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The Rearrangement of 2-Carboxymethylmercaptoimidazolidine

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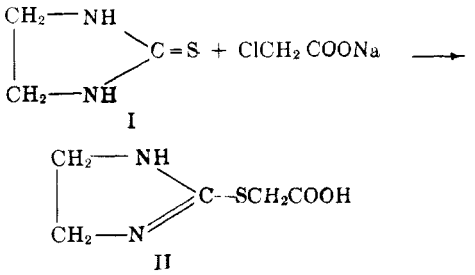
2-Mercaptoimidazoline reacts with chloroacetic acid under acidic conditions to give 3-(β-aminoethyl)-2,4-thiazolidinedione hydrochloride. The structure of the latter substance is established by its chemical reactions and by comparison of its spectrum with that of known compounds.

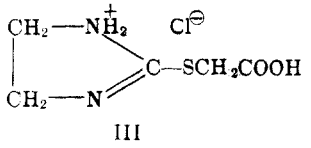
In an earlier paper,[1] a substance shown to be 2 - carboxymethylmercaptoimidazoline (II) was obtained by the interaction of 2-mercaptoimidazoline (ethylenethiourea, I) and aqueous sodium chloroacetate.

By mildly treating substance II with hydrochloric acid or chloroacetic acid, two salts, which may be represented by III or IV, resulted. Prolonged heating of either of these two mixtures gave

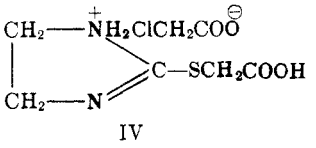


I

II



III

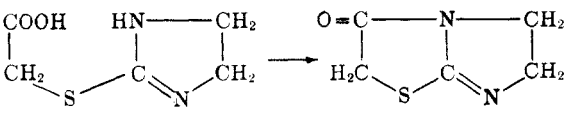


IV

a third product, a salt melting at 223° with decomposition. Johnson and Edens[2] also obtained a salt melting at 223° with decomposition, to which they assigned structure III, by refluxing three hours one equivalent of 2-mercaptoimidazoline[3] with two of chloroacetic acid in aqueous solution. As it appeared that these two salts were the same and could not also be represented as the simple hydrochloride, III, it was necessary to investigate them further.

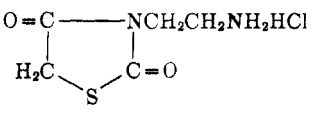
A structure that is in agreement with most of the observed properties of the product is that of the thiazolidinedione (V). Its formation can be reasonably accounted for as proceeding through the bicyclic intermediate (VI);[1] this involves ring closure followed by ring cleavage in a different way.

Evidence for structure V includes formation of a monobenzoyl derivative (VII), trimethylammonium salt (VIII), on exhaustive methylation, and an *o*-methoxybenzal derivative, (IX); the latter was also prepared by the action of dilute hydrochloric



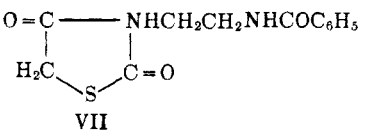
II

VI

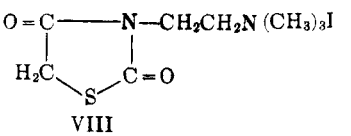


V

acid on the thiadiazapentalene derivative (X).[1] On treatment with benzoyl chloride in pyridine, the benzal derivative (IX) yields the benzoyl derivative (XI) identical with the one obtained by condensing the aldehyde with the benzoyl derivative (VII) in acetic acid. Finally, substance V gives a positive Feigl test for a sulfhydryl group, as does the unsubstituted 2,4-thiazolidinedione itself.



