[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Synthesis of Derivatives of Pyrimidine-5-carboxylic Acid[1]

BY ELIZABETH BALLARD[2] AND TREAT B. JOHNSON

Biochemical interest was really first focused upon pyrimidine carboxylic acids in 1907 when Wheeler and co-workers considered the possibility of such constructions of uracil, thymine, etc., as functioning in the organic constitution of nucleic acids[3]; and later when it was shown that uracil-4-carboxylic acid[4] is identical with the naturally occurring substance—*orotic acid*—isolated from milk whey by the Italian chemists Biscaro and Belloni in 1905.[5] As a result of contemporary biochemical research in the expanding fields of enzyme, vitamin and plant hormone chemistry,[6] heterocyclic constructions of this class are now attracting attention. It is important, therefore, that practical methods of synthesis be developed for making such heterocyclic constructions easily available for future research.

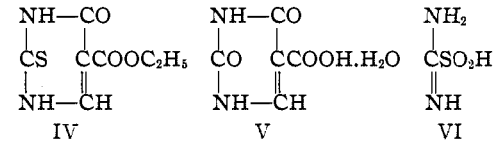
The three esters, namely: diethyl ethoxymethylene malonate (I),[3,7] ethyl ethoxymethylene cyanoacetate (II),[8] and carbethoxymalonic aldehyde (III),[9] have all been used with success in the Yale Laboratory for pyrimidine syntheses by condensation with pseudothioureas. The resulting 2-mercaptopyrimidine derivatives are all easily con-

$C_2H_5OCH{=}C(COOC_2H_5)_2$ (I) $\quad C_2H_5OCH{=}C(CN)COOC_2H_5$ (II)

$HOCH{=}C(CHO)COOC_2H_5$ (III)

verted into pyrimidine carboxylic acids by acid hydrolysis.

Wheeler, Johnson and Johns[3] reported that diethyl ethoxymethylene malonate (I) does not react with urea at 140°, and undergoes no condensation with it in the presence of alkali to form a pyrimidine. The authors now find that this ester (I) condenses smoothly with thiourea in the presence of sodium ethylate to give in excellent yield the sodium salt of ethyl 2-thiouracil-5-carboxylate (IV).



IV V VI

Desulfurization of this pyrimidine to uracil-5-carboxylic acid (V) is accomplished quantitatively by interaction with chloroacetic acid.[10] Desulfurization by treatment with hydrogen peroxide was unsuccessful.[11]

A satisfactory condensation of formamidine sulfinic acid[12] (VI) with the ester (I), either in concentrated sulfuric acid or in alkaline solutions, was not obtained. The acid condensation yielded a trace of uracil, the alkaline only a small quantity of *diethylureido-malonate*.[7]

Our study of these condensation reactions has now been extended to include practical methods for synthesizing new and important derivatives of pyrimidine-5-carboxylic acid (VIII), the pyrimidine analog of nicotinic acid (VII). The authors are now prepared to report that the 2-mercapto-6-oxypyrimidine-5-carboxylates (IX) are practical reagents serving as starting points for the synthesis of many new derivatives of this acid (VIII). Ethyl 2-ethylmercapto-6-chloropyrimidine-5-carboxylate (X)[13] and the corresponding 2-benzylmercapto- derivative, described for the first time in this paper, are formed smoothly by interaction of phosphorus oxychloride and pentachloride with the corresponding 2-mercapto-6-oxypyrimidines (IX). The uracil-5-carboxylates, however, do not undergo chlorination smoothly by interaction

(1) Researches on Pyrimidines, CLXXVII. This paper was constructed from a dissertation presented by Miss Elizabeth Ballard in June, 1940, to the Graduate Faculty of Yale University in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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(3) Wheeler, Johnson and Johns, *Am. Chem. J.*, **37**, 392 (1907); Wheeler and Johns, *ibid.*, **38**, 594 (1907).

(4) Müller, *J. prakt. Chem.*, **56**, 488 (1897); Wheeler, *Am. Chem. J.*, **38**, 358 (1907); Johnson and Schröeder, THIS JOURNAL, **53**, 1989 (1931).

(5) Biscaro and Belloni, *Estratto dell-Annuario della Soc. Chim. di Milano*, **XI**, 1-15 (1905); Johnson and Caldwell, THIS JOURNAL, **51**, 873 (1929); Bachstez, *Giornale di Chim. Ind. ed Applicata*, **12**, 174 (1930).

