[CONTRIBUTION FROM THE ORGANIC RESEARCH LABORATORY, NATIONAL OIL PRODUCTS CO.]

Studies on Pyrimidines Related to Vitamin B_1. I. A New Synthesis of 2-Methyl-6-aminopyrimidine-5-aldehyde

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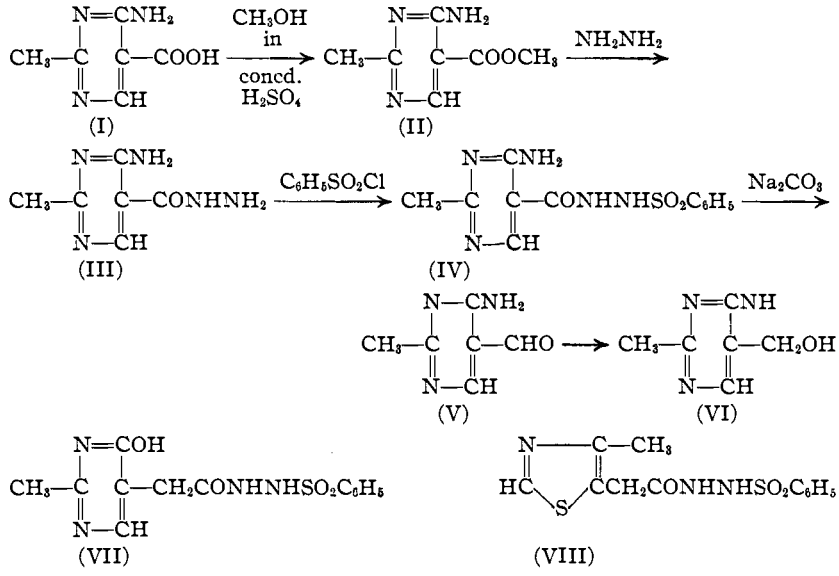
McFadyen and Stevens recently reported[1] an interesting method for the conversion of carboxylic acids into aldehydes through the benzenesulfonhydrazides, which decompose readily under the action of sodium carbonate to yield the aldehydes. The method gave excellent results where the carboxyl group was attached directly to the aromatic nucleus but failed completely where it was present in a side chain, as well as in the case of aliphatic acids. Buchman and Richardson[2] extended the method to thiazoles in the synthesis of 4-methylthiazole-5-aldehyde where the initial carboxyl group was directly attached to the ring.

We have successfully applied the method to the pyrimidine series as indicated herewith.



In agreement with the results of McFadyen and Stevens, the sulfonhydrazide of 2-methyl-5-carboxymethyl-6-oxypyrimidine (VII) failed to give the desired aldehyde when treated with sodium carbonate under the conditions used by them. Moreover, the same holds true for thiazoles as is shown by the fact that the benzenesulfonhydrazide of 4-methylthiazole-5-acetic acid (VIII), the next higher homolog to that used by Buchman and Richardson, also failed to yield an aldehyde under the same conditions.

(1) McFadyen and Stevens, *J. Chem. Soc.*, 584 (1936).

(2) Buchman and Richardson, THIS JOURNAL, **61**, 891 (1939).

2-Methyl-6-amino-5-carboxypyrimidine (I) proved to be highly resistant to esterification by the ordinary methods. Prolonged heating with methanol in the presence of anhydrous hydrochloric acid in various concentrations, sulfuric acid, or *p*-toluenesulfonic acid only yielded back the unchanged acid quantitatively. Treatment of the sodium salt with dimethyl sulfate, however, did give the ester in very small yield. For a suitable preparation of the ester, therefore, it was necessary to resort to a modification of the method reported by Meyer[3] for the esterification of *o*-aminobenzoic acid, which consists in adding dropwise a mixture of methanol and sulfuric acid to a warm solution of the acid in a large excess of concentrated sulfuric acid. The remaining steps in the synthesis gave no unusual difficulties but went smoothly with satisfactory yields.

2-Methyl-6-aminopyrimidine-5-aldehyde (V) was previously reported by Delépine,[4] who isolated it in the form of a nickel complex as a by-product during the hydrogenation of 2-methyl-5-cyano-6-aminopyrimidine with Raney nickel. We found that the catalytic reduction of this aldehyde proceeded smoothly to give 2-methyl-5-hydroxymethyl-6-aminopyrimidine (VI).

