[CONTRIBUTION NO. 18 FROM THE L. G. RYAN RESEARCH LABORATORIES OF MONSANTO CANADA LTD.]

Amino Acids. VIII. 2-Thiazoline and Δ^2-Dihydro-1,3-thiazine Derivatives of ω-Amino Acids

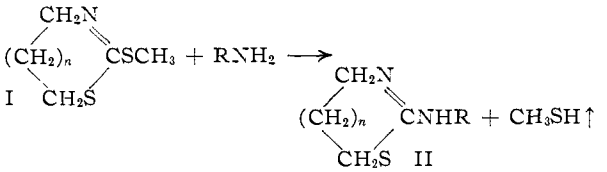
BY A. F. MCKAY, D. J. WHITTINGHAM AND M.-E. KRELING

RECEIVED DECEMBER 16, 1957

ω-Amino acids on condensation with 2-methylmercapto-2-thiazoline and 2-methylmercapto-Δ^2-dihydro-1,3-thiazine gave a new series of N-substituted amino acids. 2-(β-Carboxyethylamino)-2-thiazoline was converted by way of its ethyl ester into a bicyclic compound, 5-keto-2,3,6,7-tetrahydro-5(H)-thiazolo[3,2-a]pyrimidine. This bicyclic compound on treatment with primary amines in absolute ethanol gave good yields of the corresponding substituted amides of 2-(β-carboxyethylamino)-2-thiazoline.

Recently[1,2] the preparation and properties of 2-(ω-carboxyalkylamino)-2-imidazolines and 2-(ω-carboxyalkylamino)-Δ^2-tetrahydropyrimidines were described. The present work is an extension of these studies to similar derivatives of 2-thiazoline and Δ^2-dihydro-1,3-thiazine.

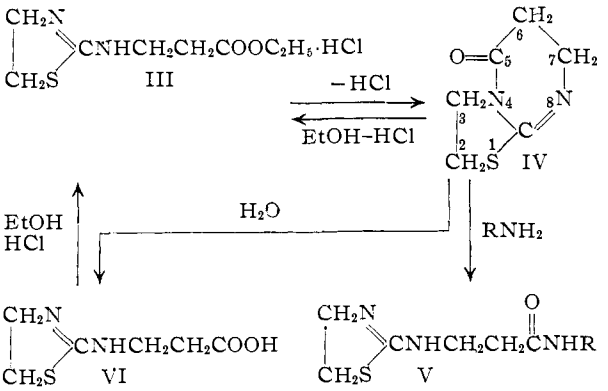
Good yields of the 2-alkylamino- or 2-aralkylamino- derivatives of either 2-thiazoline or Δ^2-dihydro-1,3-thiazine could be obtained by the reaction of the corresponding amine with the hydroiodide salts of either 2-methylmercapto-2-thiazoline or 2-methylmercapto-Δ^2-dihydro-1,3-thiazine, respectively. However, in order to obtain good yields of the 2-(ω-carboxyalkylamino)- derivatives (II, n = 0 or 1; R = $-(CH_2)_mCOOH$) the amino acid had to be condensed with the free base of the methylmercapto- derivative I (n = 0 or 1).



n = 0 or 1; R = alkyl, aralkyl or carboxyalkyl

The derivatives of 2-thiazoline and Δ^2-dihydro-1,3-thiazine prepared during this investigation are listed in Tables I and II.

2-(β-Carboxyethylamino)-2-thiazoline (VI) was converted into its ethyl ester hydrochloride salt III in the usual manner by heating with an ethanolic solution of hydrogen chloride. When 2-(β-carbethoxyethylamino)-2-thiazoline hydrochloride (III) in solution was passed through a column of IR-A 400 resin to remove the hydrogen chloride, cyclization occurred.



