[CONTRIBUTION FROM THE KODAK RESEARCH LABORATORIES]

2-Carboxymethylmercaptobenzimidazole and Related Compounds*

J. A. VANALLAN

* Communication No. 1737 from the Kodak Research Laboratories

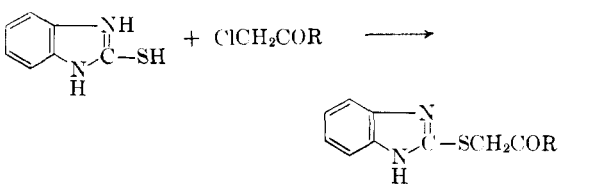
Received July 14, 1955

2-Mercaptobenzimidazole, 2-mercaptotetrahydropyrimidine, and 2-mercaptoimidazoline react with chloroacetic acid to give the corresponding 2-carboxymethylmercapto derivatives. These may be cyclized to thiazolidones. The formation of benzal derivatives of the thiazolidones and quaternary salts is described.

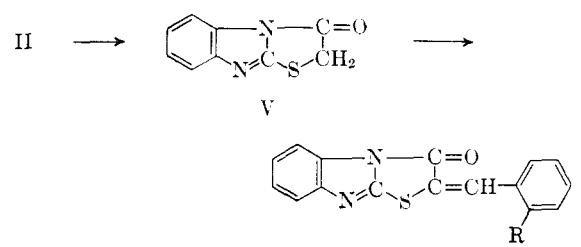
In an earlier paper[1] the failure of 3-carboxymethyl-2-iminobenzothiazoline to cyclize was mentioned, and this behavior was contrasted with the heterolog in the pyridine series. Attention subsequently was turned to the isomeric system that results from the addition of chloroacetic acid to 2-mercaptobenzimidazole.[2] This adduct was expected to be comparable to the isomeric 3-carboxymethyl-2-iminobenzothiazoline. This present paper contains observations on the reaction of 2-mercapto benzimidazole and related compounds with sodium chloroacetate and with ethyl chloroacetate.

Sodium chloroacetate in aqueous alcoholic solution reacts with the mercapto group of 2-mercaptobenzimidazole to give 2-carboxymethylmercaptobenzimidazole (I) with the elimination of sodium chloride. Ethyl chloroacetate gives the addition product from which the free ester (II) is obtained by the action of dilute sodium carbonate. Warm potassium hydroxide in methanol converts the ester into I. The ester (II) with ammonia and piperidine gives, respectively, the amide (III) and the piperidide (IV). On refluxing, the ester (II) in *o*-dichlorobenzene cyclization[3] occurs in poor yield, with the formation of 3-oxo-2,3-dihydro-1-thia-3a,8-diazacyclopent[*a*]indene (V). This latter compound is essentially a thiazolidone fused by means of a phenylene group through the 2- and 3-positions and as such may be condensed with aldehydes to form the corresponding benzal derivative. Thus, V with benzaldehyde and *o*-methoxybenzaldehyde gives, respectively, the 2-benzal- (VI) and the 2-(2-methoxybenzal)-3-oxo-2,3-dihydro-1-thia-3a,8-diazacyclopent[*a*]indene (VII). More conveniently VI and VII may be obtained directly from II and the appropriate aldehyde in methanol, with piperidine as a catalyst. The heterocyclic compound VII is readily cleaved with alcoholic potassium hydroxide to the corresponding acid; however, recrystallization of this acid regenerates VII.

The benzal derivatives VI and VII do not form quaternary salts with methyl iodide. The ester (II), however, on treatment with methyl iodide, undergoes an unusual cleavage between the methylene group and the sulfur, with the formation of 1-methyl-2-methylmercaptobenzimidazole hydriodide. This latter salt was synthesized independently from 2-mercaptobenzimidazole and methyl iodide.



