1.0 g. (63%) of white prisms was obtained which melted at 170–171° dec., λ_{infl} 220 mμ (ε 38,000), $\lambda_{\max}$ 253 mμ (ε 13,000).

Anal. Calcd. for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; N, 8.90. Found: C, 65.44; H, 5.22; N, 8.87.

5-Chloro-3-phenylindole-2-carboxaldehyde Dimethylacetal (IV).—A solution of 4.5 g. (0.13 mole) of IIb in 150 ml. of methanol and 50 ml. of 1 *N* aqueous sodium hydroxide was refluxed for 3 hr. The solution was concentrated *in vacuo* and extracted with methylene chloride. The methylene chloride was removed and on addition of petroleum ether 3.1 g. of crystals were obtained which, on recrystallization from a mixture of ether and petroleum ether gave 0.1 g. of yellow needles melting at 231–237° (see Vb below).

From the mother liquor, 2.6 g. (69%) of white prisms was obtained which melted at 134–137°, $\lambda_{\max}$ 229 mμ (ε 35,000) and 267 (11,000).

Anal. Calcd. for $C_{17}H_{16}ClNO_2$: C, 67.66; H, 5.34; N, 4.64; CH_3O, 20.6. Found: C, 68.11; H, 5.80; N, 4.68; CH_3O, 20.9.

This compound was also obtained from Vb by heating in methanol with *p*-toluenesulfonic acid as catalyst.

5-Chloro-1-methyl-3-phenylindole-2-carboxaldehyde (Va). A. From Vb.—To a solution of 0.5 g. (0.002 mole) of Vb in 10 ml. of dimethylformamide was added 0.2 g. (0.004 mole) of a 50% suspension of sodium hydride in mineral oil. The mixture was kept for 15 min. at 36–40°, cooled to 25°, and 0.28 ml. of methyl iodide was added. After 15 min. the solution was poured into water and filtered from the precipitate, which was recrystallized from a mixture of methylene chloride and petroleum ether to give 0.23 g. (43%) of yellow needles melting at 156–159°, $\lambda_{\max}$ 252 mμ (ε 30,000) and 318 (22,500).

Anal. Calcd. for $C_{16}H_{12}ClNO$: C, 71.25; H, 4.48; N, 5.19. Found: C, 71.42; H, 4.72; N, 5.04.

B. From IIIa.—Hydrolysis of IIIa under basic conditions gave Va in moderate yield. However, an almost quantitative yield of Va was obtained in an attempt to distil IIIa in a bulb tube (0.1 mm., bath temp. *ca.* 150°).

5-Chloro-3-phenylindole-2-carboxaldehyde (Vb). A. From IIIb.—A solution of 0.5 g. (0.0016 mole) of IIIb in 10 ml. of methanol, 1 ml. of water, and 2 ml. of 1 *N* aqueous sodium hydroxide was refluxed for 2.5 hr., and evaporated. The residue was taken up in methanol, and hydrochloric acid was added. A yellow precipitate which formed was collected on a filter and recrystallized from methylene chloride to give 0.2 g. of yellow needles (Vb) melting at 237–240°, $\lambda_{\max}$ 251 mμ (ε 31,000) and 320 (24,000).

Anal. Calcd. for $C_{15}H_{\ 0}ClNO$: C, 70.46; H, 3.94; N, 5.48. Found: C, 70.56; H, 3.96; N, 5.49.

B. From IV.—A solution of 0.5 g. of IV in 15 ml. of methanol and 15 ml. of 1 *N* hydrochloric acid was heated to reflux for 5 min. Yellow crystals precipitated which melted at 235–240° and were identified with Vb.

