[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE JOHNS HOPKINS UNIVERSITY]

THE HYDROGENATION OF OXALOACETONE. A NEW SYNTHESIS OF β-THIOLIMIDAZOLYLPROPIONIC ACID[1]

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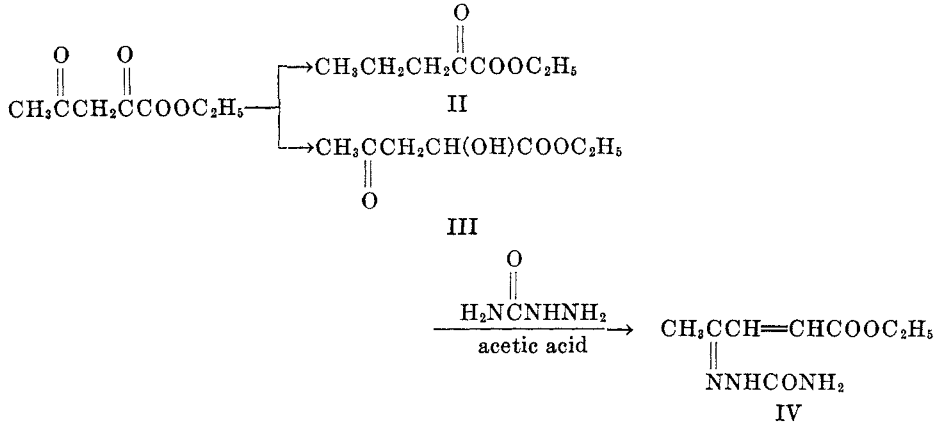
As a possible intermediate in the synthesis of ergothioneine we were interested in the preparation of an ester of α-hydroxylevulinic acid. Although the free acid has been prepared by Wolff (1) by the action of boiling water on bromolevulinic acid there is no record of its esters.

Attempts to add water across the double bond of ethyl acetylacrylate in a sealed tube at elevated temperatures resulted only in hydrolysis of the ester. This led us to believe that preparation of ethyl α-bromolevulinate and exchange of hydroxyl for bromine would also fail due to hydrolysis.

The hydrogenation of oxaloacetone, I (2), in absolute ethanol using platinum oxide (Adams') catalyst yielded a mixture of three products which were separated by fractionation at reduced pressure. The reaction was stopped after addition of one mole of hydrogen. The lowest-boiling fraction (79–80° at 18 mm.) was ethyl α-ketovalerate, II. It was identified by preparation of the semicarbazone, which melted at 138.5–139.5° (3). The second fraction (b.p. 60.5–61.5° at 2–3 mm.) was unreduced starting material. The highest-boiling fraction (77–78° at 2–3 mm.) was ethyl α-hydroxylevulinate. When the semicarbazone was prepared in 6 *M* acetic acid, dehydration occurred, leading to the formation of the derivative from ethyl β-acetylacrylate, IV. This was identified as the correct semicarbazone, m.p. 203.0–204.5°. The isomeric compound, ethyl α-keto-γ-hydroxyvalerate, could not have formed this semicarbazone by dehydration. These reactions are summarized in Chart I.

CHART I



$$CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}COOC_2H_5 \longrightarrow \begin{cases} CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}COOC_2H_5 & \text{II} \\ CH_3\underset{O}{\underset{\|}{C}}CH_2CH(OH)COOC_2H_5 & \text{III} \end{cases}$$

$$\xrightarrow[\text{acetic acid}]{H_2N\overset{O}{\overset{\|}{C}}NHNH_2} CH_3\underset{NNHCONH_2}{\underset{\|}{C}}CH{=}CHCOOC_2H_5 \quad \text{IV}$$

