tions over a period of 5 to 10 min. After each addition dark fumes were evolved. The mixture was heated for about 5 min. more in this temp. range and then filtered hot from 0.07 g. of dark yellow material which was discarded. From this filtrate upon cooling came 2.97 g. of yellow solid. A portion of this solid was purified by dissolving in dilute NaOH solution and precipitating with acetic acid followed by crystallization from water. The ultraviolet absorption spectrum of the purified material in an aqueous carbonate–bicarbonate buffer of pH 10.5 showed maxima at 241 mμ and 277–278 mμ (log ϵ values 3.92 and 3.95, respectively) and was identical with the spectrum of an authentic sample of xanthine.

2-Mercapto-4,5-diamino-6-hydroxypyrimidine.—This compound was prepared by the method of Traube[15] using certain modifications including those of Elion.[14] The condensation of thiourea and ethyl cyanoacetate was carried out on a 5-mole scale using sodium in absolute methanol in place of absolute ethanol. A reflux period of 2.5 hours was employed, and the resulting reaction mixture was poured into enough water to dissolve the solid. Acidification with acetic acid gave 641 g. (80%) of 2-mercapto-4-amino-6-hydroxypyrimidine. Using the modifications of Elion[14] 640 g. of this compound gave 546 g. (87%) of crude 2-mercapto-4,5-diamino-6-hydroxypyrimidine.

2-Mercapto-6-hydroxypurine (V).—Crude 2-mercapto-4,5-diamino-6-hydroxypyrimidine (40.0 g.) and 400 ml. of C.P. formamide were added to a 1-l., three-necked flask fitted with a sealed stirrer and reflux condenser with drying tube. The mixture was stirred and heated, and just after reflux began, the solid completely dissolved. After 30 minutes reflux, the reaction mixture was allowed to cool. The solid which formed weighed 24.3 g. after washing with water and acetone and drying. Evaporation of the formamide to dryness at reduced pressure gave a further 18.1 g. making the crude yield 99%. Purification by dissolving in a warm dilute solution containing an equivalent amount of sodium hydroxide, treating with charcoal, and acidifying the boiling filtrate from the charcoal with acetic acid gave 28.0 g. (66%) of material having the same ultraviolet absorption spectrum as the 2-mercapto-6-hydroxypurine prepared by the method of Traube.[15] In another run refluxing 100 g. of crude 2-mercapto-4,5-diamino-6-hydroxypyrimidine with 500 ml. of formamide for 30 minutes gave 61.9 g. (58%) of purified 2-mercapto-6-hydroxypurine.

2,6-Dimercaptopurine (IV).—2-Mercapto-6-hydroxypurine (50.0 g.) and 200 g. of phosphorus pentasulfide were added to 1750 ml. of stirred, dry reagent pyridine in a 3-l., three-necked flask fitted with a sealed stirrer and reflux condenser with drying tube. The mixture was refluxed for 1.5

hours and the resulting red-black solution allowed to cool about 10 minutes with stirring. It was then poured with stirring into a solution of 663 g. of sodium hydroxide in 5 l. of water plus ice. The two layers which formed were thoroughly shaken in a separatory funnel and separated. The pyridine layer was washed with a cold solution of 70 g. of sodium hydroxide in 500 ml. of water, and this wash combined with the main aqueous layer which was then acidified with 1200 ml. of glacial acetic acid. The mixture was cooled in ice, and the brown solid which formed was collected and washed with water. After air drying it weighed 44.0 g. (80% crude yield). For purification the crude material was dissolved in a solution of 22 g. of sodium hydroxide in about 4 l. of water and the solution filtered from a little insoluble solid. The filtrate was treated with charcoal, filtered, and the boiling filtrate acidified with acetic acid. The solid which formed on cooling was purified again in the same way to give 30.7 g. (56%) of pure light yellow crystalline material. 2,6-Dimercaptopurine is unchanged upon heating to 330°. It may be recrystallized from about 2000–3000 parts of boiling water.

Anal. Calcd. for $C_5H_4N_4S_2$: C, 32.60; H, 2.19; N, 30.41; S, 34.80. Found: C, 32.63; H, 2.19; N, 30.02; S, 34.50.

Purine (II) from 2,6-Dimercaptopurine.—2,6-Dimercaptopurine (15.0 g.) was dissolved in a mixture of 250 ml. of distilled water plus 50 ml. of concd. ammonia by warming. Then 100 g. of ethanol-wet Raney nickel was rinsed in with about 100 ml. of water, and the mixture refluxed 1.5 hours. The catalyst was filtered hot, washed with a little water, and the filtrate plus water wash returned to the reaction flask and refluxed one hour with a second 100 g. of ethanol-wet Raney nickel plus 30 ml. of additional concd. ammonia. The catalyst was filtered as before and the initially colorless filtrate evaporated to dryness at reduced pressure to give 3.42 g. (35%) of crude purine. It is possible that the low yield is a result of the very large quantities of Raney nickel employed. However, a single treatment with 125 g. of Raney nickel (2 hours reflux) gave a crude product containing a considerable quantity of unreacted starting material. The optimum quantity of Raney nickel (and the number of treatments therewith) have not been determined. The crude product could be purified as described above to give purine m.p. 216–216.5° which was not depressed upon admixture with a sample prepared from 6-mercaptopurine. The ultraviolet absorption spectrum of the purine obtained from 2,6-dimercaptopurine was the same as that of the purine from 6-mercaptopurine.