(6) (*Isosterism*): Erlenmeyer, Berger and Leo, *Helv. Chim. Acta*, **16**, 733 (1933); Erlenmeyer, *ibid.*, **21**, 1013 (1938); *ibid.*, **20**, 204 (1937); Schmelkes, *Science*, **90**, 113 (1939); Langmuir, THIS JOURNAL, **41**, 1543 (1919); Grimm, Gunther and Tittus, *Z. physik. Chem.*, **B14**, 189 (1931); Landsteiner, *Naturwiss*, **18**, 653 (1930); Woolley, Strong, Madden and Elvehjem, *J. Biol. Chem.*, **124**, 715 (1938).

(7) Claisen, *Ann.*, **297**, 75 (1897).

(8) Johnson, *Am. Chem. J.*, **42**, 303 (1909).

(9) Dyer and Johnson, THIS JOURNAL, **56**, 222 (1934).

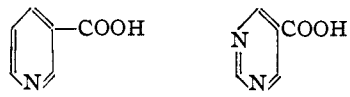
(10) Wheeler and Liddle, *Am. Chem. J.*, **40**, 547 (1908).

(11) Wheeler, *J. Biol. Chem.*, **3**, 285 (1907).

(12) Barnett, *J. Chem. Soc.*, **97**, 63 (1910); Vanino and Schinner, *Ber.*, **47**, 703 (1914); Böeseken, *Rec. trav. chim.*, **55**, 1040 (1936). "Imino-amino-methane-sulfinic acid," United States Patent 2,150,-921; granted March 21, 1939, to E. Havas, assigner to E. I. du Pont de Nemours and Co., Wilmington, Delaware.

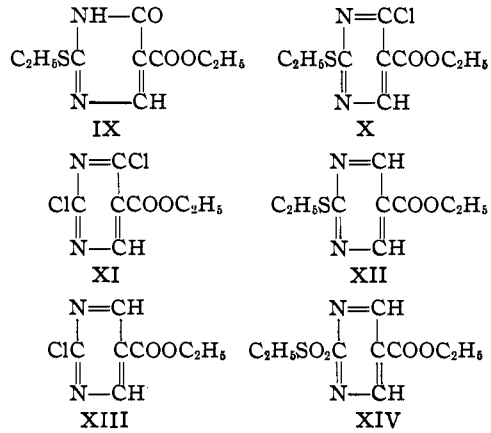
(13) Wheeler and Johns, *Am. Chem. J.*, **38**, 597 (1907).

with the phosphorus halides. Wheeler, Johnson and Johns[3] met with unexpected difficulties in their attempts to chlorinate uracil-5-carboxylic acid (V) or its ethyl ester. The authors repeated this work and attempted also to accomplish the desired change by using the methyl ester of uracil-5-carboxylic acid, but without success.



VII VIII

Ethyl 2,6 - dichloropyrimidine - 5 - carboxylate (XI) can be prepared easily in quantity from ethyl 2-ethylmercapto-6-chloropyrimidine-5-carboxylate (X) by an improvement in the original technique described by Sprague and Johnson.[14] Reduction of this same 2-mercaptopyrimidine (X) by digestion in dilute alcohol with zinc dust gave ethyl 2-ethylmercaptopyrimidine-5-carboxylate (XII). The latter compound on chlorination yields, in accordance with the Sprague–Johnson technique, the desired ethyl 2-chloropyrimidine-5-carboxylate (XIII) in a yield of 79%. Ethyl 2-ethylsulfon-pyrimidine-5-carboxylate (XIV) is formed as a secondary product of the reaction. The 2-chloropyrimidine ester (XIII) interacts quantitatively with ammonia to form ethyl 2-aminopyrimidine-5-carboxylate, which is converted by hydrolysis into the corresponding free acid.



