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THE SYNTHESIS OF RHODANINES WITH POSSIBLE ANTIMETABOLIC ACTIVITY

III. The Condensation of 3-β-Carboxyethylrhodanines With Oxo-compounds Unrelated to Aromatic Aldehydes*

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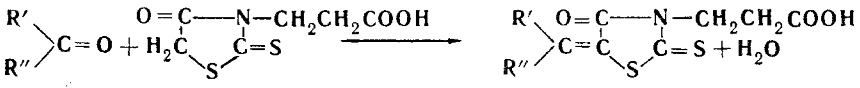
Eighteen new derivatives of rhodanine were obtained by the reaction of 3-β-carboxyethylrhodanine with various oxo-compounds. The condensation proceeded fairly readily in glacial acetic acid with enanthaldehyde, acetal, diacetyl, pyruvic acid, furfural, anthraquinone, β-chloroanthraquinone, isatin, 5-bromoisatin, acenaphthenequinone, isobutyraldehyde, cyclopentanone, and cyclohexanone. The condensations with acetone, ethyl methyl ketone, acetoacetic ester, acetophenone, and 2-acetylnaphthalene were carried out by heating in ammoniacal solution.

A number of compounds with considerable antimicrobial activity have been found among a series of 5-arylidene derivatives of 3-β-carboxyethylrhodanine which we have prepared [1]. It was consequently thought worthwhile to investigate the condensation of 3-β-carboxyethylrhodanine with other oxo-compounds unrelated to aromatic aldehydes. With this aim in view, we have attempted to condense 29 different representative aldehydes, ketones, ketoacids, and quinones with 3-β-carboxyethylrhodanine.

It is well known that rhodanine and its derivatives react readily with aromatic aldehydes in boiling acetic acid, in the presence of sodium acetate [1, 2]. Our investigations show that the condensation of 3-β-carboxyethylrhodanine with enanthaldehyde, diacetyl, pyruvic acid, furfural, anthraquinone, β-chloroanthraquinone, isatin, 5-bromoisatin, and acenaphthenequinone with 3-β-carboxyethylrhodanine takes place under similar conditions. The reaction is usually complete in 1-3 hr. The products are shown in the table.

The condensation may be represented by the general equation



I

II

The condensation with acetal proceeds with the elimination of two molecules of ethanol, with the formation of 3-β-carboxyethyl-5-ethylidenerhodanine (II, R' = CH_3, R" = H). Diacetyl, β-chloroanthraquinone, and acenaphthenequinone react with only one molecule of I, with the formation of 3-β-carboxyethyl-5-α-acetylethylidenerhodanine (II, R' = CH_3CO, R" = CH_3), 3-β-carboxyethyl-5-(2'-chloro-9'-oxo-9',10'-dihydro-10'-anthraceneylidene)rhodanine and 3-β-carboxyethyl-5-(9'-oxo-10'-acenaphthylidene)rhodanine. Under similar conditions, anthraquinone reacted with 2 moles of the rhodanine derivative, with the formation of 9, 10-bis(3'-β-carboxyethyl-2'-thiothiazolid-4'-one-5'-ylidene)dihydroanthracene. Thus, a chlorine atom in the β-position deactivates one of the CO-groups.

Condensation of 3-β-carboxyethylrhodanine with isobutyraldehyde, cyclopentanone, and cyclohexanone proceeded with much more difficulty, requiring the reaction mixture to be heated for 10 hr to complete the reaction.

Under the above reaction conditions, the condensation with acetone, ethyl methyl ketone, acetophenone, 2-acetylnaphthalene, and acetoacetic ester did not take place. We obtained the condensation products of these oxo-compounds with I by the Girard method [3], i.e., in ammoniacal solution. The products obtained are shown in the table.

Even prolonged boiling of 3-β-carboxyethylrhodanine in acetic acid or ammoniacal solution failed to effect the condensation with isovaleraldehyde, benzoin, xanthone, acetylacetone, diacetone alcohol, alizarin, camphor, benzophenone, acridone, benzanthranone, and Michler's ketone.

The condensation products of I with oxo-compounds are crystalline compounds of shades of yellow, orange, or red. They are practically insoluble in water except for the 5-ethylidene-, 5-α-acetylethylidene-, and 5-furfurylidene-

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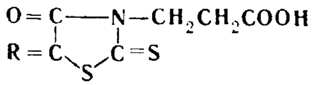
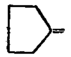
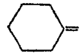
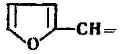
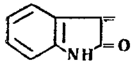
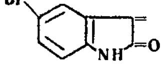
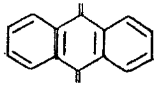
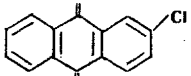
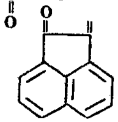
* For part II see [1]