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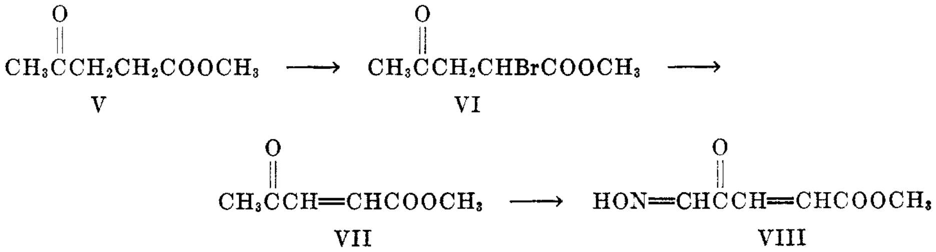
We next desired to prepare β-thiolimidazolylacrylic acid, a product of the degradation of ergothioneine by strong caustic (4). An examination of the literature revealed no synthetic source. Our attempts to nitrosate α-hydroxylevulinic ester were not encouraging but results on ethyl acetylacrylate were promising. The methyl ester was chosen because of its higher melting point and a more direct method of preparation was sought. Accordingly it was decided to attempt the synthesis from methyl acetylacrylate prepared from levulinic acid by esterification (5), bromination, and dehydrobromination (6).

The isonitrosation of ketones is a very sensitive reaction (7). The concentration of acid catalyst is critical. Traces of water are disastrous. A scheme was finally worked out whereby yields ranging from 45–64% could be consistently obtained. The conversion of levulinic ester to the isonitroso ketone is summarized in Chart II.

CHART II

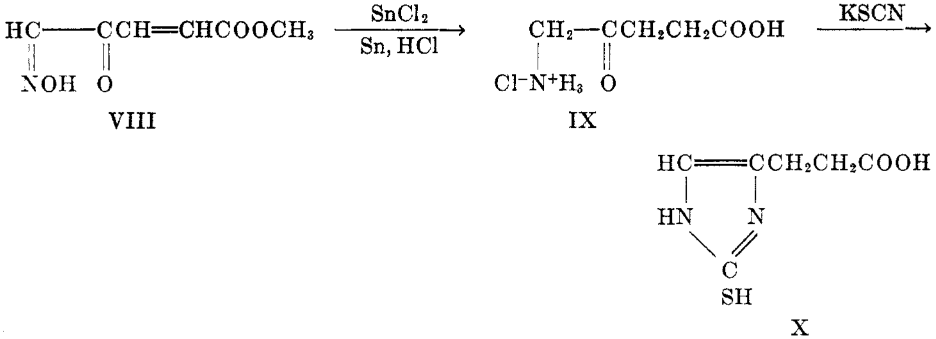


$$\underset{\text{V}}{CH_3\overset{\overset{O}{\|}}{C}CH_2CH_2COOCH_3} \longrightarrow \underset{\text{VI}}{CH_3\overset{\overset{O}{\|}}{C}CH_2CHBrCOOCH_3} \longrightarrow$$

$$\underset{\text{VII}}{CH_3\overset{\overset{O}{\|}}{C}CH{=}CHCOOCH_3} \longrightarrow \underset{\text{VIII}}{HON{=}CH\overset{\overset{O}{\|}}{C}CH{=}CHCOOCH_3}$$

Selective reduction of the isonitroso group was attempted (8, 9). The reduction was tried chemically with two equivalents of sodium amalgam and with two equivalents of stannous chloride in hydrochloric acid. These reactions led to tarry products. Catalytic reduction with Adams' catalyst led to oils. After making a polarographic study of the reduction potentials of the various groups in the molecule (10, 11) attempts at electrolytic reduction resulted in unrecognizable oils.

CHART III



$$\underset{\text{VIII}}{\underset{\overset{\|}{NOH}}{HC}{-\!-}\underset{\overset{\|}{O}}{C}CH{=}CHCOOCH_3} \xrightarrow[\text{Sn, HCl}]{\text{SnCl}_2} \underset{\text{IX}}{\underset{\overset{|}{Cl^-N^+H_3}}{CH_2}{-}\underset{\overset{\|}{O}}{C}CH_2CH_2COOH} \xrightarrow{\text{KSCN}}$$

By using as reducing agent an excess of tin and stannous chloride in concentrated hydrochloric acid it was possible to isolate a white, crystalline material, δ-aminolevulinic acid hydrochloride, IX. Indirect proof of the structure of this compound lies in the fact that on treatment with potassium thiocyanate the product obtained was β-thiolimidazolylpropionic acid, X. Thus not only the isonitroso group but also the double bond had been reduced and the reaction had taken the course shown in Chart III.