Peekskill, N. Y.

Study of the Bromination of 5-Alkylhydantoins; Conversion of 5-Propylhydantoin into 5-Propylidenehydantoin and 5-(α-Bromopropylidene)-hydantoin[1]

By Eugene J. McMullen,[2] Henry R. Henze and B. Woodrow Wyatt[3]

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Bromination of a 5-alkylhydantoin leads to the formation of a 5-alkylidenehydantoin which then is converted into a 5-(α-bromoalkylidene)-hydantoin. 5,5-Dialkylhydantoins are not thus attacked by bromine.

An attempt in this Laboratory to synthesize 5-alkyl-5-aminohydantoins, as intermediates in the formation of some sulfanilamidohydantoins, involved the preparation of 5-alkyl-5-bromohydantoins which, subsequently, were to be converted by treatment with ammonia into the corresponding

(1) From the Ph.D. dissertations at The University of Texas, respectively, of B. Woodrow Wyatt (1943) and Eugene J. McMullen (1947).

(2) Parke, Davis and Company Fellow, 1945–1946; Reseach Assistant, Project 175, The University of Texas Research Institute, 1946–1947.

(3) Cotton Research Foundation Fellow, 1938–1940; Parke, Davis and Company Fellow, 1942–1943.

amino derivatives. This sequence seemed plausible for Gabriel[4] had shown that bromination of 5-phenylhydantoin yielded 5-bromo-5-phenylhydantoin, and that the latter reacted with ammonia to form 5-amino-5-phenylhydantoin. However, in the present investigation, several 5-alkylhydantoins upon treatment with bromine yielded products which could be shown to be unsaturated as well as to contain bromine. Thus, for example, 5-propyl-hydantoin (I) was converted into a compound II of molecular formula $C_6H_7BrN_2O_2$. Under identical conditions, of exposure to bromine, several repre-

(4) S. Gabriel, *Ann.*, **350**, 118 (1906).

sentative 5,5-disubstituted hydantoins did not enter into reaction with the halogen.

A survey of the literature revealed the previous preparation of only a small number of unsaturated bromohydantoin derivatives. Omitting from consideration those containing bromine directly attached to an aromatic nucleus, only twelve compounds remain; of the twelve, but five[5] have structures plausibly analogous to the products of our bromination experiments. In general, only rather meager details of the chemical behavior of these hydantoin derivatives have been recorded in support of the structural formulas assigned by the several investigators. As an approach to proof of structure of this series, cleavage has been utilized but once; thus, Davidson[5c] stated that his ureide was easily hydrolyzed to yield parabanic acid and nitromethane. Gabriel[5a] resorted to hydrogenolysis of his "brompyvureid," utilizing the action of hydriodic acid and red phosphorus to produce 5-methylhydantoin. However, when the "N-methyl-brompyvureid" was exposed to the action of these reagents, although iodine was liberated, no organic product seems to have been recovered.

Davidson and Johnson[6] cited the work of Gabriel[4] and of Wheeler, et al.,[7] in support of their conclusion that 5-alkylhydantoins (of type X) react with one molecular equivalent of bromine to form 5-alkylidenehydantoins (of type Y). The latter, in turn, were assumed to react with another molecular equivalent of bromine to yield 5-(α-bromoalkylidene)-hydantoins (of type Z). How-
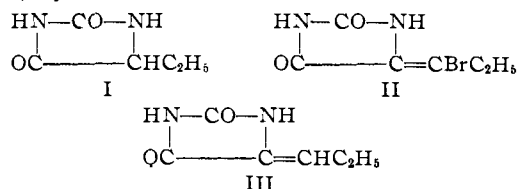
$$
\begin{array}{cc}
\text{HN—CO—NH} & \text{HN—CO—NH} \\
| \qquad\qquad | & | \qquad\qquad | \\
\text{OC———CHCH}_2\text{R} & \text{OC———C=CHR} \\
\text{Type X} & \text{Type Y}
\end{array}
$$

