boiled over a free flame with 100 cc. of concd. hydrochloric acid until crystallization started. The mixture was then evaporated to a small volume, cooled and filtered; yield 0.32 g. It was recrystallized from hot water, in which it is moderately soluble, and did not melt below 280°. It was readily decomposed by hot, dil. alkali and was dried at 100–104° for analysis.

Anal. Subs., 0.1681: CO_2, 0.3143; H_2O, 0.0774. Subs., 0.1315: N, 27.6 cc. (21°, 769.6 mm.). Calcd. for $C_{10}H_{12}O_3N_4$: C, 50.83; H, 5.12; N, 23.72. Found: C, 50.98; H, 5.15; N, 24.07.

Optical Properties.—Habit, rectangular plates; extinction, parallel, α-parallel to elongation; interference figure, biaxial; indices, $\alpha = 1.665$, $\gamma = 1.730$.

Summary

1. The action of alkali on 1,3,7-trimethyl-9-phenyl-uric acid has been studied, and the course of the reaction and the nature of the decomposition products have been determined.

2. The primary decomposition product is 1-methyl-3-phenylhydantoyl-methylamide. This is further decomposed by alkali to methylamine, carbon dioxide and methyl-phenylhydantoin.

3. Methyl-phenylhydantoyl-methylamide is oxidized by hydrogen peroxide to 1-methyl-3-phenyl-5-hydroxyhydantoyl-methylamide, which is readily hydrolyzed by alkali to mesoxalic acid methylamide and α,β-methyl-phenyl-urea.

4. An attempt to synthesize 3-phenylhydantoyl-methylamide was not successful.

5. 1,3-Dimethyl-9-allyl-uric acid has been prepared for the first time and characterized.

NEW HAVEN, CONNECTICUT

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

THE ACTION OF ALKALI ON SUBSTITUTED URIC ACIDS. III. 1,3,7,9-TETRAMETHYL-URIC ACID AND 1,3,9-TRIMETHYL-URIC ACID

BY ELIZABETH STUART GATEWOOD[1]

RECEIVED MARCH 5, 1925 PUBLISHED AUGUST 5, 1925

The stability of substituted uric acids toward alkali is dependent on their ability to form salts. As the acidity of the uric acid decreases, its salts become correspondingly less stable and the ease of decomposition is thereby increased. Thus, the neutral tetramethyl-uric acid is decomposed almost instantly by hot dil. alkali, while only 9% of the unsubstituted acid is attacked by alkali after boiling for 36 hours. Fischer[2]

[1] National Research Fellow in Chemistry.

[2] Fischer, *Ber.*, **33**, 3266 (1899).

has determined the stability of most of the methyl-substituted uric acids when boiled with N potassium hydroxide solution, and a comparison of his results with the recent work of Biltz[3] on the relative acidity of the four hydrogen atoms of uric acid shows a close relationship between the stability toward alkali and the strength of the acid, as is clear from Table I.

TABLE I

Uric acid	P_H	Decomposition, %	Uric acid	P_H	Decomposition, %
Uric Acid	4.66	8.7	3,7-Dimethyl-	4.91	12.8
7-Methyl-	4.68	9.3	1,3-Dimethyl-	5.08	36.2
1-Methyl-	4.87 (?)	16.4	3,9-Dimethyl-	5.54	..
9-Methyl-	4.54 (?)	28.0	1,7,9-Trimethyl-	4.71	22.1
3-Methyl-	4.88	..	1,3,7-Trimethyl-	4.97	32.9
7,9-Dimethyl-	4.76	9.3	3,7,9-Trimethyl-	5.59	37.3
1,9-Dimethyl-	4.77	..	1,3,9-Trimethyl-	5.64	81.7
1,7-Dimethyl-	4.81	14.8	1,3,7,9-Tetramethyl-	5.67	100.0

P_H (Sörensen value) is the negative exponent of the hydrogen-ion concentration. Hydrogen-ion concn. for water = $10^{-5.68}$; P_H = 5.68.

