portion of the reaction product consisting partly of unchanged starting material and partly of unidentified products.

Summary

1. A 45–50% solution of nitrosulfonic acid in fuming nitric acid, prepared by passing sulfur dioxide into cold fuming nitric acid, is a better nitrating agent than the usual mixture of nitric and sulfuric acids.
2. This reagent has been employed to nitrate various phenols, anilines, aromatic acids and hydrocarbons, as well as benzanilide and benzaldehyde.
3. It is suggested that nitrosulfonic acid functions because of its dehydrating action. In this respect it is more efficacious than sulfuric acid; hence the amount of nitrosulfonic acid necessary is considerably less than that of sulfuric acid ordinarily employed in nitrating mixtures.

BENARES, INDIA

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF MOUNT HOLYOKE COLLEGE]

SYNTHESIS OF THE POLYPEPTIDE-HYDANTOIN: N-1-METHYL-TYROSYL-HYDANTOIN-3-ACETIC ACID

BY DOROTHY A. HAHN AND ALICE G. RENFREW[1]

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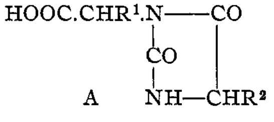
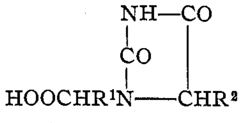
The combination of α-amino acids in such a manner as to produce cyclic urea combinations has been discussed in an earlier paper by Treat B. Johnson.[2] Such substances on hydrolysis yield α-amino acids and carbon dioxide as the sole products of decomposition and, since they may be regarded as representatives of a new class of hydantoins, have been given the name of *polypeptide-hydantoins*. Compounds of this type in all cases contain an acid group in place of a hydrogen atom in the N-1 position of the hydantoin ring as indicated by the general formula, A



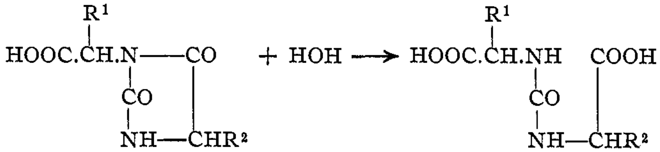
$$\begin{array}{l} \mathrm{HOOC.CHR^1.N{-}{-}CO} \\ \quad\quad\quad\quad\quad \mathrm{CO} \\ \mathrm{A} \quad\quad \mathrm{NH{-}CHR^2} \end{array}$$



$$\begin{array}{l} \quad\quad\quad\quad \mathrm{NH{-}CO} \\ \quad\quad\quad\quad \mathrm{CO} \\ \mathrm{B} \quad \mathrm{HOOCHR^1N{-}{-}CHR^2} \end{array}$$

When subjected to intense hydrolysis such substances undergo a decomposition of the hydantoin ring which may be regarded as taking place in two stages according to the following mechanism,

(a)



$$\mathrm{HOOC.\overset{R^1}{C}H.N{-}{-}CO\ (CO,\ NH{-}CHR^2)} + \mathrm{HOH} \longrightarrow \mathrm{HOOC.\overset{R^1}{C}H.NH\ \ COOH\ (CO,\ NH{-}CHR^2)}$$

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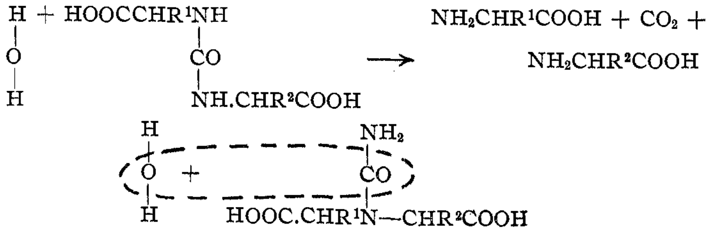
[1] The work which is embodied in this paper is being offered in partial fulfilment of the requirements for the degree of Master of Arts at Mount Holyoke College.

[2] Johnson, *Proc. Nat. Acad. Sci.*, **2**, 69 (1916).

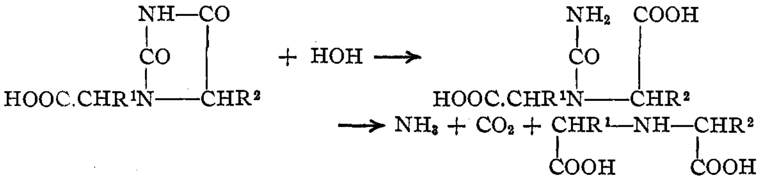
(b)



$$H{-}O{-}H + HOOCCHR^1NH{-}CO{-}NH.CHR^2COOH \longrightarrow NH_2CHR^1COOH + CO_2 + NH_2CHR^2COOH$$

Three polypeptide-hydantoins of the above type have now been synthesized and studied, namely (a) glycyl-phenylalanine-hydantoin,[3] (b) glycyl-tyrosine-hydantoin,[4] and (c) alanyl-tyrosine-hydantoin.[5] The constitution of each of these three substances has been fully established by the fact that they decompose on hydrolysis to give, respectively, (a) glycine + phenylalanine + carbon dioxide, (b) glycine + tyrosine + carbon dioxide, and (c) alanine + tyrosine + carbon dioxide.