IX X

XI XII

XIII XIV

Experimental

Diethyl Ethoxymethylene Malonate, $C_2H_5OCH{=}C(COOC_2H_5)_2$.—This malonic ester derivative was prepared according to slight modifications in the Claisen technique,[7] as proposed by Wheeler and Johns.[15]

Ethyl 2-Thio-6-oxypyrimidine-5-carboxylate (IV).—Several condensation experiments were conducted by the authors before the optimum conditions were established for carrying out successfully the condensation of thiourea with Claisen's ester. The procedure finally adopted was as follows: sodium ethylate was first prepared by dissolving 5.4 g. of metallic sodium in 300 cc. of absolute ethanol. Finely pulverized thiourea (17.6 g.) was then dissolved in the warm sodium ethylate solution and the required proportion of diethyl ethoxymethylene malonate (50 g.) added slowly to the alcohol solution during continuous agitation. Much heat was evolved. After final addition of the malonic ester the mixture was refluxed for one hour at 100° and then allowed to stand overnight at ordinary temperature. The weight of sodium salt of the crude condensation product that deposited was practically the theoretical (51 g.). This was dissolved in 400 cc. of hot water, the solution acidified with 25 cc. of concentrated hydrochloric acid, and the free pyrimidine ester that separated, on cooling, was then recrystallized from boiling water. This pyrimidine crystallized from boiling water in the form of needles without water of crystallization, and melted at 245° to a clear oil. The yield was 85%.

Anal. Calcd. for $C_7H_8O_3N_2S$: C, 41.98; H, 4.03; N, 14.00. Found: C, 42.09, 42.15; H, 4.05, 4.25; N, 13.89, 14.04, 14.12.

$C_6H_5CH_2S$—CNCCOC($COOC_2H_5$)=CH.N, Ethyl 2-Benzylmercapto - 6 - oxypyrimidine - 5 - carboxylate.—This mercaptopyrimidine was obtained according to the technique applied by Wheeler, Johnson and Johns[3] by condensation of benzylpseudothiourea with diethyl ethoxymethylene malonate. The compound crystallized from 95% ethanol in prismatic crystals and melts at 174–179°. The yield was 40%.

Anal. Calcd. for $C_{14}H_{14}O_3N_2S$: N, 9.67. Found: N, 9.60, 9.61.

$C_6H_5CH_2SCN$=CClC($COOC_2H_5$)=CHN, Ethyl 2-Benzylmercapto-6-chloropyrimidine-5-carboxylate.—This pyrimidine was obtained by warming ethyl 2-benzylmercapto-6-oxypyrimidine-5-carboxylate (10 g.) with phosphorus oxychloride (30 cc.) at 130–135° for seven hours. After distilling off the excess of phosphorus oxychloride *in vacuo*, the resulting reaction product was poured onto finely crushed ice and the chlorinated pyrimidine extracted with ether. The yield of the crude pyrimidine was 7.5 g. On distillation it boiled without decomposition at 248° (11 mm.).

Anal. Calcd. for $C_{14}H_{13}O_2N_2SCl$: N, 9.08. Found: N, 8.97, 9.05.

Desulfurization of Ethyl 2-Thio-6-oxypyrimidine-5-carboxylate (IV). (1) The Formation of Uracil-5-carboxylic Acid (V) by the Action of Chloroacetic Acid.—A description of one experiment will serve to demonstrate the practicality of this method of synthesis. Digestion of 3 g. of the sulfur pyrimidine with a boiling solution of 3 g. of chloroacetic acid in 25 cc. of water for one and one-half hours led to complete solution, desulfurization and saponification of the pyrimidine ester. On evaporating the solution to dryness, sulfur-free uracil-5-carboxylic acid was obtained. This melted at 268–270° with effervescence

(14) Sprague and Johnson, THIS JOURNAL, **57**, 2252 (1935); United States Patents, 2,146,744 (Feb. 14, 1939); 2,147,346 (Feb. 14, 1939).

(15) Wheeler and Johns, *Am. Chem. J.*, **40**, 233 (1908).

after recrystallization from boiling water. It contained water of crystallization and crystallized in the form of diamond-shaped prisms as previously described by Wheeler and co-workers.[3] The yield of purified acid was 85%.

Anal. Calcd. for $C_5H_4O_4N_2 \cdot H_2O$: H_2O, 10.3. Found: H_2O, 10.1, 10.2. Calcd. for $C_5H_4O_4N_2$: N, 17.95. Found: N, 18.07, 17.99.

No success resulted from the authors' attempts to convert, by the action of dilute nitric acid, ethyl 2-thio-6-oxypyrimidine-5-carboxylate into 6-oxypyrimidine-5-carboxylic acid. Using nitric acid of different concentrations the only sulfur-free product obtained by digestion was uracil-5-carboxylic acid (V), or its ethyl ester.