I R = OH III R = NH_2
II R = OC_2H_5 IV R = $C_5H_{10}N$



V

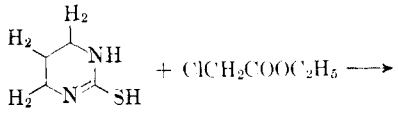
VI R = H
VII R = OCH_3

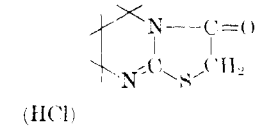
The ready cyclization of the benzal derivatives as just described led to the investigation of two other hetero-logs. 2-Mercapto-3,4,5,6-tetrahydropyrimidine with sodium chloroacetate gave a product which could not be purified. However, 3-oxo-2,3,3a,4,5,6-hexahydro-1-thia-3a,7-diazaindene hydrochloride (VIII)[4] is obtained in 97% yield when 2-mercapto-3,4,5,6-tetrahydropyrimidine is heated for a few hours with excess ethyl chloroacetate. Here again VIII as a thiazolidone is reactive as evidenced by its ready condensation with benzaldehyde and *o*-methoxybenzaldehyde to give, respectively, 2-benzal- (IX) and 2-(2-methoxybenzal)-3-oxo-2,3,-3a,4,5,6-hexahydro-1-thia-3a,7-diazaindene (X).

2-Mercaptoimidazoline and sodium chloroacetate in water react to give 2-carboxymethylmercaptoimidazoline (XI). The structure of an inner isothiouronium salt is assigned to XI, since it may be

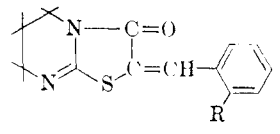
(1) Allen and VanAllen, *J. Org. Chem.*, **13**, 603 (1948).
(2) VanAllan and Deacon, *Org. Syntheses*, **30**, 56 (1950).
(3) Wilson and Stephen, *J. Chem. Soc.*, 2532 (1926).

(4) Dr. A. M. Patterson recommends the name 5*H*-thiazolo[3,2-*a*]pyrimidine-3[2*H*]-one,6,7-dihydro for VIII. Private communication.



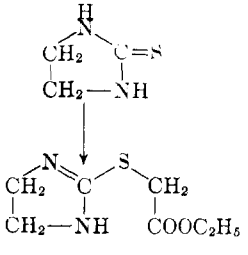


VIII

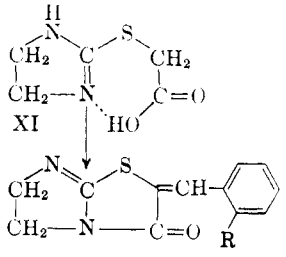


IX R=H
X R=OCH$_3$

crystallized unchanged[1] from dilute sodium carbonate. Ethyl chloroacetate likewise reacts readily with the thione in alcoholic solution. Since the reaction product is difficult to isolate, benzaldehyde or *o*-methoxybenzaldehyde is added to the solution of the addition product, the structure of which is assumed to be XIa by analogy with II, to give, respectively, 2-benzal- (XII), and 2-(2-methoxybenzal)-3-oxo-3,3a,4,5-tetrahydro-2H-1-thia-3a,6-diazapentalene (XIII). The condensation of XI with the appropriate aldehyde in acetic acid with a small amount of sodium acetate likewise gives the unsaturated compounds XII and XIII.[5] The benzal



XIa



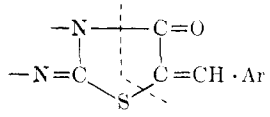
XII R=H XIII R=OCH$_3$

derivatives (IX, X, XII, XIII), in contrast to their open-chain analogs, readily form salts with methyl iodide.

The following evidence is advanced for the structures assigned to V and VIII: 1. It is well known that ethyl chloroacetate forms thiazolidones from various thioureas, a carbon-sulfur linkage being formed. Since the thiones used in this work are, in reality, symmetrical cyclic thioureas, there is no ambiguity as to the direction of cyclization. 2. The ultraviolet absorption spectra of the benzal derivatives IX and XII are essentially identical with their open-chain analog, 3-ethyl-2-ethylimino-5-benzalthiazolidone, the structure of which is established. It follows from ultimate analyses that the adducts of the benzal derivatives with methyl iodide are simple salts. Which nitrogen is quaternized is, of course, doubtful, but the nitrogen atom not common to two rings is assumed to be the more basic nitrogen since it is not adjacent to a carbonyl group; as a consequence of its greater basicity, it should quaternize more readily.