The possibility of another somewhat different general type of α-amine acid combination has been considered in an earlier paper[6] and differs from the polypeptide-hydantoin which has just been described in the fact that the substituting acid group occupies the N-3 instead of the N-1 position in the hydantoin ring, B. The products which might be expected to result from the decomposition of a substance of this character when subjected to intense hydrolysis would be quite different from those that have been described as resulting from the decomposition of Type I and would consist of ammonia (or of an amine), carbon dioxide and an imino acid.



$$\text{HOOC.CHR}^1\text{N(CO{-}NH{-}CO{-}CHR}^2) + HOH \longrightarrow \text{HOOC.CHR}^1\text{N(CO{-}NH}_2)\text{{-}CHR}^2\text{COOH} \longrightarrow NH_3 + CO_2 + \text{CHR}^1(COOH){-}NH{-}\text{CHR}^2(COOH)$$

Since imino dibasic acids represent a class of α-amino acid derivatives which is extremely interesting in itself and one in which relatively few examples have been studied, the decomposition of hydantoins of the second type (B) suggested a practical method for preparing these substances. And since the N-1 position in the hydantoin ring is the one most favored by entering groups in the formation of all mono-substitution products, it was found expedient to protect this position by replacing the hydrogen by a methyl group in the N-3 position. For the purpose already outlined

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[3] Johnson and Bates, This Journal, **38**, 1087 (1916).

[4] Johnson and Hahn, *ibid.*, **39**, 1255 (1917).

[5] Hahn and Gilman. This substance is under investigation and will be described in a paper which will appear shortly.

[6] Hahn, Kelley and Schaeffer, *ibid.*, **45**, 843 (1923).

in the present investigation, N-1-methyl-anisal-hydantoin was, therefore, prepared and made the starting point for other preparations. This substance, I, had been previously prepared[7] and its constitution had been definitely established. For purposes of checking experimental results the corresponding saturated compound, N-1-methyl-anisyl-hydantoin, II was also prepared. This substance had not as yet been described, but it was readily obtained in good yield. The course which the investigation took is outlined by means of the accompanying chart from which it will be seen that a barium salt and an ethyl ester of the desired imino dibasic acid were separated. It may be added that the free imino acid itself has since been isolated and is at present under investigation in this Laboratory.[5] The results of this work will be published shortly, but it may be said at this time that the acid corresponds on analysis to the formula $HOOC.CH_2NHCH(COOH)CH_2C_6H_4OH$ and that when titrated against 0.1 *N* alkali it appears to be monobasic in character. Its existence affords further corroboration of the relationships which are described in the present publication.

Experimental Part

1-Methyl-anisal-hydantoin (I) was prepared by the same general method as that which has been described by Johnson and Nicolet.[7] The substance was found to melt at 218° but is not so soluble in alcohol as these investigators seemed to indicate since it dissolves in boiling alcohol, in about the proportions of one part in one hundred of the solvent. The solubility in boiling alcohol is in fact not such as to make this a convenient medium for purifying the compound by recrystallization and boiling acetic acid was, therefore, used in preference. Methyl-anisal-hydantoin dissolves in the latter solvent in the proportions of about one part to three, and crystallizes almost completely on cooling.

In working with large quantities of material it was found convenient to proceed in the following way.

One hundred g. of anisal-hydantoin was suspended in 1000 g. of 50% aqueous alcohol in which 30 g. of solid potassium hydroxide (1.2 equivalents) had been dissolved. The mixture was then connected with a return condenser and heated on a steam-bath until solution was complete. This process usually required from three-quarters of an hour to an hour depending upon whether the anisal-hydantoin used for the experiment had been finely powdered or not. As soon as the anisal-hydantoin had entirely disappeared, the solution was cooled and 76 g. of methyl iodide (a slight excess over 1.2 molecular equivalents) was added with constant shaking and very gentle warming. Under this treatment the separation of a precipitate was usually observed within 10 to 15 minutes. The contents of the flask rapidly assumed a semisolid consistency so that the operation was interrupted and the hot mixture was filtered and washed first with hot and then cold alcohol. The precipitate, which consisted of long, white needles or plates, m. p. 214–216°, was practically pure and usually represented about 50 g.