EXPERIMENTAL

Attempted hydration of ethyl-β-acetylacrylate. Five grams of ethyl-β-acetylacrylate and 55 ml. of water were sealed in a tube and heated at 135–140° for thirteen hours. The *p*H of the resulting solution was 3. This was extracted once with 25 ml. of ether. Evaporation of the ether solution yielded 1.5 g. of a solid residue, m.p. 109–120°. On recrystallizing from boiling chloroform, white crystals of acetylacrylic acid, m.p. 122–125°, were obtained.

The aqueous solution was concentrated over a free flame and dried in a vacuum desiccator. The residue was a syrupy mass containing some crystals. The crystals were triturated with ethyl acetate and recrystallized from boiling chloroform; 0.4 g. of acetylacrylic acid was recovered.

Hydrogenation of oxaloacetone. To a solution of 31.6 g. (0.2 mole) of oxaloacetone in 200 cc. of absolute ethanol was added 2 cc. of moistened Raney nickel and the mixture was shaken for five minutes. The solution was filtered and 200 mg. of Adams' catalyst (PtO_2) added. The solution was hydrogenated at 50–70 p.s.i. until 1 mole of hydrogen was absorbed (3 hours). The catalyst was filtered off and the alcohol removed on the steam cone. The residue was fractionated at 9 mm. (4-plate column) to give (a) ethyl α-ketovalerate, 6.8 g., b.p. 67–70°; (b) starting material, 7.2 g., b.p. 101–105°; and (c) ethyl α-hydroxylevulinate, 7.8 g., b.p. 122–123°.

Ethyl-α-hydroxylevulinate. An analytical sample of (c) was prepared by redistillation at 2–3 mm.; b.p. 77–78°.

Anal. Calc'd for $C_7H_{12}O_4$: C, 52.49; H, 7.55.
Found: C, 52.03, 52.04; H, 7.49, 7.52.

The technique used for weighing was as described by Niederl and Niederl (12). In order to prevent explosions it was necessary to control the temperature by using a metal block until all the sample had evaporated from the weighing tube. This required about one hour at 140°. After volatilization was complete the combustion was performed as usual.

Ethyl-α-ketovalerate semicarbazone. Ethyl-α-ketovalerate (2 cc.) was dissolved in 20 cc. of water containing just enough alcohol to make the ester completely soluble. To the solution were added 2 g. of semicarbazide hydrochloride and 3 g. of sodium acetate. It was placed in a beaker of water at 80° and allowed to cool slowly to 40°, when the tube was immersed in ice-water. The white crystals were recrystallized twice from boiling water; m.p. 138.5–139.5°.

Attempted formation of the semicarbazone of ethyl-α-hydroxylevulinate (Ethyl acetylacrylate semicarbazone). A mixture of 1 cc. of ethyl-α-hydroxylevulinte, 10 cc. of 6 *M* acetic acid, and 1 g. of semicarbazide hydrochloride was immersed in a beaker of boiling-water for five minutes and then allowed to cool slowly to room temperature. On cooling in an ice-water bath white needles precipitated; recrystallized from an alcohol-water mixture; m.p. 201.5–203.0°.

Anal. Calc'd for $C_8H_{13}N_3O_4$: N, 21.09. Found: N, 21.00.

The compound was again crystallized from an alcohol-water mixture; m.p. 203.5–205.5°.

Anal. Found: N, 21.21.

A small quantity of the material was mixed with an approximately equal amount of *ethyl acetylacrylate semicarbazone* (m.p. 203.0–204.5°) prepared as was ethyl-α-ketovalerate semicarbazone described above. The melting point of the mixture showed no depression.

Methyl-δ-isonitrosoacetylacrylate. In a 125-cc. Erlenmeyer flask fitted with a two-hole rubber stopper which had a ground-glass stopcock through one hole and through the other a glass tube drawn to a capillary reaching almost to the bottom was placed 6.40 g. (0.05 mole) of methyl acetylacrylate; 75 cc. of anhydrous ether was added through the stopcock.

