drill rod, which is available in a wide range of diameters, has been found satisfactory for most organic solvents. The meniscus in the measuring capillary may be adjusted to any desired position by raising or lowering the metal rod. This permits the use of the osmometer as a dynamic instrument by the method of Fuoss and Mead[1] or as a static instrument in which the level may be set at the expected equilibrium position with consequent saving of time.

As an alternative level changing device, the rod may be omitted and a blind piece of rubber tubing R slipped over the filling tube instead. A screw clamp S on the rubber tube is then used to adjust the level. This has been found satisfactory with aqueous solutions where corrosion of the steel rod presents difficulties.

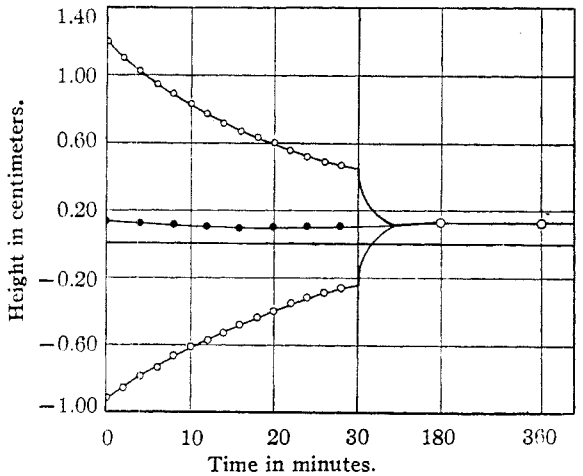

Fig. 2.—Meniscus height *versus* time, polystyrene–toluene: O, experimental points; ●, half sum values.

The osmometer filled with the solution is placed in a glass cylinder containing the solvent. A short length of capillary tubing D, of the same internal diameter as the measuring capillary, is immersed in the solvent for the purpose of correcting for capillary rise. When equilibrium has been established, the difference in level of the menisci in the measuring and reference capillaries (determined with a cathetometer) is the osmotic head. It is desirable to place the apparatus in a glass-walled thermostat held constant to within 0.01° to avoid variations due to thermal expansion of the solution in the osmometer.

When volatile solvents are being used a drop of mercury may be placed in the funnel to prevent evaporation around the rod. As so constructed the capacity of the osmometer cell is about 3 ml. Because of the absence of narrow channels, the interior may be adequately rinsed with not more than 2 ml. of solution.

Operation.—The general procedure of measuring osmotic pressure has been described previously, *e. g.*, Flory,[2] Fuoss and Mead,[1] and Wagner,[3,4] from which no essential changes have been made by us. The glass construction of the cell simplifies the elimination of bubbles in filling.

It has been found that aqueous solutions tend to stick in the fine capillary. In such cases the use of an immiscible liquid, *e. g.*, hexane or toluene, as a pressure indicator is desirable. The cell is filled about seven-eighths full with the aqueous solution and the remaining portion of the cell and capillaries filled with the manometric liquid. In such cases, the correction for capillary rise (of the manometric liquid) is determined separately.

The approach of the meniscus to equilibrium is shown in Fig. 2. These data were obtained on a solution of polystyrene in toluene using a denitrated collodion membrane. The equilibrium value, which was attained within three hours in this case, was reproducible on subsequent resettings within 0.02 cm. This is the order of reproducibility that is generally attained even when the total rise is greater.

(2) P. J. Flory, THIS JOURNAL, **65**, 372 (1943).

(3) H. Wagner, *Ind. Eng. Chem., Anal. Ed.*, **16**, 520 (1944).

(4) H. Wagner, "Physical Methods of Organic Chemistry," Vol. I, Chap. VIII, Weissberger, editor, Interscience Publishers, Inc., New York, N. Y., 1945.

POLYTECHNIC INSTITUTE OF BROOKLYN
BROOKLYN 2, N. Y.

RECEIVED MARCH 9, 1946

Convenient Syntheses of Thymine and 5-Methylisocytosine

BY HENRY W. SCHERP

Davidson and Baudisch[1] found that uracil could be synthesized conveniently by heating a solution of malic acid and urea in concentrated sulfuric acid. By substituting guanidine hydrochloride for urea, Caldwell and Kime[2] utilized this reaction for the synthesis of isocytosine. The present communication concerns the preparation of thymine and 5-methylisocytosine (2-amino-5-methyl-4(3)-pyrimidone) by the reaction between β-methylmalic acid and urea or guanidine, respectively. Thymine was synthesized also by the reaction between diethyl β-methylmalate and urea. This alternative procedure eliminated one step in the synthesis, but the yield was about one-sixth less.

