SYNTHESIS OF RHODANINE DERIVATIVES OF POTENTIAL ANTIMETABOLITE ACTIVITY

VI. 3-(α, γ-Dicarboxypropyl)Rhodanine and its 5-Arylidene Derivatives*

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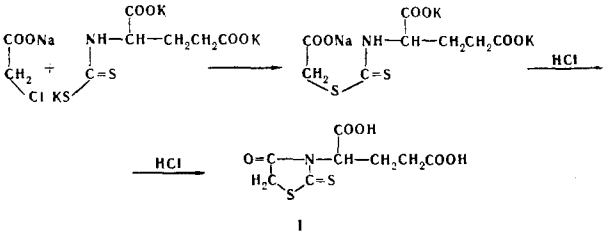
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 3, No. 4, pp. 657–660, 1967

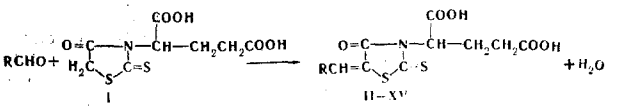
UDC 547.78:542.953.3:543.420.62

Condensation of monochloroacetic acid with the dithio-carbaminate, prepared by reacting carbon disulfide with an alkaline solution of glutaminic acid and then treating the condensation product with hydrochloric acid, gives 3-(α, γ-dicarboxypropyl)rhodanine. Its reaction with aromatic aldehydes in glacial acetic acid gives the 5-arylidene derivatives. The electronic absorption spectra of the compounds are characterized by high-intensity maxima in the 360–473 nm region.

Previous papers [1–5] described a synthesis of rhodanine derivatives based on β-alanine, whose grouping occurs in the structure of one of the vitamins, pantothenic acid. A study has been made of 3-β-carboxyethylrhodanine, its condensation products with some oxo compounds, and of electronic absorption spectra. To extend the work to a study of rhodanine derivatives of potential antimetabolite activity with respect to vitamins, we set out to synthesize 3-(α-γ-dicarboxypropyl)rhodanine, starting from glutaminic acid, whose grouping is known to be present in the molecules of folic acid and contergan, the latter being responsible, in Western countries, for the extensive phenomenon of phocomelia. Reaction of glutaminic acid with carbon disulfide in alkaline solution gave the tripotassium salt of N-(α,γ-dicarboxypropyl) dithiocarbaminic acid, which without being isolated, was condensed with sodium monochloroacetate, and the resultant salt of N-α,γ-dicarboxypropyl-S-thiocarbaminylthioglycolic acid cyclized by heating with hydrochloric acid, the equations being



It is to be noted that it takes about a month to carry out the cyclization and subsequent isolation. The 3-(α,γ-dicarboxypropyl)rhodanine (I) obtained is a colorless crystalline compound mp 98°–99°. Compound I condenses comparatively easily with aromatic aldehydes when refluxed with them in glacial acetic acid in the presence of fused sodium acetate (Table 2).



Owing to the presence of two carboxyl groups, compounds I–XV are readily soluble in saturated $NaHCO_3$ solution, ammonia (1:1), and in 10% Na_2CO_3 and NaOH. In alkaline solution compound I readily hydrolyzes to thioglycolic acid (positive nitroprusside reaction). Substituents at position 5 considerably strengthen the thiazolidine ring, since 5-arylidene derivatives do not give a positive nitroprusside reaction.

The electronic absorption spectrum of 3-(α,γ-dicarboxypropyl)rhodanine consists of 4 bands, and differs only slightly from that of 3-β-carboxyethylrhodanine. Only the maximum of the second band, due the chromophores —CO—NH— and —CS—S—, is displaced bathochromically by 4 nm compared with the same maximum for 3-β-carboxyethylrhodanine, and the intensity of the absorption of a 4th band is reduced [2]. Introduction of arylidene groups of position 5 of molecule I often displaces the maximum of the first band bathochromically, so that a maximum that is absent from the absorption plot of the starting compound appears at 229–240 nm. Simultaneously, due to the presence of a long conjugated chain, there is a high-intensity maximum at 360–473 nm, due to superposition of the K bond maximum on the corresponding maximum of the 4th band of starting compound I.

EXPERIMENTAL

3-(α, γ-Dicarboxypropyl)rhodanine (I). A solution of 50.49 g (0.9 mole) KOH in 45 ml water was added to a solution of 44.1 g (0.3 mole) glutaminic acid in 150 ml water, followed by 22.8 CS_2, and the mixture stirred for 6 hr until a homogeneous phase formed. Then a solution of 28.35 g (0.3 mole) monochloracetic acid in 60 ml water, neutralized with 15.9 g (0.15 mole) anhydrous Na_2CO_3, was added. The mixture was shaken for 30 min, left for 15 min, neutralized with HCl, and 180 ml 6 N HCl added, then heated to boiling, kept on a water bath for 2 hr, and then left to stand. Only after standing for a month did the mixture crystallize, giving a mass of minute crystals which were filtered off and washed with water. Yield 53.3 g almost colorless crystalline compound I, mp 98–99°.

