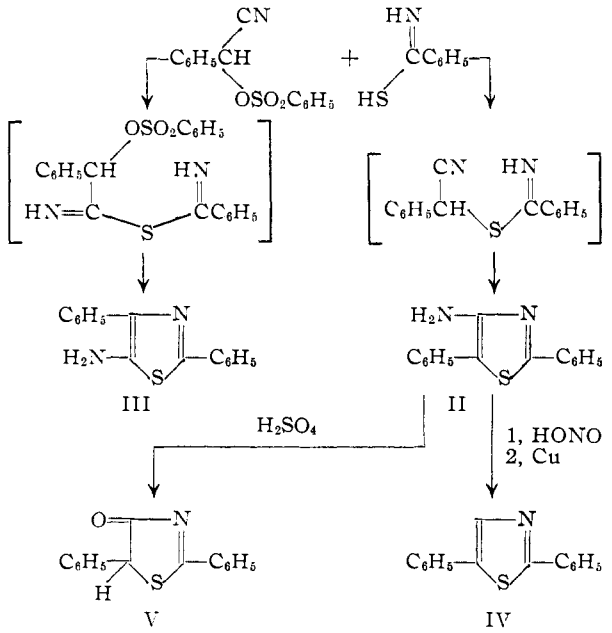
tion sequence may prove to be of interest for the synthesis of 2,5-diarylthiazoles; the only previously recorded synthesis of 2,5-diphenylthiazole involved the reaction of benzaminoacetophenone with phosphorus pentasulfide.[4]



In contrast to the extreme lability of the majority of previously prepared 4-aminothiazoles toward acid hydrolysis,[2,3,5-8] 4-amino-2,5-diphenylthiazole (prepared from the benzenesulfonic acid salt by treatment with ammonium hydroxide) proved to be remarkably stable and could be recovered unchanged after treatment with boiling alcoholic hydrochloric acid for ten minutes. It was converted in 95% yield to 2,5-diphenyl-4(5)-thiazolone (V) by heating under reflux with 40% sulfuric acid for ten hours.

Attempts to condense I with thioacetamide and α-phenylthioacetamide were unsuccessful, the only products isolated being ammonium chloride, ammonium benzenesulfonate and indefinite sulfur-containing oils.

Experimental

4-Amino-2,5-diphenylthiazole Benzenesulfonate.—A mixture of 5.46 g. (0.02 mole) of α-cyanobenzyl benzenesulfonate and 2.76 g. (0.02 mole) of thiobenzamide in 50 ml. of absolute ethanol was warmed on a steam-bath for about one minute to effect solution and then allowed to stand at 0° overnight. The yellow solid which had separated was collected by filtration, washed with cold absolute ethanol and recrystallized three times from absolute ethanol to give 3.02 g. (37%) of light yellow crystals, m.p. 198–199°.

Anal. Calcd. for $C_{15}H_{12}N_2S \cdot C_6H_6O_3S$: C, 61.4; H, 4.4; N, 6.8. Found: C, 61.7; H, 4.3; N, 6.9.

4-Amino-2,5-diphenylthiazole.—A mixture of 6.15 g. of 4-amino-2,5-diphenylthiazole benzenesulfonate and 50 ml. of aqueous ammonia (1:1) was shaken for about five minutes and the yellow solid then collected by filtration, washed with water and dried; yield 3.74 g. (99%), m.p. 103.5–104.5°.

Anal. Calcd. for $C_{15}H_{12}N_2S$: C, 71.1; H, 5.2; N, 11.1. Found: C, 71.3; H, 4.9; N, 10.9.

2,5-Diphenylthiazole.—One gram of 4-amino-2,5-diphenylthiazole was dissolved in a mixture of 30 ml. of ethanol and 15 ml. of concentrated hydrochloric acid. The solution was cooled to 0° and 4 ml. of a 20% solution of sodium nitrite added. After the mixture had stood for one hour, 0.1 g. of powdered copper was added and the solution was warmed to 50°. It then was filtered and the filtrate evaporated to about 20 ml. and cooled. The crystals which separated were recrystallized twice from absolute ethanol to give 0.27 g. (29%) of 2,5-diphenylthiazole, m.p. 103–104°. The reported melting point for 2,5-diphenylthiazole is 103–104°.[4]

Anal. Calcd. for $C_{15}H_{11}NS$: C, 75.9; H, 4.7; N, 5.9. Found: C, 76.0; H, 4.5; N, 5.8.