$$
\begin{array}{c}
\text{HN—CO—NH} \\
| \qquad\qquad | \\
\text{OC———C=CBrR} \\
\text{Type Z}
\end{array}
$$
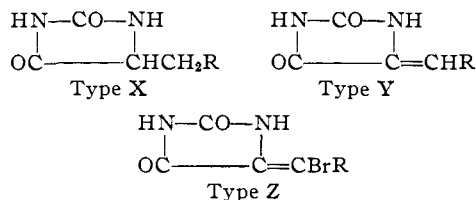
ever, the only experimental evidence[8] suggestive of the formation of a 5-alkylidenehydantoin (type Y) was obtained through bromination of 5-methylhydantoin; actually, in this instance the reaction product isolated was a *dimer* of 5-methylidenehydantoin and not of the monomeric type Y. Hydantoins of type Y, but in which R is an aryl group, have often been obtained by condensation of the appropriate aromatic aldehyde with hydantoin.[9,10] So far as the authors are aware, there is but one published reference to the isolation of a 5-alkylidenehydantoin[11] from condensation of an aliphatic aldehyde and hydantoin, and no record of formation of such a compound from interaction of bromine with a 5-alkylhydantoin. Seemingly, only one 5-

(α-arylmethylidene)-hydantoin has been prepared as a product of the bromination of a 5-(α-aralkyl)-hydantoin.[12]

Our unsaturated, brominated product II was inert toward both aqueous and alcoholic solutions of sodium hydroxide, ammonia or silver nitrate, and did not liberate iodine from iodide solutions. This product II was best obtained by warming a glacial acetic acid solution containing 5-propylhydantoin (one equivalent) and bromine (two equivalents); after a characteristic, brief period of inaction, an abrupt evolution of hydrogen bromide occurred, the solution became practically colorless, and the mono-bromo derivative would separate upon cooling the solution. However, if all the bromine was slowly added dropwise, reaction was sluggish and incomplete and there was evidence both of unreacted 5-propylhydantoin and of some other product.

In another experiment, a stream of ozonized oxygen was bubbled through the solution of 5-propylhydantoin and bromine in glacial acetic acid at room temperature; now, an unsaturated, bromine-free compound III, $C_6H_8N_2O_2$, could be obtained. This product III was demonstrated to be 5-propylidenehydantoin by its reduction to 5-propylhydantoin and its ozonolysis to yield parabanic acid and propionaldehyde. Addition of very small amounts of III to a warmed glacial acetic acid solution of 5-propylhydantoin and bromine definitely shortened the characteristic period of inaction and brought about a higher yield of 5-α-bromopropylidenehydantoin (II) and a considerable production of 5-propylidenehydantoin (III).

5-Propylidenehydantoin (III) in glacial acetic acid reacted, on being warmed, with an equivalent amount of bromine to yield II in excellent yield. Compound II, suspended in nitroethane, or dissolved in ethyl acetate, was exposed to a stream of ozone–oxygen; bromine was liberated immediately and the reaction mixture yielded parabanic acid. From these data, it was concluded that the product II has the structure of 5-(α-bromopropylidene)-hydantoin.

$$
\begin{array}{cc}
\text{HN—CO—NH} & \text{HN—CO—NH} \\
| \qquad\qquad | & | \qquad\qquad | \\
\text{OC———CHC}_2\text{H}_5 & \text{OC———C=CBrC}_2\text{H}_5 \\
\text{I} & \text{II}
\end{array}
$$

$$
\begin{array}{c}
\text{HN—CO—NH} \\
| \qquad\qquad | \\
\text{OC———C=CHC}_2\text{H}_5 \\
\text{III}
\end{array}
$$

Absorption in the ultraviolet region by alcoholic solutions of various aryl-substituted hydantoins of type Y has been studied by Seikel,[13] by Hahn and co-workers,[14] and McLean and Seeger.[15] More recently, ultraviolet absorption characteristic of aqueous solutions of 5-(α-carboxymethylidene)-hydantoin and 5-(α-carbethoxymethylidene)-hydantoin have been recorded by Mitchell and Nyc.[16]

(5) These five compounds include (a) the "brompyvureid," the "N-methylbrompyvureid," and the "methylbrompyvureid" of S. Gabriel (ref. 4); (b) the "chlorobromopivurina" reported by M. Garino and I. Muzio, *Gazz. chim. ital.*, **52II**, 226 (1922); and (c) the "bromonitropyruvic ureide" of D. Davidson, THIS JOURNAL, **47**, 1722 (1925).

(6) D. Davidson and T. B. Johnson, *ibid.*, **47**, 561 (1925).

(7) H. L. Wheeler, C. Hoffman and T. B. Johnson, *J. Biol. Chem.*, **10**, 147 (1911).

(8) R. Andreasch, *Monatsh.*, **23**, 803 (1902).

(9) H. L. Wheeler and C. Hoffman, *Amer. Chem. J.*, **45**, 368 (1911).

(10) E. Ware, *Chem. Revs.*, **46**, 304 (1950).

(11) T. B. Johnson, THIS JOURNAL, **61**, 2485 (1939).

(12) H. E. Wheeler and C. Hoffman, ref. 9, reported that *p*-hydroxybenzylhydantoin reacted with bromine in glacial acetic acid to yield 5-(3,5-dibromo-4-hydroxybenzal)-hydantoin.