VII



VIII

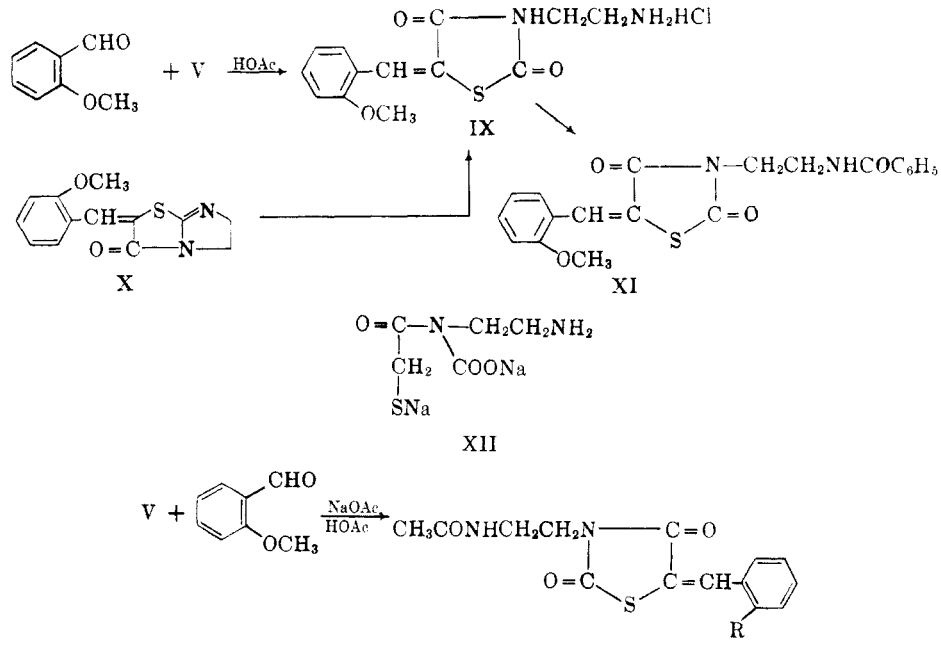
Titrations of substances V and VIII show that three equivalents of alkali are consumed (Fig. 1), whereas only one is required by a structure such as II. This is interpreted as one equivalent for the halogen acid and two to open the ring and neutralize the resulting sulfhydryl and carboxyl groups. Easy ring cleavage is a characteristic property of thiazolidones, as is shown by the Feigl test. Presumably, the salt resulting from the cleavage of V has the structure shown in XII.

It is interesting to note that if the condensation

(1) VanAllan, *J. Org. Chem.*, **21**, 24 (1956).

(2) Johnson and Edens, *J. Am. Chem. Soc.*, **64**, 2708 (1942).

(3) Allen, Edens, and VanAllan, *Org. Syntheses*, **26**, 34 (1946).

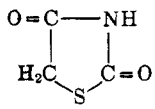


XIV R = OCH_3

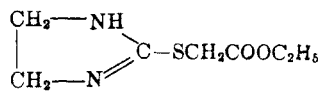
XIVa R = H

of *o*-methoxybenzaldehyde with V is carried out in acetic acid and in the presence of one equivalent of sodium acetate, the acetamido derivative (XIV) is formed. The latter is also formed by heating IX in acetic acid containing one equivalent of sodium acetate. It is a remarkably stable substance. It is unchanged by recrystallization from acetic anhydride or boiling with methanolic hydrogen chloride or thionyl chloride. It distills unchanged at 10 mm., and even survives heating to 250–270° for 1.5 hr. If the condensation is carried out in propionic or valeric acid, the corresponding propionyl and valeryl derivatives are obtained.

Discussion of ultraviolet and infrared absorption spectra. The ultraviolet absorption curves are very similar in the cases of substances V and 2,4-thiazolidinedione (XIII), but different from those of the



XIII



XV

imidazole (II) and its ethyl ester (XV) (Table I). In the benzal series, the close similarity between the ultraviolet curves of IX and XIV and that of 5-(*o*-methoxybenzal)-2,4-thiazolidinedione (XVI) (see Fig. 2) clearly supports the structure assigned here.