Experimental

2-Methyl-5-carboxy-6-aminopyrimidine (I).—Two and five-tenths grams of 2-methyl-5-cyano-6-aminopyrimidine was refluxed for two hours with 20 cc. of 10% potassium hydroxide and the solution filtered and acidified while warm with glacial acetic acid. The amino acid precipitated almost immediately and after thorough cooling was collected on a filter. The yield of acid melting at 269–270° was 2.8 g. (about 90%). Recrystallized from water it appeared as fine needles of m. p. 270–270.5° (decompn.).

(3) Meyer, *Monatsh.*, **25**, 1202 (1904).

(4) Delépine, *Compt. rend.*, **206**, 865 (1938); *Bull. soc. chim.*, [5] **5**, 1539 (1938).

Anal. Calcd. for $C_6H_7O_2N_3 \cdot H_2O$: C, 42.12; H, 5.30. Found: C, 42.23; H, 5.36.

The hydrochloride melted at 238–239°.

2-Methyl-5-carbomethoxy-6-aminopyrimidine (II).—Five grams of the preceding amino acid was dissolved in 15 g. of concentrated sulfuric acid and while stirring and warming gently, a mixture of 4 g. of methanol and 1 g. of sulfuric acid added dropwise. The heating and stirring were continued for about two and one-half hours during which time 3 g. of methanol in a little sulfuric acid was added in three portions at about forty-five minute intervals. The clear brown reaction mixture was cooled, poured into ice-water and the solution neutralized with sodium carbonate. The precipitated ester was filtered and dried, and the filtrate extracted with ether. The total yield of almost pure white ester was 3.8 g. (76%). Upon recrystallization from water it appeared in the form of colorless plates, m. p. 184–184.5°. This was not raised by further crystallization.

Anal. Calcd. for $C_7H_9O_2N_3$: C, 50.30; H, 5.43. Found: C, 50.55; H, 5.40.

The hydrochloride crystallized from methanol–ether in clusters of large needles, m. p. 181°.

Anal. Calcd. for $C_7H_{10}O_2N_3Cl$: C, 41.29; H, 4.95. Found: C, 41.33; H, 5.25.

The ethyl ester which has been reported by Todd and Bergel[5] was also prepared by the above method although the yield was not as good as that of the methyl ester, m. p. 120°. Todd and Bergel reported 120°.

Hydrazide of 2-Methyl-5-carboxy-6-aminopyrimidine (III).—A mixture of 3 g. of the methyl ester, 10 cc. of 95% ethanol and 4.5 g. of 42% hydrazine hydrate was refluxed on the steam-bath for two hours. Some hydrazide separated from the reaction mixture during heating. After thorough cooling the hydrazide was collected and weighed. The yield was 2.7 g. or 90% of the theoretical. It crystallized from 95% ethanol in colorless needles, m. p. 220–221° (decompn.).

Anal. Calcd. for $C_6H_9ON_5$: C, 43.11; H, 5.43. Found: C, 43.13; H, 5.77.

The ethyl ester was also converted to the hydrazide with about the same success (1.3 g. of hydrazide from 1.5 g. of ethyl ester).

Benzenesulfonhydrazide of 2-Methyl-5-carboxy-6-aminopyrimidine (IV).—To a suspension of 4 g. of the hydrazide in 80 cc. of dry pyridine, 4.32 g. of benzenesulfonyl chloride was added dropwise during fifteen minutes with stirring, the temperature being maintained at 17–18°. Simultaneously with the disappearance of the hydrazide, finely divided pyridine hydrochloride separated. The stirring was continued for three and one-half hours while allowing the reaction to come to room temperature. Evaporation of the solvent under reduced pressure left a semisolid mass which became crystalline on treatment with water; yield 5.3 g. (73%). It crystallized from 95% ethanol in slender white needles, m. p. 228.5–229° (decompn.).

Anal. Calcd. for $C_{12}H_{13}O_3N_5S$: C, 46.89; H, 4.26. Found: C, 47.00; H, 4.61.

(5) Todd and Bergel, *J. Chem. Soc.*, 366 (1937).