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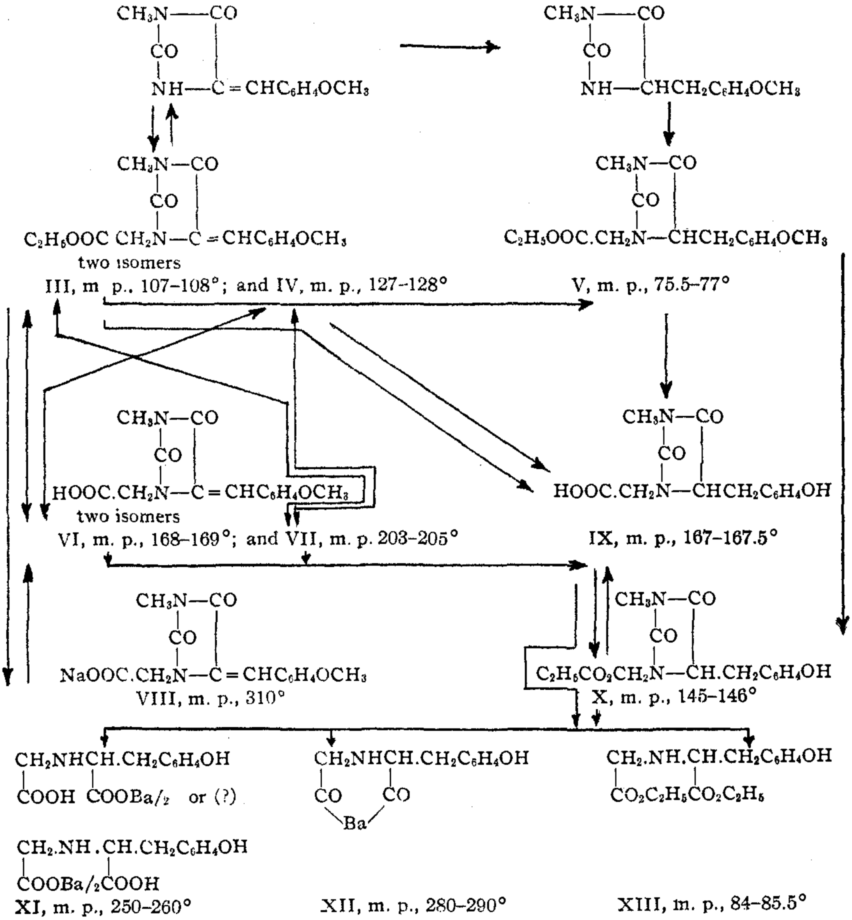
[7] Johnson and Nicolet, *Am. Chem. J.*, **47**, 469 (1912).

The filtrate which was observed to be still slightly alkaline was then heated with 5 cc. more of methyl iodide for half an hour and the mixture allowed to cool. The precipitate which was deposited was in this case slightly yellow; m. p., 190–215°. Its weight averaged about 20 g. and it was readily purified without appreciable loss in weight by recrystallization from acetic acid. Concentration of the mother liquor gave an additional precipitate of about 30 g. This melted at 70° to 200° and consisted of a very impure mixture of dimethyl-anisal-hydantoin, methyl-anisal-hydantoin, anisal-hydantoin and possibly other substances.



In a series of experiments, yields of methyl-anisal-hydantoin averaging about 70% of the calculated quantity were obtained. The identity of the substance was fully established by analyses. It might be added that methyl-anisal-hydantoin was observed to crystallize from its reaction mixture in a meshwork of long, fine, soft, white needles which suggested the texture of asbestos and which required a relatively long time for filtration. In recrystallizing the substance from alcohol or acetic acid the general appearance of the substance was so strikingly different as almost to suggest another substance. Under these conditions it separated from its solutions in the form of short, hard, well-defined plates.

1-Methyl-anisyl-hydantoin (II) was obtained by reducing 1-methyl-anisal-hydantoin with tin and hydrochloric acid in alcohol solution. The end of the reaction was recognized by the final disappearance of the last traces of methyl-anisal-hydantoin since the latter substance is almost insoluble in boiling alcohol while its reduction product is readily soluble in the hot solvent. The procedure was to suspend a mixture of 50 g. of methyl-anisal-hydantoin and 25 g. of tin (one atomic equivalent) in 250 cc. of 95% alcohol. The mixture was saturated with dry hydrogen chloride and then heated on a water-bath with a return condenser, the operation being repeated at intervals during the course of about 72 hours when the reaction was complete. The solution which was perfectly clear but was slightly green, was poured into an equal volume of water and set aside to await crystallization. This was unusually slow and even after crystals began to form was frequently not complete until after four or five hours. The crude product obtained in this way melted at 110–113° and weighed about 40 g. It was purified by recrystallization from a mixture of alcohol and water from which it separated in the form of long, soft, white needles or plates. These crystals grow in rosets and spread throughout the solution to give the effect of a dense meshwork of fine threads. After four recrystallizations the substance appeared to be pure and melted at 116–118°.

Anal. Calcd. for $C_{12}H_{14}O_3N_2$: N, 11.96. Found: 12.35, 12.36.

