adjusting the *p*H to approximately 4 with 40% sodium hydroxide, 8.8 g. of 4-chlorocoumarin was added and reflux was continued for seventeen hours. The reaction mixture was made basic with concentrated ammonium hydroxide and extracted with 400 ml. of chloroform in three equal portions. After drying the chloroform solution over magnesium sulfate, the solution was concentrated to 250 ml. and dry ether was added until the solution became cloudy. On cooling 5.0 g. of brown solid separated which on recrystallization from 500 ml. of methanol gave 4.0 g. (23.6%) of light-green solid, m. p. 210–211°.

Anal. Calcd. for $C_{20}H_{22}O_3N_2$: N, 8.27. Found: N, 8.38.

DEPARTMENT OF CHEMISTRY AND PHYSICS
THE PENNSYLVANIA STATE COLLEGE
STATE COLLEGE, PENNA.
RECEIVED MAY 27, 1950

Modified Synthesis of Pteroylglutamic Acid

BY SHOJIRO UYEO, SATOSHI MIZUKAMI, TOKUO KUBOTA AND SHUZO TAKAGI

The use of trihaloacetones in the synthesis of pteroylglutamic acid from 2,4,5-triamino-6-hydroxypyrimidine (I) and *p*-aminobenzoylglutamic acid (II) has been described by Hultquist and Dreisbach[1] and by Weygand and Schmied-Kowarzik[2].

This method seems preferable to the standard method of Waller, *et al.*,[3] in which α,β-dihalopropionaldehyde is used in place of trihaloacetone. In the latter case dihydropteroylglutamic acid should result initially and this intermediate should be dehydrogenated automatically in the reaction medium or oxidized chemically with iodine,[4] sodium bichromate[5] or mercuric acetate[6] to the aromatic pteridine.

The details of the original procedures were not available to us, but the condensation of equivalent quantities of (I), (II) and 1,1,3-trichloroacetone in water at room temperature for several days while the *p*H was maintained at 4 by the addition of sodium bicarbonate solution gave crystalline pteroylglutamic acid of about 85% purity in a yield of only 1.4%. Under these conditions the solution and product darken, so the reaction was modified by adding sodium bisulfite in order to avoid the oxidation of (I) by trichloroacetone. This was found to have a pronounced beneficial effect, giving after purification a 37% yield of crystalline pteroylglutamic acid of about 80% purity. In a similar manner, the same product was obtained in a 15% yield when 1,1-dichloro-3-bromoacetone was substituted for trichloroacetone.

It seems that the sodium bisulfite may play a role not merely as an antioxidant, but also as a catalyst to effect the combination of the three components to give pteroylglutamic acid. Semb[7] found that 2-amino-4-hydroxy-6-methylpteridine, instead of the 7-methyl derivative, was the principal product when methylglyoxal was allowed to react with 2,4,5-triamino-6-hydroxypyrimidine in water solution at *p*H 7 in the presence of sodium sulfite. Seeger, *et al.*,[4] obtained chiefly 2,4-diamino-6-methylpteridine by using 2,4,5,6-tetraaminopyrimidine in place of the triamine in the same reaction. These results seem to be in accordance with ours, although our finding was done before the appearance of their papers.

Other reducing agents, such as sodium hydrosulfite or ascorbic acid did not show any appreciable influence on the yield.

Experimental

1,1-Dichloro-3-bromoacetone (III) and 1,1,3-Trichloroacetone (IV).—These two compounds were prepared according to the procedure of Cloez.[8] III was recrystallized from petroleum ether forming colorless needles, m. p. 28–30°.

Anal. Calcd. for $C_3H_3OCl_2Br$: C, 17.5; H, 1.5. Found: C, 17.6; H, 1.6.

IV distilled at 77–79° at 25 mm. and crystallized on cooling as colorless needles melting at 13.6–15.5°.

Anal. Calcd. for $C_3H_3OCl_3$: C, 22.3; H, 1.9. Found: C, 22.3; H, 1.9.

Both III and IV formed dihydrates when each compound was poured into the same amount of water. III dihydrate formed colorless plates, m. p. 53–55°.