When XVI is used as a comparison material to determine the position of carbonyl absorption in the infrared region for this type of compound, it is seen that in both V and XIV, the position of carbonyl absorption is approximately the same as in XIII, *i.e.*, at 5.8 and 6.0 μ.

TABLE I

ABSORPTION OF HETEROCYCLIC SUBSTANCES IN 0.1 *N* HCl

No.	$\lambda_{max.}$ mμ	ϵ at $\lambda_{max.}$
V	230	3620
XIII	229	3800
II	223	8650
XV	221	8500

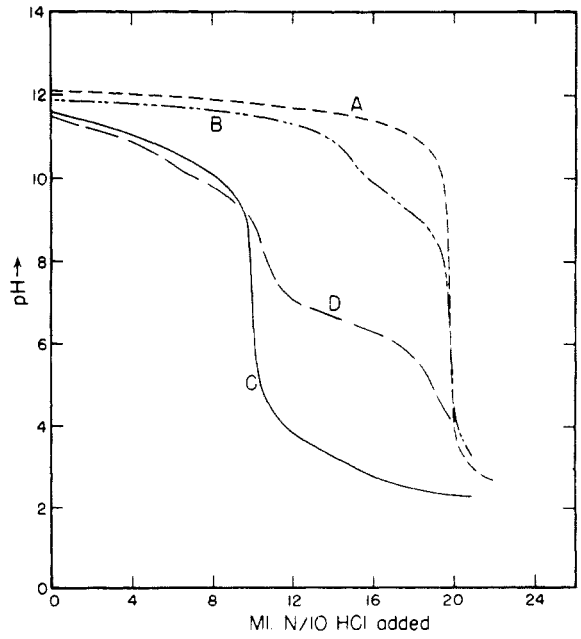


FIG. 1.—BACK-TITRATION OF SAMPLES II, V AND VIII DISSOLVED IN EXCESS SODIUM HYDROXIDE A: 2.00 meq. NaOH; B: 2.00 meq. NaOH + 0.50 mmol. of II; C: 2.00 meq. NaOH + 0.50 mmol. of V; D: 2.00 meq. NaOH + 0.50 mmol. of VIII.

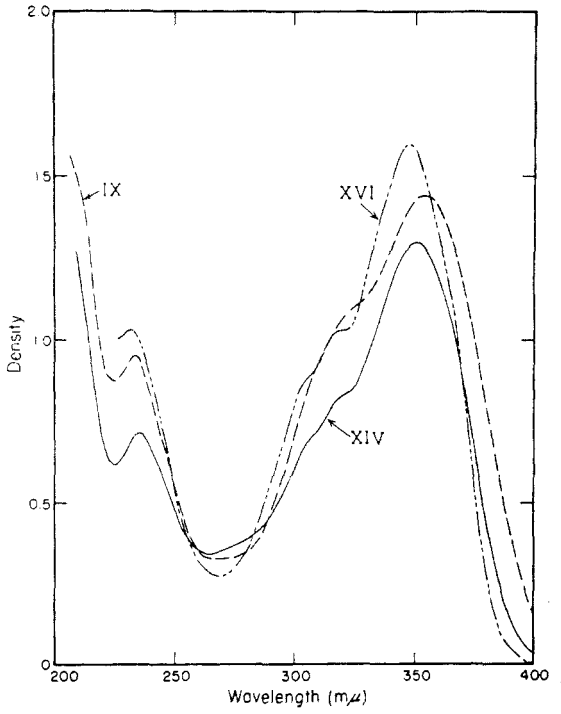


FIG. 2 —ULTRAVIOLET ABSORPTION SPECTRA OF IX (IN WATER); XIV (IN METHANOL) AND XVI (IN DIOXANE) ALL AT A CONCENTRATION OF 5×10^{-5} MOLAR

These results establish beyond a reasonable doubt that the hydrochloride, m.p. 223°, described by Johnson and Edens[2] as having structure III, has the structure V.