From a consideration of the values given in the second column, Biltz concludes that the hydrogen atom in Position 3 is the most acidic. It is replaced by metals to give the acid salt of uric acid. Next to it in acidity is the hydrogen in Position 9. The replacement of both atoms gives the neutral salt. The two hydrogens in Positions 1 and 7 are much weaker; that in Position 7 is the less acidic. The Sörensen values for 1-methyl- and 9-methyl-uric acid are apparently abnormal, as they do not agree with the relative effects of these positions as indicated by the values obtained for the di- and trisubstituted acids. Biltz suggests that the abnormality may be due to impurities in these acids. It is evident that those uric acids in which the most strongly acidic hydrogen atoms have been replaced by methyl groups will give the most unstable salts and these, as the table shows, are the ones that are most readily decomposed by alkali. When 1,3,9-trimethyl-uric acid, the weakest of the trisubstituted acids, is boiled for one hour, 81.7% is decomposed, while only 22% of 1,7,9-trimethyl-uric acid is changed after it is boiled for 15 hours. With tetramethyl-uric acid there is no possibility of salt formation; hence, it is most unstable toward alkali and instantly decomposes.

While the salts of uric acid have the lactim form, the resistance to the action of alkali does not depend on this change in configuration. This is shown by the fact that methoxycaffein[4] is as completely decomposed by alkali as its isomer, tetramethyl-uric acid. The comparative stability of the closely related hydroxycaffein results from the presence of a replace-

[3] Biltz and Herrmann, *Ber.*, **54**, 1676 (1921).

[4] Fischer, *Ber.*, 31, 3269 (1899).

able hydrogen, for it differs in no other way from methoxycaffein. Caffein, 1,7-dimethylhypoxanthine and 1,7-dimethylguanine, none of which can give salts, are also entirely decomposed by hot alkali.[4]

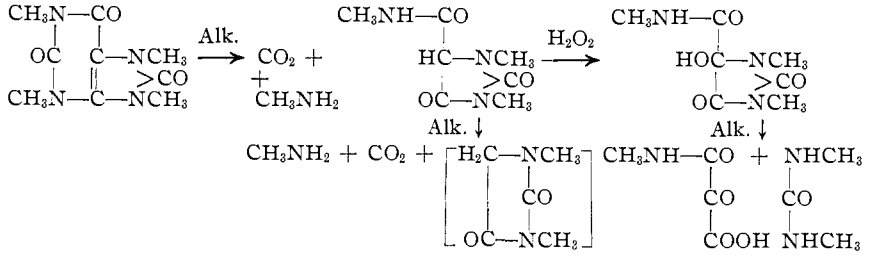
From a careful study of Table I it also appears that the stability of the uric acids toward alkali depends not only upon their salt-forming powers, but also upon whether the substituents are in the pyrimidine or the glyoxalone ring. Thus, although 3,7,9-trimethyl-uric acid has a Sörensen value only slightly less than that of 1,3,9-trimethyl-uric acid, the extents of their decomposition are not correspondingly close. As the acidity of the hydrogens in Positions 1 and 7 is about the same, this difference in decomposition must be due to their substituents being in different rings. A study of the course of these alkaline decompositions shows that the pyrimidine ring is the first one to be attacked. Hence, a substituent in Position 1 increases the instability of this ring more than one in 7, and thus the greater percentage decomposition of 1,3,9-trimethyl-uric acid may be accounted for. Likewise in the case of the disubstituted acids, 1,3-dimethyl-uric acid is only slightly more acidic than 3,7-dimethyl-uric acid, yet its percentage decomposition is thrice as great. Again, 1,3-dimethyl-uric acid forms a more stable salt than 3,7,9-trimethyl-uric acid, yet alkali decomposes them to about the same extent.

The investigation of the stability of uric acids toward alkali has been extended to the phenyl-uric acids and the decomposition of the most unstable of the methyl- and methyl-9-phenyl-uric acids has been studied. Of the latter, 9-phenyl-, 7-methyl-9-phenyl-, 1,7-dimethyl-9-phenyl-, 1,3-dimethyl-9-phenyl-, and 1,3,7-trimethyl-9-phenyl-uric acids have been synthesized. Of these, only the last two, in which not only the strongly acidic hydrogens in Positions 3 and 9 have been replaced by a methyl or phenyl group but also the two hydrogens of the pyrimidine ring, are noticeably affected by alkali. An account of their decompositions has already been given.[5]

The decomposition products of tetramethyl-uric acid and 1,3,9-trimethyl-uric acid have now been isolated and studied. Fischer, in the paper referred to above,[4] gave merely the percentage decomposition of the various methyl-uric acids, determined by acidifying the alkaline solutions and weighing the acids regained, and recorded whether the gas observed was ammonia or methylamine. The gas given off in every case shows that it is the pyrimidine that is invariably attacked, and in almost all cases it is the group in Position 3 that is lost. Whether the gas was ammonia or methylamine was apparently determined only by its odor, so that the observations are not entirely dependable.

