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Methylene-hydantoin and Related Compounds. I. On the Reaction of Pyruvic Acid and Urea: The Synthesis of 5-Methylene-hydantoin

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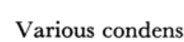
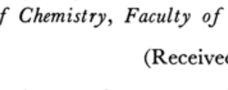
Various condensation products were obtained by the reaction between pyruvic acid and urea. They are 5-hydroxy-5-methyl-hydantoin, homoallantoin, homoallantoic acid, and dipyruvic triureide. 5-Methylene-hydantoin was prepared from some of these compounds, or directly from pyruvic acid and urea, by reactions in organic acid. The most convenient method was the dehydration of 5-hydroxy-5-methyl-hydantoin, which is a new compound melting at 166°C. 5-Methylene-hydantoin, m. p. 214°C, is a new monomer of the vinylidene type which polymerizes easily by means of a free radical mechanism. 3-Methyl-5-methylene-hydantoin was also prepared from 5-hydroxy-5-methyl-hydantoin through its 3-methyl derivative.

The derivatives of 5-methylene-hydantoin may be vinylidene-type monomers of some interest because they give polymers containing hydantoin groups along the hydrocarbon main chains. However, 5-methylene-hydantoin (I) itself has not been prepared, although the preparation of substituted 5-methylene-hydantoins, such as 1-phenyl-5-methylene-hydantoin[1] and 3-phenyl-5-methylene-hydantoin,[2] has been reported in the literature.



$$\begin{array}{l} CH_2{=}C - CO\diagdown \\ \quad\;| \qquad\qquad\;\; NH \\ \quad NH{-}CO\diagup \end{array}$$

(I)



$$\begin{array}{l} \qquad\qquad\;\; Y \\ \qquad\qquad\;\; | \\ XCH_2{-}C - CO\diagdown \\ \qquad\quad\; | \qquad\qquad\;\; NH \\ \qquad\; NH{-}CO\diagup \end{array}$$

(II)

Various attempts to derive I from the compounds represented by formula II, such as 5-bromo-5-methyl-hydantoin ($X{=}H$, $Y{=}Br$),[3] 5-bromomethyl-hydantoin ($X{=}Br$, $Y{=}H$),[4] 5-hydroxymethyl-hydantoin ($X{=}OH$, $Y{=}H$),[5] and 5-carboxymethylene-hydantoin,[6] by the elimination of XY or by decarboxylation in the case of 5-carboxymethylene-hydantoin were not successful because of the difficulty of the elimination reaction and/or the polymerization of the product during the reaction.

5-Methylene-hydantoin is considered to be the condensation product of equimolar amounts of pyruvic acid and urea; this suggests the possibility of its formation from these compounds. It was found that 5-methylene-hydantoin could be prepared from pyruvic acid and urea directly or through their reaction products as intermediates. In this paper, the synthesis of 5-methylene-hydantoin and, in connection with this, the results of the investigation of the reaction of pyruvic acid and urea will be described.

Results and Discussion

The prolonged reaction of equimolar amounts of pyruvic acid and urea in water at room temperature gave 5-hydroxy-5-methyl-hydantoin (III) in a fairly good yield. If the reaction was carried out with higher concentrations of the reagents, homoallantoic acid (α, α-diureidopropionic acid) (IV) was produced predominantly, and at higher temperatures mainly homoallantoin (5-methyl-5-ureido-hydantoin) (V) and dipyruvic triureide (VI) were obtained. The reaction probably proceeded by the course shown in Fig. 1. The condensation product (VII) of pyruvic acid and urea is converted into 5-hydroxy-5-methyl-hydantoin by cyclization in a dilute solution, but at

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[1] R. K. Ralph, G. Shaw and R. N. Naylor, *J. Chem. Soc.*, **1959**, 1169.
[2] M. Bergmann and D. Delis, *Ann.*, **458**, 82 (1927).
[3] S. Gabriel, ibid., **348**, 50 (1906).
[4] G. Nadeau and R. Gaudry, *Can. J. Research*, **27B**, 421 (1949).
[5] D. Billet, *Bull. soc. chim. France*, **1954**, 815.
[6] J. E. Nyc and H. K. Mitchell, *J. Am. Chem. Soc.*, **69**, 1382 (1947).

higher concentrations of the reagents urea may attack VII and give homoallantoic acid. This acid is slightly soluble in water and is precipitated from a cold solution. At higher temperatures, homoallantoic acid is converted into homoallantoin by dehydration or into dipyruvic triureide through condensation with VII.