In addition to the chemistry described below, the structure of this cyclization product IV was verified by its infrared spectrum. This spectrum showed the absence of N–H stretching and bending vibrations and it possessed strong bands at 1686 and 1640 cm.$^{-1}$ indicative of the presence of a C=O group and a C=N group, respectively. This cyclic product, 5-keto-2,3,6,7-tetrahydro-5(H)-thiazolo[3,2-a]pyrimidine (IV), was more stable than the similar bicyclic compound, 3-keto-2,3,5,6-tetrahydro-1-imidaz[1,2-a]imidazole, previously[1] described. It could be isolated as its free base in well formed crystals melting at 104.5–105.5°. This bicyclic compound IV was hydrolyzed completely to 2-(β-carboxyethylamino)-2-thiazoline (VI) after heating its aqueous solution under reflux for five minutes. When 5-keto-2,3,6,7-tetrahydro-5(H)-thiazolo[3,2-a]pyrimidine (IV) was heated in absolute ethanol in the presence of one equivalent of hydrogen chloride, it was converted into the hydrochloride salt of 2-(β-carbethoxyethylamino)-2-thiazoline (III). Primary amines such as N,N-dimethylethylenediamine, n-butylamine and benzylamine in absolute ethanol solution added to 5-keto-2,3,6,7-tetrahydro-5(H)-thiazolo-(3,2-a)pyrimidine to give good yields of the corresponding 2-(β-(N-substituted carbamyl)-ethylamino))-2-thiazolines (V). These amides are described in Table I. Morpholine, diisopropylamine and diethylamine under similar conditions failed to combine with the bicyclic compound IV.

Experimental[3]

Tetrahydro-1,3-thiazine-2-thione.—Jansen's method[4] was used to prepare tetrahydro-1,3-thiazine-2-thione (m.p. 131–133°) in 62% yield. One crystallization from methanol raised the melting point to 134–134.5°. The previously reported[5] melting points are 132° and 129–131°.

Anal. Calcd. for $C_4H_7NS_2$: C, 36.06; H, 5.30; N, 10.52; S, 48.13. Found: C, 36.10; H, 5.13; N, 10.47; S, 48.26.

2-Methylmercapto-2-thiazoline.—Methyl iodide (87.5 g., 0.62 mole) was added dropwise over a period of 15 minutes to a refluxing solution of thiazolidine-2-thione[6] (66.5 g., 0.56 mole) in absolute methanol (150 ml.). After a further 2

(1) A. F. McKay and W. G. Hatton, THIS JOURNAL, **78**, 1618 (1956).

(2) D. L. Garmaise, S. O. Winthrop, G. A. Grant and A. F. McKay, *Can. J. Chem.*, **34**, 743 (1956).

(3) All melting points are uncorrected. The microanalyses were determined by Micro-Tech Laboratories, Skokie, Ill.

(4) J. E. Jansen, U. S. Patent 2,293,465, August 18, 1942.

(5) (a) S. Gabriel and W. E. Lauer, *Ber.*, **23**, 92 (1890); (b) P. Hirsch, *ibid.*, **23**, 967 (1890); (c) F. M. Hamer and R. J. Rathbone, *J. Chem. Soc.*, 243 (1943).

(6) (a) S. Gabriel, *Ber.*, **22**, 1152 (1889); (b) S. Gabriel and R. Stelzner, *ibid.*, **28**, 2929 (1895); (c) L. Maquenne and R. Roux, *Compt. rend.*, **134**, 1589 (1902); (d) L. Knorr and P. Rössler, *Ber.*, **36**, 1278 (1903); (e) M. E. Roux, *Ann chim.*, [8] **1**, 72 (1904).