N-1-Methyl-anisyl-hydantoin is slightly soluble in hot water, 1.5 g. dissolving in 50 cc. The substance separates from its aqueous solutions on cooling in the form of an oil which gradually solidifies. It is very soluble in hot alcohol, dissolving in about its own weight of this solvent. For recrystallizing the substance it was, therefore, found convenient to use mixtures of water and alcohol. Fifty g. of the compound was usually dissolved in 200 cc. of hot alcohol to which solution an equal volume of boiling water was then added. As the solution cooled, about 40 g. separated in the form of fine, white crystals. The remainder was recovered when the filtrates were concentrated. The substance is very soluble in ether and may be extracted from the reaction mixture (after its dilution with an equal volume of water) by use of this solvent.

Derivatives of N-1-Methyl-anisal-hydantoin

Ethyl N-1-Methyl-4-anisal-hydantoin-3-acetate (III) was prepared by alkylating the sodium derivative of N-1-methyl-anisal-hydantoin with ethyl chloro-acetate. The reaction was complete after the mixture had been heated for four days, and a remarkably pure product, m. p. 107–108°, was obtained in yields which averaged approximately 80% of those calculated. The reaction mixture was always found to contain small quantities of N-1-methyl-anisal-hydantoin, but the solubility of this substance in boiling alcohol was so different from that of ethyl N-1-methyl-anisal-hydantoin-3-acetate that a separation of the two compounds was easily and speedily effected.

Fifty g. of N-1-methyl-anisal-hydantoin was suspended in 500 cc. of 95% alcohol to which 6 g. of metallic sodium (1.2 equivalent) had previously been added. The mixture was heated for a period varying from 12 to 18 hours in order to insure the complete conversion of the hydantoin into the sodium derivative. At the end of this time the heating was interrupted and 32 g. of ethyl chloro-acetate (a little more than the calculated quantity) was added. The heating was then resumed and continued for four days. Either of two methods of procedure could then be followed with equally satisfactory results. (a) The reaction mixture could be filtered hot, in which case about 14 g. of sodium chloride (containing practically no trace of organic material) was obtained as a precipitate. The filtrate on cooling deposited from 50 to 59 g. of crystalline solid which melted between 115° and 170°. Evaporation of the filtrate gave additional quantities of material which melted over about the same range of temperature. (b) The reaction mixture could be poured into an equal volume of water, in which case the sodium chloride dissolved and a crystalline solid was precipitated. The latter was formed in about the same amounts and melted over the same range of temperature that was observed in the previous experiment.

The mixture which was obtained by either of these methods was found to consist of but two substances which could be readily separated if advantage was taken of the relatively great difference in their solubilities in boiling alcohol. For example, 59 g. of a mixture melting at 115–170° was boiled for several minutes with 80 cc. of hot alcohol. The solution was allowed to settle and then decanted from a heavy granular precipitate that remained on the bottom of the beaker. The latter was washed twice with small quantities of hot alcohol which were also decanted and added to the original solution. On cooling, this solution precipitated 51 g. of a crystalline solid; m. p., 104–106°. The residue after extraction with boiling alcohol was dissolved in 30 cc. of boiling acetic acid. From this solution 7 g. of material, m. p. 215–217°, consisting of almost pure methyl-anisal-hydantoin was obtained.

Ethyl N-1-methyl-anisal-hydantoin-3-acetate was best purified by recrystallizing from small quantities of boiling alcohol. After four or five recrystallizations it melted to a clear liquid at 107–108° without showing any traces of a higher-melting residue.

Anal. Calcd. for $C_{16}H_{18}O_5N_2$: N, 8.80. Found: 8.82, 8.81.

Ethyl N-1-methyl-anisal-hydantoin-3-acetate is very soluble in boiling alcohol, dissolving in about its own weight of solvent. It is only very slightly soluble in cold alcohol and therefore may be recrystallized conveniently from this solvent. Since hot concentrated solutions in alcohol were difficult to filter, solutions that contained one part in ten of the solvent were used in cases where filtration was found to be necessary. In all cases the substance separates from its solutions in the form of hard, compact, well-defined prisms. The compound is slightly soluble in cold ether, from which it crystallizes on evaporation.

This ester is readily hydrolyzed by the action of both alkali and acids. In the first case an acid melting at 168–169° was formed, and in the second case a mixture of this acid with a higher-melting modification (m. p., 203–205°) was obtained. The separation and properties of these substances will be considered in detail later.

Since the higher melting of the two acids obtained by the hydrolysis of ethyl N-1-methyl-anisal-hydantoin-3-acetate gave an ester melting at 131° (IV) which was isomeric with the ester melting at 107–108° (III), an attempt was made to convert the latter into the former by heating. Two g. of substance, m. p. 107–108°, was placed in a small beaker and held at a temperature between 130° and 140° for six hours. At the end of that time the material was allowed to solidify. Upon examination its melting point was found to have suffered no change.

The ester is readily transformed into the polypeptide-hydantoin (IX) when heated with hydrogen iodide and red phosphorus.