EXPERIMENTAL

3-(β-Aminoethyl)-2,4-thiazolidenedione hydrochloride (V). A mixture of 100 g. each of 2-mercaptoimidazoline and chloroacetic acid in 100 ml. of water was heated to boiling. Solution was complete in about 3 min.; 20 ml. of concentrated hydrochloric acid then was added and the mixture was refluxed for 3 hr. The water was removed under a vacuum, leaving a crystalline residue; 350 ml. of ethyl alcohol was added to this and the mixture was boiled for 20 min. After chilling, the product was collected by filtration. The yield was 178 g., m.p. 221–223°. A sample was crystallized from methanol, m.p. 227–228°.

Anal. Calc'd for $C_5H_9ClN_2O_2S$: C, 30.5; H, 4.6. Found: C, 30.7; H, 5.0.

2-Carboxymethylmercaptoimidazoline, chloroacetic salt (IV). 2-Mercaptoimidazoline (4 g.) and 6 g. of chloroacetic acid in 15 ml. of water were heated to boiling for 5 min. and then were cooled in the ice chest. The product separated as white crystals. The yield was 3.1 g. A sample for analysis was crystallized from water; m.p. 134°.

Anal. Calc'd for $C_7H_{11}ClN_2O_4S$: C, 33.1; H, 4.3. Found: C, 33.4; H, 4.5.

2-Carboxymethylmercaptoimidazoline hydrochloride (III). 2-Carboxymethylmercaptoimidazoline (II) (2 g.) was added to 5 ml. of concentrated hydrochloric acid; the solid quickly went into solution. The mixture was heated on the steam-bath for 5 min., and the excess hydrochloric acid then was removed under a vacuum. The crystalline residue was crystallized from isopropyl alcohol; m.p. 128–129°.

Anal. Calc'd for $C_5H_9ClN_2O_2S$: C, 30.6; H, 4.6. Found: C, 30.9; H, 4.8.

3-(β-Benzamidoethyl)-2,4-thiazolidinedione (VII). To a stirred solution of 10 g. of 3-(β-aminoethyl)-2,4-thiazolidinedione hydrochloride (V) and 12 g. of sodium acetate in 50 ml. of water was added slowly, and with stirring, 8 g. of benzoyl chloride, at 15–20°. After 2 hours, 4 g. of sodium bicarbonate was added and stirring was continued for 0.5 hr. more. The white solid which had separated was removed by filtration, resuspended in a dilute aqueous solution of sodium bicarbonate, and again filtered. Two crystallizations from ethanol yielded 6 g. of white crystals, m.p. 135–136°.

Anal. Calc'd for $C_{12}H_{12}N_2O_3S$: C, 54.6; H, 4.6. Found: C, 54.7; H, 4.9.

β-(2,4-Thiazolidinedione-3)ethyltrimethylammonium iodide (VIII). A mixture of 9.8 g. of V, 23 g. (10 ml.) of methyl iodide, and 16.4 g. of sodium acetate in 100 ml. of methyl alcohol was refluxed for 5 hr. The alcohol was evaporated and 100 ml. of cold water was added. The insoluble portion (18 g.) was filtered off and dried. One crystallization from water gave 11 g. of product, m.p. 300° dec.

Anal. Calc'd for $C_8H_{15}IN_2O_2S$: C, 29.6; H, 4.8; N, 8.5; S, 9.7. Found: C, 29.3; H, 4.9; N, 8.6; S, 9.8.

3-(β-Aminoethyl)-5-(2-methoxybenzal)-2,4-thiazolidinedione hydrochloride (IX). This compound was prepared by two methods: (a) A solution of 40 g. of V and 35 ml. of 2-methoxybenzaldehyde in 250 ml. of acetic acid was refluxed for 4 hr. The mixture was cooled to room temperature and the yellow precipitate was filtered. One crystallization from water gave 59 g. of IX, m.p. 285–286° dec. (b) A solution of 4 g. of 2-(2-methoxybenzal)-3-oxo-4,5-dihydro-1-thia-3a,6-diazapentalene (X)[1] in 60 ml. of water and 20 ml. of concentrated hydrochloric acid was refluxed for 2 hr. On initial warming, complete solution ensued. After about 1 hr., a heavy yellow precipitate formed. The precipitate was collected by filtration and crystallized from water to give 3.5 g. of IX.