β-Methylmalic acid was prepared by the hydrolysis of diethyl β-methylmalate, which was in turn prepared by the reduction of ethyl ethoxalylpropionate by catalytic hydrogenation at low pressures. This method of reduction was found to be superior to other methods used previously.[3]

Experimental

Ethyl Ethoxalylpropionate.—This substance was synthesized by the Claisen condensation of diethyl oxalate and ethyl propionate.[4] Decomposition of the sodium salt

(1) Davidson and Baudisch, THIS JOURNAL, **48**, 2379 (1926).

(2) Caldwell and Kime, *ibid.*, **62**, 2365 (1940).

(3) (a) Wislicenus, *Ber.*, **25**, 196 (1892); (b) Abbott and McKenzie, *ibid.*, **71B**, 1214 (1938); (c) Wojcik and Adkins, THIS JOURNAL, **55**, 4939 (1933).

(4) "Organic Syntheses," Coll. Vol. II, 1943, p. 272.

of the addition product with acetic acid, as described in the reference quoted, produced emulsions. Decomposition with dilute sulfuric acid[5] was entirely satisfactory.

Diethyl β-Methylmalate.—Using a proportion of 1 g. of platinum oxide catalyst per mole of ethyl ethoxalylpropionate and an initial hydrogen pressure of from 3 to 4 atmospheres, the reduction of from 0.1 to 0.5 mole of the ester was complete within from two to three hours, as shown by the cessation of the uptake of hydrogen and a negative color test with ferric chloride. The use of a greater proportion of catalyst accelerated the reaction but resulted in heating of the reaction mixture. The use of a solvent (ethanol redistilled from sodium hydroxide) was disadvantageous: in several runs, the reaction slowed sharply when two-thirds complete and reached completion only after many hours; addition of fresh catalyst was ineffective.

In six runs, yields of from 88 to 92% were obtained of material boiling at 121–124° (10 mm.) and having $n^{25}D$ 1.4332–1.4338. Extrapolation from the data of Wislicenus[3a] indicated a b. p. of 125° (10 mm.); Wojcik and Adkins[3c] gave 109–113° (5 mm.); Abbot and McKenzie[3b] gave 116° (11.5 mm.).

β-Methylmalic Acid.—In a typical experiment, a mixture of 20.4 g. (0.10 mole) of diethyl β-methylmalate, 80 ml. of water and 1 ml. of 12 *N* hydrochloric acid was boiled under reflux and the course of the hydrolysis was followed by titrating samples against 0.05 *N* sodium hydroxide. There was no increase in acidity after five hours. The contents of the flask were reduced *in vacuo* to a sirup, and dehydrated by placing the flask in a vacuum desiccator containing sodium hydroxide and connected to a vacuum pump (Hyvac). After twenty-four hours, the product formed a very viscous colorless sirup weighing 15.16 g., compared with a theoretical recovery of 14.50 g.

Thymine.—Six grams (0.10 mole) of urea was added in small increments to 25 ml. of fuming sulfuric acid (15% SO_3) cooled in a bath of ice and salt. The mixture was brought to room temperature, stirred until all of the urea dissolved, and poured onto 7.4 g. (0.05 mole) of β-methylmalic acid prepared in the manner described above. After the latter had dissolved, the mixture was heated on a steam-bath for an hour. The reaction mixture was cooled, poured into 75 ml. of water and cooled to 0°. The product was filtered off, washed with water and recrystallized from the minimal volume of water (120 ml.) that would dissolve it at the boiling point. Yield, dried over phosphorus pentoxide *in vacuo*, was 3.15 g., or 50%, based on the amount of diethyl β-methylmalate taken at the start; m. p. 313–314° (uncor.) with decomposition.

Anal. Calcd. for $C_5H_6O_2N_2$: N, 22.23. Found: N, preparation 1, 22.28; preparation 2, 22.16 (micro-Kjeldahl; each value is the mean of four determinations).

Synthesis Directly from Diethyl β-Methylmalate.—The foregoing procedure was modified by substituting for β-methylmalic acid an equimolar amount of diethyl β-methylmalate, which was added to the solution of urea in sulfuric acid with stirring and cooling. The yield was 39%. In a second experiment, the amount of sulfuric acid was increased by one-third and the yield was 42%. Evidently, the concentration of acid was not critical.