7-Chloro-2,3,4,5-tetrahydro-1-methyl-1*H*-1,4-benzodiazepine (VI).—A solution of 1.7 g. (0.006 mole) of IIIa in 50 ml. of acetic acid was hydrogenated at 25° and 1 atm. using 0.2 g. of platinum oxide as catalyst. After an uptake of 335 ml. (*ca.* 0.014 mole) the hydrogen absorption had slowed down to a rate of *ca.* 20 ml. per hr. The solution was poured on ice, made basic with aqueous sodium hydroxide, and extracted with ether. The ether solution was evaporated, and the residue was extracted with boiling heptane. Addition of hydrogen chloride in ether precipitated crystals which, after recrystallization from a mixture of ethanol and ether, melted at 240–250° (VI).[5]

3-Phenylindole-2-carboxaldehyde (VII).—A solution containing 2.4 g. (0.008 mole) of IV and 8 ml. of 1 *N* sodium hydroxide in 100 ml. of ethanol was hydrogenated at atmospheric pressure and 25° using *ca.* 5 g. of Raney nickel as catalyst. The uptake stopped after the consumption of 170 ml. (*ca.* 0.007 mole) of hydrogen. The solution was filtered from the catalyst and evaporated *in vacuo*. The residue was shaken with dilute hydrochloric acid and extracted with ether. The ether solution on evaporation gave a crystalline residue which, after recrystallization from a mixture of methylene chloride and methanol, gave pale yellow needles melting at 195–197°. The yield was 1 g. (56%); $\lambda_{\max}$ 230 mμ (ε 16,500), 250 (22,500), and 320 (21,000).

Anal. Calcd. for $C_{15}H_{11}NO$: C, 81.43; H, 5.01. Found: C, 81.51; H, 4.95.

3-Phenylindole-2-carboxylic Acid (VIII).—To a solution of 0.11 g. of VII in a mixture of 30 ml. of ethanol and 20 ml. of acetone was added 0.17 g. of silver nitrate and 15 ml. of 0.1 *N* aqueous sodium hydroxide. The solution was stirred at 25° for 17 hr. and filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in dilute sodium hydroxide, and the solution was extracted with ether. On acidification of the aqueous layer a precipitate formed which was collected on a filter, dried, and recrystallized from a mixture of ether and petroleum ether. White prisms melting at 188–190° were obtained in *ca.* 34% yield (*ca.* 0.04 g.) and found to be identical with an authentic specimen.[6]

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Formation of 3-Substituted 2-Thio-4-oxo-hexahydro-1,3-diazines and 2-Substituted Imino-6-oxo-1,3-thiazanes from 1-Substituted 3-Carboxyethylthioureas and Interconversion of Both Cyclic Systems

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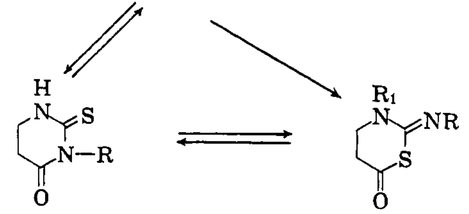
Recently we have described the cyclization of 3-carboxyethylthioureas (I),[1] and as a part of a continuing study we wish to report some further details and the interconversion of both cyclic systems, *e.g.*, 3-substituted 2-thio-4-oxo-hexahydro-1,3-diazines (II) to 2-substituted imino-6-oxo-1,3-thiazanes (III, $R_1 = H$) and *vice versa.*

$R-NH-CS-NH-CH_2CH_2COOH$

I



II

III

When the cyclization is carried out in acetic anhydride at 90–95°, the preponderant product is the thiazine derivative. From the mother liquor it is possible to isolate the diazine. Presented in Table I

TABLE I

SIMULTANEOUS FORMATION OF THIAZINE AND DIAZINE DERIVATIVES

R	Thiazines (III), yield, % $R_1 = H$	Thiazines (III), yield, % $R_1 = CH_3CO$	Diazines (II), yield, %	Ratio of III-II, mole
o-Tolyl	70		17	1:0.24
p-Methoxyphenyl		72.5	3.9	1:0.06
p-Ethoxyphenyl	68		7.6	1:0.11
o-Chlorophenyl	89.5		∽1	1:0.01
m-Chlorophenyl		54.5	12.8	1:0.28
p-Chlorophenyl	90		8	1:0.10

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[1] M. Derzaj-Bizjak, S. Oblak, and M. Tišler, *J. Org. Chem.*, **27**, 1343 (1962).