Table I

-2-Thiazoline Derivatives

-2-Thiazoline	M.p., °C.	Yield, %	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
2-Allylamino-	43–44	78.6	$C_6H_{10}N_2S$	50.67	50.38	7.08	7.11	19.70	19.66	22.55	22.59
	74–75[a]	85.4	$C_6H_{11}IN_2S$	26.67	26.68	4.10	4.38	10.37	10.11	11.87	12.11
	162–163[b]	75.8	$C_{12}H_{12}N_8O_7S$	38.81	39.34	3.53	3.80	18.86	19.00	8.63	8.88
2-Octadecylamino-	74.5–75.5	26.6	$C_{21}H_{42}N_2S$	71.12	71.25	11.94	11.99	7.90	7.94	9.04	8.62
	124–125[b]	100	$C_{27}H_{45}N_5O_7S$	55.55	55.32	7.77	7.96	12.00	12.06	5.49	5.66
2-Benzylamino-	82.5–83.5	72.0	$C_{10}H_{12}N_2S$	62.46	62.67	6.29	6.28	14.57	14.59	16.67	16.68
	168.5–169.5[b]	90.9	$C_{16}H_{15}N_5O_7S$	45.60	45.52	3.59	3.50	16.62	16.56	7.61	7.54
2-(β-Diethylaminoethylamino)-		58.0[c]	$C_9H_{19}N_3S$	53.69	53.88	9.51	9.67	20.87	20.48	15.92	15.66
	171–172[d]	100	$C_{21}H_{25}N_9O_{14}S$	38.24	38.66	3.82	3.94	19.11	19.18	4.86	4.88
2-(Carboxymethylamino)-	224–225 d.	84.0	$C_5H_8N_2O_2S$	37.49	37.48	5.03	5.09	17.49	17.78	20.01	20.20
	195–196[b]	68.0	$C_{11}H_{11}N_5O_9S$	33.94	34.18	2.85	3.10	17.99	17.66	8.24	8.33
2-(Carbomethoxymethylamino)-	75–76	65.8	$C_6H_{10}N_2O_2S$	41.36	41.52	5.79	5.84	16.09	16.03	18.40	18.18
	179–181 d.[b]	75.0	$C_{12}H_{13}N_5O_9S$	35.73	35.47	3.25	3.54	17.37	17.60	7.95	8.18
2-(Carbethoxymethylamino)-	167–168[b]	90.0	$C_{13}H_{15}N_5O_9S$	37.41	37.21	3.62	3.64	16.78	16.50	7.68	7.54
2-(β-Carboxyethylamino)-	198–199 d.	88.0	$C_6H_{10}N_2O_2S$	41.36	41.14	5.79	5.72	16.09	16.20	18.40	18.55
	177.5–179[b]	41.5	$C_{13}H_{13}N_5O_9S$	35.73	35.74	3.25	3.32	17.37	17.40	7.95	8.00
2-(β-Carbethoxyethylamino)-	129–130[b]	83.0	$C_{14}H_{17}N_5O_9S$	38.98	38.95	3.98	4.25	16.24	15.95	7.43	7.36
2-(ε-Carboxypentylamino)-	126–127	88.0	$C_9H_{16}N_2O_2S$	49.97	50.19	7.45	7.75	12.95	12.88	14.82	14.42
	167–168[b]	47.5	$C_{15}H_{19}N_5O_9S$	40.45	40.44	4.30	4.43	15.72	15.67	7.20	7.30
2-Benzylamino-5-methyl-	64.5–65.5	59.5	$C_{11}H_{14}N_2S$	64.04	63.92	6.84	6.71	13.58	13.32	15.54	15.63
	138–139[b]	100	$C_{17}H_{17}N_5O_7S$	46.89	47.21	3.94	4.22	16.08	16.42	7.36	7.17
2-(3,4-Dichlorobenzylamino)-	119.5–120.5[e]	92.6	$C_{10}H_{10}Cl_2N_2S$	45.98	45.86	3.86	3.78	10.73	10.90	12.28	12.27
	172.5–173.5[b,f]	98.9	$C_{16}H_{13}Cl_2N_5SO_7$	39.19	39.22	2.67	2.69	14.29	14.60	6.54	6.52
	159.5–160[a,g]	95.0	$C_{10}H_{11}Cl_2IN_2S$	30.86	30.77	2.85	2.87	7.20	7.55	8.24	8.22
2-(β-(N-n-Butylcarbamyl)-ethylamino)-	116.5–118.5	55.7	$C_{16}H_{19}N_5OS$	52.37	51.95	8.35	8.48	18.33	18.24	13.98	14.02
	167.5–168.5[b]	97.4	$C_{16}H_{17}N_4O_8S$	41.91	41.68	4.84	5.03	18.33	18.28	6.99	6.80
2-(β-(N-Dimethylaminoethylcarbamyl)-ethylamino)-	97.5–98.5	99.6	$C_{10}H_{20}N_4OS$	49.15	48.81	8.25	8.10	22.93	23.04	13.12	12.98
	157.5–158.5[d]	63.2	$C_{22}H_{26}N_{10}O_{16}S$	37.61	37.48	3.73	4.13	19.94	20.37	4.56	4.73
2-(β-(N-Benzylcarbamyl)-ethylamino)-	150.5–151.5	94.6	$C_{18}H_{17}N_5OS$	59.28	59.11	6.51	6.22	15.95	16.10	12.18	11.93
	166.5–167 5[b]	94.4	$C_{19}H_{20}N_6O_8S$	46.33	46.22	4.09	4.15	17.07	17.09	6.51	6.46
2-(β-(N-(9-Phenanthrylmethyl)-carbamyl)-ethylamino)-	187.5–188.5	47.0	$C_{21}H_{21}N_5OS$	69.39	69.32	5.82	6.02	11.56	11.76	8.82	8.36
	218–219[b]	100	$C_{27}H_{24}N_6O_8S$	54.73	54.89	4.08	4.39	14.19	14.03	5.41	5.43

[a] Hydroiodides. [b] Picrates. [c] B.p. 109–110° (0.37 mm.), $n^{25}D$ 1.5298, d^{25} 1.046. [d] Dipicrate. [e] Cl calcd. 27.15, found 27.14. [f] Cl calcd. 14.46, found 14.43. [g] Total halogen calcd. 50.85, found 51.04.