(13) M. D. Seikel, THIS JOURNAL, **59**, 436 (1937).

(14) D. A. Hahn and J. Evans, *ibid.*, **50**, 306 (1928); D. Hahn and E. Dyer, *ibid.*, **52**, 2505 (1930); D. Hahn, M. J. McLean and H. T. Murphy, *ibid.*, **60**, 1927 (1938).

(15) M. J. McLean and D. R. Seger, *ibid.*, **62**, 1416 (1940).

(16) H. K. Mitchell and J. F. Nyc, *ibid.*, **69**, 674 (1947).

Apparently, this study was the first involving ultraviolet absorption spectra of hydantoins of type Y in which R is not phenyl or a substituted-phenyl grouping.

In the present investigation, a study of the ultraviolet absorption by solutions of 5-propylhydantoin (I), 5-(α-bromopropylidene)-hydantoin (II), 5-propylidenehydantoin (III) and 5-(2-methylpropenyl)-5-methylhydantoin[17] in ethyl alcohol and in 0.1 N aqueous sodium solution revealed certain striking similarities and dissimilarities. The absorptions of compounds II and III are quite alike, in the region 2250–3500 Å., the bromoderivative absorbing the more strongly. The absorption by propylhydantoin and 5-(2-methylpropenyl)-5-methylhydantoin in this region is scarcely noticeable. The strong absorption by 5-(α-bromopropylidene)-hydantoin (II) and 5-propylidenehydantoin (III) in all probability is due to the conjugation of unsaturation of the nuclear carbonyl group with that of the side chain; in the methylpropenylhydantoin there is no such conjugation.[18]

Experimental

Bromination of 5-Propylhydantoin. A.—A solution of 40 g. (0.25 mole) of bromine in 130 ml. of glacial acetic acid was added to a well-stirred solution of 35.5 g. (0.25 mole) of 5-propylhydantoin[19] in the same solvent, and the mixture was heated at 85–90° causing complete solution of the hydantoin. After 11 minutes[20] of stirring and warming, the characteristic evolution of gas began and the solution became nearly colorless. The vigorous evolution of hydrogen bromide continued for about one minute. A solution of 43.9 g. (0.27 mole) of bromine in 130 ml. of glacial acetic acid was added dropwise over a period of 45 minutes, the solution remaining a light yellow amber color during this time. Heating and stirring were continued for about an hour before the solution was cooled and filtered; the cream colored solid was washed with 50 ml. of petroleum ether (b.p. 40–60°) and dried; weight 38.5 g. The product sintered at 196° and melted with decomposition at 204–205°. After recrystallization from 50% alcohol, the m.p. was 218–219° (cor.), with decomposition at 222°. The m.p. was not raised by further recrystallizations, nor by sublimation at 5 mm.; the yield of purified product was 31.7 g. (58%).

Anal. Calcd. for $C_6H_7BrN_2O_2$: C, 32.90; H, 3.22; Br, 36.48; N, 12.79. Found: C, 32.96; H, 3.18; Br, 36.63; N, 12.50.

B.—Fifteen grams (0.105 mole) of 5-propylhydantoin was dissolved in 100 ml. of glacial acetic acid and treated with 40 g. (0.25 mole) of bromine in 75 ml. of glacial acetic acid. Through this solution was bubbled vigorously a mixture of oxygen and ozone during a period of about 23 hours; the solution progressively lightened until it became colorless. The solution (170 ml.) was diluted with an equal volume of water and was then steam distilled. After 1 l. of distillate had been collected, refrigeration of the residue caused precipitation of 2.69 g. of solid which sintered at 193° and melted at 209–213°. Further, similar treatments of the filtrate produced 2.12 g. more of the same material. All fractions were combined and recrystallized from alcohol and sublimed *in vacuo* without significant effect upon the m.p.

(17) H. R. Henze, T. R. Thompson and R. J. Speer, *J. Org. Chem.*, **8**, 17 (1943).

(18) Mitchell and Nyc, ref. 16, reported that an α-carboxy or an α-carbethoxy group serves to enhance the absorption in the ultraviolet. However, absorption in the case of the 5-(α-carboxymethylidene)- and 5-(α-carbethoxymethylidene)-hydantoins actually was not greater than that exhibited by 5-propylidenehydantoin (III) and 5-(α-bromopropylidene)-hydantoin (II).

(19) H. R. Henze and R. J. Speer, This Journal, **64**, 522 (1942).

(20) With fixed amounts of 5-alkylhydantoin and bromine and glacial acetic acid, and rate of heating, the period of inaction preceding evolution of hydrogen bromide was reproducible within about one minute.

