m.p. was 103–104° and was not depressed when mixed with an authentic sample.[4]

Anal.[5] Calcd. for $C_5H_8N_2S$: C, 46.83; H, 6.29; N, 21.83; S, 25.05. Found: C, 47.27; H, 6.36; N, 21.61; S, 24.54.

2-Mercaptoimidazole and Ethyl Benzoate.—A suspension of 8 g. of 2-mercaptoimidazole in 20 g. of ethyl benzoate was heated up to the boiling point (215°) and held at reflux for ten minutes. The cooled mixture was extracted with 50 ml. of 2 *N* hydrochloric acid. After separation and washing with ether the aqueous extract was made basic with sodium carbonate and a crystalline precipitate of 2-ethylmercaptoimidazole separated. The product was recrystallized from ether–petroleum ether. It melted at 103–104° and the m.p. was not depressed when mixed with authentic 2-ethylmercaptoimidazole.[4] The yield was 4 g. (39%).

From the ethyl benzoate solution was isolated benzoic acid by extraction with sodium bicarbonate solution and acidification of the aqueous extract.

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[4] Prepared from 2-mercaptoimidazole and ethyl iodide by the procedure of ref. 3; m.p. 103.5–104.5°.

[5] The author is indebted to W. L. Brown, H. L. Hunter and W. J. Schenck for the analysis.

THE LILLY RESEARCH LABORATORIES
INDIANAPOLIS, INDIANA

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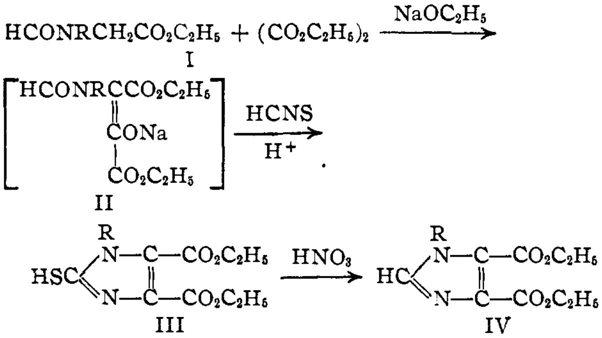
Studies on Imidazoles. VI. Synthesis of 4,5-Imidazoledicarboxylates

BY REUBEN G. JONES

Imidazoledicarboxylic acids and their derivatives with substituents in the 1-position (III and IV) are of interest for the preparation of purines[1] and related compounds. A general method for the synthesis of such 1-substituted-4,5-imidazoledicarboxylic acid derivatives is reported here. This is an extension of an earlier method for the synthesis of 1-substituted-4(or 5)-imidazolecarboxylates.[2] The steps involved are indicated by the accompanying series of reactions.



N-Formylglycine esters (I) are readily obtained by methods previously outlined.[2] The esters such as I have been found to undergo the Claisen condensation with oxalic acid esters to give the intermediates, II. As in the related reactions described previously,[2] it is possible to use N-acetylglycine esters in place of the N-formyl esters (I). Compounds II have not been isolated but have been allowed to react with thiocyanic acid in aqueous solution, and 1-substituted-2-mercapto-4,5-imidazoledicarboxylates, III, have been obtained in good yields. Oxidation of compounds III with nitric acid[2] led to the 1-substituted-4,5-imidazoledicarboxylates, IV.

Several of the compounds had unexpected solubility properties. Whereas 1-methyl-4,5-imidazoledicarboxylic acid, like 4,5-imidazoledicarboxylic acid[3] itself, was rather sparingly soluble in water; 2-mercapto-4,5-imidazoledicarboxylic acid and 1-phenyl-2-mercapto-4,5-imidazoledicarboxylic acid were soluble in water. They were precipitated when the solution was made strongly acidic with hydrochloric acid. Dimethyl 1-methyl-4,5-imidazoledicarboxylate was soluble in water, but dimethyl 1-phenyl-4,5-imidazoledicarboxylate and diethyl 4,5-imidazoledicarboxylate were water insoluble.

Acknowledgment.—The author is grateful to W. L. Brown, H. L. Hunter and W. J. Schenck for the microanalyses.

