[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TEXAS]

MESITYL OXIDE AND DIACETONE ALCOHOL IN THE BUCHERER SYNTHESIS OF HYDANTOINS

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In connection with a study of the identification of carbonyl compounds through conversion into hydantoins (1), we had occasion to investigate the behavior of mesityl oxide and diacetone alcohol, respectively, with potassium cyanide and ammonium carbonate in diluted alcohol at about 60°, these being the conditions developed by Bucherer (2) for the synthesis of hydantoins. During the earlier portion of this investigation we read the report by Marsh and Lazzell (3) of their synthesis of 5-methyl-(2-methylpropenyl)hydantoin and 5-methyl-5-(2-hydroxy-2-methylpropyl)hydantoin by the Bucherer method. Since the data recorded for these hydantoins differed from those which we had noted (4) for the compounds, we have repeated our study and succeeded only in confirming our previous findings. A partial explanation of the apparent discrepancy between the data of Marsh and Lazzell and our own may be had from a consideration of the behavior of mesityl oxide and diacetone alcohol towards dilute alkali, ammonia, and cyanides.

Diacetone alcohol (II) is prepared (5) by a condensation of two molecules of acetone (I) in the presence of alkali; this reaction is reversible, the equilibrium depending on the *p*H and salt concentration of the medium. Koelichen (6) observed that for dilute aqueous solutions of diacetone alcohol the equilibrium was so far displaced toward acetone that the decomposition might be considered as proceeding to completion, and in dilute solutions of alkali hydroxides the rate of reactions is proportional to the concentration of hydroxyl ions. French (7) reported the effect of potassium ions in catalyzing the conversion of diacetone alcohol to acetone, and Miller and Kilpatrick (8) described the catalytic action of ammonia.

In addition, diacetone alcohol is in equilibrium also with mesityl oxide (III). Harries (9) found that in regenerating mesityl oxide from its bisulfite addition compound by means of aqueous sodium hydroxide, the expected yields of oxide were considerably reduced by conversion of oxide into acetone. The above relationships may be formulated as follows:

$$\underset{\text{I}}{2CH_3COCH_3} \rightleftarrows \underset{\text{II}}{(CH_3)_2COHCH_2COCH_3} \rightleftarrows \underset{\text{III}}{(CH_3)_2C{=}CHCOCH_3} + H_2O$$

Since it is an α,β-unsaturated ketone, mesityl oxide is able to add to itself the elements of hydrogen cyanide, not only at the carbonyl grouping to form the cyanhydrin but also at the ethylenic linkage. Lapworth (10) has discovered that "... hydrogen cyanide is more efficient as an additive reagent when its

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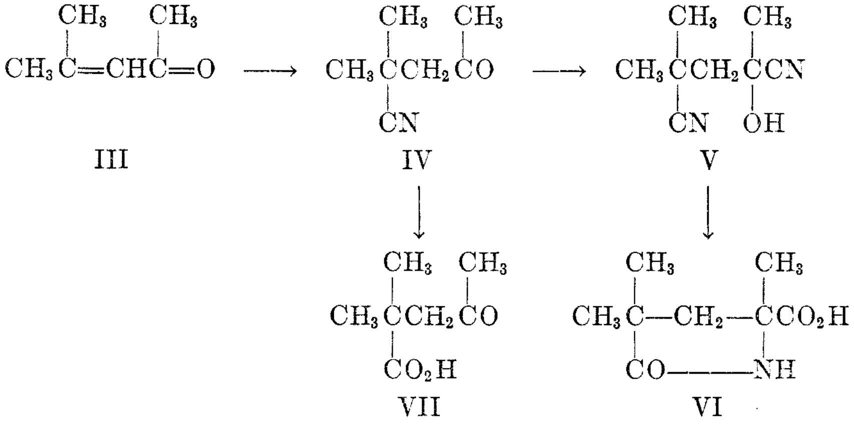
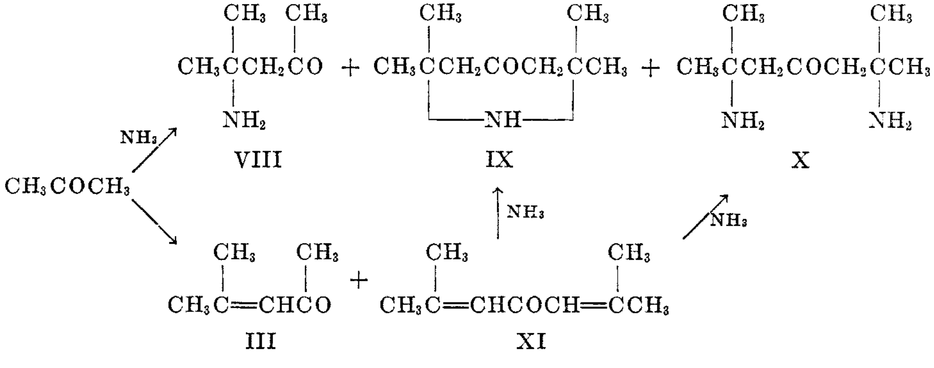
own salts are present." When mesityl oxide is mixed with an aqueous solution of potassium cyanide several products are formed depending on the concentration of reactants and the temperature. Mesitonitrile (IV) is first formed but reacts much more rapidly with potassium cyanide solution to form mesitonitrile cyanhydrin (V) than does mesityl oxide to form additional mesitonitrile. Mesitylic acid (VI) is produced to some extent by hydrolysis of mesitonitrile cyanhydrin in the alkaline potassium cyanide. The hydrolysis of mesitonitrile to mesitonic acid (VII) is possible, especially if the concentration of potassium cyanide is too low to convert the nitrile to cyanhydrin.