Table II

-Δ^2-Dihydro-1,3-thiazine Derivatives

-Δ^2-Dihydro-1,3-thiazines	M.p., °C.	Yield, %	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
2-Benzylamino-	95.5–96.5	75.0	$C_{11}H_{14}N_2S$	64.04	64.15	6.84	6.76	13.58	13.68	15.54	15.47
	165.5–166.5[a]	100	$C_{17}H_{17}N_5O_7S$	46.89	47.12	3.94	4.01	16.08	16.19	7.36	7.54
2-(β-Diethylamino-ethylamino)-		4.3[c]	$C_{10}H_{21}N_3S$	55.76	55.72	9.83	10.02	19.51	19.60	14.89	14.87
	169–170.5[b]	48.0	$C_{22}H_{27}N_9O_{14}S$	39.23	39.51	4.04	4.24	18.72	19.18	4.76	4.90
2-(ε-Carboxypentyl-amino)-	181–182	94.4	$C_{10}H_{18}N_2O_2S$	52.14	51.67	7.88	7.88	12.16	12.16	13.92	13.92
	161–163[a]	95.2	$C_{16}H_{21}N_5O_9S$	41.83	41.85	4.61	4.69	15.25	14.94	6.98	7.10
2-(ε-Carbomethoxy-pentylamino)-	54–55	81.8	$C_{11}H_{20}N_2O_2S$	54.06	54.48	8.25	8.09	11.46	11.24	13.12	12.81
	87–87.5[a]	100	$C_{17}H_{23}N_5O_9S$	43.12	43.17	4.89	4.84	14.79	14.82	6.77	6.65
2-(ε-(N-Methylcar-bamyl)-pentyl-amino)-	136.5–137.5	56.9	$C_{11}H_{21}N_3OS$	54.28	54.28	8.70	8.93	17.26	17.76	13.17	13.43
	124.5–125[a]	91.5	$C_{17}H_{24}N_6O_8S$	43.21	42.84	5.12	5.10	17.79	17.47	6.78	6.77

[a] Picrates. [b] Dipicrate. [c] Viscous liquid was distilled in a collar flask at a bath temperature of 152–154° at 0.05 mm., $n^{25}D$ 1.5170.

hours of refluxing, the solution was cooled and then diluted with absolute ether (150 ml.). The crystals (m.p. 111–114°) were recovered by filtration, yield 127 g. (87%). A small sample (1 g.) of these crystals was crystallized from ethanol to a constant melting point of 112–114°.

Anal. Calcd. for $C_4H_8INS_2$: C, 18.39; H, 3.09; N, 5.36; S, 24.55. Found: C, 18.39; H, 3.08; N, 5.55; S, 23.90.

2-Methylmercapto-2-thiazoline hydroiodide (50 g., 0.19 mole) in methanol (1000 ml.) was passed through a column of IR-A 400 resin (400 ml.) in the hydroxyl form which had been previously washed with methanol (700 ml.). The column was washed with methanol (750 ml.) and the eluate and washings were evaporated *in vacuo* to remove the methanol. The oily residue was fractionally distilled *in vacuo*. The main fraction (b.p. 64.5–65.5° (0.24 mm.)) was obtained in 74% (18.89 g.) yield.

Two similar preparations of 2-methylmercapto-2-thiazoline gave 99% (b.p. 74° (0.31 mm.)) and 86% (b.p. 67.5–68° (0.16 mm.)) yields. Gabriel[6a] reported a boiling point of 216–217° at 760 mm. A sample (0.2 g.) of 2-methylmercapto-2-thiazoline was converted into its picrate from aqueous solution in the usual manner. It melted at 144–146°. Crawhall and Elliott[7] report a melting point of 123° for this picrate.

Anal. Calcd. for $C_{10}H_{10}N_4O_7S_2$: C, 33.15; H, 2.78; N, 15.46; S, 17.70. Found: C, 33.36; H, 2.88; N, 15.39; S, 17.91.