(2) **Desulfurization by Treatment with Hydrogen Peroxide.**—Under none of the experimental conditions applied by the authors did the action of hydrogen peroxide on ethyl 2-thio-6-oxypyrimidine-5-carboxylate proceed in such a manner as to give a uniform product. Superoxol (30% hydrogen peroxide) diluted with several volumes of water interacted with the sulfur pyrimidine in 10% sulfuric acid solution at 90–100° to give uracil-5-carboxylic acid (V) in a yield of 50%. Action of hydrogen peroxide at a lower temperature was productive of the ethyl ester in about the same percentage yield. In one experiment the oxidation with hydrogen peroxide was applied for only fifteen minutes at steam-bath temperature. Sulfur was precipitated immediately in about 25% yield. After removal of the sulfuric acid by precipitation as barium sulfate and evaporation of the resulting solution to dryness *in vacuo* at 60°, the residue on extraction with ethyl acetate yielded ethyl uracil-5-carboxylate. This was contaminated with a small quantity of a basic compound melting at 185° with sintering. The analytical results indicated that we were dealing here with the ethyl ester of 6-oxypyrimidine-5-carboxylic acid.

Anal. Calcd. for $C_7H_8O_3N_2$: N, 16.67. Found: N, 16.89, 16.7.

Condensation Experiments with Formamidine-sulfinic Acid (VI).[7] Interaction with Ethyl Ethoxymethylene Malonate.—(1) Two grams of the sulfinic acid (VI) and 4 g. of this ester (I), were dissolved in 5 cc. of cold concd. sulfuric acid. This solution was then allowed to stand at room temperature for twelve hours and poured onto crushed ice. One ml. of the unaltered ester was recovered by extraction with ether. The aqueous solution was treated with barium chloride to remove sulfuric acid, filtered, and then concentrated by warming on a steam-bath. This yielded no organic substance that could be definitely identified.

(2) Two grams of the sulfinic acid was suspended in absolute alcohol containing one equivalent of sodium ethylate, and 4 g. of ethyl ethoxymethylene malonate added. This mixture was then digested at 100° for one hour, allowed to cool and then filtered. Sulfur dioxide was evolved when the solution was acidified with hydrochloric acid. Upon evaporation of this solution to a small volume there finally separated a crystalline product which decomposed without melting at about 300°. This behaved in every way like slightly impure uracil-5-carboxylic acid (V).

Anal. Calcd. for $C_5H_4O_4N_2$: N, 17.95. Found: N, 18.10, 18.30.

(3) In this experiment the sulfinic acid (VI) was dissolved in water containing two equivalents of potassium hydroxide. To this aqueous solution while heating on a steam-bath was added one equivalent of ethyl ethoxymethylene-malonate (I). Aside from free sulfur, potassium sulfate and sulfite, the only organic product identified was **ureidomethylene-malonic ethyl ester**, $NH_2CONHCH{=}C(COOC_2H_5)_2$ in 10% yield. This melted at 207–212° after thorough washing with carbon bisulfide and two recrystallizations from 95% alcohol.

Anal. Calcd. for $C_9H_{14}O_5N_2$: C, 46.94; H, 6.13; N, 12.18. Found: C, 46.74, 47.19; H, 5.86, 5.92; N, 12.15, 12.19.

This experiment was repeated without heating, the solution being allowed to stand at room temperature for one day. The clear solution was then acidified with hydrochloric acid and evaporated to dryness. A mixed residue of organic and inorganic material was obtained, which gave after solution in water and cooling a small quantity of an organic product having all the properties of uracil. It gave a strong Wheeler and Johnson color test for this pyrimidine.[16]