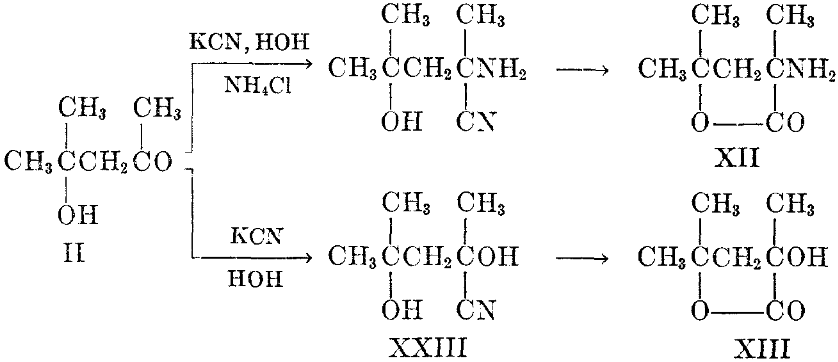

III IV V VII VI

Since in the synthesis of hydantoins by the Bucherer procedure it is the common practice to acidify the reaction mixture and to remove the solvent partially before crystallization begins, acid hydrolysis of nitriles is possible, also.

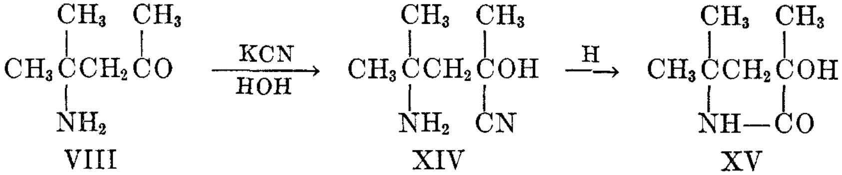
The presence of ammonia under the conditions of the Bucherer procedure affords the possibility of amine production. Indeed, diacetone amine (VIII) is prepared readily from mesityl oxide and aqueous ammonia (11) and also by the interaction of acetone and ammonium hydroxide, the latter method also producing triacetoneamine (IX) and triacetonediamine (X) (12). Triacetoneamine may also be formed (13) by the interaction of acetone and diacetoneamine. In addition, phorone (XI), which may arise from condensation of three molecules of acetone, likewise reacts (14) with ammonia to yield a mixture of IX and X. The relationships of these amines are sketched below.


VIII IX X III XI

Cyanhydrin and amino nitrile formation are plausible intermediates in hydantoin synthesis but, should the final conversion of the nitriles to hydantoin derivatives be incomplete, subsequent acid hydrolysis should convert these to acids. In cases where a gamma hydroxyl or amino group is present in the nitrile, lactonization or lactamization would result. As a case in point, Kohn (15) reported the preparation of α-amino-α,γ-dimethyl-γ-valerolactone (XII) and α-hydroxy-α,γ-dimethyl-γ-valerolactone (XIII).



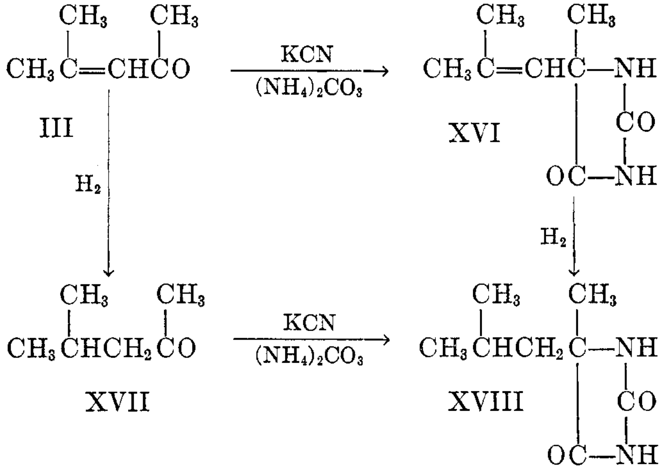
Should diacetoneamine (VIII) be present, a reaction analogous to that pictured above could occur, as described by Weil (16), to produce 3-hydroxy-3,5,5-trimethyl-2-pyrrolidone (XV) as indicated below.

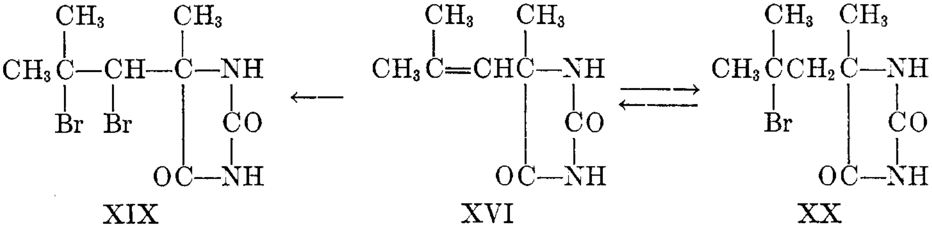


Since the various possibilities cited are to a greater or lesser degree plausible under the conditions of the Bucherer procedure (2), investigations of the behavior of mesityl oxide and diacetone alcohol, in their possible conversion into hydantoins, had the added purpose of determining whether the presence of any of these by-products could be detected.