TABLE II

THIAZINES AND DIAZINES

					Carbon, %		Hydrogen, %		Nitrogen, %	
Compound	R	R_1	M.p., °C.	Formula	Calcd.	Found	Calcd.	Found	Calcd.	Found
II	*o*-Tolyl		172	$C_{11}H_{12}N_2OS$	59.99	59.47	5.49	5.49	12.76	12.89
III	*p*-Tolyl	CH_3CO	156	$C_{13}H_{14}N_2O_2S$	59.52	59.40	5.38	5.74	10.68	10.75
III	*p*-Methoxyphenyl[a]	CH_3CO	167	$C_{13}H_{14}N_2O_3S$	56.09	56.22	5.07	5.41	10.07	10.07
III	*o*-Chlorophenyl[b]	H	136	$C_{10}H_9ClN_2OS$	49.83	49.98	3.76	3.91	11.63	11.50
III	*m*-Chlorophenyl	CH_3CO	143	$C_{12}H_{11}ClN_2O_2S$	50.97	51.18	3.92	4.20	9.91	9.73
II	*p*-Chlorophenyl		204	$C_{10}H_9ClN_2OS$	49.83	49.60	3.76	4.01	11.63	11.60
III	*p*-Chlorophenyl	H	182	$C_{10}H_9ClN_2OS$	49.83	50.01	3.76	4.04	11.63	11.39

[a] Ultraviolet spectrum: λ_{max}^{EtOH} 2410 Å. (ϵ 16,700) and 2950 Å. (ϵ 11,500). [b] Ultraviolet spectrum: λ_{max}^{EtOH} 2450 Å. (ϵ 11,850) and 2950 Å. (ϵ 9860).

is the corresponding ratio for each pair of cyclic compounds. Besides reaction temperature,[1] we have also observed that the reaction time greatly influences the yield of the two products II and III. Thus yields of III in the 25–30% range were observed at 90° and a 30-min. reaction time and they are raised to 90% at the same temperature but prolonging the reaction time to 90 min. However, such conditions have led in some cases to acetylated products (III, $R_1 = CH_3CO$), which are readily distinguished from the unacetylated thiazines by means of their infrared spectra, exhibiting an additional peak in the 8.10-μ region and lacking NH stretching absorption.[2]

The passage from one cyclic system into the other is possible by different means. Acetic anhydride transforms the diazines into thiazines under conditions similar to those of the direct cyclization. On the other hand, diazines can be obtained from thiazines by treatment with dilute acetic acid or with pyridine; with the acetylated compounds the same conversion takes place. Although the diazines are readily hydrolyzed with aqueous alkali or acid, giving rise to the starting carboxyethylthioureas,[1] we were unable to isolate such compounds during the above-mentioned mutual conversions of both ring systems.

The interconversion of both ring systems can be followed spectrophotometrically as both heterocyclic systems are readily distinguished on the basis of their ultraviolet spectra. 1,3-Diazine derivatives have absorption characteristics almost identical with those of 2-thiouracil, whereas derivatives of 1,3-thiazine exhibit two maxima, one at about 2450 Å. and the second one at about 2950 Å. The first one apparently corresponds to the thiolactone group for maxima in this region (2350 Å.) have been registered with simple γ-thiolactones.[3] Thus we have followed spectrophotometrically the formation of a diazine (II, R = *o*-tolyl) from the corresponding thiazine with 10% acetic acid at 60° and the optimum conversion (88%) is achieved after 80 min. On the other hand the diazine (II, R = *o*-tolyl) is transformed into the thiazine by means of acetic anhydride at 60° after 120 min. (83% conversion). These results, representing optimum conversion, are most probably due to an equilibrium-controlled process.