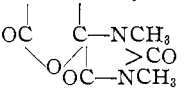
Tetramethyl-uric acid is instantly decomposed by boiling alkali. The course of the decomposition is shown in the following scheme.

[5] (a) Gatewood, THIS JOURNAL, **45**, 3056 (1923); (b) **47**, 2175 (1925) (preceding paper).



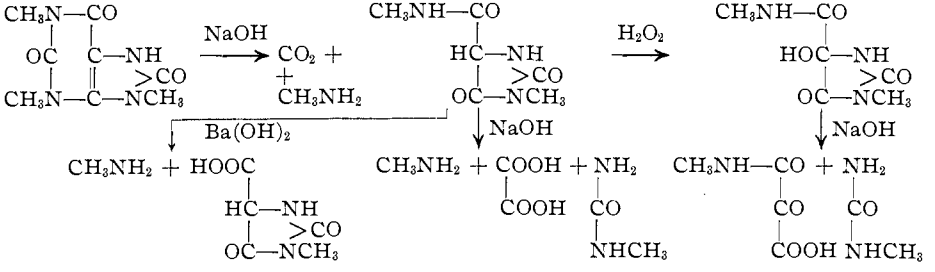
Methylamine is first evolved, and then, when the solution is acidified, carbon dioxide. The solution, when evaporated to dryness and extracted with chloroform, gives a sticky, crystalline mass, from which, by rubbing with ethyl acetate and recrystallizing repeatedly from acetone, a well-crystallized substance of empirical formula $C_7H_{11}O_3N_3$ is obtained; m. p., 180°. These and other properties agree with those of 1,3-dimethyl-hydantoyl-methylamide, which Biltz[6] has obtained from allocaffuric acid by reduction with hydrogen iodide. It is easily decomposed by cold alkali. Methylamine is given off but, as Biltz found, 1,3-dimethyl-hydantoin cannot be isolated. However, the solution does not contain dimethyl-urea, oxalic acid or formic acid.

Dimethylhydantoyl-methylamide is oxidized by hydrogen peroxide in alkaline solution to 1,3-dimethyl-5-hydroxyhydantoyl-methylamide (allocaffuric acid). It is isolated by evaporating the acidified solution to dryness and extracting with ethyl acetate; m. p., 164–165°; empirical formula, $C_7H_{11}O_4N_3$. Biltz[7] obtained this same substance from trimethyl-caffolide, $CH_3N{-}CO$, by boiling with water. It is hydrolyzed



by alkali to dimethyl-urea and the methylamide of mesoxalic acid.

The action of alkali on 1,3,9-trimethyl-uric acid is shown in the following scheme.



Hot alkali decomposes the acid readily. Methylamine and carbon dioxide are split off, and the substance obtained when the solution is evaporated to dryness and extracted with absolute alcohol has the composition and melting point (235–237°) of 3-methylhydantoyl-methylamide, which Biltz[8] has obtained by reducing isocaffuric acid. He found that this substance was hydrolyzed by barium hydroxide to methylamine and 3-methylhydantoin-5-carboxylic acid. He did not hydrolyze it further. The decomposition product hydrolyzes in the same way when barium hydroxide is used, but with sodium hydroxide the products obtained are methylamine, oxalic acid and methyl-urea.

---

[6] Biltz, *Ber.*, **43**, 1610 (1910).

[7] Ref. 6, p. 1608.

[8] Biltz, *Ber.*, **46**, 3409 (1913).

This shows that the decomposition is like that of 3-phenylhydantoyl-methylamide.[9] When oxidized with hydrogen peroxide, methylhydantoyl-methylamide gives 3-methyl-5-hydroxyhydantoyl-methylamide (isocaffuric acid).