From a mixture, resulting from interaction of mesityl oxide, potassium cyanide and ammonium carbonate in diluted alcohol warmed at 60°, a compound was readily isolated; data for analyses and molecular weight determination of this compound are in agreement with those for 5-methyl-5-(2-methylpropenyl)hydantoin (XVI). However, the melting point of this compound, namely, 194° (corr.), does not agree very well with that of 210° reported by Marsh and Lazzell (3) for a product claimed by them to be 5-methyl-5-(2-methylpropenyl)hydantoin and prepared by the same method. These authors record only the determination of molecular weight and percentage of nitrogen to substantiate their claim. Because of the difference of sixteen degrees in melting point temperatures, additional proof was obtained for the validity of the structure postulated for XVI.

Low-pressure catalytic hydrogenation of mesityl oxide yielded isobutyl methyl ketone (XVII). The latter was converted into 5-isobutyl-5-methylhydantoin (XVIII) by the Bucherer method (2). Next, the unsaturated hydantoin XVI, produced from mesityl oxide, was catalytically hydrogenated to yield a product identical with XVIII. The presence of the ethylenic linkage in XVI was also shown by addition of bromine and of hydrogen bromide to yield 5-methyl-5-(1,2-dibromo-2-methylpropyl)hydantoin (XIX) and 5-methyl-5-(2-bromo-2-methylpropyl)hydantoin (XX), respectively. The structure of XX is predicated upon normal addition of hydrogen bromide to an ethylenic linkage.





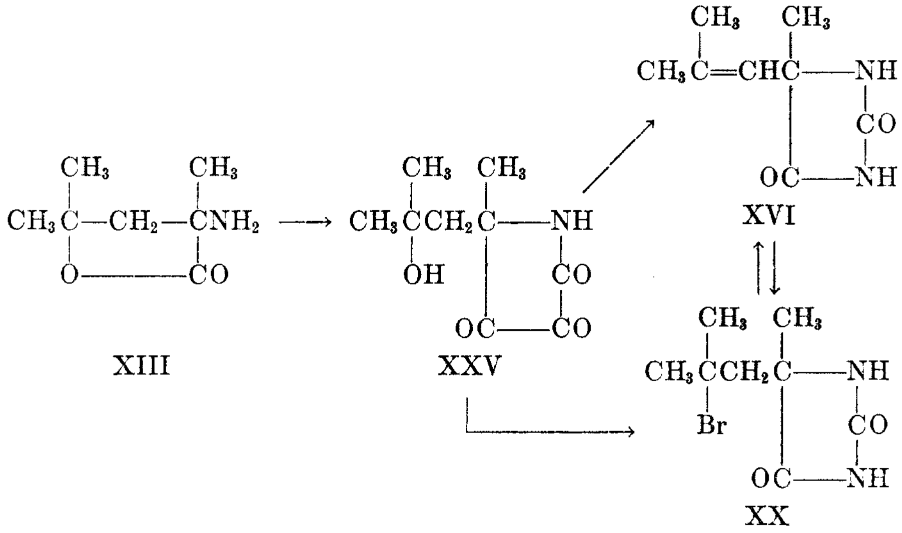
After separation of XVI from the reaction mixture, concentration of the mother liquor yielded a hygroscopic solid which could not be purified by recrystallization. However, when subjected to vacuum sublimation, a product was obtained which melted at 209–210° (corr.) and possessed the molecular formula $C_7H_{13}NO_2$. This compound has been identified as 3-hydroxy-3,5,5-trimethyl-2-pyrrolidone (XV) which Weil[3] had prepared from the cyanhydrin of diacetoneamine.

[3] Weil (16) reported m.p. 202°. It was found that Weil's method for preparing XV could be shortened and the yield improved by treating diacetoneamine hydrogen oxalate with aqueous potassium cyanide, followed by acid hydrolysis.

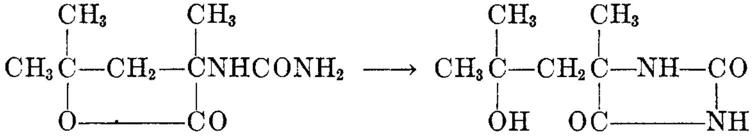
The utilization of diacetone alcohol in the Bucherer synthesis has been found to yield a mixture of products, the time of heating having considerable effect upon the nature as well as the amounts of the products formed. After thirty-six hours of reaction time, a 22% yield of 5,5-dimethylhydantoin (XXI) and 24.3% yield of α-hydroxy-α,γ-dimethyl-γ-valerolactone (XIII) were obtained. However, after fifty hours the reaction mixture yielded 6% of XXI, 21% of XIII, and 8.6% of a compound (XXII) melting at 210° (corr.) and having the composition, $C_8H_{14}N_2O_3$, anticipated for 5-methyl-5-(2-hydroxy-2-methylpropyl)-hydantoin. Since acetone can be converted into XXI under the conditions of the Bucherer synthesis, it is logical to assume that this hydantoin is formed from acetone which results from the decomposition of diacetone alcohol (II). Since XIII can be prepared by acid hydrolysis of diacetone alcohol cyanhydrin (XXIII), it is quite probable, under the Bucherer conditions, that any cyanhydrin formed from diacetone alcohol and not converted into a hydantoin is hydrolyzed, by subsequent acidification, yielding the hydroxy lactone (XIII).