2-Methylmercapto-5-methyl-2-thiazoline.—5-Methyl-2-thiazolidinethione[8] was converted into 2-methylmercapto-5-methyl-2-thiazoline hydroiodide in 83% yield by the method described above for the preparation of 2-methylmercapto-2-thiazoline hydroiodide. The melting point was raised from 108–113° to 113.5–115° by 3 crystallizations from methanol–ethyl ether (1:3.5) solution.

Anal. Calcd. for $C_5H_{10}INS_2$: C, 21.82; H, 3.66; N, 5.09. Found: C, 21.95; H, 3.74; N, 5.42.

A sample of 2-methylmercapto-5-methyl-2-thiazoline hydroiodide in water was converted into its picrate (m.p. 127–

(7) J. C. Crawhall and D. F. Elliott, *J. Chem. Soc.*, 3094 (1952).

(8) A. A. Rosen, This Journal, **74**, 2994 (1952).

130°) in the usual manner, yield 76%. One crystallization from water raised the melting point to a constant value of 129–130°. A melting point of 122° was reported by Crawhall and Elliott.[7]

Anal. Calcd. for $C_{11}H_{12}N_4O_7S_2$: C, 35.10; H, 3.22; N, 14.89; S, 17.04. Found: C, 35.14; H, 3.42; N, 14.95; S, 17.10.

2-Methylmercapto-Δ²-dihydro-1,3-thiazine.—Tetrahydro-1,3-thiazine-2-thione was methylated with methyl iodide under the conditions described above for the preparation of 2-methylmercapto-2-thiazoline hydroiodide. The crude product (m.p. 136–145°) was obtained in 87% yield. Crystallization from ethanol gave a constant melting point of 142–143°.

Anal. Calcd. for $C_5H_{10}INS_2$: C, 21.82; H, 3.66; N, 5.09; S, 23.30. Found: C, 22.15; H, 3.86; N, 4.91; S, 23.10.

The picrate formed from water in the usual manner melted at 122–123°, yield 78%.

Anal. Calcd. for $C_{11}H_{12}N_4O_7S_2$: C, 35.10; H, 3.22; N, 14.89; S, 17.04. Found: C, 35.25; H, 3.30; N, 14.82; S, 16.87.

2-Methylmercapto-Δ²-dihydro-1,3-thiazine hydroiodide (55 g., 0.2 mole) in absolute methanol (1375 ml.) was passed through a column of IR-A 400 resin (400 ml. in the hydroxyl form) which had been previously washed with methanol. After the column was washed with methanol (1000 ml.), the combined eluate and washings were taken to dryness *in vacuo* under nitrogen. The residual liquid was distilled *in vacuo*. The main colorless fraction had the following physical constants; b.p. 79–80° (0.9 mm.), $n^{25}D$ 1.5962, d^{25}_4 1.216; MD calcd. 41.5, obsd. 41.2. The yield was 27.34 g. (93%). Hamer and Rathbone[5c] reported a boiling point of 155–160° at 50 mm.

Anal. Calcd. for $C_5H_9NS_2$: C, 40.78; H, 6.16; N, 9.51; S, 43.54. Found: C, 40.85; H, 6.11; N, 9.70; S, 43.47.

2-Substituted Amino-2-thiazolines and -Δ²-dihydro-1,3-thiazines.—The 2-alkylamino- and 2-aralkylamino- derivatives of 2-thiazoline and Δ²-dihydro-1,3-thiazine were prepared under the conditions described below in method A while the 2-(ω-carboxyalkylamino)-derivatives were prepared by method B. These compounds are described in Tables I and II.

Method A. 2-(3,4-Dichlorobenzylamino)-2-thiazoline.—2-Methylmercapto-2-thiazoline hydroiodide (2.61 g., 0.01 mole) and 3,4-dichlorobenzylamine (1.76 g., 0.01 mole) in methanol (20 ml.) were heated together under reflux for 3.5 hours. The evolved methyl mercaptan was absorbed in sodium hydroxide solution. After the reaction mixture was evaporated to dryness *in vacuo*, the semi-crystalline residue (3.69 g.) was crystallized from methanol–ether solution, yield 3.28 g. (84.4%). The melting point was raised from 155–157.5° to 159.5–160° by three recrystallizations from methanol–ether (1:2) solution.

Its picrate (m.p. 170–172°) was formed in 98.9% yield in the usual manner from water. Crystallization from absolute ethanol raised the melting point to 172.5–173.5°.