However, boiling an aqueous solution of the product (1.3 g./100 ml.) for 13 hours allowed isolation of a white solid (0.72 g.) melting at 211–214° without sintering or decomposition. The bromine-free product was insoluble in benzene, ether and carbon tetrachloride; slightly soluble in cold water, methanol, acetic acid and ethyl acetate; soluble in ethyl alcohol, dioxane and very soluble in dilute sodium hydroxide solution. Aqueous solutions of this material were neutral to litmus, and readily decolorized solutions of potassium permanganate and bromine, respectively. The total weight of 7.8 g. of this material, melting at 208 ± 4°, represented 53% yield.

Anal. Calcd. for $C_6H_8N_2O_2$: mol. wt., 140.14; C, 51.42; H, 5.75; N, 19.99. Found: mol. wt. (ebulliometric in acetone), 142; C, 51.01; H, 5.89; N, 19.90. This product subsequently was demonstrated to be 5-propylidenehydantoin (III).

Bromination of 5-Propylhydantoin in the Presence of 5-Propylidenehydantoin. A.—A solution of 10 ml. (31.2 g., 0.195 mole) of bromine in 100 ml. of glacial acetic acid was added to 28.5 g. (0.20 mole) of 5-propylhydantoin. The mixture was heated at 85–95° for three minutes and formed a homogeneous solution. At this time, 0.075 g. (0.0005 mole) of 5-propylidenehydantoin (the $C_6H_8N_2O_2$ product from the preceding experiment) was added to the hot solution, after four minutes the usual vigorous evolution of hydrogen bromide began and continued for about one minute, while the solution became nearly colorless. A solution of 11 ml. (34.3 g., 0.214 mole) of bromine in 100 ml. of glacial acetic acid was added dropwise over a period of about 20 minutes; vigorous stirring was maintained during this period and for 20 minutes longer. The solution was chilled and filtered to remove white crystals. The latter were washed with petroleum ether (b.p. 90–120°) and dried with suction for 3 hours; weight 36.3 g. (83% yield); m.p. 218–219° with decomposition at 222–223° (cor.). The m.p. behavior was not altered by subsequent recrystallizations. Additional crops of this material ($C_6H_7BrN_2O_2$) were obtained; total amount, 39.5 g. (90% yield).

B.—In another experiment, 42 g. (0.295 mole) of 5-propylhydantoin and 96.7 g. (0.604 mole) of bromine were brought together in glacial acetic acid. After this solution had been warmed for 4 minutes at 85–95°, 0.073 g. (0.0005 mole) of 5-propylidenehydantoin was added; the usual gas evolution and decolorization occurred 2 minutes later. After a total period of heating of 90 minutes, the solution was cooled and treated with 300 ml. of water; immediate precipitation of a white, flocculent mass occurred. The latter was removed, washed and dried to leave 51 g. of material melting at 218–219° and decomposing at 223°. From the mother liquor was obtained 3.3 g. of the same product ($C_6H_7BrN_2O_2$) to bring the total yield to 84%.

Further investigation of the mother liquor gave 4.3 g. of a white solid which did not contain bromine, and readily decolorized a solution of bromine in glacial acetic acid. After recrystallization from water, there was left 2.33 g. of material which sintered at 180° and melted at 191–197°. The recovery of this bromine-free material represented an 11% conversion of 5-propylhydantoin into 5-propylidenehydantoin.

Hydrogenation of 5-Propylidenehydantoin (III).—A solution containing 0.2093 g. (0.0015 mole) of III in 50 ml. of ethyl alcohol was hydrogenated over a small amount of Raney nickel catalyst. During 105 minutes the mixture absorbed 38 ml. (0.0015 mole) of hydrogen at 23° and 742 mm. The mixture was filtered from the catalyst and evaporated to dryness; the residual solid was recrystallized from toluene to yield 0.1313 g. (62% conversion) of 5-propylhydantoin of m.p. 136–137°.

Ozonolysis of 5-Propylidenehydantoin (III).—Two grams of III was dissolved in 125 ml. of glacial acetic acid and a stream of oxygen containing ozone was bubbled through this solution until, seven hours later, ozone was detected in the effluent gas. The system was then swept with oxygen for two hours; at no time during the treatment with ozone or oxygen was any color noted in the reaction mixture.

The clear liquid was diluted with an equal volume of water and subjected to steam distillation; the tip of the condenser dipped into a solution of 2,4-dinitrophenylhydrazine hydrochloride. A yellow precipitate formed immediately in the carbonyl reagent solution; this product was washed free of chloride and dried to weigh 0.48 g.; m.p. 122–130°.

Chromatography on talc–calcium carbonate[21] in benzene yielded 0.057 g., m.p. 153–154°, undepressed by mixture with authentic propionaldehyde 2,4-dinitrophenylhydrazone. The total weight of crude dinitrophenylhydrazone (0.48 g.) represents 14% yield.

The residue from the steam distillation was concentrated by means of an air jet to about 8 ml., diluted with 15 ml. of water, reconcentrated, and this procedure repeated several times. Chilling resulted in the precipitation of 0.26 g. of white needles melting at 230–233° dec. Recrystallization raised the m.p. to 246–248° dec.; mixture of a portion of this material with authentic parabanic acid[22] did not depress the m.p. of the latter. Additional material, totalling 0.9 g., represented a 56% recovery of parabanic acid. These data indicate that this $C_6H_8N_2O_2$ material is 5-propylidenehydantoin.