Experimental

Diethyl 2-Mercapto-4,5-imidazoledicarboxylate.—In a dry, three-liter, three-necked flask provided with a stirrer, dropping funnel and reflux condenser were placed 700 ml. of anhydrous ether and 29 g. (1.25 g. atom) of clean sodium cut in small pieces. Absolute ethanol, 58 g. (1.25 moles), was added followed by 182 g. (1.25 moles) of ethyl oxalate added slowly so that the reaction did not become too vigorous. To the resulting solution was added from the dropping funnel with stirring 131 g. (1.0 mole) of N-formylglycine ethyl ester.[2] A precipitate formed which turned to a dark red-brown gummy mass after standing. After the mixture had stood overnight 1 liter of ice water was added, and the mixture was agitated until the solid dissolved. The aqueous layer was separated, and to it was added 170 g. (1.75 moles) of potassium thiocyanate followed by 240 ml. (3.0 moles) of 12 *N* hydrochloric acid.

The resulting solution was warmed on the steam-bath under reduced pressure for a few minutes to remove dissolved ether, and then it was kept at about 40–60° for five or six hours during which time a heavy yellow crystalline precipitate separated. The mixture was cooled, and the product was collected on a filter and washed with a little ice-water. By evaporating the filtrate under reduced pressure to a volume of about 700 ml. an additional quantity of the product was obtained. The total yield of crude product was 165 g. (68%), and the yield from a similar experiment in which N-acetylglycine ethyl ester was used in place of N-formylglycine ethyl ester was 54%.

The diethyl 2-mercapto-4,5-imidazoledicarboxylate was appreciably soluble in water or alcohol, and recrystallization from either of these solvents resulted in large losses of material. A sample for analysis was recrystallized from water m.p. 204–205° dec. (uncor.).

Anal. Calcd. for $C_9H_{12}N_2O_4S$: C, 44.25; H, 4.95; N, 11.47. Found: C, 44.50; H, 4.93; N, 11.62.

2-Mercapto-4,5-imidazoledicarboxylic Acid.—A solution of 9 g. of crude diethyl 2-mercapto-4,5-imidazoledicarboxylate in 30 ml. of 6 *N* sodium hydroxide was heated on the steam-bath for one hour. The solution was clarified with carbon, filtered and the carbon washed with 20 ml. of water. The combined filtrate and washing was acidified with 17 ml. of 12 *N* hydrochloric acid. A canary-yellow, crystalline precipitate separated. The product was recrystallized by dissolving in 125 ml. of cold water and adding 100 ml. of 12 *N* hydrochloric acid. After standing, 5 g. (71% yield) of yellow crystalline powder separated; m.p. 251–252° dec. (uncor.).

Anal. Calcd. for $C_5H_4N_2O_4S$: N, 14.90. Found: N, 15.02.

Diethyl 4,5-Imidazoledicarboxylate.—Diethyl 2-mercapto-4,5-imidazoledicarboxylate was oxidized with dilute nitric acid in a manner previously described for the oxidation of similar 2-mercaptoimidazoles.[2] When the reaction was complete the solution was treated with excess sodium carbonate. An oil separated which quickly crystallized.

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[1] R. A. Baxter and F. S. Spring, *J. Chem. Soc.*, 232 (1945); 378 (1947); R. A. Baxter, A. C. McLean and F. S. Spring, *ibid.*, 523 (1948); G. A. Howard, A. C. McLean, G. T. Newbold, F. S. Spring and A. R. Todd, *ibid.*, 232 (1949).

[2] R. G. Jones, THIS JOURNAL, **71**, 644 (1949).

[3] R. G. Fargher and F. L. Pymann, *J. Chem. Soc.*, **115**, 217 (1919).

The mixture was extracted with chloroform and the dried extract was evaporated to a small volume. Addition of petroleum ether caused the ester to crystallize. The yield was 71% of white powder readily soluble in chloroform or alcohol, sparingly soluble in ether or cold water and insoluble in petroleum ether. A sample was recrystallized from water; m.p. 151–152°.

Anal. Calcd. for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.21. Found: C, 51.21; H, 5.87; N, 13.47.