It is of interest that refluxing VIII or XI for a few minutes with acetic anhydride gives very intense yellow dyes, the structures of which are uncertain.

Discussion of the ultraviolet absorption spectra. In discussing the ultraviolet spectra of these compounds, it is convenient to consider them as 2-iminothiazolidones in which the principal site of ultraviolet absorption lies in the α,β-unsaturated carbonyl group as indicated below. The residue of



the molecule would be expected to be relatively unimportant in respect to absorption. However, the substituents on the nitrogen in this series do have considerable influence on the absorption.

3-Ethyl-2-ethylimino-5-benzalthiazolidone (XIV) (λ = 326 mμ, log ϵ 4.40) was chosen as a reference compound. In XII (λ = 320 mμ, log ϵ 4.46), the

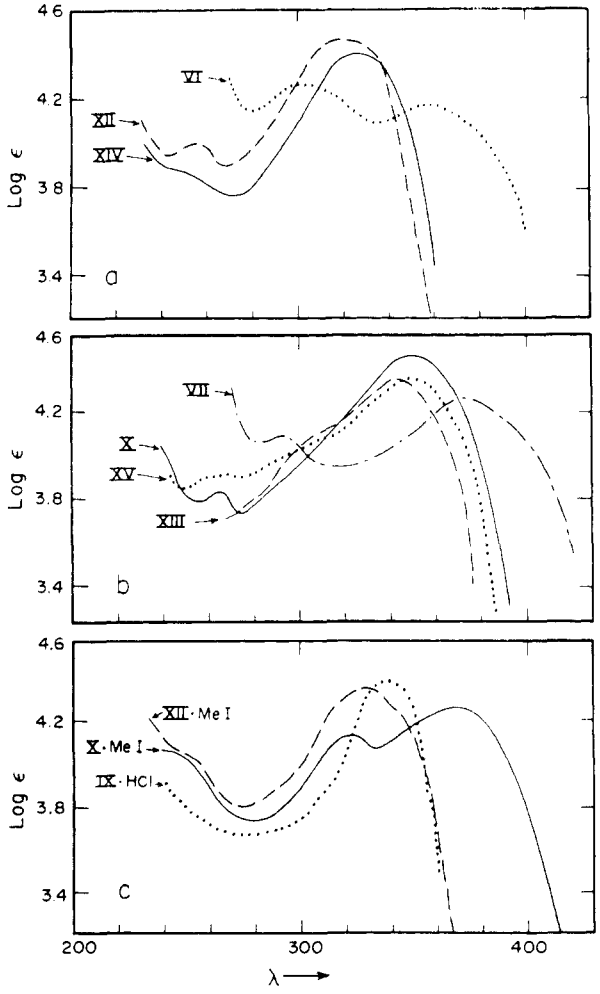


FIG. 1.—ULTRAVIOLET-ABSORPTION CURVES AS DETERMINED IN METHANOL AS A SOLVENT.

(5) Dr. A. M. Patterson recommends the name imidazo-[2,1-β]thiazol-3(2H)-one,5,6-dihydro for the parent base of XII and XIII. Private communication.