Although the molecular formula of compound XXII is in agreement with that for 5-methyl-5-(2-hydroxy-2-methylpropyl)hydantoin described by Marsh and Lazzell (3), its melting point is 28° higher than that reported by these authors. Therefore, attempts were made to synthesize XXII by another method or to convert it into some other substance of established configuration. It was visualized that the bromine atom of 5-methyl-5-(2-bromo-2-methylpropyl)hydantoin (XX) might be replaced by a hydroxyl group; however, attempts to accomplish this with aqueous sodium hydroxide, moist silver oxide, or aqueous sodium acetate resulted only in formation of 5-methyl-5-(2-methylpropenyl)hydantoin (XVI). It was found also that XX in aqueous solution loses the elements of hydrogen bromide even at room temperature. Since XX thus can be converted readily into XVI, compound XXII was treated with thionyl chloride in the hope that its postulated hydroxyl group could be replaced by chlorine and the chloro compound by subsequent treatment with water yield XVI. It was noted, with some surprise, that boiling thionyl chloride caused no change and XXII was recovered unaltered. Since the hydantoin nucleus is rather stable to mineral acids, in an attempt at dehydration of XXII to produce XVI the former was warmed with 60% sulfuric acid. The product obtained was not XVI, but was an acidic material $C_8H_{13}NO_4$, in all probability α-carbamido-α,γ-dimethyl-γ-valerolactone (XXIV).

In order to synthesize 5-methyl-5-(2-hydroxy-2-methylpropyl)hydantoin by another method, XIII was treated with potassium cyanate essentially according to the method used by Boyd (17) in preparing hydantoins from amino acids. A product (XXV) was obtained which melted at 147° (corr.), and was shown to have the composition represented by $C_8H_{14}N_2O_3$. This compound was readily soluble in acetone, and reacted vigrously in the cold with thionyl chloride to yield, after subsequent hydrolysis, hydantoin XVI. The latter was also obtained from XXV by reaction with a solution of hydrogen bromide in glacial acetic acid. These facts are evidence that XXV is 5-methyl-5-(2-hydroxy-2 methylpropyl)hydantoin.



Insight into the structure of the $C_8H_{14}N_2O_3$ compound (XXII), of m.p. 210°, was gained by its ready conversion into XXV. This transformation was accomplished by heating the former with 10% sodium hydroxide on the steam-bath for two hours, with subsequent neutralization with hydrochloric acid (under similar conditions a typical hydantoin, such as 5-isobutyl-5-methylhydantoin (XVIII) is unchanged). This behavior, together with the data concerning the behavior of XXII towards thionyl chloride and mineral acids is best explained on the assumption that XXII is α,γ-dimethyl-α-ureido-γ-valerolactone.


XXII, m.p. 210° XXV, m.p. 147°

In order to obtain additional information about the production of the ureido lactone (XXII), diacetone alcohol (II) was mixed with potassium cyanide and ammonium carbonate, as in the Bucherer synthesis, except that the solution was allowed to stand for two days at room temperature; a 20.3% yield of (XXI) and a 26.4% yield of XIII were isolated, but no ureido lactone could be detected. In contrast, diacetone alcohol cyanhydrin (XXIII) was prepared and then mixed with a diluted alcohol solution of ammonium carbonate at 58° for from seventeen to fifty-one hours; acidification was omitted and directly from the reaction mixtures was obtained the ureido lactone (XXII) in 16% yield and dimethylhydantoin (XXI) in 8% yield, but no α-hydroxy-α,γ-dimethyl-γ-valerolactone (XIII). Thus, since this reaction mixture was not acidified, this hydroxy lactone (XIII) in previous experiments must arise from acid hydrolysis of the cyanhydrin (XXIII). On the other hand, the production of the ureido lactone (XXII) shows that the latter can be formed in the Bucherer synthesis and does not depend on acid hydrolysis for its production. The isolation of XXI indicates that the cyanhydrin dissociates into diacetone alcohol which in turn decomposes to form acetone.

We desire to acknowledge our indebtedness to the Research Institute of the University of Texas for financial support of this investigation.

EXPERIMENTAL

5-Methyl-5-(2-methylpropenyl)hydantoin (XVI). Ninety-eight grams (1 mole) of mesityl oxide was placed in a 2-liter flask, equipped with a mechanical stirrer and a reflux condenser, together with 1 liter of 50% aqueous alcohol, 87 g. (1.3 mole) of potassium cyanide, and 342 g. (3 moles) of ammonium carbonate (cubes). The flask was kept at 58° for fifty hours. After three hours the mixture was homogeneous and the stirring was discontinued. On cooling to 5°, 53.5 g. of inorganic material crystallized. The filtrate was acidified and after evaporation 17 g. of organic material, m.p. 189–194°, was obtained. Purification with charcoal and crystallization from diluted alcohol yielded 16 g. (9.5% yield) of white crystals melting at 194° (corr.).

Anal. Calc'd for $C_8H_{12}N_2O_2$: Mol. wt. 168.19; C, 57.12; H, 7.19; N, 16.66.

Found: Mol. wt. (b.p. elevation of acetone) 175; C, 57.30, 57.09; H, 7.40, 7.39; N, 16.80, 16.80.