5-Hydroxy-5-methyl-hydantoin is a new compound whose melting point is 166°C. The reduction of 5-hydroxy-5-methyl-hydantoin with hydroiodic acid gave 5-methyl-hydantoin. It has been known that homoallantoic acid itself can be prepared from one mole of pyruvic acid and two of urea.⁷⁾ When heated at 100°C in 80% formic acid, 5-hydroxy-5-methyl-hydantoin easily gave 5-methylene-hydantoin in a 60% yield. The prolonged reaction did not improve the yield, but by the addition of acetic anhydride to the reaction mixture as a dehydrating agent, 5-methylene-hydantoin was obtained almost quantitatively, even in several minutes. The reaction carried out in acetic acid or in 1 N hydrochloric acid gave 5-methylene-hydantoin in only low yield. However, 5-methylene-hydantoin was obtained in a high yield when a mixture of glacial acetic acid and a small amount of concentrated hydrochloric acid was used as the solvent. 5-Methylene-hydantoin gave 5-methyl-hydantoin by reduction with hydroiodic acid.

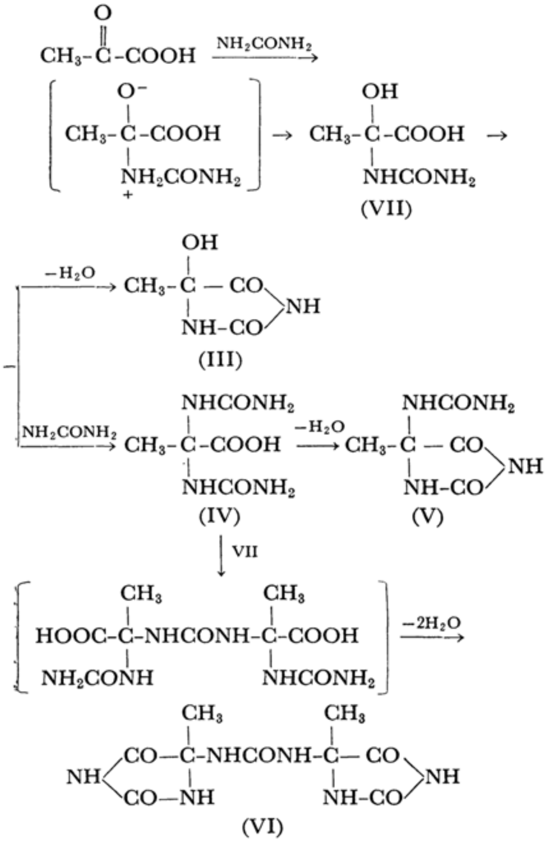
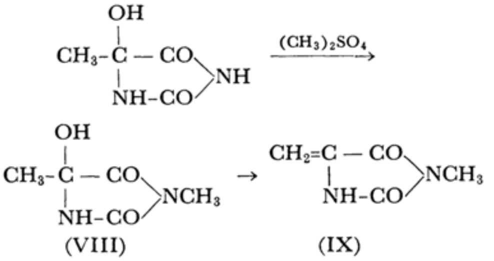


Fig. 1. Reaction of pyruvic acid and urea.

TABLE I. THE REACTION OF PYRUVIC ACID AND UREA
Pyruvic acid, 5.0 g.; Urea, 3.4 g. (1 : 1 molar ratio)

Solvent	ml.	Temp. °C	Time	Product (% Yield)			
				III	IV	V	VI
H_2O	5	20	2 days	—	40	—	—
H_2O	25	20	14 days	69	—	10	—
H_2O	5	90	2 hr.	—	—	10	22
H_2O	20	90	2 hr.	30	—	10	11
1/100 N HCl	20	20	3 days	21	—	—	—
1 N NaOH	15	20	3 days	48	—	7	—

3, 5-Dimethyl-5-hydroxy-hydantoin (VIII) was prepared by the methylation of 5-hydroxy-5-methyl-hydantoin with dimethyl sulfate. The dehydration of this compound gave 3-methyl-5-methylene-hydantoin (IX) under the same conditions as produced 5-hydroxy-5-methyl-hydantoin.



