[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Researches on Pyrimidines. CXLIII. The Preparation of Some New Derivatives of Uracil[1]

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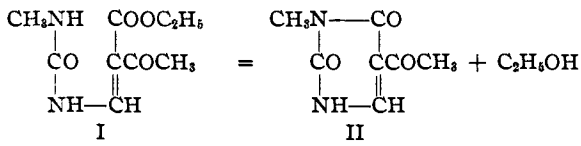
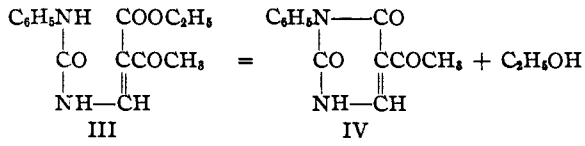
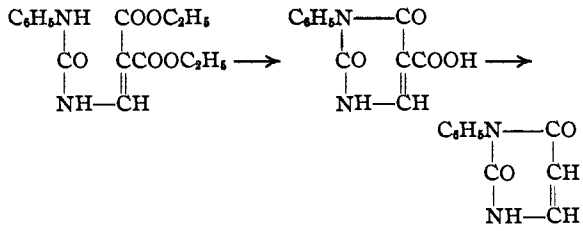
The behavior of the acyclic ureido compound formed by the interaction of ethyl ethoxy-methylene-acetoacetate with urea when treated with sodium ethylate and dilute potassium hydroxide, respectively, has been described in a previous paper by Johnson and Bergmann.[2] We now find that if a mixture of N-methylurea and the same acyclic ester is heated to 140° for about fifteen minutes, ethyl methylureidomethylene-acetoacetate I is formed in good yield. The subsequent treatment of this acyclic ureide I with dilute potassium hydroxide at 75° followed by acidification with glacial acetic acid produces 1-methyl-5-acetyluracil II. That the course of the



reaction leads to the formation of this ketone was shown by treating the pyrimidine II with fuming nitric acid. This reacted to form a N-methyl-nitrouracil which was identical with that described by Johnson and Heyl.[3] We also found that if ethyl aminomethylene-acetoacetate is allowed to interact with phenyl isocyanate in an anhydrous solvent such as benzene or ether, ethyl phenylureidomethylene-acetoacetate III is formed in good yield. This compound is converted smoothly into 1-phenyl-5-acetyluracil by treatment with dilute alkali according to the reaction



We have studied also the corresponding derivatives of malonic ester, and find that if ethyl aminomethylene-malonate in xylene solution be heated with phenyl isocyanate, ethyl phenylureidomethylene-malonate is formed. The subsequent treatment of this compound with dilute potassium hydroxide produces 1-phenyluracil-5-carboxylic acid. The latter is converted easily into 1-phenyluracil by the action of concentrated hydrochloric acid. These changes are shown below



Experimental Part

Ethyl Methylureidomethylene-acetoacetate.—A mixture of 7 g. of ethyl ethoxymethylene-acetoacetate and 3 g. of N-methylurea was heated to 140° in an oil-bath for fifteen minutes. The ureido compound was obtained as a solid. After cooling it was washed several times with dry ether and with ethyl alcohol, and finally purified by recrystallization from hot water; melting point 133–134°; yield, 2 g.

Anal. Calcd. for $C_9H_{14}N_2O_4$: N, 13.08. Found: N, 12.90, 12.97.

This imido derivative is soluble in cold ethyl acetate, benzene, methyl alcohol, ethyl alcohol, acetone, chloroform and pyridine. It is slightly soluble in cold ether. It is insoluble in cold petroleum ether and water. It is slightly soluble in hot water and insoluble in hot petroleum ether.

Formation of 1-Methyl-5-acetyluracil.—Ten cc. of a 5% aqueous solution of potassium hydroxide was heated to 75° and 1 g. of ethyl methyl-ureido-methylene-acetoacetate added. Solution took place in a few minutes. This was acidified with glacial acetic acid and allowed to cool, when the above pyrimidine separated in a crystalline condition. It was purified by crystallization from hot water and melted at 197°.

Anal. Calcd. for $C_7H_8N_2O_3$: N, 16.77. Found: N, 16.60, 16.67.

This keto-pyrimidine is soluble in cold ethyl alcohol, and slightly soluble in cold ethyl acetate and water. It is insoluble in cold benzene, ether and chloroform; soluble in hot ethyl acetate and water and slightly soluble in boiling ether and chloroform.

Ethyl Phenylureidomethylene-acetoacetate.—A solution of 7.9 g. of ethylaminomethylene-acetoacetate in 75 cc. of dry xylene and 1.5 g. of dry pyridine was prepared. Then 10 g. of phenyl isocyanate was added and the mixture refluxed for two hours. After cooling, the solvent was removed under reduced pressure and the residue washed several times with ether and finally crystallized

(1) From a thesis presented by Louis R. Buerger to the Graduate Faculty of Yale University in June, 1934, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

(2) Bergmann and Johnson, *Ber.*, **66**, 1492 (1933).