Bromination of 5-Propylidenehydantoin (III).—One gram (0.007 mole) of III and 5 ml. of glacial acetic acid were warmed at 85–95° until solution occurred; 1.07 g. (0.0073 mole) of bromine in 1 ml. of glacial acetic acid was then added dropwise to the agitated solution, during a 5-minute period. The bromine solution was readily decolorized and evolution of hydrogen bromide occurred. The solution was heated for 15 minutes, cooled, and a white precipitate formed in such amount as to make the mixture nearly solid. The latter was washed into 20 ml. of water, shaken well and filtered, washed and dried under vacuum; weight 1.32 g. (88% yield) of 5-(α-bromopropylidene)-hydantoin (II): m.p. 215–215° dec.

Oxidation of 5-(α-Bromopropylidene)-hydantoin (II) by Ozone in Nitroethane Solution.—A mixture of oxygen and ozone was passed through 10 g. of II suspended in 500 ml. of nitroethane (redistilled, b.p. 112–114°). The mixture became light yellow in color within a few minutes: the intensity of color increased with the time of exposure to ozone. The solid dissolved completely in 4 hours; introduction of ozone–oxygen was continued for an additional 2 hours, in which time a white, crystalline solid had appeared. The mixture was filtered; the dried solid weighed 1.4 g.; sintered at 171°, melted at 183–187° dec. After recrystallization, the product ($C_6H_8Br_2N_2O_3$) melted at 186.5–187.5° dec. Partial evaporation of the nitroethane solution filtrate yielded 0.28 g. of white solid which sintered at about 180°, but melted with vigorous decomposition at 244°.[23]

Other Attempts to Cleave 5-(α-Bromopropylidene)-hydantoin (II). A.—Attempted oxidation of a hot aqueous solution of II by sodium bismuthate resulted only in recovery of 39% of the starting material.

B.—Attempted oxidation by potassium permanganate gave no isolable products. Manganese dioxide formed and 34.5% of the starting material was recovered.

C.—Attempted cleavage by treatment with hot, 47% nitric acid resulted in the isolation of 2.53 g. (69% yield) of a substance melting with decomposition at 182.0–182.5°.

Anal. Calcd. for $C_6H_8Br_2N_2O_3$: mol. wt., 315.96; C, 22.80; H, 2.55; Br, 50.57; N, 8.87. Found: mol. wt. (ebullioscopic in acetone), 350 ± 30; C, 22.92; H, 2.74; Br, 50.72; N, 9.15.

A sample of this material was analyzed after being dried for 3.5 hours at 110°; found: C, 22.99; H, 2.72. After drying for 16 hours in a vacuum oven (75° and 29.8″), a sample was found to contain 9.14% N. Analysis of two samples which had been recrystallized from water and dried with suction for 2 hours gave: C, 22.81, 22.85; H, 2.59, 2.53. Digestion of a hot aqueous solution of this material with silver oxide resulted in precipitation of silver bromide in amount corresponding to 98% removal of bromine from the sample. The oxidation product evidenced no unsaturation toward solutions of bromine or potassium permanganate; it was soluble in alcohol, acetic acid, ethyl acetate, dioxane and pyridine; slightly soluble in water; insoluble in benzene, cyclohexane, nitroparaffins and halogenated hydrocarbons.

D.—In another experiment, 5 g. (0.023 mole) of II in 100 ml. of water was heated on a steam-cone for 10 minutes before addition of bromine was begun; a total of 2 ml. (6.2 g., 0.039 mole) of bromine was added in six approximately equal portions, the mixture becoming colorless after each addition except the last. At no time was the mixture free of undissolved solid, but the appearance of the suspended material changed during the course of the experiment. Initially, the undissolved solid was fluffy in appearance; in the later part of the heating period (ten minutes) the undissolved solid was more dense and flaky. The suspended material was filtered and dried to weigh 5.14 g.; m.p. 200–201° dec. All crops of material were recrystallized from water to yield the $C_6H_8Br_2N_2O_3$ compound of m.p. 190–192°[24]; the conversion represented 94%.

E.—A solution of II in ethyl acetate was treated with ozonized oxygen; evaporation of the solution, which had become amber in color, caused deposition of a white solid which melted at 190–191° dec. This product, $C_6H_6Br_2N_2O_3$, was thus obtained in 20% yield. At no time was the presence of an ozonide detected. Essentially the same result was obtained when 2-nitropropane was used as solvent.