Decomposition of the Sulfonhydrazide.—Five and three-tenths grams of the sulfonhydrazide was suspended in 60 cc. of ethylene glycol and the mixture heated to 160°, 4.8 g. of sodium carbonate was then added to this solution surrounded by a bath maintained at 157–160°. When the brisk evolution of gas ceased at the end of about three to five minutes, water was added and after cooling the solution extracted with 200 cc. of chloroform in six portions. After drying and removal of the chloroform, the yellow solid was taken up in the minimum amount of 95% ethanol, from which it crystallized. The yield was 1.05 g. (44%). After a second recrystallization using animal charcoal the aldehyde (V) separated in the form of fine white needles, m. p. 195–196°. The melting point reported by Delépine was 192°.

Anal. Calcd. for $C_6H_7ON_3$: C, 52.52; H, 5.15. Found: C, 52.76; H, 5.28.

The aldehyde reduced Fehling solution.

In one run less ethylene glycol was used as a solvent and ethyl acetate was used for extraction. In this case, besides the aldehyde an appreciable amount of a highly insoluble yellow material (m. p. above 300°) was isolated. It reduced Fehling solution and dissolved in hydrochloric acid but was insoluble in water and organic solvents and, therefore, could not be purified further. On the basis of these facts and the following analysis, this compound probably consists of a condensation product of two moles of the amino aldehyde, wherein water has been eliminated between the amino group of one and the aldehyde group of another.

Anal. Calcd. for $C_{12}H_{14}O_2N_6 - H_2O$: C, 56.24; H, 4.72. Found: C, 55.67; H, 5.33.

A Schiff base of the aldehyde (V) with *p*-toluidine was prepared in almost quantitative yield by heating equal weights of *p*-toluidine and the aldehyde in about 50% ethanol until complete solution took place. At the end of about fifteen minutes of standing the Schiff base began to separate. On crystallization from 80% ethanol it formed long silky needles, m. p. 196–197°.

Anal. Calcd. for $C_{13}H_{14}N_4$: C, 69.01; H, 6.24. Found: C, 69.18; H, 6.63.

Reduction of 2-Methyl-6-aminopyrimidine-5-aldehyde (V).—A mixture of 0.3 g. of the aldehyde in 10 cc. of 95% ethanol, and 0.02 g. of platinum oxide catalyst were shaken with hydrogen at slightly more than one atmosphere pressure until the uptake had almost ceased (about 10% in excess of one mole). After filtration and evaporation of the solvent under reduced pressure, the solid residue was recrystallized from isopropyl alcohol. The yield of alcohol (VI) was 0.21 g. (70%), m. p. 193–194°. The melting point reported by Andersag and Westphal[6] is 194°. A mixed melting point with a known sample of the alcohol gave no observable depression.

The benzenesulfonhydrazide of 2-methyl-6-oxypyrimidine-5-acetic acid (VII) was prepared by a procedure almost identical with that described for the sulfonhydrazide of 2-methyl-5-carboxy-6-aminopyrimidine (IV), m. p. 238°.

Anal. Calcd. for $C_{13}H_{14}O_4N_4S$: C, 48.45; H, 4.38. Found: C, 48.28; H, 4.68.

(6) Andersag and Westphal, *Ber.*, **70**, 2048 (1937).

Treatment of this substance with sodium carbonate under the conditions which yielded 2-methyl-6-aminopyrimidine-5-aldehyde gave reaction products from which no trace of an aldehyde could be obtained.

The sulfonhydrazide of 4-methylthiazole-5-acetic acid (VIII) was also prepared according to essentially the same procedure as that used for the preceding compound, m. p. 122°.

Anal. Calcd. for $C_{12}H_{18}O_3N_8S_2 \cdot H_2O$: C, 43.77; H, 4.56. Found: C, 43.83; H, 4.83.

This substance likewise failed to give any trace of an aldehyde when treated with sodium carbonate under the conditions previously used.