Products of the Condensation of 3-β-Carboxyethylrhodanine with Oxo-Compounds



Comp. no.	R	Color of Comp.	Mp, ° C	Formula	Found, % C	Found, % H	Found, % N	Calculated, % C	Calculated, % H	Calculated, % N	Yield, %
1	$CH_3—CH=$	Orange	>240 decomp	$C_8H_9NO_3S_2$	41.61	3.91	6.02	41.54	3.92	6.06	61.5
2	$CH_3—C(CH_3)=$	Flesh	194—195	$C_9H_{11}NO_3S_2$	44.16	4.60	5.79	44.06	4.52	5.71	67.7
3	$CH_3—C(COCH_3)=$	Deep-yellow	144—145	$C_{10}H_{11}NO_4S_2$	44.01	4.03	5.10	43.94	4.06	5.12	38.0
4	$CH_3—C(COOH)=$	Deep-yellow	>220 decomp	$C_9H_9NO_5S_2$	39.38	3.34	5.15	39.26	3.29	5.09	43.6
5	$CH_2(COOC_2H_5)—C(CH_3)=$	Pale-lemon	112—113	$C_{12}H_{15}NO_5S_2$	45.52	4.77	4.49	45.41	4.76	4.41	88.8
6	$CH_3—C(C_6H_5)=$	Yellow	216—217	$C_{14}H_{13}NO_3S_2$	54.80	4.21	4.60	54.70	4.26	4.56	63.8
7	$CH_3—C(C_{10}H_7)=$	Yellow	177—178	$C_{18}H_{15}NO_3S_2$	60.60	4.21	3.99	60.48	4.23	3.92	86.7
8	$CH_3—CH_2—C(CH_3)=$	Yellow	168—170	$C_{10}H_{13}NO_3S_2$	46.39	4.96	5.42	46.31	5.05	5.40	74.8
9	$CH_3—CH(CH_3)—CH=$	Yellow	132—133	$C_{10}H_{13}NO_3S_2$	46.22	5.47	5.30	46.13	5.42	5.38	49.2
10	$CH_3—(CH_2)_5—CH=$	Lemon	117—119	$C_{13}H_{19}NO_3S_2$	51.65	6.43	4.53	51.80	6.35	4.65	63.1
11		Yellowish-orange	200—201	$C_{11}H_{13}NO_3S_2$	48.59	4.77	5.22	48.68	4.83	5.16	23.6
12		Pale-yellow	146—148	$C_{12}H_{15}NO_3S_2$	51.35	3.66	5.03	51.41	3.60	5.00	94.2
13		Yellow	192—193	$C_{11}H_9NO_4S_2$	46.77	3.22	5.01	46.63	3.20	4.94	93.3
14		Claret	>240 decomp	$C_{14}H_{10}N_2O_4S_2$	50.43	3.07	8.42	50.29	3.01	8.38	92.7
15		Deep-claret	>240 decomp	$C_{14}H_9BrN_2O_4S_2$	40.81	2.19	6.76	40.68	2.19	6.78	45.5
16		Pale-lemon	160—162	$C_{26}H_{18}N_2O_6S_4$	53.70	3.20	4.83	53.59	3.11	4.81	48.7
17		Pale-cream	181—183	$C_{20}H_{12}ClNO_4S_2$	55.99	2.81	3.35	55.87	2.81	3.28	60.0
18		Deep-claret	247—249	$C_{18}H_{11}NO_4S_2$	58.40	3.04	3.78	58.52	3.00	3.79	31.4

derivatives, which are soluble in boiling water. Most of the compounds are soluble in methanol, acetone, benzene, and chloroform. By virture of the presence of a free carboxyl group, the compounds are as a rule soluble not only in solutions of NaOH, ammonia, and sodium carbonate, but also in saturated sodium bicarbonate solution. Only the condensation products from anthraquinone, β-chloroanthraquinone, acenaphthenequinone, isatin, and 5-bromoisatin are soluble with difficulty in the latter solution.

We have shown previously [1] that 3-β-carboxyethylrhodanine, unsubstituted in the 5-position, is unstable in alkaline solution, undergoing hydrolysis to thioglycolic acid as shown by the positive reaction to sodium nitroprusside. Our experiments with the condensation products of 3-β-carboxyethylrhodanine show that the introduction of radicals derived from oxo-compounds in the 5-position results in considerable stabilization of the thiazolidine ring, with the result that alkaline solutions of these compounds in sodium carbonate do not give a positive nitroprusside reaction. The condensation products of anthraquinone and β-chloroanthraquinone are exceptional in that they give an intense violet coloration, those of acenaphthenequinone and 2-acetylnaphthalene giving weak reactions only. Thus, radicals derived from condensed aromatic rings, as opposed to the residues from all the other oxo-compounds, do not stabilize the thiazolidine ring to any extent.

Experimental

Condensations of 3-β-carboxyethylrhodanine in acetic acid. A mixture of 5 mM of 3-β-carboxyethylrhodanine, 5 mM of the oxo-compound, 10 ml of glacial acetic acid, and 1 g of anhydrous sodium acetate were boiled under reflux for 1–10 hr. In many cases the condensation product separated after a short time from the clear solution which formed initially. The reaction mixture was treated with 30 ml of water in the cold, the precipitate filtered off, washed with water, dried, and recrystallized from glacial acetic acid.

Condensation of 3-β-carboxyethylrhodanine in ammoniacal solution. 5 mM of the oxo-compound, a solution of 0.32 g of ammonium chloride in 0.65 ml of water and 0.85 ml of concentrated ammonia solution were added to a solution of 5 mM of 3-β-carboxyethylrhodanine in 5 ml of ethanol. The mixture was boiled for 2 hr under reflux, and the resulting clear solution treated with 30 ml of water and acidified with hydrochloric acid. The precipitate which separated was filtered off, washed with water and recrystallized from glacial acetic acid.

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