Anal. Calcd. for $C_3H_3OCl_2Br \cdot 2H_2O$: C, 14.9; H, 2.9. Found: C, 14.9; H, 2.9.

IV dihydrate, m. p. 47–48°, was isomorphous with the trichloro compound and did not depress the melting point when admixed with III dihydrate.

Anal. Calcd. for $C_3H_3OCl_3 \cdot 2H_2O$: C, 18.2; H, 3.6. Found: C, 18.4; H, 3.7.

Both dihydrates are easily soluble in water.

Pteroylglutamic Acid.—To a solution of 1.13 g. of 2,4,5-triamino-6-hydroxypyrimidine,[9] 2.13 g. of *p*-aminobenzoyl-L-glutamic acid[10] and 1.5 g. of sodium bisulfite in 150 cc. of water was added a solution of 1.3 g. of 1,1,3-trichloroacetone in 60 ml. of water. The acidity of the resulting mixture was adjusted and maintained at *p*H 4 throughout the reaction with frequent addition of sodium bicarbonate solution. After standing for ninety-five hours at room temperature the precipitation was complete. The product was then filtered off and washed with water, alcohol and ether. The crude material was purified twice according to the method of Waller, *et al.*,[3] by reprecipitation and 1.30 g. of yellowish-orange crystals were obtained. The purity by chemical assay[11] was about 80%. The substance was reprecipitated once more in a similar manner and the purity was raised to about 92%; yield 1.04 g. For analysis it was further reprecipitated thrice and dried at 140° *in vacuo* for five hours. The dried pale yellow crystals were very hygroscopic and on exposure to air they gained in weight quite rapidly, changing color to yellow. The analyses agreed with values calculated for partially rehydrated material.

---

(1) Hultquist and Dreisbach, U. S. Patent 2,443,165, June 8, 1948.

(2) Weygand and Schmied-Kowarzik, *Ber.*, **82**, 333 (1949).

(3) Waller, *et al.*, THIS JOURNAL, **70**, 19 (1948).

(4) Seeger, *et al.*, *ibid.*, **71**, 1753 (1949).

(5) Boothe, *et al.*, *ibid.*, **71**, 2304 (1949).

(6) Uyeo and Mizukami, *Jap. J. Pharmacy and Chemistry*, **21**, 237 (1949).

(7) Semb, U. S. Patent 2,477,426, July 26, 1949; *cf.* Seeger, *et al.*, ref. 4.

(8) Cloez, *Ann. chim. phys.*, [6] **9**, 176 (1886); King and Spensley (*Nature*, **164**, 574 (1949)) gave for 1,1-dichloro-3-bromoacetone m. p. 31° and b. p. 92–93° (25 mm.).

(9) Traube, *Ber.*, **33**, 1371 (1900).

(10) Van der Scheer and Landsteiner, *J. Immunology*, **29**, 373 (1935).

(11) "New and Nonofficial Remedies," J. B. Lippincott Company, New York, N. Y., 1948, p. 618.

Anal. Calcd. for $C_{19}H_{19}O_6N_7 \cdot 1.5H_2O$: C, 48.6; H, 4.7; N, 20.9. Found: C, 48.4; H, 5.0; N, 20.9.

The crystal form, ultraviolet absorption spectrum and paper partition chromatography (R_f, 0 (*n*-butanol); 0.11 (collidine–lutidine, 1:1); 0.22 (acetic acid–*n*-butanol–water, 1:4:1); 0.40 (phenol–water–ammonia solution, 80:18:2))[12] showed the identity of this product with an authentic sample of pteroylglutamic acid.

---

[12] Kuwada, Mizuno and Masuda read a paper on the paper partition chromatography of folic acid and related compounds at the meeting of the Pharmaceutical Society of Japan in September, 1949.

THE DEPARTMENT OF PHARMACY
FACULTY OF MEDICINE
UNIVERSITY OF KYOTO
KYOTO, JAPAN
RECEIVED MARCH 29, 1950

Adsorption Effects in the Decomposition of Hydrogen Peroxide Vapor

BY MILTON TAMRES AND ARTHUR A. FROST

Adsorption phenomena in studying the kinetics of hydrogen peroxide vapor decomposition were reported by MacKenzie and Ritchie[1] and by Giguère[2] who investigated extensively the sensitivity of the reaction to surface conditions. The reaction was studied at this Laboratory by a static method employing an oil (Nujol heavy mineral oil) manometer to follow the reaction rate. Results at 45° and room temperature showed a pressure increase during a run in excess of the 50% expected for a homogeneous reaction. This can only be explained by adsorption effects of hydrogen peroxide and water.