The conclusion to be drawn from these alkaline decompositions is that the primary decomposition is the same in all cases—the loss of methylamine and carbon dioxide and the formation of an hydantoyl-methylamide. The difference comes in the further decomposition. 1,3-Disubstituted-hydantoyl-methylamides give hydantoins on hydrolysis with alkali while 3-mono-substituted-hydantoyl-methylamides always give ureas. In the first case it is the bond between Carbon 5 and the carboxyl group that is the least stable; in the second case it is the 1–5 bond that breaks first. This difference seems to depend solely on whether Position 1 is substituted or not.

All the hydantoyl-methylamides are oxidized by hydrogen peroxide to 5-hydroxyhydantoyl-methylamides, and these are easily hydrolyzed by alkali to the corresponding ureas and the methylamide of mesoxalic acid.

To make the study of the action of alkali on substituted uric acids complete, one must know where the first break in the uric acid ring occurs. Is it at the 3–4 bond, as Biltz finds it is in the uric acid glycol ring when it undergoes the caffolide decomposition, and more recently, in the hydroxy-dihydro-uric acid ring, both of which first give hydroxyhydantoyl-ureas?[10] Or is it at the 2–3 bond as in the caffeine ring, which Maly and Andreasch[11] found gave caffeidine-carboxylic acid and then caffeidine,[12] $CH_3NH—CO—CNCH_3$, by loss of carbon dioxide?

$$\begin{array}{l} \quad\quad\quad\quad\ \| \ \rangle CO \\ CH_3NH—CNH \end{array}$$

To try to determine where the first break in the uric acid ring occurs, attempts were made to isolate an intermediate by milder treatment with alkali. Many experiments were carried out with more dilute alkali solution or at lower temperatures or both, but all four uric acids gave only the products obtained originally. No trace of any intermediate could be found.

Fischer[13] found that under certain conditions tetramethyl-uric acid lost only carbon dioxide and gave a product melting at 165–167° and having the formula $C_8H_{14}N_4O_2$. He considered it to be analogous to caffeidine and called it tetramethyl-ureidine. This preparation could not be repeated. The substance obtained from tetramethyl-uric acid always melted at 180° when it was finally pure and was identical with dimethylhydantoyl-methylamide.

[9] Ref. 5 a, p. 3057.

[10] Biltz, *Ann.*, **432**, 162 (1923).

[11] Maly and Andreasch, *Monatsh.*, **4**, 369 (1883).

[12] Strecker, *Ann.*, **123**, 361 (1862).

[13] Fischer, *Ber.*, **30**, 3009 (1897).

Experimental Part

1,3,7,9-Tetramethyl-uric Acid

Tetramethyl-uric acid was prepared from caffeine by the method of Biltz.[14] 8-Chlorocaffeine[15] was obtained by the action of chlorine on caffeine. This when refluxed with potassium hydroxide and methyl alcohol gave 8-methoxycaffeine,[16] which rearranges smoothly to tetramethyl-uric acid when heated.

Optical Properties.—Habit, needles and small plates; extinction, parallel, α-parallel to elongation; indices, $\alpha = 1.455$, $\gamma = 1.710$.

Action of Alkali.—Five g. of finely powdered tetramethyl-uric acid was boiled with 25 cc. of 4 *N* sodium hydroxide solution. It was decomposed after a few seconds and an odor of methylamine was evident. The solution, when cold, was made distinctly acid with dil. nitric acid. A vigorous evolution of carbon dioxide resulted. The solution was evaporated to dryness in a vacuum desiccator and then extracted several times with warm chloroform. A sticky, crystalline product remained when the chloroform had evaporated. It was rubbed with ethyl acetate and recrystallized from acetone. The residue after the chloroform extraction was dissolved in water, the solution was made weakly alkaline with ammonia, evaporated to dryness and extracted with chloroform. Only a little more of the same substance was obtained. The yield varied from 0.8 to 1.8 g. After a second recrystallization from acetone the substance sintered at 175° and melted at 179–180°. Analysis showed that it was 1,3-dimethylhydantoyl-methylamide.

Anal. Subs., 0.1883, 0.1603: CO_2, 0.3142, 0.2685; H_2O, 0.1013, 0.0849. Subs., 0.1486, 0.1361: N, 29.3 cc. (22°, 766.5 mm.), 28.3 cc. (26°, 756.8 mm.). Calcd. for $C_7H_{11}O_3N_3$: C, 45.40; H, 5.93; N, 22.70. Found: C, 45.50, 45.67; H, 6.02, 5.93; N, 22.41, 22.87.