Dipyruvic triureide has been known to be easily obtainable by a reaction of 2 moles of pyruvic acid and 3 of urea in concentrated hydrochloric acid.⁸⁾ Dipyruvic triureide was hydrolyzed to give 5-hydroxy-5-methyl-hydantoin and homoallantoin almost quantitatively by boiling it in water for several hours. By a prolonged reaction at a much slower rate, homoallantoin could be hydrolyzed to 5-hydroxy-5-methyl-hydantoin and urea.

5-Methylene-hydantoin could also be obtained from dipyruvic triureide and from homoallantoin by hydrolysis in organic acid under conditions similar as those in the dehydration of 5-hydroxy-5-methyl-hydantoin. In these cases, however, some difficulties were encountered in isolating 5-methylene-hydantoin from the other hydrolysis products, urea and homoallantoin, while 5-methylene-hydantoin might polymerize during the isolation if it requires too long a time.

Davidson⁸⁾ has reported that dipyruvic triureide was converted by concentrated sulfuric acid into dipyruvic ureide (X), the dimer of 5-methylene-hydantoin, which is stable and almost insoluble in cold water. In this reaction the initial product must be 5-methylene-hydantoin, which dimerizes in sulfuric acid by the cationic mechanism.

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7) I. J. Simon, *Compt. rend.*, **133**, 587 (1901).

8) D. Davidson, *J. Am. Chem. Soc.*, **47**, 255 (1925).

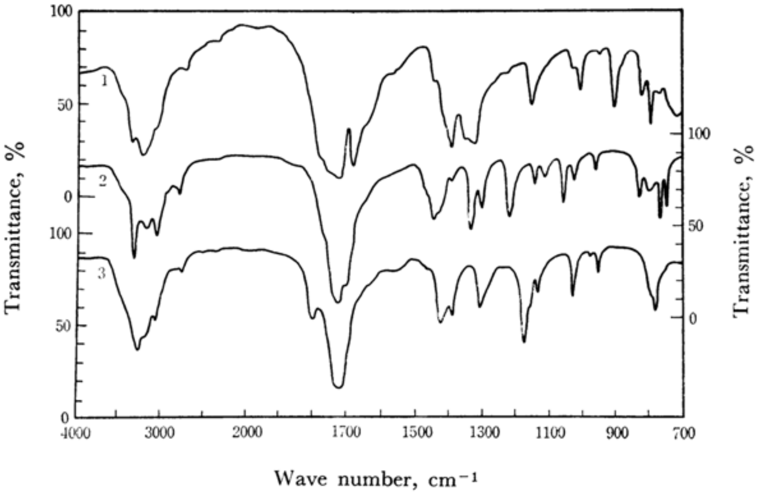
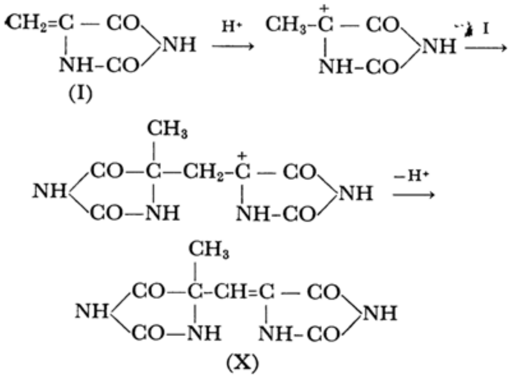


Fig. 2. Absorption spectra of: 1, 5-methylene-hydantoin; 2, 5-methyl-hydantoin; 3, 5-hydroxy-5-methyl-hydantoin (in KBr disks).



(I)

(X)

Directly from pyruvic acid and urea, 5-methylene-hydantoin could be prepared in a low yield by heating it in acetic acid containing a small amount of hydrochloric acid. However, the slow rate of reaction left the reagents unreacted, or resulted in the polymerization of the hydantoin produced during the long period of reaction.