5-Arylidene-3-(α, γ-dicarboxypropyl)rhodanine (II–XV). 5 mm compound I, 5 mm aldehyde, 1.5 g fused NaOAc, and 10 ml glacial AcOH were refluxed together for 2 hr, cooled, and diluted with 50 ml water. Compounds IV, XI, XII, XIII gradually separated in the form of a finely-divided powder, and the rest of the condensation products as oils crystallizing only after several days. The reaction products were filtered off and crystallized from glacial AcOH.

*For part V see [5]

Table 1

5-Arylidene-3(α,γ-dicarboxypropyl)Rhodanines

Compound	R in formulas II–XV	Color	Mp, °C	Formula	Found, %			Calculated, %			Yield, %
					C	H	N	C	H	N	
I	R—CH=H_2	Pale cream	98—99	$C_8H_9NO_5S_2$	36.67	3.50	5.41	36.49	3.44	5.32	67.5
II	C_6H_5	Lemon yellow	207	$C_{15}H_{13}NO_5S_2$	51.42	3.80	4.10	51.27	3.73	3.99	68.9
III	o-$O_2NC_6H_4$	Brown	212—213	$C_{15}H_{12}N_2O_7S_2$	45.35	3.10	7.17	45.45	3.05	7.07	94.0
IV	m-$O_2NC_6H_4$	Lemon Yellow	228—229	$C_{15}H_{12}N_2O_7S_2$	45.60	3.15	7.20	45.45	3.05	7.07	95.9
V	p-$O_2NC_6H_4$	Orange	198—200	$C_{15}H_{12}N_2O_7S_2$	45.39	3.13	7.01	45.45	3.05	7.07	84.3
VI	p-ClC_6H_4	Pale yellow	220—221	$C_{15}H_{12}ClNO_5S_2$	46.80	3.20	3.87	46.69	3.13	3.63	92.8
VII	p-BrC_6H_4	Pale yellow	217—218	$C_{15}H_{12}BrNO_5S_2$	41.95	2.90	3.39	41.87	2.81	3.25	93.9
VIII	p-$(CH_3)_2NC_6H_4$	Bordeaux red	225	$C_{17}H_{18}N_2O_5S_2$	51.60	4.52	7.05	51.76	4.60	7.10	74.0
IX	p-$(C_2H_5)_2NC_6H_4$	Bordeaux red	201—202	$C_{19}H_{22}N_2O_5S_2$	54.10	5.30	6.75	54.01	5.25	6.63	85.2
X	C_6H_5CH=CH	Yellowish green	173—174	$C_{17}H_{15}NO_5S_2$	54.20	4.10	3.59	54.09	4.01	3.71	84.3
XI	3-CH_3O-4-HOC_6H_3	Yellow	241—242	$C_{16}H_{15}NO_7S_2$	48.48	3.90	3.56	48.35	3.80	3.52	68.4
XII	3,4-$(CH_3O)_2C_6H_3$	Yellow	130—132	$C_{17}H_{17}NO_7S_2$	49.75	4.10	3.52	49.62	4.16	3.40	84.1
XIII	3,4-$CH_2O_2C_6H_3$	Yellow	204—205	$C_{16}H_{13}NO_6S_2$	48.55	3.37	3.60	48.60	3.31	3.54	78.9
XIV	α-$C_{10}H_7$	Dark green	171—173	$C_{19}H_{15}NO_5S_2$	56.90	3.75	3.60	56.84	3.77	3.49	82.5
XV	9′-$C_{14}H_9$	Orange	196—197	$C_{23}H_{17}NO_5S_2$	61.30	3.85	3.20	61.18	3.79	3.10	87.4

Table 2

UV Spectra of 3-(α,γ-Dicarboxypropyl)Rhodanine and its 5-Arylidene Derivatives

Compound	1st band		2nd band		3rd band		4th band	
	λ_{max}, nm	lge	λ_{max}, nm	lge	λ_{max}, nm	lge	λ_{max}, nm	lge
I	<220	—	265	3.93	295.5	4.03	379	1.65
II	236.5	4.00	273	4.44	Hump	3.8	376	4.57
III	228	4.05	267	3.90	—	—	360	4.30
IV	236	4.11	267	4.06	—	—	372	4.43
V	229	3.92	278.5	3.98	—	—	380.5	4.48
VI	237	3.98	277	4.02	—	—	381	4.54
VII	240	3.99	278	4.06	—	—	381	4.57
VIII	229.5	3.97	253	3.96	318	4.15	464	4.69
IX	229.5	3.92	256	3.89	321	4.12	473	4.71
X	<220	—	244	4.09	297	4.20	401	4.67
XI	<220	—	264.5	3.93	292.5	4.05	406	4.52
XII	<220	—	262	3.95	292	3.96	406	4.52
XIII	<220	—	261	3.95	293	3.92	401.5	4.50
XIV	<220	—	269	3.93	306.5	3.98	390.5	4.32
					330 Hump	4.0		
XV	<220	—	253	3.95	338	3.18	415.5	2.82

The electronic absorption spectra were measured with a SF-4 spectrophotometer. The compounds measured were dissolved in MeOH, 1 mg in 100 ml twice-distilled solvent.

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21 December 1965

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