Anal. Calc'd for $C_{13}H_{14}N_2O_3S{\cdot}HCl$: C, 49.8; H, 4.5. Found: C, 50.0; H, 4.7.

3-(β-Benzamidoethyl)-5-(2-methoxybenzal)-2,4-thiazolidinedione (XI). This compound was prepared by two methods: (a) To a solution of 1 ml. of benzoyl chloride in 20 ml. of pyridine was added 1.5 g. of IX. The mixture was warmed on a steam-bath for 1 hr., then poured into water. The precipitate was filtered, washed with dilute hydrochloric acid, and then with dilute aqueous sodium bicarbonate. The product was recrystallized first from butanol, then from xylene to give XI, m.p. 174–175°. (b) A solution of 1.5 g. of VII and 1.5 ml. of 2-methoxybenzaldehyde in 25 ml. of acetic acid was refluxed for 4 hr. The acetic acid was removed under reduced pressure and the residue was crystallized from butanol to give XI as shown by mixture melting-point determination.

Anal. Calc'd for $C_{20}H_{18}N_2O_4S$: C, 62.8; H, 4.7. Found: C, 62.5; H, 4.7.

3-(β-Acetamidoethyl)-5-(2-methoxybenzal)-2,4-thiazolidinedione (XIV). This compound was prepared in two ways: (a) A solution of 40 g. of V, 35 ml. of *o*-methoxybenzaldehyde and 30 g. of sodium acetate in 250 ml. of acetic acid was refluxed for 4 hr. The acetic acid was removed under reduced pressure and water was added to the residue. The insoluble portion was filtered, dried, and crystallized from xylene or methanol to give 59 g. of XIV, m.p. 178–179°. (b) A solution of 2.0 g. of IX and 2.0 g. of sodium acetate in 25 ml. of acetic acid was refluxed for 2 hr. and the product was isolated as above. It was identified as XIV by mixture melting-point determination.

Anal. Calc'd for $C_{15}H_{16}N_2O_4S$: C, 56.6; H, 5.0. Found: C, 56.4; H, 5.6.

3-(β-Propionamidoethyl)-5-(2-methoxybenzal)-2,4-thiazolidinedione (XVII); *m.p. 150°, and 3-(valeramidoethyl)-5-(2-methoxybenzal)-2,4-thiazolidinedione* (XVIII); *m.p. 139°*. These compounds were synthesized using method (a), but using propionic and valeric acids, respectively.

Anal. (XVII) Calc'd for $C_{16}H_{18}N_2O_4S$: C, 57.5; H, 5.4. Found: C, 57.8; H, 5.5.

Anal. (XVIII) Calc'd for $C_{18}H_{22}N_2O_4S$: C, 60.3; H, 6.1. Found: C, 60.0; H, 6.5.

5-(2-Methoxybenzal)-2,4-thiazolidinedione (XVI). A mixture of 23.4 g. of 2,4-thiazolidinedione, 27 g. of 2-methoxybenzaldehyde, 12 ml. of piperidine, and 200 ml. of methanol was refluxed for 4 hr. The yellow solid which settled out was filtered off and crystallized from xylene to give 8 g. of XVI, m.p. 235°.

Anal. Calc'd for $C_{11}H_{10}NO_3S$: C, 55.8; H, 4.2. Found: C, 55.7; H, 4.4.

Acknowledgments. We are indebted to C. W. Zuehlke and M. Hill, of the Analytical Chemistry Department, of these Laboratories, for the titration curves, and to L. Weisler, of the Paper Service Division of the Eastman Kodak Company, for the spectral data.

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