An Attempt to Chlorinate Methyl Uracil-5-carboxylate by Interaction with Phosphorus Oxychloride.—Wheeler, Johnson and Johns[8] reported difficulty in accomplishing smooth chlorinations by interaction of both uracil-5-carboxylic acid (V) and its ethyl ester with phosphorus oxychloride. The authors likewise met with similar difficulties in their work with the corresponding methyl ester. When methyl uracil-5-carboxylate (5 g.) was refluxed with 25 cc. of pure phosphorus oxychloride for five hours, there was no evidence of a reaction. Upon the addition of phosphorus pentachloride (5 g.) to the phosphorus chloride solution hydrochloric acid was immediately evolved and on heating at 130° the pyrimidine completely dissolved. After the evolution of hydrochloric acid had ceased the excess of phosphorus chloride was removed *in vacuo* and the resulting oil then poured over finely crushed ice. A thick oil insoluble in water resulted which refused to solidify. This reaction product was dissolved in ether and dried over calcium chloride. Attempts to purify it by distillation were unsuccessful. Only a small quantity of a colorless product was obtained boiling at 130–135° (16 mm.). The major portion refused to distill and decomposed completely at 200°. Evidence that this small fraction boiling at 130–135° was the desired methyl ester of 2,6-dichloropyrimidine-5-carboxylic acid was revealed by its behavior toward concentrated ammonia. They interacted at ordinary temperatures to give an amino derivative to which was assigned the formula of methyl 2-chloro-6-aminopyrimidine-5-carboxylate. This compound was purified by recrystallization from commercial xylene and melted at 159–161°. It dissolved immediately in dilute hydrochloric acid, but was insoluble in cold alkali as expected.

Anal. Calcd. for $C_6H_6O_2N_3Cl$: N, 22.41. Found: N, 22.49, 22.56.

Experiments with Ethyl 2-Ethylmercapto-6-chloropyrimidine-5-carboxylate (X).[13] The Formation of Ethyl 2-Ethylmercaptopyrimidine-5-carboxylate by Reduction with Zinc Dust (XII).—One part by weight of the pyrimidine

(16) Wheeler and Johnson, *J. Biol. Chem.*, **3**, 183 (1907).

ester and 5 parts by volume of ethyl alcohol and water respectively were used. A solution of the ester in alcohol was first prepared and kept at the boiling point while the zinc dust and water were added in portions. Refluxing was continued for three hours and the solution then filtered from excess of zinc. Removal of alcohol left behind a tarry product suspended in water which was extracted with ether to remove the desired reduction product. Much of this tar refused to dissolve in the ether and the amount varied in quantity in each experiment. With units of 5 g. of the 6-chloropyrimidine derivative (X) about 2 g. of the reduction product was obtained which crystallized from dilute alcohol in colorless crystals melting at 49–51°. The compound proved to be identical with the ethyl 2-ethylmercaptopyrimidine-5-carboxylate (XII) previously described by Dyer and Johnson.[9] Separation of this reduced pyrimidine from the tarry reaction product was also accomplished by distillation. The reduced pyrimidine boiled at 172° (14 mm.) and the yield in the different experiments varied between 40–50%. Attempts to apply this technique of reduction to ethyl 2,6-dichloropyrimidine-5-carboxylate (XI) with any practical success were unsuccessful.

Reduction of Ethyl 2,6-Dichloropyrimidine-5-carboxylate (XI) with Hydriodic Acid. Formation of 6-Oxypyrimidine-5-carboxylic Acid.—A mixture of this pyrimidine (2 g.) with red phosphorus (2 g.), hydriodic acid of sp. g. 1.7 (12 cc.) and glacial acetic acid (12 cc.) was refluxed at the boiling point for fifteen minutes, filtered and the resulting solution finally evaporated to dryness in a vacuum. Treatment of the residue with cold water precipitated 0.9 g. of a crystalline product which was easily recrystallized from hot water. This reaction product was free from chlorine, was soluble in both acid and alkali solutions and decomposed, on heating, at about 238° with evolution of carbon dioxide. This decomposition point varied in the different preparations between 220–250°. The analytical values confirmed the conclusion that we were dealing here with the unknown **6-oxypyrimidine-5-carboxylic acid.**

Anal. Calcd. for $C_5H_4O_3N_2$: N, 20.01. Found: N, 20.14, 20.18.

A sample of this pyrimidine acid was decomposed by heating in a sealed tube at 250°. Carbon dioxide was evolved and the residue badly charred. Extraction of this fused residue with boiling ethyl acetate yielded crystalline 6-oxypyrimidine which melted at 163–165°. It was identical with the sulfur-free pyrimidine prepared by Wheeler[17] by desulfurization of 2-thiouracil with hydrogen peroxide.