TABLE I
PHYSICAL PROPERTIES OF COMPOUNDS STUDIED

Compound	M.P., °C.	Emp. formula	Calc'd C	Calc'd H	Found C	Found H	Yield, %
I	228–230 dec[a]	$C_9H_8N_2O_2S$[d]	51.9	3.8	51.9	3.7	82
II	93–94[a]	[e] and [f]					83
III	218[a]	$C_9H_9N_3OS$	52.2	4.4	52.1	4.7	94
IV	158–159[a]	$C_{14}H_{17}N_3OS$[d]	60.8	6.2	60.6	6.3	91
V	182[a]						30
VI	226[b]	$C_{16}H_9N_2OS$[i]	69.2	3.3	69.2	3.7	85
VII	210[c]	$C_{17}H_{12}N_2O_2S$[i]	66.2	3.9	66.4	3.8	87
VIII·HCl[k]	260[a]	$C_6H_8N_2OS\cdot HCl$[g]	37.5	4.7	37.4	4.5	97
VIII·Picrate[l]	195[c]	$C_{12}H_{11}N_5O_8S$[j]	37.4	2.9	37.8	2.9	
IX	135[a]	$C_{13}H_{12}N_2OS$[g]	64.0	4.9	63.8	4.8	83
IX·HCl[m]	223–225[a]	$C_{13}H_{12}N_2OS\cdot HCl\cdot H_2O$[h]	52.7	4.0	52.8	4.4	71
X	132–133[b]	$C_{14}H_{14}N_2O_2S$[d]	61.2	5.1	61.3	5.1	84
X·MeI[n]	235–237 dec[c]	$C_{15}H_{17}O_2N_2SI$[g]	43.2	4.1	43.3	4.4	70
XI	185–187 dec[a]	$C_5H_8N_2O_2S$[h]	37.5	5.0	37.7	5.1	62
XII	180[b]	$C_{12}H_{10}N_2OS$[i]	62.6	4.3	63.0	4.3	67
XIII	214–215[c]	$C_{13}H_{12}N_2O_2S$[i]	59.8	4.3	59.7	4.5	73
XIII MeI[o]	243–245 dec[c]	$C_{13}H_{15}IN_2O_2S$[h]	40.0	3.8	40.2	3.5	78
XIV	74[b]	$C_{14}H_{16}N_2OS$[g]	64.5	6.2	64.4	6.1	48
XV	85[c]	$C_{15}H_{18}N_2O_2S$[g]	62.0	6.2	62.1	6.2	57
IX·MeI[p]	272–275[c]	$C_{14}H_{15}IN_2OS$[h]	43.5	3.9	43.3	3.8	91
XII·MeI	238[c]	$C_{13}H_{13}IN_2OS$[h]	41.9	3.5	41.9	3.9	88

[a] White. [b] Pale yellow. [c] Yellow. [d] Butanol. [e] Benzene. [f] Ligroin, b.p. 90–120°. [g] Ethanol. [h] Water. [i] Xylene. [j] Acetonitrile. [k] Calc'd: N, 14.5; S, 16.5. Found: N, 14.5; S, 15.5. [l] Calc'd: N, 18.2. Found: N, 18.6. [m] Calc'd: N, 9.4. Found: N, 9.4. [n] Calc'd: I, 30.0. Found: I, 30.1. [o] Calc'd: I, 32.6. Found: I, 32.4. [p] Calc'd: N, 7.3. Found: N, 7.4.

nitrogen atoms are joined by an ethylene group, which introduces strain in the molecule, resulting in a small (6 mμ) hyposochromic shift of the maximum. In VI, the nitrogens are fused through a phenylene group, which results in the splitting of its absorption spectra into two bands, λ = 300 mμ, log ε 4.22 and λ = 357 mμ, log ε 4.17, indicating considerable contribution of the phenylene group to the hybrid structures (Figure 1a).

The same relationship as described for XII and XIV exists between 3-ethyl-2-ethylimino-5- (2-methoxybenzal)thiazolidone XV; (λ = 348 mμ, log ε 4.13) and XIII; (λ = 342 mμ, log ε 4.12). There is, of course, a large bathochromic shift (22 mμ) as a consequence of the introduction of the *ortho*-methoxy group in these compounds. The less strained X (λ = 350 mμ, log ε 4.44) has its $\lambda_{max.}$ shifted 8 mμ toward longer wavelengths than XIII. In comparing VI with VII, it will be noted that the peaks in VII are farther apart. The short-wavelength band is shifted bathochromically about 10 mμ and the long-wavelength band about 12 mμ (Figure 1b).

The quaternization of XII to its methiodide (λ = 330 mμ, log ε 4.36) produces a small (10 mμ) bathochromic shift but does not otherwise appreciably alter the shape of the curve. The hydrochloride salt of IX (λ = 340 mμ, log ε 4.37) absorbs at slightly longer wavelength than XII·MeI as a consequence of its less-strained structure. The spectrum of the methiodide salt of X (λ = 322 mμ, log ε 4.13 and λ = 370 mμ, log ε 4.26) again reflects the powerful auxochromic effect of the *ortho* methoxy group.

