[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Researches on Pyrimidines. CXXXII. A New Synthesis of Thymine

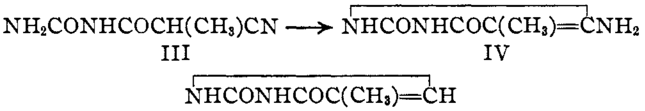
BY WERNER BERGMANN[1] AND TREAT B. JOHNSON

When in 1900 Wilhelm Traube[2] made his important contributions to our knowledge of pyrimidine chemistry, he was particularly interested in developing a new technique for the synthesis of purines of the uric acid type comparable to the classical methods of preparation previously described by Emil Fischer.[3] The compound which served as the starting point of his researches was cyanacetic acid. He found that this reagent combined smoothly with urea, thiourea and guanidine, giving acyclic ureides which easily undergo cyclic condensations, giving pyrimidine combinations that are easily transformed into purines. Traube's method of purine synthesis is limited to the use of cyanacetic acid or its ester and is applicable, therefore, only to oxypyrimidines, which are unsubstituted in position 5 of the pyrimidine ring. Presumably for this reason the action of the homologs of cyanacetic acid on urea, thiourea and guanidine, and the rearrangement of their respective condensation products have thus far been neglected. The development of a program of work in fields of heterocyclic chemistry calling for the application of new methods of pyrimidine syntheses is now leading to a study in this Laboratory of cyclic ureides derived from substituted cyanacetic acids of types I and II.

$\mathrm{NCCHXCOOH}$ I $\qquad$ $\mathrm{NCCX_2COOH}$ II

The use of a substituted cyanacetic acid of type I for the synthesis of thymine is described below.

As the rearrangement of cyanacetyl-urea leads to 4-aminouracil, that of methyl cyanacetyl-urea III should be productive of the corresponding amino derivative of thymine IV. Moreover, if as Rupe[4] found, cyanacetyl-urea is transformed by catalytic hydrogenation in the presence of platinum into uracil, then methyl cyanacetyl-urea III should under the same conditions be transformed into thymine V. Since thymine is not easily obtainable in quantity and any improvement in present methods of synthesis, therefore, is desirable, it seemed worth while to study these new reactions.



$$\underset{\text{III}}{\mathrm{NH_2CONHCOCH(CH_3)CN}} \longrightarrow \underset{\text{IV}}{\overline{\mathrm{NHCONHCOC(CH_3)=C}}\mathrm{NH_2}}$$

$$\underset{\text{V}}{\overline{\mathrm{NHCONHCOC(CH_3)=CH}}}$$

---

[1] Sterling Professorship of Chemistry Research Assistant.

[2] Traube, *Ber.*, **33**, 1374 (1900).

[3] Fischer, *ibid.*, **30**, 2251 (1897).

[4] Rupe, *Helv. Chim. Acta.*, **8**, 850 (1925).

Methyl cyanacetic acid, which can be prepared very easily according to the method of Hessler,[5] condenses smoothly with urea in the presence of acetic anhydride, forming the ureide III. We now find that this compound, when reduced catalytically, is transformed with evolution of ammonia into thymine as represented by the formulas above. The thymine prepared by this new method is obtainable in good yield, and free from sulfur and the pyrimidine uracil. It did not respond to the Wheeler–Johnson[6] color test for uracil and cytosine. There is no doubt that this technique when developed will serve for the preparation of many other uracil derivatives substituted in position 5 of the pyrimidine ring. Many of the combinations desired for our work cannot be prepared successfully through the usual methods calling for application of a Claisen ketone ester condensation with ethyl formate, followed by condensation with thiourea or a pseudo-thiourea to give a pyrimidine.

When treated with alkali methyl cyanacetyl-urea III undergoes a molecular rearrangement with cyclization to a pyrimidine ring forming 4-aminothymine or 2,6-dioxy-4-amino-5-methylpyrimidine IV, in the same way as cyanacetyl-urea is transformed into 4-amino uracil or 2,6-dioxy-4-aminopyrimidine.[7]

Experimental Part

Methyl Cyanacetyl-urea, III.—One mole of methyl cyanacetic acid[5] and 1.1 mole of urea are heated with 1.25 moles of distilled acetic anhydride on a steam-bath. After twenty minutes' heating crystals begin to separate which increase in quantity very rapidly as the heating is continued until the liquid assumes a solid condition, when the reaction is complete. This ureide is purified by crystallization from hot water, in which it is very soluble. On cooling, it deposits in the form of plates melting at 192°. The crystals contained water of crystallization. For analysis the compound was dried at 100° in a vacuum.