The Formation of Ethyl 2,6-Dichloropyrimidine-5-carboxylate (XI) by Direct Chlorination of Ethyl 2-Ethylmercapto-6-chloropyrimidine-5-carboxylate (X).—Sprague and Johnson have reported[14] that according to the temperature conditions ethyl 2-ethylmercapto-6-chloropyrimidine-5-carboxylate may give upon direct chlorination either ethyl 2,6-dichloropyrimidine-5-carboxylate or 2-ethylsulfon-6-chloropyrimidine-5-carboxylate. Some difficulty was first encountered by the authors in controlling the two changes and in spite of variations of both temperature and acidity of solution over a wide range the formation of the dichloropyrimidine was completely suppressed in favor of the sulfone. A simple modification in experimental technique, however, corrected this difficulty. If the mercaptopyrimidine was kept immersed in a good volume of water and the chlorine gas admitted directly into the ester layer freely through a perforated disk and without stirring, we always obtained a satisfactory yield of the desired chloropyrimidine. The best results were obtained by keeping the reaction temperature between 40–50°. The end of the chlorination was indicated by the separation of the emulsified mixture into two layers and the bubbling off of excess chlorine. The dichloropyrimidine was extracted by petroleum ether and distilled. It boiled at 145° (11 mm.) and the yield was 76%.

Chlorination of Ethyl 2-Ethylmercaptopyrimidine-5-carboxylate (XII).—The authors have extended the application of the Sprague–Johnson chlorination technique, and applied it with success to ethyl 2-ethylmercaptopyrimidine-5-carboxylate.

An emulsion of ethyl 2-ethylmercaptopyrimidine-5-carboxylate (3.3 g.) in 30 cc. of water was chlorinated at 45° at which temperature the ester was melted. The reaction products were then extracted as usual with petroleum ether. During this extraction operation 0.6 g. of crystalline material separated which proved to be ethyl 2-ethylsulfonpyrimidine-5-carboxylate. This crystallizes nicely from 95% ethanol and melted at 87–89° to an oil.

Anal. Calcd. for $C_9H_{12}O_4N_2S$: N, 11.47. Found: N, 11.42, 11.51.

Evaporation of the petroleum ether extract gave a crystalline product which was easily purified by crystallization from 95% ethanol. It melted at 61° to an oil and was identified as *ethyl 2-chloropyrimidine-5-carboxylate* (XIII). In subsequent preparations 10-cc. units of the 2-mercaptopyrimidine were chlorinated at 40–70° and the yields of this ethyl 2-chloropyrimidine-5-carboxylate averaged about 79%. New research with this important pyrimidine derivative will be undertaken when time permits.

Anal. Calcd. for $C_7H_7O_2N_2Cl$: N, 15.02. Found: N, 15.02, 15.08.

$NH_2\overline{C—N=CHC(COOC_2H_5)=CH.N}$, Ethyl 2-Aminopyrimidine-5-carboxylate.—2-Ethylmercapto-5-carbethoxypyrimidine (XII) was recovered unchanged by heating with aqueous or alcoholic ammonia solution at 100°. 2-Chloro-5-carbethoxypyrimidine (XIII) (0.1 g.) and saturated alcoholic ammonia (2 cc.) were heated at 100°. On cooling, this 2-aminopyrimidine derivative separated in the form of colorless needles. The ester was purified by crystallization from hot water and melted at 147–149°.

Anal. Calcd. for $C_7H_9O_2N_3$: N, 25.15. Found: N, 25.10, 25.14.

$H_2N\overline{C—N=CHC(COOH)=CHN}$, 2-Aminopyrimidine-5-carboxylic Acid.—The above ester (0.32 g.) was saponified by dissolving in 5 cc. alcohol and 3 cc. of 10% potassium hydroxide solution and heating the solution to the boiling temperature. An insoluble potassium compound was formed which was separated by filtration. This salt was then dissolved in water and hydrochloric acid added in exact quantity to liberate the pyrimidine acid. The latter separated in quantitative yield, and was purified by crystallization from boiling water. It crystallized in

(17) Wheeler, *J. Biol. Chem.*, **8**, 285 (1907).

needles which showed no change when heated at 300°. The acid is insoluble in alcohol and dissolves immediately in hydrochloric acid.

Anal. Calcd. for $C_5H_5O_2N_3$: N, 30.21. Found: N, 30.27, 20.15.

This same new pyrimidine acid is also formed by boiling a strong hydrochloric acid solution of its ethyl ester.