Optical Properties.—Habit, thick needles; extinction, (1) parallel, (2) angle 41°, γ-parallel to elongation; interference figure, biaxial; indices, $\alpha = 1.520$, $\beta = 1.565$, $\gamma = 1.645$.

When dimethylhydantoyl-methylamide was dissolved in a little sodium hydroxide solution, a strong odor of methylamine developed after a short time, or at once when the mixture was warmed. The solution gave negative tests for oxalic acid and formic acid. 1,3-Dimethylhydantoin could not be isolated when the solution was acidified, evaporated to dryness and extracted with anhydrous ether. A colorless liquid was obtained which may have been the impure substance, as it melts at 41° when pure.[17]

Oxidation of 1,3-Dimethylhydantoyl-methylamide.—Two g. of the alkaline decomposition product was dissolved in 25 cc. of water and the solution cooled with ice; 5.4 g. of potassium hydroxide and 130 cc. of 3% hydrogen peroxide were then added and the temperature was kept below 15°. After five minutes the solution was acidified with dil. hydrochloric acid, cooled for one hour and finally evaporated to dryness in a vacuum desiccator. The residue was extracted several times with ethyl acetate. A crystalline product separated on standing, which sintered at 155° and melted at 164–165° after recrystallizing from ethyl acetate; yield, 1 g. It was 1,3-dimethyl-5-hydroxyhydantoyl-methylamide.

Anal. Subs., 0.1621: CO_2, 0.2471; H_2O, 0.0794. Subs., 0.1646, 0.1676: N, 31.1 cc. (18°, 742.9 mm.), 31.1 cc. (21°, 767 mm.). Calcd. for $C_7H_{11}O_4N_3$: C, 41.78; H, 5.5; N, 20.89. Found: C, 41.58; H, 5.34; N, 21.21, 21.14.

[14] Biltz, *Ann.*, **413**, 200 (1917).

[15] Fischer, *Ann.*, **221**, 336 (1883).

[16] Fischer, *Ber.*, 17, 1785 (1884).

[17] Ref. 10, p. 168.

Optical Properties.—Habit, hexagonal plates; extinction, symmetrical, α-parallel to elongation; interference figure, biaxial, large optic angle; indices, $\alpha = 1.460$, $\gamma = 1.590$ (?).

When dimethylhydroxyhydantoyl-methylamide was treated with 4 *N* sodium hydroxide solution no odor could be detected. After several minutes the solution was neutralized with acetic acid, and a solution of phenylhydrazine in acetic acid was added. A yellow precipitate formed. The solution was warmed until clear, cooled and hydrochloric acid added. A heavy, bright yellow precipitate resulted which melted at 167–168°; when this was mixed with the phenylhydrazone of mesoxalic acid methylamide, the melting point was unchanged. The optical properties of the two agreed. Dimethylurea was not isolated from the filtrate.

1,3,9-Trimethyl-uric Acid

Preparation.—Pure trimethyl-uric acid was prepared by the recent method of Biltz,[18] in which 9-methyl-pseudo-uric acid is methylated in Positions 1 and 9 by dimethylsulfate and then boiled with concd. hydrochloric acid.

The preparation of 9-methyl-pseudo-uric[19] acid involved the methylation of large amounts of uric acid with methyl iodide. The methylations were carried out in 30g. lots in a 4-liter copper flask closed with a clamp having a pressure gage, heated internally by a small coil, and shaken mechanically. The pressure was kept at about 1.6 atmospheres. The yields varied from 20 to 25 g. of the mixed 3- and 9-methyl-uric acids. Chlorine changes the latter into 9-methyl-5-chloro-pseudo-uric acid, from which 9-methyl-pseudo-uric acid is obtained by treatment with stannous chloride. This must be purified before methylating further.

Optical Properties.—Habit, hexagonal plates; extinction, symmetrical, γ-parallel to elongation; interference figure, biaxial; indices, $\alpha = 1.525$, $\gamma = 1.705$.