F.—Two and one-half grams (0.011 mole) of II was dissolved in hot glacial acetic acid (20 ml.) and treated with 57% hydriodic acid (5 ml.) containing 5.85 g. (0.038 mole) of hydrogen iodide. The solution became dark brown. Red phosphorus (2 g., 0.065 mole) was added and the mixture refluxed for 2.5 hours; evolution of iodine vapor was noted. The mixture was filtered through sintered glass and the filtrate subjected to steam distillation until about 4 l. of distillate had been collected. The residue from steam distillation was fractionally evaporated, five crops of solid (total weight 0.73 g., 43% yield) were collected; all such material melted at 133–135°. After recrystallization from toluene the product melted at 136–137°; a mixture with authentic 5-propylhydantoin showed no depression in m.p.

G.—A catalyst mixture[25] obtained by the reduction, by means of hydrogen, of 25 mg. of palladium(II) chloride and 3.5 mg. of platinum(IV) oxide in the presence of 250 mg. of activated charcoal was used in this experiment. The charcoal had been activated by maintaining a sample of decolorizing charcoal at 150° in a stream of methane for 8 hours. A solution containing 0.2521 g. (0.00115 mole) of 5-(α-bromopropylidene)-hydantoin in 50 ml. of ethyl alcohol was hydrogenated; in 34 minutes, 55.1 ml. (0.0023 mole) of hydrogen at 16° and 754 mm. was taken up.[26] The mixture was filtered, and the filtrate evaporated to dryness; there remained 0.1553 g. (95% yield) of 5-propylhydantoin of m.p. 134–135°.

Hydrogenation of 5-(α-Bromobenzal)-hydantoin.—A similar palladium-on-charcoal catalyst was added to a solution of 1.34 g. (0.005 mole) of 5-(α-bromobenzal)-hydantoin[7] in 300 ml. of alcohol. When shaken under 857 mm. of hydrogen, the solution absorbed hydrogen rapidly and smoothly; a pressure drop of 14 mm. (corresponding to 0.0084 mole) of hydrogen was observed in 7 minutes. Shaking was continued for 77 minutes longer but no further drop in pressure occurred. The product of the reaction (63% yield) was 5-benzylhydantoin, m.p. 192–193°.

Comparison of the Behavior of Certain Unsaturated Bromo Derivatives toward Catalytic Hydrogenation (or Hydrogenolysis) with the Palladium Catalyst. A.—Approximately 2.72 g. (0.02 mole) of 2-bromopropene[27] (b.p. 47.5–48.3° (748 mm.)) was dissolved in 80 ml. of alcohol and added to the catalyst prepared from reduction of 56.5 mg. of palladium(II) chloride in the presence of 1 g. of activated charcoal. Hydrogen under 86 cm. pressure was introduced; 0.03 mole of hydrogen was absorbed during 7 hours. The gaseous effluent was bubbled through a very dilute potassium permanganate solution and caused precipitation of only a very small amount of brown solid. The alcoholic suspension was filtered and an aliquot portion of the filtrate was treated with concentrated nitric acid and silver nitrate

(21) H. H. Strain, "Chromatographic Adsorption Analysis," Interscience Publishers, Inc., New York, N. Y., 1942, p. 60.

(22) L. Simonsen, *Ann.*, **333**, 101 (1904).

(23) The vigorous decomposition at this temperature is suggestive of the behavior of parabanic acid m.p. 244° dec., an expected oxidative cleavage product.

(24) The m.p. could be made to vary between 181 and 208° depending upon the rate of heating.

(25) Directions for the preparation of this extremely active catalyst were furnished by the courtesy of Dr. P. L. Pickard.

(26) When the volume of hydrogen absorbed was plotted against the time elapsed, there was obtained a smooth, steep curve indicative of single stage absorption of hydrogen, to the extent of two moles of hydrogen per mole of $C_6H_7BrN_2O_2$ material.

(27) M. Reboul, *Ann. chim. phys.*, [5] **14**, 453 (1878), reported b.p. 47–48° (742 mm.).

solution.[28] The precipitated silver bromide was processed in a suitable fashion; from its weight, the total content of bromide ion in the reaction mixture was calculated and accounted for 93.4% of the bromine in the 2-bromopropene used.
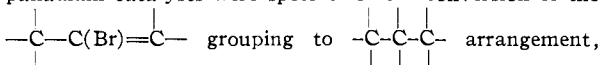
B.—3-Bromopropene (allyl bromide) was not altered by contact with this palladium-on-charcoal catalyst. The catalyst was removed by filtration, washed with alcohol, and was then shown to catalyze actively the conversion of the $C_6H_7BrN_2O_2$ material into 5-propylhydantoin.

C.—2,3-Dibromopropene in alcohol in the presence of this catalyst readily absorbed *one* mole equivalent of hydrogen. The reaction mixture was filtered; no evidence of bromide ion could be detected in the diluted filtrate.

D.—1,3-Dibromo-2-propanol (α,γ-glyceroldibromohydrin) in alcohol did not utilize any hydrogen in the presence of either the palladium or palladium–platinum catalysts. The former was recovered and shown still to be active in the hydrogenation and debromination of 5-(α-bromopropylidene)-hydantoin.