N-1-Methyl-anisal-hydantoin-3-acetic Acid; M. p., 203–205° (VII).—This substance represents one of the two modifications of an acid corresponding to this formula obtained by hydrolyzing ethyl N-1-methyl-anisal-hydantoin-3-acetate (III) in the presence of hydrochloric or of hydrobromic acid. The ester used in these experiments was obtained by alkylation of the sodium derivative of N-1-methyl-anisal-hydantoin with ethyl chloro-acetate; m. p., 107–108°. When boiled with concd. aqueous solutions of the above-mentioned mineral acids for periods of two to three hours it was transformed into a somewhat gummy mass that melted over a relatively wide range of temperature, namely, 145–205°. The product was found to consist of a mixture of two isomeric acids that differed considerably in their relative solubilities in hot glacial acetic acid. The resolution of the mixture into its two components was, therefore, first attempted by recrystallization from this solvent. Thus, for example, a weighed quantity of material melting at 145–205° was dissolved in the least possible quantity of boiling, glacial acetic acid. The white, crystalline solid that separated immediately on cooling represented about half the weight of the dissolved substance; m. p., 190–205°. This melting point was not improved by repeated recrystallizations from acetic acid or from alcohol, but extractions with ether left a residue that melted at 203–205°. This represented the purest form in which the higher-melting of the two isomeric acids was obtained. The filtrates from this substance contained the lower-melting acid, but a detailed account of the methods which were used for the separation of the latter substance must be reserved for discussion later.

Ten g. of ethyl N-1-methyl-anisal-hydantoin-3-acetate was suspended in 100 cc. of concd. hydrochloric acid and heated on an oil-bath at 130–140°. During this process the ester first melted to a clear oil that settled on the bottom of the flask. This gradually disappeared and at the end of about an hour and a half crystals began to form throughout the solution. After continued heating for another hour the contents of the flask presented the appearance of an almost solid mass of crystals and the reaction was, therefore, interrupted at this point. The mixture was cooled to room temperature, filtered, washed with water and dried. It consisted of about 7 g. of material that melted between 145° and 205°. The hydrochloric acid filtrate on evaporation gave an additional quantity of crystals; m. p., 140–160°. The mixture melting at 145–205° was dissolved in the least possible quantity of boiling glacial acetic acid, which was found to be roughly about 25 cc. for 7 g. As this solution cooled it precipitated approximately 3.5 g. of an acid melting at 190–205°. Since recrystallizing from acetic acid did not improve the melting point of this substance although it separated from the solvent in the form of small, well-defined needles or plates which appeared to be perfectly homogeneous, the solvent was changed and ethyl alcohol substituted. The use of this solvent proved of no advantage, however, since when 6 g. of acid melting at 190–205° was dissolved in 50 cc. of boiling alcohol, 4.1 g. having exactly the same melting point crystallized upon cooling. Extractions with ether afforded the only means by which it was possible to sharpen the melting point of this acid. After digesting twice with small quantities of ether a substance melting at 203–205° was obtained and analyzed.

Anal. Calcd. for $C_{14}H_{14}O_5N_2$: N, 9.65. Found: 9.72, 9.57.

The acid prepared in this way crystallized from acetic acid in the form of glistening plates that were distinctly yellow. When digested with hydrogen iodide it was transformed into the polypeptide-hydantoin; m. p., 167–167.5°. Thus, for example, 2 g. of acid melting at 203–205° gave about 1 g. of the polypeptide-hydantoin (IX). The weight of the product in this case represents only that portion of the material which crystallized at once from the hydriodic acid mixture. No attempt was made to separate additional quantities of the product present in the filtrates, since the experiment was undertaken merely with the object of determining whether this modification of N-1-methyl-4-anisal-hydantoin-3-acetic acid gave the same polypeptide-hydantoin that had been obtained previously from the ester melting at 107–108°.

Ethyl N-1-Methyl-anisal-hydantoin-3-acetate (IV), m. p. 127–128°, was prepared by passing hydrogen chloride into alcohol containing N-1-methyl-anisal-hydantoin-3-acetic acid melting at 203–205° (VI).

Two g. of acid was suspended in 50 cc. of absolute alcohol and hydrogen chloride was conducted into the mixture while it was kept cool. In the course of an hour the substance gradually dissolved, this process being coincident with the separation of what appeared to be another and a different crystalline compound. The latter was not filtered at once but hydrogen chloride was allowed to pass into the cooled solution for another hour. The mixture was then heated to boiling on a water-bath and filtered hot. An almost negligible quantity of acid melting at 200–205° was retained by the filter. As the filtrate cooled it deposited 1.3 g. of a white, crystalline substance; m. p., 120–125°. This was dissolved in 30 cc. of boiling alcohol from which as the solution cooled it separated in the form of soft, white, needle-like crystals that melted sharply at 127–128°. A second recrystallization failed to change its melting point and it was therefore considered to be pure and was analyzed in this form.

Anal. Calcd. for $C_{16}H_{18}O_5N_2$: N, 8.80. Found: 8.82, 8.84.

The ester obtained in this way was almost insoluble in hot water, and the aqueous filtrates from it were neutral to litmus paper. It was fairly soluble in hot alcohol and only slightly soluble in the cold solvent.