As has been described above, there are various routes possible in the synthesis of 5-methylene-hydantoin from pyruvic acid and urea as starting materials. However, the most convenient route among these is that via 5-hydroxy-5-methyl-hydantoin because of its high yield and the simple procedure.

The infrared spectra of 5-methylene-hydantoin, 5-methyl-hydantoin and 5-hydroxy-5-methyl-hydantoin are shown in Fig. 2.

Experimental

5-Hydroxy-5-methyl-hydantoin.—A solution of pyruvic acid (50 g., 0.57 mol.) and urea (34 g., 0.57 mol.) in water (250 ml.) was allowed to stand at room temperature for 14 days and then evaporated under reduced pressure. Methanol (350 ml.) was added to the residue, and the insoluble materials were filtered off. Then the unreacted urea was removed by precipitation by adding dry ether to the filtrate. When the solution was evaporated, crude crystals of 5-hydroxy-5-methyl-hydantoin were obtained. Recrystallization from acetic acid gave colorless crystals; yield, 51 g. (69%); m. p. 166°C. This compound was soluble in water, alcohol, acetone, and tetrahydrofuran, sparingly soluble in ethyl ether, and insoluble in petroleum ether.

Found: C, 36.82; H, 4.61; N, 21.62. Calcd. for $C_4H_8N_2O_3$: C, 36.93; H, 4.65; N, 21.53%.

The reaction carried out at a higher concentration of the reagents, at a higher temperature or in the presence of an acid or a base did not improve the yield of 5-hydroxy-5-methyl-hydantoin. The results of the reaction under varying conditions are shown in Table I.

Homoallantoic Acid.—This compound was prepared according to Simon.7) It was converted into homoallantoin in hot water in a 50% yield.

5-Methylene-hydantoin from 5-Hydroxy-5-methyl-hydantoin.—5-Hydroxy-5-methyl-hydantoin (10 g., 0.077 mol.) was dissolved in a mixture of 80% formic acid (100 ml.) and acetic anhydride (120 ml.), and then heated at 100°C for 5 min. in the presence of a small amount of hydroquinone. The solution was then cooled and evaporated under reduced nitrogen pressure. The residue was recrystallized from acetic acid. 5-Methylene-hydantoin (8 g.) was thus obtained almost quantitatively; m. p. 214°C.

Found: C, 42.80; H, 3.62; N, 25.13. Calcd. for $C_4H_4N_2O_2$: C, 42.86; H, 3.60; N, 25.00%.
5-Methylene-hydantoin was soluble in water, alcohol, and acetone, sparingly soluble in ethyl ether, and insoluble in hexane and benzene. It polymerized easily when heated in the presence of a radical initiator. The polymerization and the properties of the polymer will be described in a following paper.9)

To a solution of 5-methylene-hydantoin (0.05 g.) in acetic acid (2 ml.), hydroiodic acid (2 ml., $d=1.6$)

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9) S. Murahashi, H. Yuki, K. Kosai and F. Doura, This Bulletin, **39**, 1563 (1966).

was added. Immediately the brown color of iodine appeared. The solution was heated at 100°C for 10 min. and then concentrated under reduced pressure. Water was added to the residue, and the solution was evaporated. This procedure was repeated five times in order to remove the iodine. Colorless crystals of 5-methyl-hydantoin were thus obtained; m. p. 142°C. They showed the same infrared spectrum as an authentic sample, and their melting points were undepressed on admixture.

The reaction of 5-hydroxy-5-methyl-hydantoin and hydroiodic acid gave the same product as that described above.

3, 5-Dimethyl-5-hydroxy-hydantoin. — 5-Hydroxy-5-methyl-hydantoin (20 g., 0.15 mol.) was dissolved in 1 N sodium hydroxide, after which dimethyl sulfate (21 g., 0.17 mol.) was stirred in drop by drop. The temperature was then kept at 35°C for about one hour. The evaporation of the solvent left a syrupy residue, which was extracted with absolute alcohol. Dry ether was added to the solution, and the precipitates produced were filtered off. When the filtrate was evaporated, a white solid (18 g.) was obtained. Recrystallization from acetone-petroleum ether gave pure 3, 5-dimethyl-5-hydroxy-hydantoin; yield, 17 g. (77%); m. p. 104°C. The compound was soluble in water, alcohol and acetone, slightly soluble in ether, and insoluble in petroleum ether.