Dimethyl 1-Methyl-2-mercapto-4,5-imidazoledicarboxylate.—This was prepared by the condensation of methyl oxalate with N-formylsarcosine methyl ester[2] using sodium methylate, followed by treatment of the aqueous solution of the product with thiocyanic acid. The procedure was essentially the same as that described above for the preparation of diethyl 2-mercapto-4,5-imidazoledicarboxylate. The product was obtained as a finely divided, white, crystalline precipitate in a yield of 70% based on the formylsarcosine ester. A sample for analysis was recrystallized from ethyl acetate containing a little methanol. It separated as fine white needles; m.p. 173.5–174° (uncor.).

Anal. Calcd. for $C_8H_{10}N_2O_4S$: C, 41.73; H, 4.38; N, 12.17. Found: C, 41.52; H, 4.69; N, 12.62.

Dimethyl 1-Methyl-4,5-imidazoledicarboxylate and 1-Methyl-4,5-imidazoledicarboxylic Acid.—To a solution of 20 ml. of concentrated nitric acid in 60 ml. of water was added a few crystals of sodium nitrite and then 23 g. of dimethyl 1-methyl-2-mercapto-4,5-imidazoledicarboxylate was added in small portions with stirring. The mixture was cooled in an ice-bath to keep the temperature at 30–40°. After the reaction was complete the resulting clear solution was chilled to 10°, and a white crystalline solid separated. This was the nitrate salt of dimethyl 1-methyl-4,5-imidazoledicarboxylate. It was collected on a filter and air-dried. The yield was 17 g. (65%). It was readily soluble in water, alcohol or acetone. A sample for analysis was recrystallized from a little water; m.p. 154–155°.

Anal. Calcd. for $C_8H_{10}N_2O_4 \cdot HNO_3$: C, 36.79; H, 4.25; N, 16.09. Found: C, 36.94; H, 4,57; N, 15.63.

The 17 g. of nitrate salt was dissolved in 30 ml. of water and an excess of sodium carbonate was added. An oily layer separated to the top, but it was only sparingly soluble in ethyl acetate or chloroform. The mixture was extracted with two 150-ml. portions of ethyl acetate. This extract was dried and evaporated leaving a colorless oil which crystallized after cooling for several hours. The yield of dimethyl 1-methyl-4,5-imidazoledicarboxylate was 10 g. (77% based on the nitrate salt). The compound was readily soluble in benzene, ethyl acetate or water from which it would not separate again on cooling. A sample was recrystallized from benzene-petroleum ether; m.p. 46.5–47°.

Anal. Calcd. for $C_8H_{10}N_2O_4$: N, 14.14. Found: N, 13.98.

The above aqueous sodium carbonate solution and the original nitric acid filtrate, from which the nitrate salt was obtained, were combined, made basic with sodium hydroxide solution and heated to boiling. After cooling, the solution was acidified to *p*H 2 with hydrochloric acid and chilled in the ice-box. The white crystalline precipitate of 1-methyl-4,5-imidazoledicarboxylic acid which separated was collected on a filter, washed with a little ice-water and air-dried. The yield was 7.5 g. (44% based on the original dimethyl 1-methyl-2-mercapto-4,5-imidazoledicarboxylate). A sample was recrystallized from water and separated as fine, lustrous needles, m.p. 261–262° dec. (uncor.).

Anal. Calcd. for $C_6H_6N_2O_4$: C, 42.36; H, 3.56. Found: C, 42.52; H, 4.01.

Diethyl 1-Phenyl-2-mercapto-4,5-imidazoledicarboxylate.—This was prepared by the same procedure as described above for the preparation of diethyl 2-mercapto-4,5-imidazoledicarboxylate, using N-formyl-N-phenylglycine ethyl ester[2] in place of N-formylglycine ethyl ester. In the condensation with thiocyanic acid, an equal volume of alcohol was added to the water solution in order to maintain homogeneity. At the end of the reaction the mixture was evaporated under reduced pressure to remove most of the alcohol. The product was obtained as a brown crystalline solid which was collected on a filter, washed well with water and air-dried. The yield was 86%. A sample was recrystallized from alcohol; m.p. 146–147°.