2,5-Diphenyl-4(5)-thiazolone.—A mixture of 3.78 g. of 4-amino-2,5-diphenylthiazole and 80 ml. of 40% sulfuric acid was heated under reflux for ten hours. The yellow product started separating from the hydrolysis mixture after about one hour. The cooled mixture then was filtered and the collected solid washed well with water and recrystallized from absolute ethanol to give 3.62 g. (95%) of bright yellow crystals, m.p. 215–215.5°.

Anal. Calcd. for $C_{15}H_{11}ONS$: C, 71.1; H, 4.4; N, 5.5. Found: C, 71.2; H, 4.6; N, 5.5.

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The Synthesis of N-Methyl-3-cyano-4-methoxy-6-pyridone, a Structural Isomer of Ricinine

BY E. C. TAYLOR, JR.,[1] ALDO J. CROVETTI AND HARVEY M. LOUX

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During the course of a program concerned with the chemistry of pyridine-N-oxides, which recently has led to a new synthesis of the alkaloid ricinine (I),[2] we had occasion to prepare for comparison purposes a hithertofore unknown structural isomer of this alkaloid. The condensation of diethyl acetonedicarboxylate with ethyl orthoformate and ammonia was carried out according to the method of den Hertog[3] to give ethyl 4,6-dihydroxynicotinate (II), which was converted to the corresponding amide III with anhydrous ammonia in a sealed steel bomb at 150°. Treatment of III with a mixture of phosphorus oxychloride and phosphorus pentachloride effected chlorination and simultaneous dehydration to give 4,6-dichloronicotinonitrile (IV) in an overall yield of 67%, based on II. An alternative and lengthier route to IV has been described by den Hertog.[4]

Sodium methoxide in methanol converted IV in 94% yield to 4,6-dimethoxynicotinonitrile (V), which was isomerized with methyl iodide in a sealed tube in 93% yield to N-methyl-3-cyano-4-methoxy-6-pyridone (VI), a structural isomer of ricinine. The structure of the product was confirmed by hydrolysis with concentrated hydrochloric acid to N-

(1) Frick Chemical Laboratory, Princeton University, Princeton, N. J.
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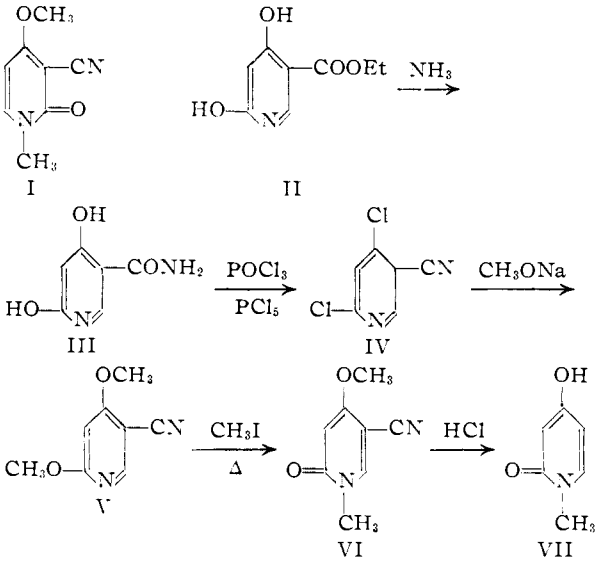
methyl-4-hydroxy-2-pyridone (VII), which also is formed by similar treatment of ricinine itself.[5]

It is of interest that the isomerization of V to VI took place much more readily than the analogous isomerization of 2,4-dimethoxynicotinonitrile to ricinine.[2,6]



Experimental

4,6-Dihydroxynicotinamide (III).—A mixture of 10 g. of ethyl 4,6-dihydroxynicotinate[3] and 70 ml. of liquid ammonia was sealed in a steel bomb and heated at 150° for a period of 3 hours (the internal pressure at this temperature is 1900 lb./sq. in.). Removal of excess ammonia gave 8.4 g. of colorless solid which darkens above 300° and has an indistinct decomposition point about 353°. Since no satisfactory method could be found for recrystallization of this material, it was used directly without further purification in the next step.

4,6-Dichloronicotinonitrile (IV).—A mixture of 5.5 g. of crude 4,6-dihydroxynicotinamide, 20 g. of phosphorus pentachloride and 75 ml. of phosphorus oxychloride was heated under reflux for 3 hours. The resulting red solution was concentrated under reduced pressure to remove excess phosphorus oxychloride and the residual sirup was poured with vigorous stirring onto ice. After this aqueous mixture had stood at 0° for 1 hour, it was extracted thoroughly with ether and the ether extracts washed with water, dried over anhydrous sodium sulfate and concentrated to give 5.23 g. of a white, crystalline solid. Sublimation of this material at 70° (0.5 mm.) gave 4.11 g. (67%, based on II) of pure 4,6-dichloronicotinonitrile, m.p. 134–136°.

