

SYNTHESIS OF RHODANINE DERIVATIVES WITH POTENTIAL ANTIMETABOLITE ACTIVITY

V. Esters of 3- β -Carboxyethylrhodanine and Their Derivatives

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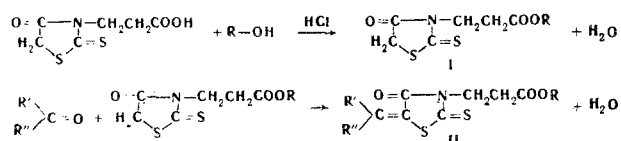
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Esterification of 3- β -carboxyethylrhodanine gives methyl, ethyl, n-propyl, n-butyl, isoamyl, and benzyl esters, liquids which vacuum-distill undecomposed. Higher atomic refractions for sulfur in these esters indicate a considerable shift of electrons from position 1. Condensation of these esters with isatin, benzaldehyde, and two derivatives of the latter gives 5-substituted derivatives with characteristic high-intensity absorption maxima in the 375-470 m μ region.

β -Alanine occupies a special place among naturally-occurring amino acids, and it enters into the compositions of the specific naturally-occurring dipeptides carnosine and anserine, and pantothenic acid. Though up to the present β -alanine metabolism has been insufficiently studied, undoubted interest attaches to synthesis and investigation of some of its complex derivatives, as they may include a compound of potential antimetabolite activity.

A previous paper [1] describes 3- β -carboxyethylrhodanine, prepared from β -alanine, as well as various 5-substitution derivatives. The compounds synthesized were found to include some of marked antitubercular activity.

The present work aimed to prepare esters of 3-carboxyethylrhodanine, to investigate their reactions with carbonyl compounds, as well as the UV spectra of the compounds synthesized. 3- β -Carboxyethylrhodanine was refluxed with various alcohols, while saturated with hydrogen chloride gas, and the resultant methyl, ethyl, n-propyl, n-butyl, isoamyl, and benzyl esters purified by vacuum-distillation. The esters were condensed with benzaldehyde, as well as with the p-nitro- and p-dimethylamino derivatives of the latter, and with isatin, in glacial acetic acid.



The esters I prepared were pale yellow liquids, which distilled undecomposed at $6 \cdot 10^{-3}$ to $2 \cdot 10^{-2}$ mm (Table 1), and which were readily soluble in the ordinary organic solvents. They were readily hydrolyzed, as shown by the good solubilities of four low molecular esters in dilute NaOH.

Determinations of the molecular refractions of the esters of 3-carboxyethylrhodanine gave interesting results. The average calculated atomic refraction for two sulfur atoms present in a molecule of the compounds under investigation, was 19.17 i. e. after deducting the refraction for thioketone sulfur (9.70), at po-

sition 2, a value of 9.47 remains for the S atom at position 1. This value is considerably above the atomic refraction for thioester sulfur, given by literature data [2]. Enhanced sulfur atomic refractions (10.5-12.6) have also been found [3] in thiazanone rings, resulting in its losing thioester character (atomic refraction 9.70).

The electronic absorption spectra of esters I consist of four bands and in respect to positions of maxima, differ but little from the spectrum of the starting 3- β -carboxyethylrhodanine (Table 3). Only the benzyl ester differs, by considerable decrease in intensities of the first two maxima (258 and 195 m μ) and increase in intensity of the third maximum (375-378 m μ).

The 5-arylidene and 5-2'-oxoindolylidene-3 derivatives (II) are crystalline compounds exhibiting different shades of yellow and red (Table 2). They are readily soluble in the usual organic solvents. Solutions of the p-nitrobenzylidene and 2'-oxoindolylidene-3 derivatives in dilute NaOH are orange or lemon colored. Introduction of substituents at position 5 in I stabilizes the thiazolidine ring, as confirmed by such substituted compounds not giving a positive nitroprusside reaction in alkaline solution.

As a rule benzylidene, p-nitrobenzylidene, and p-dimethylaminobenzylidene substituents bring about a large bathochromic displacement of the first maximum down to 23.5 m μ , compared with esters of 3- β -carboxyethylrhodanine not substituted at position 5. The first two of the above substituents also effect bathochromic displacement of the 2nd band's maximum to 273-280 m μ , while p-dimethylaminobenzylidene and 2'-oxoindolylidene-3' substituents displace this maximum hypsochromically to 252.5-257 m μ . This maximum indicates the presence of a thiomide group in thiazolid-4-one compounds [4].