Anal. Calcd. for $C_{15}H_{16}N_2O_4S$: C, 56.25; H, 5.00; N, 8.74. Found: C, 56.30; H, 5.43; N, 8.74.

1-Phenyl-2-mercapto-4,5-imidazoledicarboxylic Acid.—The above ester, 12 g., was saponified with 6 *N* sodium hydroxide solution. Acidification of the solution with a large excess of concentrated hydrochloric acid caused precipitation of a yellow solid. This was collected and taken up in 100 ml. of warm acetone. The acetone solution was filtered from some sodium chloride which was present, and evaporated under reduced pressure. The crystalline residue, 8 g., dissolved readily in 150 ml. of cold water. To this solution was added 100 ml. of concentrated hydrochloric acid which caused immediate precipitation of the 1-phenyl-2-mercapto-4,5-imidazoledicarboxylic acid as a crystalline solid; m.p. 200–201° dec.; yield 7.8 g. (74%).

Anal. Calcd. for $C_{11}H_8N_2O_4S$: N, 9.93; neut. equiv., 141.1. Found: N, 9.94; neut. equiv., 141.2.

1-Phenyl-4,5-imidazoledicarboxylic Acid and Esters.—The above diethyl 1-phenyl-2-mercapto-4,5-imidazoledicarboxylate was oxidized with dilute nitric acid and the mixture worked up as described above for the preparation of diethyl 4,5-imidazoledicarboxylate. The product, diethyl 1-phenyl-4,5-imidazoledicarboxylate, was obtained as a brown oil which eventually crystallized. The yield was 80%. A sample was recrystallized from ethyl acetate-petroleum ether mixture; m.p. 84–85°.

Anal. Calcd. for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.60; N, 9.72. Found: C, 62.40; H, 5.61; N, 10.03.

1-Phenyl-4,5-imidazoledicarboxylic acid obtained by saponification of the diethyl ester was recrystallized from water; m.p. 199–200° dec.

Anal. Calcd. for $C_{11}H_8N_2O_4$: C, 56.80; H, 3.43. Found: C, 56.84; H, 3.80.

Dimethyl 1-phenyl-4,5-imidazoledicarboxylate, obtained by esterification of the acid with methanol and hydrogen chloride, melted at 86–87° after recrystallization from alcohol.

Anal. Calcd. for $C_{13}H_{12}N_2O_4$: N, 10.77. Found: N, 10.88.

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The Density of Liquid Fluorine

BY SCOTT B. KILNER, CARL L. RANDOLPH, JR., AND ROLLIN W. GILLESPIE

Kanda[1] has reported values of the density of liquid fluorine in the temperature range −216° to −188°. The density at −196°, determined from these results, is 1.13 g./cc. We have recently redetermined the density of liquid fluorine at this temperature and have found a value of 1.54 ± 0.02 g./cc.; Kanda's result therefore appears to be in error by approximately 27%.

A hydrometer, so proportioned as to cover the density range from 1.05 to 1.60 g./cc. in a stem length of 20 cm., was constructed from Pyrex glass, and was calibrated at room temperature in solutions of known density. On the assumption that the thermal coefficient of expansion of Pyrex glass is 1×10^{-5} °C.$^{-1}$, the change of temperature would have necessitated a correction of only 0.2%, hence it was ignored. The hydrometer was enclosed in a Pyrex tube fitted with inlets for flushing and for blanketing with helium, and for the introduction of fluorine. Fluorine could be condensed in this apparatus after it had been immersed in a large unsilvered dewar flask containing liquid nitrogen. The length of the emergent stem of the hydrometer could then be measured visually with a cathetometer. The accuracy of the calibration at low temperatures was verified by the determination of the density of liquid oxygen at −196° as 1.18 ± 0.02 g./cc. (literature value, 1.20 g./cc.[2]).

Fluorine, obtained from the Pennsylvania Salt Manufacturing Company, was liquefied in the apparatus described

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(1) E. Kanda, *Bull. Chem. Soc., Japan*, **12**, 469, 473 (1937).

(2) "Int. Crit. Tables," Vol. III, McGraw-Hill Book Co., Inc., New York, N. Y., 1927.