Ethyl N-1-methyl-anisal-hydantoin-3-acetate (IV), was readily hydrolyzed to a mixture of the corresponding acids by boiling with concd. hydrochloric acid. For example, 0.8 g. of ester melting at 127–128° was treated with 15 cc. of concd. hydrochloric acid and the mixture boiled for one and one-half hours. During the process, solution did not appear to take place, but at the end of this time the appearance of the precipitate had changed from dull white to glistening yellow crystals. The reaction was therefore interrupted at this point and the resulting mixture was cooled and filtered. The precipitate, after being washed with relatively large amounts of cold water to remove any trace of hydrochloric acid, and subsequently dried on the hot-plate, melted at 195–204°; yield, 0.5 g. The solution of this substance in water was acid to litmus paper, and when the substance was melted with an analyzed specimen of N-1-methyl-anisal-hydantoin-3-acetic acid (VII), it was found to be identical with the latter substance. The filtrate from this acid on evaporation deposited well-defined, colorless prisms that melted at 165–169° and were found to be identical with an isomeric acid (VI).

Ethyl N-1-methyl-anisal-hydantoin-3-acetate, m. p. 127–128°, was also obtained by esterifying the low-melting modification of the acid. This rather remarkable observation was made in the course of two experiments in which specimens of the acid that melted at 161–169° were esterified by dissolving the substance in alcohol and treating with dry hydrogen chloride. For example, 2 g. of acid in 30 cc. of alcohol, placed in a freezing mixture which was then saturated with hydrogen chloride, was warmed on a water-bath and then cooled and resaturated, the process being repeated several times during the course of a day. The mixture was filtered cold, whereupon 0.8 g. of a white crystalline solid was obtained; m. p., 125–127°. Evaporation of the filtrate gave an additional 0.3 g. of the same substance; m. p., 127–128°. These crystals were almost insoluble in hot water, and the aqueous filtrate from them was found to be neutral to litmus; 3.3 g. of this substance was accumulated and recrystallized twice from 100 cc. of boiling alcohol. The substance separated immediately from its hot solutions as they cooled, in the form of long, white, glistening plates, m. p. 127–128°, and was found to be identical in all respects with a similar substance which was obtained by esterifying the higher-melting modification of N-1-methyl-anisal-hydantoin-3-acetic acid (VII).

Inasmuch as specimens of acid melting at 161–169° (VI) usually esterified to give quantitative yields of the ester melting at 107–108° (III) it seems probable that in this case the substance isomerized to the higher-melting acid (VII) (which seems to correspond with the ester IV melting at 127–128°) prior to esterification.

N-1-Methyl-anisal-hydantoin-3-acetic Acid (VI), m. p. 168–169°, was obtained by the hydrolysis of ethyl N-1-methyl-anisal-hydantoin-3-acetate (III) in the presence of acid and also of alkali.

When the hydrolysis was brought about by hydrochloric or hydrobromic acid, the reaction product consisted of a mixture of two isomeric acids, melting at 203–205° and 168–169°, respectively. This mixture was partially resolved into its components when dissolved in boiling glacial acetic acid and allowed to cool. Under these conditions, the higher-melting modification crystallized immediately upon cooling. Concentration of the filtrate to one-half of the original volume failed to bring about the precipitation of additional quantities of material. On dilution with water, however, a heavy crystalline precipitate was formed which represented about one-third of the reaction product and melted at 161–169°. The melting point of this substance was not greatly improved by recrystallization from alcohol-water or acetic acid-water solutions, but sharpened rapidly with only negligible loss of material upon extraction with small quantities of acetone. This was a practical method of purification, if the material was handled rapidly, although the acid was extremely soluble in this solvent. After the second extraction the melting point was found to be 168–169°. A third extraction produced no further change and the acetone filtrate on evaporation and subsequent dilution with water gave a crystalline precipitate that also melted at 168–169°. It was therefore assumed that the acid was homogeneous and practically pure at this melting point. This conclusion was borne out by the fact that material prepared in this way passes quantitatively into ethyl N-1-methyl-anisal-hydantoin-3-acetate (III) upon esterification in the presence of alcohol and dry hydrogen chloride.

When ethyl N-1-methyl-anisal-hydantoin-3-acetate was hydrolyzed by the action of sodium hydroxide the primary product of the reaction was the corresponding sodium salt. The latter could be readily purified by recrystallization from hot water or from hot alcohol, since on cooling it separated in good yield from both of these solvents. An aqueous solution of this salt when acidified gave a white, crystalline precipitate; m. p., 168–169°. This substance was identical in all respects with the acid which was formed as the result of the hydrolysis of ethyl N-1-methyl-anisal-hydantoin-3-acetate with hydrochloric or hydrobromic acid and which has just been described. The acid obtained by acidifying aqueous solutions of the salt was recrystallized once and then analyzed.

Anal. Calcd. for $C_{14}H_{14}O_5N_2$: N, 9.65. Found: 9.69, 9.55.