For experiments at 21°, a small quantity of liquid hydrogen peroxide of approximately 90% concentration was distilled at room temperature under reduced pressure until a trace of the liquid remained. Decomposition of the resulting vapor at initial pressures of 0.5 to 0.7 mm. and presumably of very high peroxide concentration. was studied in two spherical 500-cc. Pyrex vessels, The observed over-all change in pressure was approximately 62% of the initial pressure for one vessel and 50% for the other although their surfaces were treated identically. That this difference in adsorption was not due to possible slight differences in experimental conditions was shown by employing an experimental technique whereby hydrogen peroxide vapor could be introduced simultaneously into both reaction vessels, equalizing the pressure of vapor between them and following the "differential" rate of reaction with the oil manometer each end of which was connected to one of the vessels. The "differential" rate of reaction showed that initial decomposition proceeded more rapidly in the vessel where adsorption was greater, the difference in extent of adsorption being noted by the difference in final pressures in the reaction vessels. Each run required several days and consequently few were made. The results, however, seemed reproducible.

Packing the reaction vessel with approximately 5 g. of soft glass wool strikingly demonstrated this effect, approximately three times as much hydrogen peroxide being adsorbed than was present in the vapor phase.

Attempts to minimize surface effects by coating Pyrex glass surfaces with microcrystalline wax (Cerese wax AA) and with silicone (Dri-Film 9987) were unsuccessful. A comparison of the rate of decomposition at 45.0° showed that the wax only slightly decreased the rate as compared with the chromic acid cleaned surface whereas the silicone surface catalyzed the reaction.

For photochemical experiments, the reaction vessel was a cylindrical Pyrex glass cell to which a Vycor window was sealed with Apiezon W. The cell, which was 4 cm. inside diameter and of 250-cc. capacity, was jacketed with a copper coil through which water at 26.2° was circulated. The ultraviolet source was a Hanovia quartz mercury discharge lamp, emitting predominantly 2537 Å. radiation. The rate of the photochemical reaction was much faster than that of the thermal reaction, and was not influenced by the introduction of 0.05 to 8.0 mm. pressure of nitrogen (except as described below), oxygen or water vapor, nor by 0.05 to 1.0 mm. pressure of hydrogen or air. This is in agreement with results reported by Volman.[3]

The complete photolysis of the vapor from a supply of approximately 95% liquid hydrogen peroxide resulted in a pressure change which was from 49 to 61% of the initial pressure, again indicating adsorption of peroxide. The fact that Volman reported an over-all change in pressure which was less than 50% of the initial pressure, does not eliminate the possibility of adsorption in his experiments since his liquid hydrogen peroxide supply was of lower concentration.

An interesting observation in the photochemical studies should be mentioned. In the initial experiments, when nitrogen was being used as the inert gas, decomposition was very rapid for nitrogen pressures less than 0.1 mm., while at higher nitrogen pressures the rate was decreased noticeably if the nitrogen were admitted first to the cell, but was unaffected by the presence of nitrogen if peroxide were first introduced. A change to oxygen as the foreign gas showed no such pressure dependence and a return to nitrogen no longer produced this effect.

These observations confirm the heterogeneous character of the thermal reaction and indicate that the photochemical reaction also has some heterogeneous characteristics.

Acknowledgment.—This work was supported by a fellowship from the U. S. Rubber Company.

DEPARTMENT OF CHEMISTRY
NORTHWESTERN UNIVERSITY
EVANSTON, ILLINOIS
RECEIVED JUNE 23, 1950

---

[1] R. C. MacKenzie and M. Ritchie, *Proc. Roy. Soc.* (*London*), **A185**, 207 (1946).

[2] P. A. Giguère, *Can. J. Research*, **25B**, 135 (1947).

[3] D. H. Volman, *J. Chem. Phys.*, **17**, 947 (1949).