(3) Johnson and Heyl, *Am. Chem. J.*, **37**, 628 (1907).

from boiling ethyl alcohol. The final purification was made by crystallization from hot water; melting point 141°; yield 13 g.

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: N, 10.15. Found: N, 9.97, 9.98.

Ethyl phenylureidomethylene-acetoacetate ester is soluble in cold ethyl acetate, acetone, chloroform and pyridine. It is slightly soluble in cold methyl alcohol, ethyl alcohol and ether. It is insoluble in cold benzene, petroleum ether and water. It is soluble in hot methyl alcohol and ethyl alcohol and slightly soluble in hot benzene, ether and water. It is insoluble in hot petroleum ether.

1-Phenyl-5-acetyluracil.—Ten cc. of 5% aqueous potassium hydroxide solution was heated to boiling. and 1 g. of ethyl phenylureidomethyleneacetoacetate added. When solution was complete, usually in a short time, it was acidified with hydrochloric acid. Precipitation of the above pyrimidine occurred immediately. After cooling and filtering, it was crystallized from hot water; melting point 228°; yield, 5 g.

Anal. Calcd. for $C_{12}H_{10}N_2O_3$: N, 12.17. Found: N, 11.99, 12.04.

Ethyl 1-phenyl-5-acetyluracil is soluble in cold pyridine, slightly soluble in cold ethyl acetate, methyl alcohol, ethyl alcohol, acetone and chloroform, and insoluble in cold benzene, ether, petroleum ether and water. It is soluble in hot methyl alcohol, ethyl alcohol, acetone and chloroform. It is slightly soluble in hot ethyl acetate and water. It is insoluble in hot benzene, ether and petroleum ether.

Ethyl Phenylureidomethylene-malonate.—A solution of 3.74 g. of ethyl aminomethylene-malonate, 2.5 g. of phenyl isocyanate and 5 cc. of dry pyridine in 25 cc. of dry xylene was heated in a bomb tube to 160° for six and one-half hours. After cooling the solvent was removed under reduced pressure and the residue washed with dry ether and ethyl alcohol. It was purified by crystallization from hot ethyl alcohol and melted at 170–171°; yield, 1 g.

Anal. Calcd. for $C_{15}H_{16}N_2O_5$: N, 9.15. Found: N, 9.00, 9.08.

Ethyl phenylureidomethylene-malonate is soluble in cold ethyl acetate, acetone, chloroform and pyridine; slightly soluble in cold benzene, methyl alcohol, ethyl alcohol and ether, and insoluble in cold petroleum ether and water. It is soluble in hot benzene, methyl alcohol and ethyl alcohol and is slightly soluble in hot ether and water.

1-Phenyluracil-5-carboxylic Acid.—Ten cc. of 5% aqueous potassium hydroxide was heated to boiling and 1 g. of ethyl phenylureidomethylenemalonate added. Solution was complete in a short time. It was then acidified with 0.7 cc. of concentrated hydrochloric acid and allowed to cool. The pyrimidine was crystallized from hot water and melted at 239° with decomposition; yield, 0.71 g.

Anal. Calcd. for $C_{11}H_8N_2O_4$: N, 12.08. Found: N, 11.94, 11.98.

1-Phenyluracil-5-carboxylic acid is soluble in cold acetone and pyridine, slightly soluble in cold ethyl acetate, methyl alcohol, ethyl alcohol, and chloroform and insoluble in cold benzene, ether, petroleum ether and water.

1-Phenyluracil.—Two-tenths of a gram of 1-phenyluracil-5-carboxylic acid was refluxed with concentrated hydrochloric acid for eighteen hours, and the solution then evaporated to dryness. The residue of pyrimidine was crystallized from hot water and melted at 247°; yield, 0.060 g.

Anal. Calcd. for $C_{10}H_8N_2O_2$: N, 14.89. Found: N, 14.78.

Ethyl 1-phenyluracil is slightly soluble in cold methyl alcohol, ethyl alcohol, pyridine and water, and insoluble in cold ethyl acetate, chloroform, acetone, benzene, petroleum ether and ether.

Summary

Further work is reported dealing with the reactivity of Claisen's ethyl ethoxymethylene-acetoacetate and ethyl aminomethylene-malonate toward methyl urea and phenyl isocyanate, respectively. The following new uracil derivatives have been described: 1-methyl-5-acetyluracil, 1-phenyl-5-acetyl-uracil, 1-phenyluracil-5-carboxylic acid and 1-phenyluracil.

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