EXPERIMENTAL

2-Carboxymethylmercaptobenzimidazole (I). 2-Mercaptobenzimidazole[2] (15 g., 0.1 mole), 14 g. (0.11 mole) of sodium chloroacetate, and 100 ml. of 50% aqueous methanol were heated on the steam-bath for five hours. After cooling, the product was filtered off, washed with water, and dried. For yields and analytical results, see the table.

2-Carboxymethylmercaptoimidazoline (XI). This compound was prepared in the same way from 102 g. of 2-mercaptoimidazoline,[6] 140 g. of sodium chloroacetate, and 200 ml. of water which gave 102 g. of XI.

3-Oxo-2,3,3a,4,5,6-hexahydro-1-thia-3a,7-diazaindene (VIII). 2-Mercapto-3,4,5,6-tetrahydropyrimidine[7] (60 g.) (prepared in 85% yield from trimethylenediamine and carbon disulfide in a manner analogous to that of 2-mercaptoimidazoline) and 100 ml. of ethyl chloroacetate were heated to 140–145° for four hours. After cooling, the reaction mixture, which had set to a solid crystalline mass, was filtered, washed with benzene, and dried.

2-Carboethoxymethylmercaptobenzimidazole (II). This compound was prepared in a similar fashion. The hydrochloride initially obtained was dissolved in water, treated with Norit, and the free base was liberated with dilute sodium carbonate.

2-Carbamylmethylmercaptobenzimidazole (III). Compound II (4 g.) was dissolved in 10 ml. of methanol, and 25 ml. of concentrated ammonia was added, forming a clear solution. After three hours' reflux, the precipitated amide was filtered and dried.

N,N-pentamethylene-2-carbamylmethylmercaptobenzimidazole (IV). Equimolecular equivalents of the components in alcohol were refluxed for five hours. The alcohol was evaporated, and the residue was triturated with ligroin and recrystallized from benzene, and then from butanol.

3-Oxo-2,3-dihydro-1-thia-3a,8-diazacyclopent[a]indene[3] (V). 2-Carboethoxymethylmercaptobenzimidazole (30 g.) in 60 ml. of *o*-dichlorobenzene was refluxed for one hour while

(6) VanAllan, *Org. Syntheses*, **26**, 34 (1946).
(7) Duden and Scharff, *Ann.*, **288**, 232 (1895).

continuously removing the alcohol; 3.6 ml. (theory 6.8 ml.) was collected. The mixture became quite dark so refluxing was discontinued. On cooling, 10 g. of dark-colored crystals separated, m.p. 178–181°.

2-Benzal-3-oxo-2,3-dihydro-1-thia-3a,8-diazacyclopent[a]-indene (VI). 3-Oxo-2,3-dihydro-1-thia-3a,8-diazacyclopent-[a]indene (3.8 g.), 3.0 ml. of benzaldehyde, 2 ml. of piperidine, and 30 ml. of butanol were refluxed two hours and then were cooled. The product was collected, washed with methanol, and dried. Alternately, 6.0 g. of 2-carboethoxymethylmercaptobenzimidazole, 6 ml. of benzaldehyde, 6 ml. of piperidine, and 100 ml. of methanol, after refluxing for four hours, gave VI.

2-(2-Methoxybenzal)-3-oxo-2,3-dihydro-1-thia-3a,8-diazacyclopent[a]indene (VII). This compound was prepared in a manner analogous to that for VI; it may also be prepared from I. Thus, a mixture of 5.0 g. of 2-carboxymethylmercaptobenzimidazole, 4 g. of sodium acetate, 4 ml. of *o*-methoxybenzaldehyde, and 50 ml. of acetic acid was refluxed for five hours, and then was cooled to 15°. The product which precipitated was collected by filtration, washed with methanol, and dried. The yields by any of these methods varied between 80–90%.

