Moscow (1953).
2. P. Stolle and Fr. Schmidt, Ber., 45, 3116 (1912).
3. P. Andreach, Mh Chem., 27, 1211 (1906).
4. N. M. Turkevich, V. M. Vvedenskii, and L. I. Petlichnaya, Zh. Obshch. Khim. 27, 680 (1961).