Isolation of 3-hydroxy-3,5,5-trimethyl-2-pyrrolidone (XV). After the removal of XVI, as described above, further concentration and chilling of the filtrate yielded only inorganic material, a total of 240 g. being obtained. Finally, the residue was dissolved in ethanol, filtered from a few grams of inorganic material, and the filtrate was concentrated to a thick syrup on the steam-bath. Heating to 150° removed the last traces of solvent and yielded 150 g. of amorphous, hygroscopic solid. When heated to 200° under 5 mm. pressure, white solid material collected on the cold-finger type condenser. After recrystallization from ethyl acetate, 9.5 g. (6.6% yield) of white crystals, m.p. 209–210° (corr.) was obtained. This material did not lower the m.p. of an authentic sample of XV.

Anal. Calc'd for $C_7H_{13}NO_2$: Mol. wt. 143.18; C, 58.72; H, 9.15; N, 9.78.

Found: Mol. wt. (b.p. elevation of acetone) 150; C, 58.60; H. 9.29; N, 9.80.

One-tenth gram of the pyrrolidone (XV), isolated as above, was heated with 4 cc. of acetyl chloride for one hour under a reflux condenser. The sample was slow to dissolve. The excess of acetyl chloride was evaporated to leave a residue which was crystallized from benzene-petroleum ether, wt. 0.1 g. (78% yield); m.p. 138°. Mixed with an authentic sample of the acetate of XV it showed no lowering of the melting point.

Anal. Calc'd for $C_9H_{15}NO_3$: N, 7.56. Found: N, 7.70.

Twenty and one-half grams (0.1 mole) of diacetoneamine hydrogen oxalate (11) was dissolved in 100 cc. of water and a solution of 11.1 g. (0.1 mole) of calcium chloride in 20 cc. of water was added. The precipitated calcium oxalate was removed and the filtrate concentrated to 25 cc. on the steam-bath. Six grams of liquid hydrogen cyanide was added to the chilled solution which was maintained at 0° for three hours and then at room temperature for twenty-four hours. An equal volume of concentrated hydrochloric acid was added and the mixture heated under a reflux condenser for six hours. After evaporation to dryness on the steam-bath the residue was subjected to vacuum sublimation. A white powder was collected and crystallized from ethyl acetate. The yield of *3-hydroxy-3,5,5-trimethyl-2-pyrrolidone* (XV) of melting point 209–210° (corr.), was 1 g. (7%).

The yield of XV was increased by the following, better method. Twenty-five and one-half grams of diacetoneamine hydrogen oxalate was dissolved in 100 cc. of water and 6.5 g. (0.1 mole) of potassium cyanide in 50 cc. of water was added. After standing at room temperature for twenty-four hours, an equal volume of concentrated hydrochloric acid was added and the mixture heated with refluxing for six hours. The solution was concentrated on a steam-bath under an air jet, 150 cc. of ethanol was added, the organic salts were filtered, and the filtrate concentrated by evaporation. The residue was dried on a porous plate, and extracted (Soxhlet) with acetone. On evaporation, the acetone solution left a viscous, semi-solid mass which was subjected to vacuum sublimation. The light brown sublimate was crystallized from ethyl acetate; m.p. 209–210° (corr.); yield 4 g. (28%).

5-Isobutyl-5-methylhydantoin (XVIII). A. From isobutyl methyl ketone (XVII). Thirty-three grams of XVII [b.p. 115–116° (745 mm.)] was dissolved in 330 cc. of 50% aqueous alcohol to which 28.6 g. of potassium cyanide and 112 g. of ammonium carbonate had been added. The mixture was warmed at 58° for ten hours; after acidification and removal of alcohol, 45.3 g. of product was obtained. Concentration of the filtrate yielded an additional 7 g.; total yield 93%. After recrystallization from diluted alcohol, m.p. 144.5° (corr.).

Anal. Calc'd for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29; N, 16.46.
Found: C, 56.68; H, 8.39; N, 16.56.

B. Hydrogenation of 5-methyl-5-(2-methylpropenyl)hydantoin (XVI). One gram of XVI was dissolved in 40 cc. of ethanol and shaken under 70 cm. of hydrogen in the presence of 50 mg. of the Adams' platinum catalyst. The conversion was complete in one and one-half hours. The melting point of the product was 144.5° (corr.) and was unchanged by mixing with an authentic sample of XVIII.

Bromination of XVI. Six grams of the hydantoin (XVI) was dissolved in 125 cc. of glacial acetic acid and, with cooling in ice-water, a 28% solution of bromine in glacial acetic acid was added slowly until the color persisted; the time of addition was one hour. Excess bromine and the acetic acid were removed on the steam-bath under a current of air. The residue was crystallized from aqueous alcohol to give 9 g. (77% yield) of white, fluffy crystals of XIX, m.p. 185° (dec.).

Anal. Calc'd for $C_8H_{12}Br_2N_2O_2$: Br, 48.73; N, 8.54.
Found: Br, 48.52; N, 8.63.

Addition of hydrogen bromide to XVI. Fifteen grams of XVI was dissolved in 85.5 g. of a 16.2% solution of hydrogen bromide in glacial acetic acid; there was no heat of reaction and the mixture was allowed to stand for eight hours. Crystalline material separated and additional amounts were obtained by concentration of the mother liquor. The combined material, weighing 16.5 g. (76° yield), was recrystallized from glacial acetic acid as colorless, glistening, mica-like crystals (XX) melting at 193° to a clear liquid with evolution of gas. A mixture of XVI and XX melted at 170° (dec.). A sample of XX dissolved in glacial acetic acid did not discharge the color of a bromine solution.