Anal. Calcd. for $C_6H_2N_2Cl_2$: C, 41.6; H, 1.2; N, 16.2. Found: C, 41.3; H, 1.2; N, 15.9.

4,6-Dimethoxynicotinonitrile (V).—Into a 1-l. 3-necked round-bottom flask, to which was attached a liquid sealed stirrer and a reflux condenser provided with a drying tube, was placed a solution of 3.0 g. of sodium in 500 ml. of absolute methanol and 7.0 g. of 4,6-dichloronicotinonitrile. The mixture was heated under reflux with stirring for 5 hours, the excess methanol was removed by distillation until solid product started to crystallize from the solution, and 250 ml. of cold water then was added. The cooled mixture was filtered and the collected solid washed with water and dried at 100° to give 6.22 g. (94%) of colorless crystals, m.p. 153.7–155.7°. The analytical sample was prepared by recrystallization from absolute ethanol followed by sublimation *in vacuo*, m.p. 154.7–155.7°.

Anal. Calcd. for $C_8H_8N_2O_2$: C, 58.5; H, 4.9; N, 17.1. Found: C, 58.9; H, 4.9; N, 17.3.

N-Methyl-3-cyano-4-methoxy-6-pyridone (VI).—A mixture of 8.2 g. of 4,6-dimethoxynicotinonitrile and 83 ml. of methyl iodide was heated in a sealed tube at 130° for 5 hours and then evaporated to dryness. The crude product (8.04 g.) was recrystallized from water to give 7.65 g. (93%) of colorless needles, m.p. 241–242°. The analytical sample was prepared by sublimation at 175° (0.5 mm.).

Anal. Calcd. for $C_8H_8N_2O_2$: C, 58.5; H, 4.9; N, 17.1. Found: C, 58.7; H, 4.9; N, 16.9.

In a separate experiment, 0.1 g. of 4,6-dimethoxynicotinonitrile was heated alone in a sealed tube at 200–225° for 10 hours, and the resulting brown solid (0.094 g., m.p. 215–230°) was recrystallized from water and then sublimed to give VI, identical with the material prepared as described above.

1-Methyl-4-hydroxy-2-pyridone (VII).—The method used here was adapted from procedures reported for the hydrolysis of ricininic acid[7] and ricinine.[5] A mixture of 2.0 g. of N-methyl-3-cyano-4-methoxy-6-pyridone and 10 ml. of concentrated hydrochloric acid in a sealed glass tube contained in a steel pressure bomb was heated at 150° for 4.5 hours. The cooled reaction mixture was diluted with 40 ml. of water, filtered, and the filtrate evaporated to dryness. The residue was extracted with boiling absolute ethanol, the extracts evaporated to dryness, the residue triturated with dilute ammonium hydroxide and the mixture again taken to dryness. The resulting residue again was extracted with ethanol, the extracts evaporated to dryness and the residue recrystallized from water to give a white crystalline solid which melted at 60–70°, then solidified and remelted at 160–165° After sublimation at 150° (0.5 mm.), the product melted at 171–172°.

Anal. Calcd. for $C_6H_7NO_2$: C, 57.6; H, 5.6; N, 11.2. Found: C, 57.8; H, 5.6; N, 11.2.

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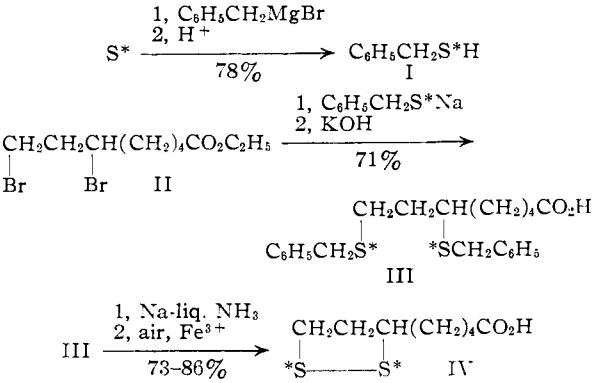
Synthesis and Properties of High Specific Activity DL-α-Lipoic Acid-S_2^{35}

BY RICHARD C. THOMAS AND LESTER J. REED

RECEIVED MAY 13, 1955

To facilitate studies of the metabolism of the biocatalyst, α-lipoic acid, in this Laboratory, a semimicro method for the synthesis of high specific activity DL-α-lipoic acid-S_2^{35} has been developed. The sequence of reactions employed in the synthesis is shown below.



Benzyl mercaptan-S^{35} was prepared by modification of the method of Wood, *et al.*[1] The recent syn-

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