Action of Alkali.—One hundred cc. of 4 *N* sodium hydroxide solution was added to 2 g. of powdered trimethyl-uric acid. The sodium salt separated, but gradually dissolved as the solution was heated to boiling. After the solution had been boiled for half a minute, it was cooled slightly and then acidified with dil. sulfuric acid; carbon dioxide was evolved. The liquid was evaporated to dryness in a vacuum desiccator and the residue was extracted several times with boiling absolute alcohol. A white, crystalline material separated from the alcohol; yield, 0.2–0.5 g.; m. p., 235–237°. It had the composition and other properties of 3-methylhydantoyl-methylamide.

Anal. Subs., 0.1613: CO_2, 0.2497; H_2O, 0.0755. Subs., 0.1252: N, 27.9 cc. (24°, 761 mm.). Calcd. for $C_6H_9O_3N_3$: C, 42.09; H, 5.26; N, 24.56. Found: C, 42.22; H, 5.24; N, 24.90.

Optical Properties.—Habit, hexagonal and octagonal plates; extinction, symmetrical (octagonal), 14° (hexagonal), α-parallel to elongation; interference figure, biaxial; indices, $\alpha = 1.485$, $\beta = 1.520$, $\gamma = 1.570+$.

Methylhydantoyl-methylamide is very soluble in water, somewhat less in alcohol, and insoluble in acetone and ethyl acetate.

When it was warmed with barium hydroxide at 80°, methyl amine was evolved. The solution was evaporated to dryness in a desiccator, the residue dissolved in water and the barium precipitated by dil. sulfuric acid and removed. The clear filtrate was then evaporated to a small volume on the water-bath and left in a vacuum desiccator. A crystalline product was obtained which, when recrystallized from water, melted at 129–130° with decomposition; this is the melting point of methylhydantoyl-carboxylic acid.

[18] Biltz, *Ann.*, **423**, 248 (1922).

[19] Ref. 14, p. 89.

Action of Alkali on 3-Methylhydantoyl-methylamide.—Two cc. of 4 *N* sodium hydroxide solution was added to 0.25 g. of the alkaline decomposition product. It dissolved at once, and when the solution was warmed on the water-bath, methylamine was given off. The solution was acidified with acetic acid and a solution of calcium chloride was added. A heavy precipitate of calcium oxalate formed at once; yield, 0.165 g. (88%). The filtrate was evaporated to dryness and extracted with absolute alcohol. After partial evaporation of the alcohol in a desiccator, a crystalline product separated; m. p., 102°. A mixed melting point showed that it was methyl-urea.

Oxidation of 3-Methylhydantoyl-methylamide.—One g. of the alkaline decomposition product was dissolved in 12 cc. of water and the solution cooled with ice water. To this, 3.8 g. of potassium hydroxide and 70 cc. of 3% hydrogen peroxide were added. The temperature was kept below 15°. After five minutes the solution was acidified with dil. hydrochloric acid and evaporated to dryness in a vacuum desiccator. The residue was then extracted with boiling absolute alcohol; a crystalline product separated as the solution cooled. It was recrystallized from a little water; m. p., 194° (sintered, 190°). Biltz[20] gives 191° as the melting point of 3-methyl-5-hydroxyhydantoyl-methylamide (isocaffuric acid), which he obtained from iso-apocaffeine.

Optical Properties.—Extinction angle, 35°, γ-parallel to elongation; interference figure, biaxial; index, $\gamma = 1.555$.

Attempts to Isolate an Intermediate Product

1,3-Dimethyl-9-phenyl-uric Acid.—(1) One g. of the acid was shaken with 50 cc. of 4 *N* sodium hydroxide solution at 20–23°. The sodium salt separated and then gradually dissolved. After four days' shaking the solution was clear and the acid was completely decomposed. The solution was acidified and allowed to stand overnight. Phenylhydantoyl-methylamide separated; yield, 0.65 g.; m. p., 250°.

(2) One g. of the acid was shaken with 50 cc. of *N* sodium hydroxide solution at 24°. The solution cleared after it had been shaken for one day but it still gave some of the unchanged acid on acidification. After shaking had been continued for two more days all the acid was decomposed. The solution was acidified and left until the next day; 0.8 g. of phenylhydantoyl-methylamide separated; m. p., 250°.

1,3,7-Trimethyl-9-phenyl-uric Acid.—(1) One g. of the finely powdered acid was shaken with 25 cc. of 2 *N* sodium hydroxide solution at 20–22°. All had dissolved after 24 hours. The solution was acidified and partially evaporated in a vacuum; 0.5 g. of methylphenylhydantoyl-methylamide separated which, after recrystallization from hot water, melted at 163°.