N-1-Methyl-anisal-hydantoin-3-acetic acid is very soluble in boiling alcohol, 10 g. dissolving in about 30 cc. It is less soluble in cold alcohol and therefore separates from this solvent to some extent on cooling. It is only slightly soluble in hot, and almost insoluble in cold water. For example, 1.5 g. of acid when dissolved in 100 cc. of boiling water gave 1.3 g. on cooling the solution. It is more soluble in hot acetic acid than in hot alcohol but does not separate readily from this solvent.

This acid when dissolved in alcohol and treated with dry hydrogen chloride passes quantitatively into ethyl N-1-methyl-anisal-hydantoin-3-acetate; m. p., 107–108°. The substance obtained in this way was melted with a specimen that had been synthesized from methyl-anisal-hydantoin and was found to be identical with it in all respects. It was observed during the reaction that concentrated solutions of the ester in alcohol saturated with hydrogen chloride were deep red. This color was discharged on dilution with alcohol and reappeared when the solutions were concentrated. The ester was observed to crystallize from concentrated solutions in the form of long, fine, soft needles that spread throughout the solvent, while it separated from dilute solutions in the form of hard, compact prisms that either appeared on the bottom of the beaker or dropped from the surface of the liquid. The appearances of these two modifications were so different that in spite of having the same melting point they were at first suspected of being two different substances.

When heated with hydrogen iodide and red phosphorus, the acid melting at 168–169° was transformed into the polypeptide-hydantoin (IX).

Since it seemed possible that this acid might isomerize into the higher-melting acid on heating, 4.2 g. of pure material was dissolved in 20 cc. of glacial acetic acid and held at the boiling point of the solvent for six hours. At the end of this time the heating was discontinued and, on cooling, a small quantity of acid crystallized. This showed no change in melting point. The remainder of the acid was recovered unchanged by precipitation with water.

Sodium N-1-Methyl-anisal-hydantoin-3-acetate (VIII), m. p., 310° with decomposition, was prepared by hydrolyzing ethyl N-1-methyl-anisal-hydantoin-3-acetate in the presence of sodium hydroxide.

For example, 1.45 g. of sodium hydroxide (1.2 equivalent) was dissolved in 60 cc. of 25% alcohol to which 10 g. of ester was then added. The mixture was connected with a return condenser and heated on a water-bath for one and a half hours. At the end of this time the ester had completely dissolved to give a perfectly clear solution. The product was then transferred to a beaker and evaporated to one-third of its volume to remove the alcohol. Since the addition of an equal volume of cold water at this point was observed to cause the separation of a precipitate, the mixture was allowed to cool and the precipitate was filtered off and washed with cold water. It consisted of 0.5 g. and, when examined on platinum, burned, leaving no residue. It was therefore a pure organic compound uncontaminated by any trace of sodium salt. In subsequent experiments this substance always appeared at this point and was always observed to form in about the same relative amounts. For example, 40 g. of ester hydrolyzed to give 2 g. of the substance. In a series of experiments a total of about 6 g. was accumulated and the compound, which had been found to be only slightly soluble in hot alcohol, was purified by recrystallization from acetic acid. During this process the melting point changed from 203–206° to 217–218° and the substance was definitely recognized as N-1-methyl-anisal-hydantoin. It was finally identified by melting with an analyzed specimen of this substance which had been obtained by synthesis from anisal-hydantoin.

In order to eliminate any possibility that N-1-methyl-anisal-hydantoin might have been present along with ethyl N-1-methyl-hydantoin-3-acetate in some form of loose chemical combination having the observed melting point of what appeared to be the pure, original ester (m. p., 107–108°) a specimen of 20 g. of this ester (which had first been recrystallized seven times) was saponified. After the methyl-anisal-hydantoin had been completely separated from the sodium salt, the latter was recrystallized from water-alcohol mixtures and finally esterified by suspending it in absolute alcohol and saturating the mixture with dry hydrogen chloride. The ester which was obtained in this way melted at 107–108° and was in all respects identical with the original ester. Specimens of this substance taken (a) before hydrolysis and (b) after hydrolysis and esterification, when melted together showed absolutely no change in melting point.

The aqueous filtrate from this substance was concentrated to small volume and on cooling gave a crystalline precipitate. This consisted of 9.1 g. (from 10 g. of ester) and had the appearance and properties of the desired sodium salt. For example, it dissolved completely in a small quantity of cold water and when burned on platinum it left a white residue which gave an alkaline reaction with turmeric paper. The salt was purified by recrystallization first from alcohol and then from water. It melted at 110°, giving off water of crystallization, solidified, and melted again at 310° when it charred and decomposed. When dried for four or five days in a desiccator the salt completely lost its water of crystallization.

Anal. Calcd. for $C_{14}H_{18}O_5N_2Na.5H_2O$: N, 6.94. Found: 7.04, 7.15.