2-Benzal- (IX) and *2-(2-methoxybenzal)-3-oxo-2,3,3a,4,5,6-hexahydro-1-thia-3a,7-diazaindene* (X). These substances were made from 3-oxo-2,3,3a,4,5-hexahydro-1-thia-3a,7-diazaindene hydrochloride and the appropriate aldehyde in methanol; enough piperidine was used to make the reaction mixture basic.

2-Benzal-3-oxo-3,3a,4,5-tetrahydro-2H-1-thia-3a,6-diazapentalene (XII). This material was prepared by the acetic acid method as described for VII, or directly from the addition product of 2-mercaptoimidazoline and ethylchloroacetate *in situ*. Thus, 2-mercaptoimidazoline (10.2 g.), ethyl chloroacetate (10.5 ml.), 8.5 ml. of pyridine, and 60 ml. of ethanol were refluxed for five hours. Then 10.5 ml. of benzaldehyde and 7 ml. of piperidine were added and refluxing was continued for three hours. On chilling, the product separated.

2-(2-Methoxybenzal)-3-oxo-3,3a,4,5-tetrahydro-2H-1-thia-3a,6-diazapentalene (XIII). When *o*-methoxybenzaldehyde was substituted for benzaldehyde in the above procedures, XIII was obtained.

2-Benzal-3-oxo-3,3a,4,5-tetrahydro-2H-1-thia-3a,6-diazapentalene methiodide (XII·MeI). Two grams of 3-oxo-3,3a,4,5-tetrahydro-1-thia-3a,6-diazapentalene was dissolved in 10 ml. of nitrobenzene and 10 ml. of methyl iodide was added; after 10 minutes on the steam-bath, the reaction mixture had set to a solid mass of yellow crystals. Warming was continued for a further hour, after which the product was filtered and dried. The methiodides of IX, X, and XIII were prepared in a similar fashion.

3-Ethyl-2-ethylimino-4-thiazolidone. A mixture of 87 g. of 1,3-diethylthiourea, 70 g. of chloroacetic acid, 63 g. of sodium acetate, and 500 ml. of alcohol was refluxed for four hours. Most of the alcohol was removed *in vacuo* and water was added to the residue; the oil which separated soon solidified. This crude product was recrystallized from methanol and water. Yield, 47 g. 41%, m.p. 38°.

Anal. Calc'd for $C_7H_{12}N_2OS$: C, 48.9; H, 6.9. Found: C, 48.7; H, 7.0.

5-Benzal (XIV) *and 5-(2-methoxybenzal)-3-ethyl-2-ethyliminothiazolidone* (XV). These compounds were prepared from 3-ethyl-2-ethylimino-4-thiazolidone and the corresponding aldehyde in methanol, with piperidine as a catalyst, in a manner analogous to that given for the preparation of VI.

1-Methyl-2-methylmercaptobenzimidazole hydriodide. Two grams of II was dissolved in 5 ml. of nitrobenzene and 4 ml. of methyl iodide was added. After warming to 50–60° for 1.5 hours, the reaction mixture was cooled and the crystals which had formed were separated by filtration and recrystallized from ethyl alcohol or water to give 0.9 g. of white crystals, m.p. 204–206° dec.

Anal. Calc'd for $C_9H_{11}IN_2S$: C, 35.3; H, 3.6; I, 41.5. Found: C, 35.7; H, 3.5; I, 41.9.

(The reaction mixture contains a strong lachrymator, probably ethyl iodoacetate.) 1-Methyl-2-methylmercaptobenzimidazole hydriodide was also synthesized by quaternization of 2-mercaptobenzimidazole with methyl iodide to give 2-methylmercaptobenzimidazole, m.p. 208°, large white crystals from ethanol.

Anal. Calc'd for $C_8H_8N_2S$: C, 58.5; H, 4.9. Found: C, 58.2; H, 5.3.

The 2-methylmercaptobenzimidazole again was quaternized with methyl iodide to give 1-methyl-2-methylmercaptobenzimidazole hydriodide, m.p. 206° dec., which gave no depression of melting point when mixed with the product from II and methyl iodide.

Acknowledgment. We are indebted to E. E. Richardson of the Physics Division, Kodak Research Laboratories, for the determination of the ultraviolet absorption spectra given in Figure 1.

ROCHESTER, NEW YORK