Found: C, 44.66; H, 5.66; N, 19.27. Calcd. for $C_5H_8N_2O_3$: C, 44.66; H, 5.59; N, 19.44%.

3-Methyl-5-methylene-hydantoin. — This compound was obtained quantitatively from 3, 5-dimethyl-5-hydroxy-hydantoin by the same procedure as that described in the synthesis of 5-methylene-hydantoin from 5-hydroxy-5-methyl-hydantoin. 3-Methyl-5-methylene-hydantoin, m. p. 142°C, was soluble in water, alcohol and acetone, slightly soluble in ether, and insoluble in petroleum ether.

Found: C, 47.52; H, 4.89; N, 22.33. Calcd. for $C_5H_6N_2O_2$: C, 47.62; H, 4.80; N, 22.22%.

Dipyruvic Triureide.—Dipyruvic triureide was prepared according to Davidson[8] as follows. To a solution of urea (75 g., 1.3 mol.) in concentrated hydrochloric acid (85 ml.), pyruvic acid (50 g., 0.57 mol.) was added. After the solution had been allowed to stand for 3 days, it solidified completely. Recrystallization from dilute aqueous ammonia and acetic acid gave long needles; yield, 73 g. (72%); m. p. above 300°C (decomp.).

Found: C, 33.88; H, 5.13; N, 26.41. Calcd. for $C_9H_{12}N_6O_5 \cdot 2H_2O$: C, 33.74; H, 5.04; N, 26.25%.

The Hydrolysis of Dipyruvic Triureide.—A suspension of dipyruvic triureide (50 g., 0.15 mol.) in water (1.2 l.) was refluxed for 5 hr. The resultant solution was evaporated to dryness. The residue was then triturated with dry methanol (130 ml.) and filtered. Homoallantoin was thus obtained as colorless crystals; yield, 24 g. (91%); m. p. 260°C (decomp.) (lit.,[7] m. p. 260°C (decomp.)).

Found: C, 34.79; H, 4.78; N, 32.69. Calcd. for $C_5H_8N_4O_4$: C, 34.88; H, 4.88; N, 32.55%.

The filtrate was concentrated after urea had been removed by adding dry ether. The crude crystals of 5-hydroxy-5-methyl-hydantoin were recrystallized from acetic acid; yield, 19 g. (91%).

The Hydrolysis of Homoallantoin.—Homoallantoin (10 g., 0.058 mol.) was dissolved in hot water (100 ml.), and the solution was refluxed for 10 hr. By the same procedure as has been described above, unreacted homoallantoin (5.5 g.) was recovered and 5-hydroxy-5-methyl-hydantoin (3.2 g.) was obtained from the mother liquor in a 94% yield (based on the consumed homoallantoin).

5-Methylene-hydantoin from Dipyruvic Triureide.—A suspension of dipyruvic triureide (5 g., 0.016 mol.) in 80% formic acid (100 ml.) or in a mixture of acetic acid (100 ml.) and concentrated hydrochloric acid (1 ml.) was heated at 100°C for 20 min. in the presence of hydroquinone. The concentration of the resultant solution under a reduced nitrogen pressure left a syrupy residue, which was dissolved in water (80 ml.) and filtered to remove homoallantoin and the polymer produced during the reaction. After the filtrate had been freeze-dried, the residual crystals were extracted with tetrahydrofuran (100 ml.) to remove the urea. When the extracted solution was evaporated, crude crystals of 5-methylene-hydantoin were obtained. Recrystallization from acetonitrile yielded 2.1 g. (60%). From the water-insoluble fraction, homoallantoin (0.5 g.) was obtained.

5-Methylene-hydantoin from Homoallantoin.—By a procedure similar to that described above, 5-methylene-hydantoin was obtained from homoallantoin in a 60% yield.

5-Methylene-hydantoin from Pyruvic Acid and Urea.—A solution of pyruvic acid (5.0 g., 0.06 mol.) and urea (3.4 g., 0.06 mol.) in acetic acid (20 mol.) containing a small amount of hydrochloric acid was heated at 100°C for 2 hr. 5-Methylene-hydantoin (1.5 g.) was thus obtained in a 24% yield.