Summary

1. The McFadyen and Stevens aldehyde synthesis has been applied to pyrimidines.

2. In two cases the reaction has been shown to fail where the carboxyl group is not directly attached to the ring.

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Oxygen Inhibition in the Photobromination of Cinnamic Acid

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Several halogenations are inhibited by oxygen[1a-g] but the reactions are not fully understood. The experiments described here were designed to study further this inhibiting effect of oxygen, as reported previously in the photobromination of cinnamic acid.[2] In order to follow the course of the reaction without exposure to atmospheric oxygen an all-glass technique was followed in which the concentration of bromine at any time was determined by the absorption of light as measured with a photoelectric cell. The intensity of light was low (170 ergs per second) so that the concentration would not be changed appreciably by photochemical reaction during the few seconds required to take a reading.

Apparatus.—A monochromator with liquid ethyl cinnamate for the refracting prism[3] was used with an 85-watt General Electric mercury vapor lamp (Type H-3). The parallel beam of light at 4360 Å. passed through a water thermostat and the cylindrical absorption cell. It then struck a photoelectric cell (Westinghouse S.R. 51) connected with an amplifying circuit containing a type no. 76 tube. The galvanometer (2.5 mm. per microvolt) was adjusted to zero by changing a shunt resistance and a resistance in series with the 90-volt batteries. An identical cell filled with carbon tetrachloride was used for the zero reading.

A multiple reaction cell was fused to the vessel in which the reaction mixture was deoxygenated, and to other chambers used for filling with the solution and adding definite quantities of oxygen. Five cylindrical cells 1.7 cm. in inside diameter with fused Pyrex windows 2.5 cm. apart permitted different measurements to be made, all with the same concentration of bromine and oxygen. The solutions of cinnamic acid and bromine in carbon tetrachloride were frozen and evacuated, then melted, frozen and evacuated again. This cycle was repeated three to five times until the emission spectrum of oxygen could no longer be obtained with a Tesla coil. Oxygen was then admitted to a predetermined pressure as read on a manometer and the concentration of dissolved oxygen was calculated from the volumes of the liquid and the gas space of the apparatus, using the distribution coefficients of Horiuti.[4] In some of the experiments the oxygen was admitted with magnetic hammers and sealed-off tubes.

It was found that a rapid diffusion of bromine occurred when there was a marked difference in concentration in the adjacent compartments of the multiple cell. The diffusion apparently took place along a surface film of solution rather than through the gas phase. Consequently it was necessary to use single absorption cells in some of the experiments.

Known solutions of purified bromine in carbon tetrachloride, ranging in concentration from 2.7 to 30.4 $\times 10^{-4}$ mole per liter, gave a straight line when the logarithm of the light transmission was plotted against concentration. The transmission was obtained by dividing the galvanometer deflection with bromine solution in the cell by the deflection with pure carbon tetrachloride in the cell. The constant k in Beer's law, $I = I_0 e^{-klc}$ was found to be 458 when l is expressed in cm. and c in moles per liter. Using a thermopile and much more intense light Bauer and Daniels[3] obtained a value of 448.

Solutions of purified carbon tetrachloride and bromine were prepared in an atmosphere of nitrogen and kept in a large storage vessel using a tightly fitting, unlubricated stopcock. Kahlbaum cinnamic acid, recrystallized several times from alcohol, gave a melting point of 133°. The stilbene and triphenylethylene were prepared by Zartman.[5] They melted at 124.4 and 69.8,° respectively. The triphenylmethane was prepared from benzene and chloroform in the presence of aluminum chloride. After

(1) (a) Luther and Goldberg, *Z. physik. Chem.*, **56**, 43 (1906); (b) Dickinson and Leermakers, THIS JOURNAL, **54**, 3852, 4648 (1932); (c) Willard and Daniels, *ibid.*, **57**, 2240 (1935); (d) Chapman, *ibid.*, **56**, 818 (1934); (e) Pease, *ibid.*, **53**, 3728 (1931); (f) Schultze, *ibid.*, **56**, 1552 (1934); (g) Heisig, *ibid.*, **58**, 1095 (1936).

(2) Bauer and Daniels, *ibid.*, **56**, 2014 (1934).

(3) Bauer and Daniels, *ibid.*, **56**, 378 (1934).

(4) Horiuti, *Sci. Papers Inst. Phys. Chem. Research* (Tokyo), **17**, 125 (1931).

(5) Adkins and Zartman, THIS JOURNAL, **54**, 1668 (1932).