The major portion of 2-(3,4-dichlorobenzylamino)-2-thiazoline hydroiodide (2.07 g., 0.005 mole) in methanol (41.5 ml.) was passed through a column of IR-A 400 resin (20 ml. in the hydroxyl form) at a rate of 2.3 ml./min. The column was washed with methanol (50 ml.) and the combined eluate and washings were evaporated to dryness *in vacuo* under nitrogen. A colorless, crystalline residue (m.p. 96–113°) was obtained, yield 1.29 g., (93%). Three crystallizations from hexane (*ca.* 100 ml./g.) raised the melting point of the 2-(3,4-dichlorobenzylamino)-2-thiazoline to 119.5–120.5°.

Method B. 2-(β-Carboxyethylamino)-2-thiazoline.—2-Methylmercapto-2-thiazoline (83.8 g., 0.63 mole) and β-alanine (56.1 g., 0.63 mole) in methanol–water (1:1) solution (1 l.) were heated under reflux for 25 hours. After the solvents were removed *in vacuo* under nitrogen, a colorless semi-crystalline residue remained, yield 125.2 g. This crude product was dissolved in water (150 ml.) and the solution was diluted with acetone (250 ml.) until turbidity appeared. The product separated out as an oil, but it crystallized slowly on standing in the refrigerator. The first crop of crystals (m.p. 193–194° dec.) weighed 85 g. When the mother liquor from the first crop was concentrated to a volume of 50 ml. and then diluted with acetone (100 ml.), a second crop of crystals (m.p. 193–194° dec.) was obtained. The total yield was 89.3 g. (81.2%). Crystallization of the crude 2-(β-carboxyethylamino)-2-thiazoline from water–acetone (1:3) solution raised the melting point to 198–199° dec.

A sample of 2-(β-carboxyethylamino)-2-thiazoline in water was converted into its picrate (m.p. 173–174°) in the usual manner. One crystallization from water raised the melting point to 177.5–179°.

5-Keto-2,3,6,7-tetrahydro-5(H)-thiazolo[3,2-a]pyrimidine.—2-(β-Carboxyethylamino)-2-thiazoline (80 g., 0.46 mole) in absolute ethanol (1 l.) containing dry hydrogen chloride (56 g., 1.53 moles) was refluxed for 2 hours. Benzene (200 ml.) was added and the solution was refluxed for another hour after which the benzene–ethanol–water azeotrope was distilled at atmospheric pressure. This procedure of adding benzene and removing the benzene–ethanol–water azeotrope was repeated three times and then the solvent was removed *in vacuo* under nitrogen. A pale-colored viscous oil remained, yield 109.4 g. (99.8%). This preparation of 2-(β-carbethoxyethylamino)-2-thiazoline hydrochloride (109.4 g., 0.45 mole) in methanol (2.2 l.) was passed through a column of IR-A 400 resin (1.4 l. in the hydroxyl form) at a rate of 45 ml./min. The resin was washed with methanol (4.0 l.) and the combined eluate and washings were evaporated to dryness *in vacuo* under nitrogen. The yield of pale yellow oil was 59.5 g. (83%). The oil solidified to a crystalline mass after it had remained in the refrigerator for four days. The crude crystalline product was crystallized twice from a minimum of absolute ethanol, yield 28 g. Addition of hexane to the ethanolic mother liquors gave a second crop of 11 g. of crystals. The total yield of product melting at 104.5–105.5° was 39 g. (54.6%). Crystallization from acetone–*n*-hexane (1:4) raised the melting point to 105–105.5°.

Anal. Calcd. for $C_6H_8N_2OS$: C, 46.13; H, 5.16; N, 17.94; S, 20.53. Found: C, 46.21; H, 5.09; N, 17.96; S, 20.60.

A sample of 5-keto-2,3,6,7-tetrahydro-5(H)-thiazolo-[3,2-a]pyrimidine (100 mg.) in absolute ethanol (5 ml.) on treatment with a saturated ethanolic solution of picric acid gave a 97.4% yield of picrate (m.p. 204–206°). Crystallization from absolute ethanol raised the melting point to 204.5–206°.

Anal. Calcd. for $C_{12}H_{11}N_5O_8S$: C, 37.40; H, 2.88; N, 18.18; S, 8.32. Found: C, 37.05; H, 2.73; N, 18.39; S, 8.34.

When 5-keto-2,3,6,7-tetrahydro-5(H)-thiazolo[3,2-a]-pyrimidine (100 mg.) in water (5 ml.) was refluxed for 3 minutes and the solution treated with aqueous picric acid solution, a picrate melting at 178–180° was obtained, yield 216 mg. (93%). A mixture melting point determination with a known sample of 2-(β-carboxyethylamino)-2-thiazoline picrate (m.p. 179°) showed no depression.