Anal. Calc'd for $C_8H_{13}BrN_2O_2$: Br, 32.08; N, 11.25.
Found: Br, 31.74; N, 11.32.

Attempt to convert XX into 5-methyl-5-(2-hydroxy-2-methylpropyl)hydantoin (XXV). Two grams of XX in 10 cc. of water was treated with 3.3 cc. of 0.2436 *N* sodium hydroxide. The mixture was warmed on a steam-bath for one hour, to complete solution, and then allowed to stand overnight. Upon concentrating and cooling, 1 g. of 5-methyl-5-(2-methylpropenyl)hydantoin (XVI) was obtained. The product alone and mixed with authentic XVI melted at 194° (corr.).

Another attempt was carried out by vigorously stirring 1 g. of XX with 1 g. of silver oxide in 50 cc. of benzene and 0.5 cc. of water for ten hours on the steam-bath. After removal of the benzene by evaporation, addition of 20 cc. of water, filtration from silver bromide, concentration and cooling, 0.5 g. of XVI (m.p. 194°) was recovered.

Finally, 0.5 g. of XX was mixed with 1.5 g. of sodium acetate and 25 cc. of water. The mixture was allowed to stand at room temperature for three days. From the concentrated solution there crystallized 0.2 g. of XVI (m.p. 194°).

Diacetone alcohol in the Bucherer synthesis. A. One hundred sixteen grams (1 mole) of diacetone alcohol (II) was dissolved in 1000 cc. of 50% alcohol containing 87 g. (1.3 mole) of potassium cyanide and 342 g. (3 moles) of ammonium carbonate (cubes) and warmed for fifty hours at 58°. The solution was acidified with concentrated hydrochloric acid, concentrated to small volume under reduced pressure on a steam-bath and diluted with 300 cc.

of ethanol. After chilling, 96 g. of inorganic material was removed and the alcoholic filtrate yielded a viscous oil upon concentration. The addition of 300 cc. of benzene caused granular solid material to separate. This material was subjected to extraction with benzene in a Soxhlet apparatus.

Upon concentrating and cooling the combined benzene extracts, a total of 16 g. of solid was obtained, which on crystallization from isoamyl alcohol and from water melted at 175–176° (corr.). The m.p. of a mixture with an authentic sample of *5,5-dimethylhydantoin* (XXI) showed no depression.

Anal. Calc'd for $C_5H_8N_2O_2$: Mol. wt. 128.13; N, 21.87.
Found: Mol. wt. (b.p. elevation in acetone) 132; N, 21.92.

The benzene filtrate, which resulted from removal of XXI, was subjected to distillation under diminished pressure; 30 g. of colorless product was collected, b.p. 109–110° (10 mm.), which on crystallization from benzene-petroleum ether melted at 65° (corr.). A mixture with an authentic sample of α-hydroxy-α,γ-dimethyl-γ-valerolactone (XIII) showed no depression in melting point.

Conversion of 3-hydroxy-3,5,5-trimethyl-2-pyrrolidone (XV) into XIII. This was carried out essentially according to Kohn's modification (18) of Tafel's method (19). Two grams of XV was dissolved in a mixture of 10 cc. of water and 10 cc. of concentrated hydrochloric acid, and with cooling in an ice-bath, a solution of 3 g. of sodium nitrite in 5 cc. of water was slowly added. After the reaction subsided, the solution was made alkaline with 50% sodium hydroxide solution. One gram of unreacted XV separated and the filtrate was acidified with dilute sulfuric acid and heated under a reuflx condenser for two hours. The acidic solution was repeatedly extracted with ether and the extract dried over anhydrous sodium sulfate. The residue which remained after evaporation of the ether was crystallized from a benzene-petroleum ether mixture. The yield was 0.1 g. of material melting at 65–66° (corr.)[4], which did not lower the melting point of an authentic sample of α-hydroxy-α,γ-dimethyl-γ-valerolactone (XIII).

The residue which remained after removal of XX and XIII was extracted with acetone in a Soxhlet apparatus. On concentrating and chilling the extract, 16 g. of solid was obtained. Recrystallization from isoamyl alcohol and finally from acetone gave a colorless, crystalline product (XXII) which melted at 209–210°.

Anal. Calc'd for $C_8H_{14}N_2O_3$: Mol. wt. 186.21; C, 51.60; H, 7.58; N, 15.05.
Found: Mol. wt. (b.p. elevation in acetone) 195; C, 51.65; H, 7.62; N, 15.19.

B. The same quantities of materials as noted in *A* were maintained at 58° for thirty-six hours. The reaction mixture was cooled and acidified before being acidified and concentrated under diminished pressure. Again, inorganic salts separated and were removed by filtration. Now, 300 cc. of benzene was added to the syrupy residue and the mixture was heated to boiling. After cooling, the precipitated solid was filtered and 250 cc. of acetone was added to redissolve the organic material leaving some insoluble inorganic salts. Concentration of the acetone extract yielded 30 g. of XXI, m.p. 175° (corr.). From the benzene filtrate was obtained an additional 21 g. of XXI, m.p. 175°. Distillation of the final benzene mother liquor produced 35 g. of XIII; b.p. 108–110°; m.p. 62–64°. The residue from the distillation was dissolved in ethanol-benzene from which 5 g. of XXI was obtained. Thus a total of 56 g. (0.44 mole) of XXI and 35 g. (0.243 mole) of XIII were recovered from the molar quantity of II used.