(2) One g. was shaken with 25 cc. of *N* sodium hydroxide solution. The solution was clear after 12 hours. Methylphenylhydantoyl-methylamide was obtained, as before; yield, 0.62 g.; m. p., 164°.

1,3,9-Trimethyl-uric Acid.—One g. of the acid was shaken with 50 cc. of 4 *N* sodium hydroxide solution at 22°. The sodium salt separated. After nine days the solution was clear. It was acidified, evaporated to dryness and extracted with absolute alcohol. Methylhydantoyl-methylamide (m. p., 237°) was obtained.

1,3,7,9-Tetramethyl-uric Acid.—Five g. of the finely powdered acid was shaken with 45 cc. of *N* potassium hydroxide solution at 25°. All had dissolved after several hours. The solution was acidified with sulfuric acid, evaporated to dryness in a vacuum, and the residue extracted with chloroform. The sticky, crystalline mass obtained was rubbed with ethyl acetate, and recrystallized many times from acetone. The product melted at 178–180°, either alone or mixed with dimethylhydantoyl-methylamide. The optical properties of the two were identical. The residue from the chloroform extract was

[20] Biltz, *Ber.*, **46**, 3408 (1913).

dissolved in water, made alkaline with aqueous ammonia, evaporated to dryness, and the residue extracted again. Only a little sirup that did not crystallize was obtained.

Summary

1. The causes for the varying stability of substituted uric acids toward alkali are discussed.

2. The action of alkali on tetramethyl-uric acid and on 1,3,9-trimethyl-uric acid has been studied. Tetramethyl-uric acid gives 1,3-dimethyl-hydantoyl-methylamide, and trimethyl-uric acid gives 3-methylhydantoyl-methylamide.

3. Tetra-substituted uric acids give hydantoins as final decomposition products; 1,3,9-tri-substituted uric acids give ureas.

4. An intermediate compound that would show where the first break in the uric acid ring occurs could not be isolated.

NEW HAVEN, CONNECTICUT

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF KENTUCKY]

SOME NEW SUBSTITUTED BENZYL ESTERS[1]

BY CHARLES BARKENBUS AND JOHN B. HOLTZCLAW

RECEIVED APRIL 24, 1925 PUBLISHED AUGUST 5, 1925

The anti-spasmodic action of opium alkaloids has been shown by Macht[2] to be due to the presence of the benzyl group in the alkaloids. Benzyl benzoate and many other benzyl esters have been shown to possess this physiological property.[3] In the last few years many benzyl esters have been made, chiefly with the desire of finding some new ester that would have the physiological properties of benzyl benzoate but have physical properties that would allow it to be more readily dispensed.

The object of this work was to prepare a substituted benzyl benzoate, namely *p*-carboxybenzyl benzoate, that would have a carboxyl group in the *para* position of the benzyl nucleus. It was hoped that this ester might form a soluble salt which would be superior to benzyl benzoate for dispensing purposes, since the latter is a water-insoluble oil. So far we have been unable to obtain this ester in a pure state but have thought it expedient to publish the results obtained, since other workers[4] are preparing esters of this kind and we do not expect to continue this work.

p-Carboxybenzyl alcohol can be esterified to give three types of esters.

$$HOOCC_6H_4CH_2OH \longrightarrow HOOCC_6H_4CH_2OOC{-}R \quad (1)$$

$$HOOCC_6H_4CH_2OH \longrightarrow HOCH_2C_6H_4COOC{-}R_3 \quad (2)$$

$$HOOCC_6H_4CH_2OH \longrightarrow R{-}COOCH_2C_6H_4COOC{-}R_3 \quad (3)$$

[1] This paper is based upon the thesis presented by John B. Holtzclaw to the Faculty of the Graduate School of the University of Kentucky in partial fulfilment of the requirements for the degree of Master of Science, June, 1924.

[2] Macht, *J. Pharmacol.*, **9**, 287 (1917); **11**, 263 (1918).

[3] Macht, *ibid.*, **13**, 509 (1919). Shonle and Row, THIS JOURNAL, **43**, 361 (1921).

[4] Case, THIS JOURNAL, **47**, 1143 (1925).