Experimental[4]

General Remarks.—1-Substituted 3-carbethoxyethylthioureas were prepared as described previously,[1] but saponification of these esters was performed by an improved procedure: 0.05 m. of the corresponding ester was refluxed with an equivalent of 2 *N* sodium hydroxide until complete dissolution (about 15 min.). On acidification with hydrochloric acid (1:1) to pH 1–2 and standing on ice the crystals were collected. If necessary the product was crystallized from ethanol, but in this case the compounds were found to be sufficiently pure for further cyclization. By this procedure 1-(2′,4′-dimethylphenyl)-3-carboxyethylthiourea was prepared, m.p. 145°, yield 90%.

Anal. Calcd. for $C_{12}H_{16}N_2O_2S$: C, 57.13; H, 6.39; H, 11.11. Found: C, 57.37; H, 6.45; N, 10.99.

1-(*o*-Chlorophenyl)-3-carboxyethylthiourea was prepared without isolating the intermediate ester which was submitted to saponification as a crude reaction product; yield 65%, m.p. 139°.

Anal. Calcd. for $C_{10}H_{11}ClN_2O_2S$: C, 46.42; H, 4.28; N, 10.83. Found: C, 46.89; H, 4.75; N, 10.67.

Cyclization of 1-Substituted 3-Carboxyethylthioureas.—A 0.02-mole sample of the corresponding acid I, 100 ml. of acetic anhydride, and few drops of concentrated sulfuric acid were heated 1.5 hr. at 90–95° on a water bath. On cooling, the reaction mixture was poured into about 300 ml. of water, stirred, and left aside for 15 min.; the upper liquid was decanted from the oily residue or filtered if the compound crystallized immediately. The crude product was left overnight for crystallization, and purification from ethanol yielded the pure thiazine derivative. The residual mother liquor was evaporated almost to dryness and the remaining crystals of the diazine were crystallized from ethanol. The cyclized products are presented in Table II. The acetylated thiazines are stable compounds and the acetyl group is not removed in the course of their isolation, but is removed during their conversion into the diazines.

Interconversions of Diazines and Thiazines. A.—A 1.2-g. sample of III (R = *o*-Cl-C_6H_4, R_1 = H) was heated with 10% acetic acid (30 ml.) on a water bath; the solution was evaporated almost to dryness. The residue was filtered and crystallized from ethanol to yield 1 g. (83%) of the diazine (II, R = *o*-Cl-C_6H_4), m.p. 189°. The ultraviolet spectrum showed λ_{max} 2800 Å. (ϵ 12,800).

Anal. Calcd. for $C_{10}H_9ClN_2OS$: C, 49.83; H, 3.76; N, 11.63. Found: C, 50.22; H, 3.27; N, 11.49.

B.—III (R = *p*-CH_3O-C_6H_4, $R_1 = CH_3CO$; 1.6 g.) was converted similarly to the diazine (II, R = *p*-CH_3O-C_6H_4), yield 1.5 g. (94%), m.p. 236°.[1]

C.—II (R = C_6H_5, 1.15 g.), acetic anhydride (57.5 ml.), and a few drops of concentrated sulfuric acid were heated on a water bath at 75° for 2 hr. The solvent was evaporated *in vacuo*; the residue was poured into 20 ml. of water. The crystals which separated were purified from ethanol to yield 0.9 g. (78.5%) of the thiazine (III, R = C_6H_5, R_1 = H), m.p. 142°.[1]

D.—III (R = C_6H_5, R_1 = H; 1.0 g.) and 20 ml. of pyridine were heated on a water bath for 15 min., the solvent was evaporated *in vacuo* to dryness, and the residue was triturated with water. The product obtained was crystallized repeatedly from ethanol, giving the diazine (II, R = C_6H_5), m.p. and m.m.p. 228°

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(2) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen and Co., London, 1960, p. 249.

(3) C. M. Stevens and D. S. Tarbell, *J. Org. Chem.*, **19**, 1996 (1954).

(4) All melting points were determined on a Kofler hot stage and are corrected.