Fifty-eight grams (0.50 mole) of II dissolved in 250 cc. of alcohol, 36 g. (0.555 mole) of potassium cyanide in 250 cc. of water, and 144 g. (1.5 mole) of ammonium carbonate were mixed and placed in a stoppered flask and permitted to stand at room temperature for two days. The solution was filtered from undissolved ammonium carbonate and acidified with concentrated hydrochloric acid while the temperature was maintained below 15°. The acidic solution was evaporated at room temperature to a thick slurry, 200 cc. of alcohol

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[4] Kohn (18) reported m.p. 66–68°.

was added and, on cooling, 20 g. of inorganic salt separated. The alcoholic filtrate was concentrated to a thick syrup. The latter was stirred and heated under reflux condenser with 150 cc. of benzene for one hour, then allowed to stand overnight before being filtered. The residue was extracted with acetone from which was obtained 26 g. (0.203 mole) of XXI. The benzene filtrate yielded 19 g. (0.132 mole) of XIII.

Interaction of diacetone alcohol cyanhydrin with ammonium carbonate. One hundred twelve grams (0.97 mole) of diacetone alcohol was dissolved in a solution of 100.8 g. (0.97 mole) of sodium sulfite and 225 cc. of water by stirring at room temperature for one hour. To this solution of the bisulfite addition product was gradually added with cooling and stirring a solution of 63.1 g. (0.097 mole) of potassium cyanide in 125 cc. of water. After one hour the mixture was poured into a separatory funnel and the upper layer of cyanhydrin (143 g.) withdrawn. Without further purification, the latter was dissolved in 500 cc. of alcohol, mixed with 186.2 g. (1.94 mole) of ammonium carbonate cubes and maintained at 58° for seventeen hours.

One-half of the solution was withdrawn and concentrated to about 100 cc. on the steam-bath. On cooling, crystals formed which were filtered and washed with acetone; yield, 12 g. of XXII; m.p. 209–210°. The filtrate was concentrated to a syrup, two volumes of benzene was added and the mixture was stirred and warmed until homogeneous. On cooling, crystals formed and were filtered and washed with a mixed solvent (1 ethanol:3 benzene); yield, 4 g. of XXI; m.p. 174–175°. The mother liquor was concentrated and gave crystalline material upon cooling; after washing with acetone, 2.5 g.; m.p. 209–210°. Further concentration and dilution with benzene yielded 2 g.; m.p. 173–174°.

The remaining half of the original reaction mixture was held at 58° for twenty-four hours longer, and treated in the same manner as the initial portion. There was thus obtained 13.2 g. of material melting at 209–210° and 9.8 g. of solid of m.p. 173–175°. The material of m.p. 174–175° was shown to be 5,5-dimethylhydantoin (XXI). The substance melting at 209–210° (corr.) is identical with a solid (XXII) isolated from interaction of diacetone alcohol with potassium cyanide and ammonium carbonate by the Bucherer procedure and shown to be of composition $C_8H_{14}N_2O_3$, that is, α,γ-dimethyl-α-ureido-γ-valerolactone (XXII).

Treatment of XXII with acid. Two grams of XXII was mixed with 2 g. of water and 3 g. of sulfuric acid and heated on the steam-bath for one day; at first solution was complete, but after one hour crystals began to form. An equal volume of water was added, and the mixture cooled and filtered, giving 1.2 g. of solid melting with decomposition at 200–202°. After crystallization from water the substance melted at 203° with evolution of gas to yield a clear liquid which did not solidify on cooling. The material is acidic to litmus and gives a neutralization equivalent of 202 when titrated in the cold. If, however, the sample is dissolved in water with warming and then cooled to room temperature, the neutralization equivalent is higher (264). The analytical data are in agreement with those calculated for α-carbamino-α,γ-dimethyl-γ-valerolactone (XXIV).

Anal. Calc'd for $C_8H_{13}NO_4$: Mol. wt. 187.19; C, 51.33; H, 7.00; N, 7.49.
Found: Neut. equiv. 202; C, 51.18; H, 7.15; N, 7.45.

In another experiment, 2 g. of XXII was dissolved in 30 cc. of concentrated hydrochloric acid and heated for twenty hours at 100°. After evaporation to dryness and crystallization, there was obtained 1 g. of XXIV melting at 203° (dec.).

Treatment of XXII with thionyl chloride. Three-tenths of a gram of XXII was mixed with 3 cc. of thionyl chloride and heated at 90°; the solid dissolved and heating was continued under water-pump vacuum to remove excess thionyl chloride. After adding 3 cc. of water and concentrating to 0.5 cc., 0.3 g. of crystals separated. The material was shown to be unchanged lactone (XXII).