Anal. (Micro.) 3.879 mg. gave 6.06 mg. of CO_2, 1.692 mg. H_2O. 2.933 mg. gave 0.759 cc. of N_2 at 22° and 746 mm. Calcd. for $C_5H_7O_2N_3$: C, 42.55; H, 4.96; N, 29.79. Found: C, 42.62; H, 4.88; N, 29.40.

Thymine V.—Methyl cyanacetyl-urea is dissolved in about thirty times its weight of hot water and the solution agitated in an atmosphere of hydrogen at 70° using platinum black (Willstätter) as the catalytic agent. When one-half the theoretical quantity of hydrogen has been absorbed, heating is discontinued and the agitation continued until one mole of hydrogen has been absorbed. The catalyst is then separated by filtration and the solution acidified with acetic acid to neutralize the ammonia liberated by hydrolysis. This base forms a salt with thymine, holding the latter in solution. The solution is finally concentrated and cooled when thymine separates. After one recrystallization from boiling water it showed a melting point of 318–320°. The thymine obtained by this procedure showed all the typical thymine reactions and was free from uracil.

2,6-Dioxy-4-amino-5-methylpyrimidine (4-Aminothymine) IV.—Methyl cyanacetyl-urea III was dissolved in three times its weight of 20% aqueous sodium hydroxide solution and the mixture allowed to stand for half an hour. On acidifying with

---

(5) Hessler, This Journal, **35**, 980 (1913).

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

(7) Traube, *Ber.*, **41**, 532 (1908).

acetic acid the 4-aminothymine separated in needles. This pyrimidine was purified by recrystallization from boiling water and melted at 355°. The rearrangement of the acylurea III into 4-aminothymine IV can also be effected by heating in aqueous solution with magnesium oxide. For analysis the compound was dried at 100° in a vacuum.

Anal. Calcd. for $C_5H_7O_2N_3$: N, 29.79. Found: N, 29.56.

Summary

1. Methyl cyanacetyl-urea can be rearranged to 2,6-dioxy-4-amino-5-methylpyrimidine by the action of alkali.
2. Methyl cyanacetyl-urea, when reduced catalytically in the presence of platinum is converted smoothly into thymine.

NEW HAVEN, CONNECTICUT

RECEIVED FEBRUARY 4, 1933
PUBLISHED APRIL 6, 1933

Notes

Preparation of Triethylsilicon Halides

BY E. A. FLOOD

It is commonly supposed that triethylsilicon halides cannot be prepared, readily, from di-triethylsilicon oxide. Nevertheless it has been found that triethylsilicon bromide, chloride and fluoride can be obtained very easily from the oxide by treating a mixture of concentrated sulfuric acid and di-triethylsilicon oxide with the corresponding sodium or ammonium halide. The mixture is allowed to stand for some hours and the product extracted with petroleum ether. The triethylsilicon halide is separated from the solvent by distillation. The yields are practically quantitative.

Triethylsilicon fluoride, prepared in this way, is a colorless mobile liquid having a very faint "camphor-like" odor. It boils at 110° (uncorr.) under atmospheric pressure. It is much more stable toward hydrolysis than is the corresponding bromide and may be distilled in air without appreciable decomposition.

Analyzed for fluorine by a modified Starck method, calcd. for $(C_2H_5)_3SiF$: F, 14.15. Found: F, 14.31, 14.63, mean 14.48.

It was shown to be a single substance as follows. About ten grams was allowed to distil under its own vapor pressure at room temperature into a receiver (volume 302 cc.) cooled to −33°. The vapor density of the first two or three drops of distillate collected was determined, as well as the vapor density of the last two or three drops of residual liquid remaining in the original container. The vapor densities of the two extreme fractions agreed within the experimental error and gave a value for the molecular weight in close agreement with that required by the formula $(C_2H_5)_3SiF$. The data follow: mol. wt. (vapor density). First fraction. Subs., 0.0534, 0.0501; vol., 302.0; pressure, mm., 24.7, 22.9; *t*, 27.7°, 28.0°.