On shaking at room temperature not all the ester dissolved. Through a calcium chloride tube attached to the capillary was blown in 1.01 g. of gaseous hydrogen chloride. The solution was cooled to 20° and 3.03 g. (0.04 mole) of ethyl nitrite was bubbled in over the absorbant during 1.5 hours; the temperature was maintained around 20°. The undissolved gas was released from the flask by slightly opening the ground-glass stopcock. At the end of the addition the solution had turned deep red and the solid ester had completely dissolved. The reaction mixture was stored in the dark at room temperature for 1¾ hours. It was necessary to release the pressure occasionally during this period. The reaction mixture had turned light yellow. A very small amount of insoluble material was filtered off and the ether was drawn off with an aspirator. The solid residue was dissolved in the minimum amount of ether and most of the solvent was evaporated off in an air stream and the residue cooled and filtered. On further evaporating the filtrate more crystals formed which were washed with benzene and combined with the first crop. Yield, 5.00 g. of a light yellow solid; m.p. 112–115° dec.; 64% (based on methyl acetylacrylate).

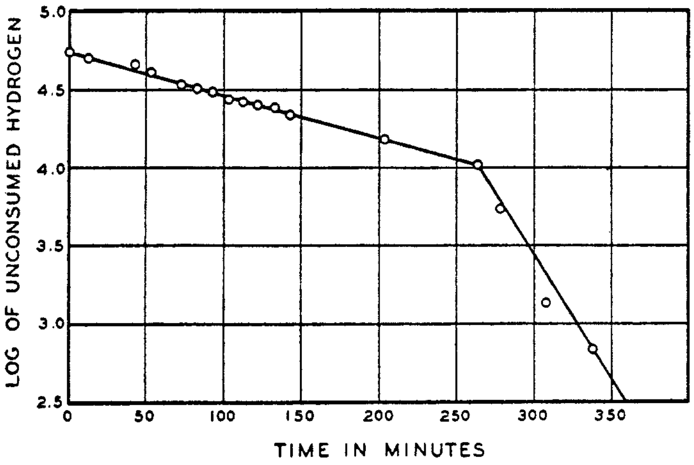


FIGURE 1.

A sample was purified for analysis by recrystallizing four times from toluene. The pure product was a very pale yellow, m.p. 114–117° dec.

Anal. Calc'd for $C_6H_7NO_4$: C, 45.86; H, 4.49; N, 8.92.

Found: C, 45.73; H, 4.45, N, 8.98, 9.05.

The compound decomposes slowly when stored in air. It is very soluble in ether and glacial acetic acid, slightly soluble in benzene and toluene, and insoluble in water. In ethanol and in concentrated sulfuric acid it turns deep red (11).

ATTEMPTED SELECTIVE REDUCTIONS OF METHYL-δ-ISONITROSOACETYLACRYLATE

(a) *By hydrogenation.* In one arm of one cup of a Warburg microhydrogenation apparatus was placed 0.532 mg. of δ-isonitrosoacetylacrylate. In the other arm a mixture of 40 mg. of Norit A, 2 ml. of distilled water, and two drops of 10% palladium chloride solution in 10% hydrochloric acid was introduced. The second capillary arm was left open to atmospheric pressure. The catalyst was hydrogenated and the solutions were then mixed and the determination started.

Figure 1 is the logarithmic plot of the unconsumed hydrogen against the time in minutes. The break in the hydrogenation occurred at 0.59 mole and the reaction ceased at 0.72 mole. This indicates partial hydrogenation of a one double bond and shows that the absorption of 2 moles required for the hydrogenation of the isonitroso group is not probable.

In spite of this, another hydrogenation was run and the product from it was treated with potassium thiocyanate. The product of the attempted condensation was a dark-colored tar from which potassium thiocyanate and no other solid material could be isolated.

(b) *With stannous chloride.* Four and one-half grams (0.02 mole) of stannous chloride dihydrate was dissolved in 8 cc. of conc'd hydrochloric acid. A solution of 1.57 g. (0.01 mole) of methyl isonitrosoacetylacrylate dissolved in 16 cc. of glacial acetic acid was poured rapidly into the hydrochloric acid solution. The mixture warmed spontaneously to about 50°. It was stirred mechanically and allowed to stand for four hours at room temperature. To the deep red solution was added 150 cc. of water and the tin precipitated with hydrogen sulfide. The tin sulfide was removed by filtration and the solvent aspirated at 40–50° until the volume was reduced to 10 cc. Then 0.97 g. (0.01 mole) of potassium thiocyanate was added and the solution evaporated to dryness on the steam-bath. The residue was a dark oil from which potassium thiocyanate could be extracted with methanol.