Summary

1. Diethyl ethoxymethylene-malonate condenses with thiourea in alcohol solution and in the presence of sodium ethylate to give ethyl 2-thiouracil-5-carboxylate. This sulfur pyrimidine is desulfurized by interaction with chloroacetic acid giving a quantitative yield of uracil-5-carboxylic acid.

2. Benzylpseudothiourea condenses with diethyl ethoxymethylene-malonate to form ethyl 2-benzylmercapto-6-oxypyrimidine-5-carboxylate.

3. Diethyl ethoxymethylene-malonate interacts with formamidine-sulfinic acid in alkaline solution to give ureido-methylene-malonic ethyl ester, $NH_2CONHCH{=}C(COOC_2H_5)_2$.

4. An improved method for the preparation of ethyl 2,6-dichloropyrimidine-5-carboxylate has been described.

5. 2-Ethylmercaptopyrimidine-5-carboxylate has been prepared by a new method. This acid is converted into ethyl 2-chloropyrimidine-5-carboxylate by treatment with chlorine gas.

6. Ethyl 2-chloropyrimidine-5-carboxylate reacts with ammonia to form ethyl 2-aminopyrimidine-5-carboxylate. The latter yields on saponification 2-aminopyrimidine-5-carboxylic acid.

7. Reduction of ethyl 2,6-dichloropyrimidine-5-carboxylate by digestion with hydriodic acid gave 6-oxypyrimidine-5-carboxylic acid.

NEW HAVEN, CONN. RECEIVED OCTOBER 22, 1941

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE MALLINCKRODT CHEMICAL WORKS]

A Study of Diethyl 1,4-Dihydroxy-2,3-naphthalate[1]

BY AUGUST H. HOMEYER AND V. H. WALLINGFORD

The chemistry of 1,4-oxygenated naphthalene derivatives has been studied extensively in recent years because of the antihemorrhagic activity of many members of the group. Yet comparatively little is known about the 1,4-dihydroxy derivatives of 2-naphthoic and 2,3-naphthalic acids. Diethyl 1,4-dihydroxy-2,3-naphthalate (I) was obtained in 5% yield by Schwerin[2] from the condensation of diethyl phthalate with diethyl succinate. The yield of the dihydroxy ester has been increased to 48% by use of an excess of diethyl phthalate and more suitable conditions for the reaction. This material being readily available, it was interesting to study its methylation and hydrolysis.

The mono- and dimethoxy derivatives (V and II) were prepared by the action of methyl iodide and sodium ethylate. The monomethoxy compound was converted smoothly to the dimethoxy derivative by the same reagents. When the dimethoxy compound was prepared directly from the dihydroxy ester (I), an oil was also produced which showed marked antihemorrhagic activity. This product was 2,3-dihydro-2,3-dimethyl-2,3-dicarbethoxy-1,4-naphthoquinone resulting from methylation of the β-keto ester form of compound I in the 2 and 3 positions. Its hydrolysis was accompanied by loss of carbon dioxide and 2,3-dimethyl-1,4-dihydroxynaphthalene was formed.

Hydrolysis of diethyl 1,4-dimethoxy-2,3-naphthalate (II) gave a stable dicarboxylic acid (III) which formed an anhydride (IV) on heating. The monomethoxy ester (V), however, lost carbon dioxide on hydrolysis yielding 1-hydroxy-4-methoxy-3-naphthoic acid (VI). Similarly, hydrolysis of the dihydroxy ester (I) was accompanied by loss of carbon dioxide giving 1,4-dihydroxy-2-naphthoic acid (VIII) which Russig[3] obtained by carbonation of the disodium salt of 1,4-dihydroxynaphthalene. The easy loss of carbon dioxide from these two naphthalic acids was surprising since other known naphthalic and dihydroxyphthalic acids that have come to our attention are stable and form anhydrides readily. Traces of substances believed to be dicarboxylic acids were mentioned by Schwerin[2] and Russig[3] but they were not characterized.

Methyl alcoholic hydrogen chloride converted 1,4-dihydroxy-2-napthoic acid (VIII) to its 4-

(1) Presented before the Division of Organic Chemistry at the Atlantic City meeting of the American Chemical Society, September 9, 1941.

(2) Schwerin, *Ber.*, **27**, 112 (1894).

(3) Russig, *J. prakt. Chem.*, [2] **62**, 33 (1900).