2-(β-Carbethoxyethylamino)-2-thiazoline Picrate from 5-Keto-2,3,6,7-tetrahydro-5(H)-thiazolo[3,2-a]pyrimidine.—An ethanolic solution of hydrogen chloride (0.001 mole) was added to a solution of 5-keto-2,3,6,7-tetrahydro-5(H)-thiazolo[3,2-a]pyrimidine (156 mg., 0.001 mole) in absolute ethanol (4 ml.). After the reaction mixture was heated under reflux for 2 hours, it was treated with saturated ethanolic picric acid solution. A crystalline picrate (m.p. 128–131°) separated slowly from the solution, yield 251 mg. A second crop of crystalline picrate (m.p. 129–131°) was obtained from the concentrated mother liquor. The total yield was 430 mg. (99.9%). A mixture melting point determination with a known sample of 2-(β-carbethoxyethylamino)-2-thiazoline picrate (m.p. 129–130°) showed no depression.

The Reaction of Amines with 5-Keto-2,3,6,7-tetrahydro-5(H)-thiazolo[3,2-a]pyrimidine.—A series of 2-(β-(N-substituted carbamyl)-ethylamino)-2-thiazolines (*cf.* Table I) were prepared by the reaction of amines with 5-keto-2,3,6,7-tetrahydro-5(H)-thiazolo[3,2-a]pyrimidine. Since the procedures used in these preparations were similar, only the preparation of 2-(β-(N-benzylcarbamyl)-ethylamino)-2-thiazoline is given in detail.

Benzylamine (0.5 g., 0.005 mole) was added to a solution of 5-keto-2,3,6,7-tetrahydro-5(H)-thiazolo[3,2-a]pyrimidine (0.78 g., 0.005 mole) in absolute ethanol (7.5 ml.). The solution was allowed to stand at room temperature for

17 hours after which the solution was evaporated to dryness *in vacuo* under nitrogen. The crystalline residue melted at 145–150°, yield 1.215 g. (94.6%). Three crystallizations from water raised the melting point to a constant value of 150.5–151.5°. Its picrate (m.p. 164–165°) was formed in 94.4% yield in the usual manner from ethanol. Two crystallizations from water raised the melting point to 166.5–167.5°.

The preparation of 2-(β-(N-(9-phenanthrylmethyl)-carbamyl)-ethylamino)-2-thiazoline was carried out under similar conditions with the exception that the ethanolic solution of reactants was refluxed for 4 hours.

Attempts to form amides with morpholine, diisopropylamine and diethylamine under similar reaction conditions gave an 80–90% recovery of unchanged 5-keto-2,3,6,7-tetrahydro-5(H)-thiazolo[3,2-a]pyrimidine.

Methyl Ester of 2-(ε-Carboxypentylamino)-Δ²-dihydro-1,3-thiazine.—2-(ε-Carboxypentyl)-Δ²-dihydro-1,3-thiazine (6 g., 0.026 mole) in absolute ethanol (100 ml.) containing 5% hydrogen chloride was converted into its ethyl ester under the conditions described above for the preparation of 2-(β-carbethoxyethylamino)-2-thiazoline. Its solution was evaporated to dryness *in vacuo* and a yellow gummy residue was obtained. The yellow gum was dissolved in methanol (200 ml.) and passed through a column of IR-A 400 resin (150 ml. of resin in the hydroxyl form) at a rate of 8.3 ml./min. After the column was washed with methanol (250 ml.), the combined eluate and washings were evaporated to dryness *in vacuo* under nitrogen. The residue crystallized (m.p. 45–50°) on standing overnight, yield 5.21 g. (77.6%). The crude free base was extracted with hot hexane (125 ml.) and the extract was concentrated to a volume of 50 ml. Crystals (m.p. 53–55°) separated from the solution on cooling, yield 4.46 g. Another crystallization from *n*-hexane raised the melting point to 54–55° (*cf.* Table II). During the passage of the ethyl ester of 2-(ε-carboxypentylamino)-Δ²-dihydro-1,3-thiazine in methanol through the column of IR-A 400 resin transesterification occurred and the methyl ester of the acid was obtained.

A sample (220 mg.) of this product on treatment with ethanolic picric acid solution gave a crystalline picrate (m.p. 80–86°), yield 100%. One crystallization from methanol (10 ml.) and three from benzene–hexane (1:1) solution (20 ml.) gave a product with a double melting point (m.p. 82–83° and 87–87.5°).