Preparation of 5-methyl-5-(2-hydroxy-2-methylpropyl)hydantoin (XXV). A. From α-amino-α,γ-dimethyl-γ-valerolactone[5] *(XII).* Fourteen and three-tenths grams (0.1 mole)

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[5] Prepared from diacetone alcohol (II) according to directions of Kohn (15).

of XII was dissolved in 15 cc. of water and treated with 19.7 g. (0.2 mole) of 37% hydrochloric acid. With cooling in an ice-bath and vigorous stirring 14.8 g. (0.2 mole) of potassium cyanate was added in small portions during about thirty minutes. After standing at 0° for two hours crystals separated and were recrystallized from isoamyl alcohol. The yield was 4.5 g. (24%) of hydantoin melting at 147° (corr.)[6].

B. From α,γ-dimethyl-α-ureido-γ-valerolactone (XXII). One and eighty-six hundredths grams of the lactone XXII was dissolved in 25 cc. of 10% sodium hydroxide solution and heated on the steam-bath for two hours. After acidification with concentrated hydrochloric acid and evaporation to dryness, the residue was extracted with 40 cc. of hot ethanol, this extract was evaporated to dryness and the solid crystallized from isoamyl alcohol. The yield was 1 g. of hydantoin melting at 146–147° (corr.). This material did not depress the m.p. of XXV prepared from XII and cyanic acid.

In another experiment, 3.8 g. of XXII was heated under reflux condenser for sixteen hours in 35 cc. of 30% alcoholic potassium hydroxide solution. After the acidification and subsequent treatment outlined above, 2.5 g. (70% yield) of XXV, m.p. 146–147°, was obtained.

Conversion of 5-methyl-5-(2-hydroxy-2-methylpropyl)hydantoin (XXV) into 5-methyl-5-(2-bromo-2-methylpropyl)hydantoin (XX). One and four-tenths grams of XXV (m.p. 147°) was dissolved in 20 g. of glacial acetic acid (from which XXIV crystallizes unchanged) and treated with 24.4 g. of a 12.3% solution of hydrogen bromide in glacial acetic acid. After standing at room temperature for sixteen hours, the solution was concentrated at 100° to a volume of 15 cc. under an air-jet. Upon cooling, 1.1 g. of mica-like crystals formed and were found to decompose at 193°. No depression of m.p. occurred as a result of mixing this sample of XX with that prepared by interaction of hydrogen bromide and XVI.

Conversion of 5-methyl-5-(2-hydroxy-2-methylpropyl)hydantoin (XXV) into 5-methyl-5-(2-methylpropenyl)hydantoin (XVI). Two grams of XXV (m.p. 147°) was treated with 5 cc. of thionyl chloride. After the initial vigorous reaction had subsided the mixture was heated to reflux for thirty minutes on the steam-bath. Excess thionyl chloride was decomposed with ethanol and finally 10 cc. of water was added. The solution was concentrated to about 3 cc. and cooled. A yield of 1.2 g. of brown colored crystals, melting at 182–185°, was collected. After vacuum sublimation, 0.8 g. of white powder was obtained; melting point and mixed m.p. with an authentic sample of XVI, 192.93°.

In another experiment, 0.7 g. of hydroxyhydantoin (XXV) was heated with 5 cc. of 40% hydrobromic acid for fifteen hours on the steam-bath, and then placed in a desiccator containing (solid) potassium hydroxide. In three days, most of the liquid had evaporated to leave a slurry of brown crystals. An attempt was made to recrystallize the material from glacial acetic acid but no crystals were obtained. On evaporation of the acid, dissolving the residue in 10 cc. of water, and concentration of this solution, crystals appeared on cooling; wt. 0.5 g. Vacuum sublimation yielded a white powder; m.p. alone or mixed with XVI, 193–194° (corr.).

SUMMARY

1. The behavior of mesityl oxide and diacetone alcohol, respectively, towards a hydroalcoholic solution of potassium cyanide and ammonium carbonate (Bucherer procedure for hydantoin formation) has been studied. The results noted differ widely from those reported by Marsh and Lazzell for these two carbonyl compounds under the same conditions.

2. Utilization of mesityl oxide led to the isolation of 3-hydroxy-3,5,5-trimethyl-2-pyrrolidone and 5-methyl-5-(2-methylpropenyl)hydantoin, m.p. 194° (corr.). The structure of the latter was confirmed through its reduction to form 5-isobutyl-5-methylhydantoin.

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[6] Marsh and Lazzell (3) report m.p. 180–181° (corr.).

3. Treatment of the propenylhydantoin with bromine or hydrogen bromide in glacial acetic acid produced dibromo and monobromo derivatives respectively.

4. Diacetone alcohol yielded 5,5-dimethylhydantoin, α-hydroxy-α,γ-dimethyl-γ-valerolactone and α,γ-dimethyl-α-ureido-γ-valerolactone.

5. 5-Methyl-5-(2-hydroxy-2-methylpropyl)hydantoin was prepared from interaction of α-amino-α,γ-dimethyl-γ-valerolactone and cyanic acid, and also from α,γ-dimethyl-α-ureido-γ-valerolactone by action of dilute sodium hydroxide solution. The structure of this hydantoin was proved by its conversion into 5-methyl-5-(2-methylpropenyl)hydantoin and 5-methyl-5-(2-bromo-2-methylpropyl)hydantoin.

6. The structure of a compound melting at 210° (corr.), isolated from utilization of diacetone alcohol in the Bucherer procedure, and isomeric with 5-methyl-5-(2-hydroxy-2-methylpropyl)hydantoin was postulated as being α,γ-dimethyl-α-ureido-γ-valerolactone.

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