(c) *Electrolytic reduction.* The apparatus used for the reduction at controlled potential was a modification of that described by Lingane (10). The first reduction was run at room temperature. After orienting polarographic studies similar to those described by Hartnell and Bricker (11) a cathode potential of 0.12 volts negative to the saturated calomel electrode was chosen. The isonitroso ester (1.57 g.) was dissolved in 500 cc. of a solution 0.018 *M* in hydrochloric acid and 2.4 *M* in acetic acid. This solution, *p*H 1.5, was placed in the cathode compartment and the anode was filled with solvent only. With the cathode solution stirred vigorously, the current was 90 milliamperes. After twelve hours the current had diminished to 2 milliamperes. The reduction was stopped and the solution, which had become yellow, was drained from the cathode compartment and the water removed by sublimation. The residue was a red oil. This was dissolved in 10 cc. of distilled water and treated as above with potassium thiocyanate. The residue was a very dark viscous material from which no solid compound could be isolated.

The second reduction was performed similarly except that the temperature was maintained at 0° during the entire reduction (20 hours). The maximum current obtainable at this temperature was 55 milliamperes. One-half of the solution was dried by sublimation of the solvent and treated with potassium thiocyanate as described above. Evaporation to dryness left a red oil. The other half was reduced further at a cathode potential of 0.65 volts. When the product of this reduction was treated as described above no imidazole derivative could be isolated.

δ-Aminolevulinic acid hydrochloride. With mechanical stirring, 9.6 g. of $SnCl_2 \cdot 2\ H_2O$ was dissolved in 16 cc. of conc'd HCl and cooled to 0° when 2.30 g. of tin was added, followed by 3.14 g. of δ-isonitrosoacetylacrylate in small portions over a period of 45 minutes. The reaction mixture was stirred at room temperature for two hours, diluted with 400 cc. of water, and hydrogen sulfide blown in until all the tin was precipitated (test sample). The precipitate was filtered off and the water removed in the lyophylizer. Absolute methanol (14 cc.) was added to the residue and some undissolved ammonium chloride filtered off. The hydrochloride was reprecipitated by the slow addition of 50 cc. of dry ether; yield, 1.23 g. (34%) of white powder.

A sample was prepared for analysis by solution in the least amount of absolute methanol possible. The solution was placed in a desiccator over dry ether. The lid was clamped down and allowed to stand for several days. Slow distillation of ether into the methanol solution caused precipitation of long white needles. These were filtered off and dried in a Fischer pistol. M.p. 144–147° dec.

Anal. Calc'd for $C_5H_{10}ClNO_3$: N, 8.36. Found: N, 8.24.

β-Thiolimidazolylpropionic acid (8): A mixture of 1.23 g. (0.0067 mole) of δ-aminolevulinic acid hydrochloride, 8.00 cc. of distilled water, and 0.65 g. (0.0067 mole) of KSCN was evaporated to dryness on the steam cone. The solid residue was redissolved in 14 cc. of boiling-water, the hot solution filtered, and the filtrate allowed to evaporate at room temperature until the volume had decreased to 7 cc. During this time beautiful rosettes of crystals formed. Further cooling in the ice box gave 0.44 g. (38%) of crude product. A sample was prepared for analysis by reprecipitating from hot water; m.p. 203–205°.

Anal. Calc'd for $C_6H_8N_2O_2S$: C, 41.85; H, 4.68; N, 16.27.
Found: C, 41.44; H, 4.61; N, 16.32.

The product showed no positive test for thiocyanate ion, decolorized ferric chloride solution slowly, and gave a gelatinous, green precipitate with cuprous chloride thiol reagent (13).

SUMMARY

1. The catalytic hydrogenation of oxaloacetone is described and the structure of the products determined.

2. A new synthesis of β-thiolimidazolylpropionic acid is outlined.

3. Several new intermediate compounds have been synthesized and described and their structures established.

BALTIMORE, MARYLAND

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