2-(ε-(N-Methylcarbamyl)-pentylamino)-Δ²-dihydro-1,3-thiazine.—A solution of 2-(ε-carbomethoxypentylamino)-Δ²-dihydro-1,3-thiazine (3 g., 0.012 mole) in absolute methanol (250 ml.) containing methylamine (14.4 g., 0.046 mole) and sodium (0.1 g., 0.004 mole) was allowed to stand at room temperature for 120 hours. The solution, which turned cloudy after 20 hours, was taken to dryness *in vacuo* under nitrogen. A white solid residue (m.p. 115–120°) was obtained, yield 3.2 g. Crystallization of the crude product from ethanol–*n*-hexane solution gave 1.70 g. (57%) of crystals melting at 131–135°. Four additional crystallizations from the same solvent combination raised the melting point to 136.5–137.5°.

A picrate (m.p. 123–124.5°) was prepared in the usual manner from aqueous solution in 92% yield. One crystallization from ethanol–water (20:1) solution raised the melting point to 124.5–125.5°. Both the free base and the picrate are described in Table II.

VILLE LASALLE, QUEBEC, CANADA

[CONTRIBUTION FROM THE OAK RIDGE NATIONAL LABORATORY,[1] BIOLOGY DIVISION]

Ion Exchange Studies of Transguanylation Reactions. II. Rearrangement of 3-Aminopropylisothiourea and N-Substituted Aminoethyl- and Aminopropylisothioureas to Mercaptoalkylguanidines and 2-Aminothiazolines or Penthiazolines

BY JOSEPH X. KHYM, DAVID G. DOHERTY AND RAYMOND SHAPIRA

RECEIVED JANUARY 27, 1958

Quantitative ion-exchange chromatography was used to establish that intratransguanylation is dependent on *p*H as well as on the number of carbon atoms between the amino and isothiourea groups. The aminoethyl- and aminopropylisothioureas intratransguanylate readily at neutral *p*H but S,4-aminobutylisothiourea does not. At *p*H's 3–6, 2-aminothiazolines and -penthiazolines are formed, whereas in strong alkali, mixtures of mercaptoguanidines and mercaptoamines are formed. N-Alkyl substitution on the various N atoms alters the *p*H at which intratransguanylation takes place as well as the rate of formation and composition of the products obtained.

Introduction

S,2-Aminoethylisothiourea (AET) undergoes a series of transformations through a cyclic intermediate to yield either 2-aminothiazoline (2-AT) or 2-mercaptoethylguanidine (MEG).[2] An ion-exchange analytical procedure, developed for examination of these reactions, established that they are *p*H dependent and that only in strongly alkaline medium does AET approach the behavior of a normal isothiourea and yield mixtures of MEG, 2-mercaptoethylamine (MEA) and dicyanodiamide (DCD).[3] Color tests showed that 3-aminopropylisothiourea (APT) as well as N-alkylamine and N′-guanyl N-substituted ethyl- and propylisothioureas can also participate in these transformations.[2] Dialkylaminoalkylisothioureas and 4-aminobutylisothiourea are stable at neutral *p*H and apparently do not intratransguanylate at any *p*H.[2] The interest in this class of compounds as potential radiation-protective agents[4] rendered their chemical properties of immediate interest. We therefore investigated the transformations of the higher homologs and variously N-substituted aminoalkylisothioureas to establish the conditions necessary for the preparation of the mercaptoalkylguanidines and thiazolines or penthiazolines in a pure state and to verify the structural limitations on the intratransguanylation reaction, which were hitherto based on color tests alone. Information of this nature may also be essential for an understanding of the biological conversions of these compounds in mammalian systems and of their pharmacological properties.

Experimental

Thiol Assay of Isothiourea Reactions.—We examined the rate of intratransguanylation and thiazoline formation

(1) Operated by Union Carbide Corporation for the U. S. Atomic Energy Commission.

(2) D. G. Doherty, R. Shapira and W. T. Burnett, Jr., THIS JOURNAL, **79**, 5667 (1957).

(3) J. X. Khym, R. Shapira and D. G. Doherty, *ibid.*, **79**, 5663 1957).

(4) D. G. Doherty and W. T. Burnett, Jr., *Proc. Soc. Exptl. Biol. Med.*, **89**, 312 (1955); R. Shapira, D. G. Doherty and W. T. Burnett, Jr., *Radiation Research*, **7**, 24 (1957).