Benzylidene and 2'-oxoindolylidene-3' substituents leave the positions of the maxima in the third band (290-297 m μ) almost unchanged, but lower their intensities. We regard this maximum as due to superposition of the dithiocarbonate—S—C=S and CONH₂ chromophores. The p-nitrobenzylidene group converts these maxima to inflections.

The p-dimethylaminobenzylidene group causes a large bathochromic shift of the third and fourth absorption bands, since quinonoid groups can arise.

The most characteristic sign of introduction of an arylidene group at position 5 is a very strong increase in intensities of maxima in the fourth band at

Table 1. Esters of 3-β-Carboxyethylrhodanine

Experimental number	R	Bp, °C (mm pressure)	n _D ²⁰	d ₄ ²⁰	MRD		Formula	Found, %			Calculated, %			Yield, %
					Found	Calculated		C	H	N	C	H	N	
1	CH ₃	117-119 (2·10 ⁻³)	1.6014	1.3844	54.51	54.81	C ₇ H ₉ NO ₃ S ₂	38.31	4.20	6.45	38.34	4.14	6.39	91.8
2	C ₂ H ₅	108-110 (7·10 ⁻³)	1.5874	1.3197	59.45	59.43	C ₈ H ₁₁ NO ₃ S ₂	41.30	4.77	6.02	41.18	4.75	6.00	85.6
3	n-C ₄ H ₇	106 (6·10 ⁻³)	1.5750	1.2778	63.96	64.05	C ₉ H ₁₃ NO ₃ S ₂	43.65	5.30	5.70	43.70	5.30	5.66	94.8
4	n-C ₆ H ₁₁	109-110 (6·10 ⁻³)	1.5648	1.2418	68.53	68.67	C ₁₀ H ₁₅ NO ₃ S ₂	45.97	5.85	5.31	45.95	5.78	5.36	95.2
5	iso-C ₆ H ₁₁	111-114 (7·10 ⁻³)	1.5573	1.2109	73.25	73.29	C ₁₁ H ₁₇ NO ₃ S ₂	47.89	6.20	5.05	47.97	6.22	5.09	94.6
6	C ₆ H ₅ CH ₂	148-152 (8·10 ⁻³)	1.6013	1.2737	79.47	78.92	C ₁₃ H ₁₅ NO ₃ S ₂	52.76	4.50	4.71	52.86	4.44	4.74	92.3