E.—Likewise, 1,3-dibromopropane was not debrominated in the presence of hydrogen and the palladium-on-charcoal catalyst, although this catalyst was active subsequently in the usual conversion of 5-(α-bromopropylidene)-hydantoin.

These experiments appear to demonstrate that these palladium catalysts were specific for the conversion of the

$$-\overset{|}{C}-\overset{|}{C}(Br)=\overset{|}{C}-\ \text{ grouping to }\ -\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-\ \text{ arrangement,}$$

and establish the presence of the former structure in the side chain of 5-(α-bromopropylidene)-hydantoin.

Solutions of the $C_6H_8Br_2N_2O_3$ material in ethyl alcohol did not absorb hydrogen in the presence of either palladium catalyst, although each catalyst was subsequently shown to retain its catalytic activity. The structure of this dibromo derivative has not been elucidated.

Attempts to Brominate 5,5-Disubstituted Hydantoins.—A solution of 5,5-dimethylhydantoin in glacial acetic acid was treated with two mole equivalents of bromine and heated to refluxing for several hours; no evolution of hydrogen bromide could be detected. After steam distillation of the mixture, to remove bromine and acetic acid, the residual material yielded unaltered dimethylhydantoin.

Similarly, no evidence was obtained of attack of bromine upon 5-methyl-5-phenylhydantoin, 5-phenyl-5-phenethylhydantoin, 5-phenyl-5-propylhydantoin, 5-isopropyl-5-phenylhydantoin or 5-methoxy-5-phenylhydantoin.[29]

Bromination of 5-Benzylhydantoin.—A mixture of 3.3 g. (0.017 mole) of 5-benzylhydantoin,[30] 2.7 g. (0.017 mole) of bromine and 10 ml. of glacial acetic acid was heated to refluxing; after about 10 minutes, evolution of hydrogen bromide began and continued for some time. Another portion of bromine (3.6 g., 0.020 mole) was added and the heating was continued. After removal of the acid, there was ob-

tained 3.5 g. (78% yield) of the known 5-(α-bromobenzal)-hydantoin[31] of m.p. 245–256°.

Bromination of Other 5-Alkylhydantoins.—5-Butylhydantoin and 5-isobutylhydantoin were heated with two equivalents of bromine in glacial acetic acid solution. In both cases, there was the characteristic delay in evolution of hydrogen bromide, followed by a vigorous evolution of this gas for a brief period. The monobrominated products are formulated as 5-(α-bromobutylidene)-hydantoin and 5-(α-bromo-β-methylpropylidene)-hydantoin, respectively, in analogy to the structure of the product of bromination of 5-propylhydantoin.

Table I

5-(α-Bromoalkylidene)-hydantoin

Alkylidene group	M.p., °C.	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Butylidene	193–194	36.07	36.33	3.89	3.95
β-Methylpropylidene	253	36.07	36.27	3.89	3.90

	Yield, %	Bromine Calcd.	Bromine Found	Nitrogen Calcd.	Nitrogen Found
Butylidene	60	34.29	34.01	12.02	12.18
β-Methylpropylidene	74	34.29	34.27	12.02	12.27

Ultraviolet Absorption Spectra.—Absorption in the ultraviolet region was determined with a Beckman Model DU spectrophotometer.[32] The measurement in certain cases was made both in ethyl alcoholic solution and in 0.1019N sodium hydroxide solution.

Table II

Ultraviolet Absorption Spectra

5-Substituted hydantoin	Maximum, Å.	$\epsilon \times 10^{-4}$	Maximum, Å.	$\epsilon \times 10^{-4}$
In alcoholic soln.				
Propylidene	2700	1.26	2400	0.44
α-Bromopropylidene	2800	1.52	2500	.47
2-Methylpropenyl	None		None	
Propyl	None		None	
α-Bromobenzal	3000	1.19	2635	.67
Benzal	3200	2.34	2550	.34
In alkaline soln.				
Propylidene	2850	0.62	2650	.47
	2400[a]	1.28		
α-Bromopropylidene	2950	0.93	2750	.76
	2550[a]	1.34		

[a] Chief maximum

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(28) A 25-ml. sample of alcohol was diluted with water and subjected to this treatment, but gave no evidence of precipitation.

(29) Prepared initially by Dr. George Rieveschl.

(30) Prepared by the hydriodic acid reduction of 5-benzalhydantoin following the method of T. B. Johnson and J. S. Bates, This Journal, **38**, 1087 (1916).

(31) H. L. Wheeler, C. Hoffman and T. B. Johnson, ref. 7, obtained this compound through interaction of 5-benzalhydantoin and bromine in glacial acetic acid solution and reported m.p. 240°.

(32) Determinations were made in the Spectrographic Laboratory of The University of Texas (Dr. F. A. Matsen, Director) by Mr. S. H. Hastings, Spectrographic Assistant.