Microbiological Assay.—Through the courtesy of Dr. I. C. Gunsalus of Cornell University, one of the present preparations of thymine was tested for its activity as a stimulant of the growth of *Streptococcus faecalis* R[6] and was found to be as effective as a sample of thymine prepared in another laboratory by the method of Johnson.[7]

5-Methylisocytosine.—Nineteen and one-tenth grams (0.20 mole) of guanidine hydrochloride was added in small increments to 54 ml. of fuming sulfuric acid (15% SO_3) cooled in a bath of ice and salt. The solution was brought to room temperature and poured onto 14.8 g. (0.10 mole) of β-methylmalic acid prepared in the manner already described. After the latter had dissolved, the solution was heated on a steam-bath for an hour, cooled, and poured into 2 liters of ice and water. Barium carbonate was added until, after stirring for half an hour, the solution was alkaline to congo red; a total of 300–325 g. of barium carbonate was required. The barium sulfate was filtered off and washed on the filter with 500 ml. of water. The filtrate was acidified with 0.2 ml. of concentrated sulfuric acid (to remove excess barium) and hydrochloric acid until acid to congo red (to hold the product in solution during subsequent concentration). The solution was reduced *in vacuo* to less than 100 ml., freed of barium sulfate by filtration, and neutralized to phenol red with concentrated ammonium hydroxide. After several hours of refrigeration, the product was filtered off and washed on the filter with 30–40 ml. of water. It recrystallized in rosets of needles from the minimal volume of water (325 ml.) that would dissolve it at the boiling point. The yield, dried over phosphorus pentoxide *in vacuo*, was 9.49 g., or 76%, based on the diethyl β-methylmalate taken at the start; m. p. 290–291° (uncor.), with slight carbonization and considerable evolution of gas.

Anal. Calcd. for $C_5H_7ON_3$: N, 33.60. Found: N, 33.67 (micro-Kjeldahl, mean of four determinations).

Acknowledgment.—The author is indebted to Dr. D. S. Tarbell for much helpful discussion and for the use of various facilities.

DEPARTMENT OF BACTERIOLOGY
SCHOOL OF MEDICINE AND DENTISTRY
UNIVERSITY OF ROCHESTER
ROCHESTER, N. Y. RECEIVED FEBRUARY 6, 1946

(5) Wislicenus and Arnold, *Ann.*, **246**, 329 (1888).

(6) Stokes, *J. Bact.*, **48**, 201 (1944).

(7) Johnson, *J. Biol. Chem.*, **3**, 299 (1907).

NEW COMPOUNDS

1-Trichloro-2,2-bis-(*p*-*t*-butylphenyl)-ethane and Degradation Products[1]

To a mixture, kept at 30°, of 13.4 g. (0.1 mole) of *t*-butyl benzene and 7.4 g. (0.05 mole) of chloral was added dropwise, with stirring, 30 ml. of 100% sulfuric acid, after which the stirring was continued for one hour. The resulting mixture was poured upon ice and the solid washed by decantation, first with water, then with sodium bicarbonate, and finally with water again. The air-dried material weighed 14.5 g. and melted at 120–139°. After several recrystallizations from 95% ethanol, the product, 1-trichloro-2,2-bis-(*p*-*t*-butylphenyl)-ethane (I), melted at 154–155° (cor.) and was obtained in 33% yield.

Anal. Calcd. for $C_{22}H_{27}Cl_3$: Cl, 26.74. Found: Cl, 26.61.

The *para* position of the *t*-butyl groups is assumed on the basis of experience in the Baeyer condensation,[2] as well as upon the correspondence between the observed and predicted reaction-rate constants for dehydrochlorination with ethanolic sodium hydroxide as reported previously.[3]

A solution of 2.0 g. (0.005 mole) of I and 1.0 g. (0.018 mole) of potassium hydroxide in 30 ml. of 95% ethanol was heated at reflux for one and one-half hours. The reaction mixture was cooled, poured into water, and extracted with ether. The solvent was removed in an air stream, and the residue was taken up in ethanol, clarified

(1) Part of a program supported by a transfer of funds, as recommended by the Committee on Medical Research, from the Office of Scientific Research and Development to the Bureau of Entomology and Plant Quarantine.

(2) (a) v. Baeyer, *Ber.*, **5**, 25, 280, 1094 (1872); (b) Fischer, *ibid.*, **7**, 1190 (1874); (c) Elbs, *J. prakt. Chem.*, [2] **47**, 68 (1893); (d) Grummitt, Buck and Stearns, THIS JOURNAL, **67**, 156 (1945); (e) Haller, Bartlett, Drake, Newman and co-workers, *ibid.*, **67**, 1591 (1945).

(3) Cristol, *ibid.*, **67**, 1494 (1945).