Table 2. Derivatives of Esters of 3-β-carboxyethylrhodanine

Experimental number	R'	R	Mp, °C	Formula	Found, %			Calculated, %			Yield, %
					C	H	N	C	H	N	
1	C ₆ H ₅ CH	CH ₃	112-113	C ₁₄ H ₁₃ NO ₃ S ₂	54.58	4.23	4.50	54.70	4.26	4.56	96.4
2	"	C ₂ H ₅	83	C ₁₅ H ₁₅ NO ₃ S ₂	55.95	4.76	4.40	56.05	4.70	4.36	91.6
3	"	n-C ₄ H ₇	74-75	C ₁₆ H ₁₇ NO ₃ S ₂	57.19	5.05	4.25	57.29	5.11	4.18	92.4
4	"	n-C ₄ H ₉	64	C ₁₇ H ₁₉ NO ₃ S ₂	58.35	5.45	4.08	58.42	5.48	4.01	94.0
5	"	iso-C ₆ H ₁₁	69	C ₁₈ H ₂₁ NO ₃ S ₂	59.60	5.80	3.90	59.47	5.82	3.85	85.4
6	"	C ₆ H ₅ CH ₂	79-81	C ₂₀ H ₁₉ NO ₃ S ₂	62.58	4.50	3.69	62.64	4.47	3.65	78.3
7	p-O ₂ NC ₆ H ₄ CH	CH ₃	155-156	C ₁₄ H ₁₂ N ₂ O ₅ S ₂	47.65	3.50	7.99	47.71	3.43	7.95	96.5
8	"	C ₂ H ₅	128-130	C ₁₅ H ₁₄ N ₂ O ₅ S ₂	49.21	3.91	7.71	49.17	3.85	7.65	95.6
9	"	n-C ₃ H ₇	121-122	C ₁₆ H ₁₆ N ₂ O ₅ S ₂	50.46	4.22	7.41	50.51	4.24	7.36	91.9
10	"	n-C ₄ H ₉	119	C ₁₇ H ₁₈ N ₂ O ₅ S ₂	51.70	4.63	7.18	51.76	4.60	7.10	90.5
11	"	iso-C ₆ H ₁₁	127-128	C ₁₈ H ₂₀ N ₂ O ₅ S ₂	52.99	4.95	6.90	52.92	4.93	6.86	89.7
12	"	C ₆ H ₅ CH ₂	96-97	C ₂₀ H ₁₈ N ₂ O ₅ S ₂	56.00	3.80	6.57	56.06	3.76	6.54	94.4
13	p-(CH ₃) ₂ NC ₆ H ₄ CH	CH ₃	169-170	C ₁₆ H ₁₄ N ₂ O ₅ S ₂	54.92	5.22	8.05	54.83	5.18	7.99	66.3
14	"	C ₂ H ₅	139	C ₁₇ H ₁₆ N ₂ O ₅ S ₂	56.17	5.62	7.65	56.02	5.53	7.69	65.4
15	"	n-C ₃ H ₇	135-135	C ₁₈ H ₁₈ N ₂ O ₅ S ₂	57.24	5.75	7.49	57.11	5.86	7.40	86.2
16	"	n-C ₄ H ₉	113-114	C ₁₉ H ₂₀ N ₂ O ₅ S ₂	58.03	6.06	7.21	58.13	6.16	7.14	88.8
17	"	iso-C ₆ H ₁₁	125	C ₂₀ H ₂₂ N ₂ O ₅ S ₂	59.18	6.35	6.93	59.08	6.45	6.89	85.2
18	"	C ₆ H ₅ CH ₂	121-122	C ₂₂ H ₂₂ N ₂ O ₅ S ₂	61.80	5.15	6.63	61.94	5.20	6.57	87.7
19	C ₆ H ₄ C NH CO	CH ₃	202-203	C ₁₅ H ₁₂ N ₂ O ₄ S ₂	51.78	3.50	8.10	51.71	3.47	8.04	93.1
20	"	C ₂ H ₅	233-234	C ₁₆ H ₁₄ N ₂ O ₄ S ₂	53.12	3.93	7.81	53.02	3.89	7.73	93.9
21	"	n-C ₄ H ₇	213-214	C ₁₇ H ₁₆ N ₂ O ₄ S ₂	54.30	4.28	7.52	54.24	4.28	7.44	91.5
22	"	n-C ₄ H ₉	198-200	C ₁₈ H ₁₈ N ₂ O ₄ S ₂	55.41	4.69	7.18	55.36	4.65	7.17	92.3
23	"	iso-C ₆ H ₁₁	208-210	C ₁₉ H ₂₀ N ₂ O ₄ S ₂	56.35	4.91	6.99	56.41	4.98	6.93	95.4
24	"	C ₆ H ₅ CH ₂	218-220	C ₂₁ H ₁₆ N ₂ O ₄ S ₂	59.38	3.75	6.64	59.41	3.80	6.60	62.4

375–479 $m\mu$, i. e. from $\log \epsilon$ 1.70–2.60 to $\log \epsilon$ 4.23–4.70. This phenomenon is connected with superposition of the second thioamide low-intensity absorption of compounds I with a K band of compound II, due to conjugation with a conjugated chain.

EXPERIMENTAL

Synthesis of esters of 3- β -carboxyethylrhodanine.

A mixture of 2.5 mmole 3- β -carboxyethylrhodanine, 30 ml alcohol was refluxed for 3 hr, while dry HCl gas was passed. The product was a viscous lemon-yellow liquid, from which, on cooling, part of the ester usually separated as large oil drops. Excess alcohol was vacuum-distilled off, the residue dissolved in 30 ml ether, and the ether solution thrice extracted with 25 ml 5% NaHCO_3 solution. The ether extracts were dried over Na_2SO_4 for 24 hr, filtered, the ether distilled off, and the residual oil vacuum-distilled.

Condensation with carbonyl compounds. A mixture of 5 mmole ester, 5 mmole carbonyl compound, 1 g fused NaOAc, and 10 ml glacial AcOH was heated for 2 hr. To isolate the benzylidene derivatives, 30 ml water was added, an oil separated, and crystallized

in 30 min. The products from 3- β -carboxyethylrhodanine and p-nitrobenzaldehyde and p-dimethylaminobenzaldehyde were precipitated from the products after they had cooled, while the isatin products were precipitated after only 10 min refluxing. The materials were twice recrystallized from glacial AcOH.

Spectrophotometric investigations. Electronic absorption spectra were determined with a SF-4 spectrophotometer. The compounds were investigated in solution, 1 mg in 100 ml twice-distilled MeOH.

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