The salt is soluble in its own weight of boiling water and separates as the solution cools. In recrystallizing the substance more dilute solutions were used. For example, 8 g. dissolved in 30 cc. of hot water gave a precipitate of 5 g. when cold. In recrystallizing it from alcohol 12 g. was dissolved in 120 cc. of hot alcohol and about two-thirds of the material separated as the solution cooled.

Suspended in hot alcohol and treated with hydrogen chloride the salt passes quantitatively into an ester melting at 107–108°. This was identified as ethyl N-1-methyl-anisal-hydantoin-3-acetate (III) by melting with an analyzed specimen of the latter substance.

Derivatives of N-1-Methyl-anisyl-hydantoin (II)

Ethyl N-1-Methyl-anisyl-hydantoin-3-acetate, V, m. p., 75.5–77°, was prepared (a) by treating N-3-sodium-N-1-methyl-anisyl-hydantoin with ethyl chloro-acetate and (b) by reducing ethyl N-1-methyl-anisal-hydantoin-3-acetate (I) with hydrogen in the presence of palladium as a catalyst. The specimens of this substance which were obtained in these two ways were found to be identical in all respects and the melting point remained unchanged when they were mixed and melted together. Of the two methods of preparation, the latter alone is practical and may be employed to great advantage since the product is practically pure and the percentage yield is very nearly quantitative.

(a) Twenty g. of methyl-anisyl-hydantoin, m. p. 116–118°, was dissolved in 80 cc. of absolute alcohol to which 1.2 equivalent of sodium had previously been added. The solution was heated on a water-bath with a return condenser for 12 hours in order to insure the formation of N-3-sodium-N-1-methyl-anisyl-hydantoin, and at the end of this time the mixture was cooled and 14 g. of ethyl chloro-acetate was added. The mixture was again heated for a period of about three hours or until tests with tumeric paper indicated a neutral reaction. The product was then poured into a beaker and set aside to await crystallization. Since, however, with the evaporation of the alcohol an oil was precipitated, an additional quantity of alcohol was added in order to redissolve the oil, and the attempt was then made to induce the separation of solid material by precipitation with water. This also proved unsuccessful and the mixture of water and alcohol was therefore set aside over summer. When examined the following autumn the separation of two quite different types of crystals was observed to have occurred and since one of these consists of long, soft needles and the other of compact, hard prisms a partial separation was effected mechanically. After purification by recrystallizing first from mixtures of water and alcohol and finally from 95% alcohol, substances were obtained which melted sharply at 116–118° and 75.5–77°, respectively. The former was identified as N-1-methyl-anisyl-hydantoin by comparison with a specimen of that compound, and the latter was shown to be the desired acetate derivative. These two substances appear to possess almost the same degree of solubility in boiling water and boiling alcohol and when mixed are extremely difficult to separate, so that only about 3 g. of ethyl N-1-methyl-anisyl-hydantoin-3-acetate was obtained in pure condition as a result of this reaction. At best, the transformation of N-1-methyl-anisyl-hydantoin into its condensation product must be regarded as very incomplete and the separation of the latter from the parent substance as very unsatisfactory and laborious.

(b) Ten g. of ethyl N-1-methyl-anisal-hydantoin-3-acetate (I), m. p. 107–108°, was dissolved in 300 cc. of boiling alcohol and added to a solution of 0.40 g. of palladium dissolved in 5 cc. of water. The mixture was shaken constantly at room temperature in the presence of hydrogen under slight pressure for about five hours, when it was observed that hydrogen was no longer absorbed. The solution was then poured into a beaker, acidified by adding a few drops of acetic acid while it was slightly warmed in order to precipitate the palladium, and filtered. The filtrate on evaporation deposited 9.2 g. of the crystalline reduction product in practically pure condition, and the mother liquor from these crystals yielded slight additional amounts of the same substance on precipitation with water. No trace of the original substance was observed.

Anal. Calcd. for $C_{16}H_{20}O_5N_2$: N, 8.75. Found: 8.55, 8.79.

Ethyl N-1-methyl-anisyl-hydantoin-3-acetate is very soluble in hot alcohol and in hot water and when pure separates from both solvents as the solutions cool in the form of hard, compact, transparent prisms. When heated with hydrogen iodide and red phosphorus at 135°, it is readily transformed into N-1-methyl-tyrosyl-hydantoin-3-acetic acid (IX).

Derivatives Common to Both N-1-Methyl-anisal-hydantoin and N-1-Methyl-anisyl-hydantoin

The Polypeptide-hydantoin, N-1-Methyl-4-hydroxy-benzyl-hydantoin-3-acetic Acid (IX), M. p. 167–167.5°.—This substance was obtained in a variety of ways, such as from either of the two isomeric N-1-methyl-4-anisal-hydantoin-3-acetic acids (VI and VII), from the corresponding ethyl esters (III and IV) and also from ethyl N-1-methyl-4-anisyl-hydantoin-3-acetate (V). In all cases the procedure was the same, the substance being heated with hydrogen iodide and red phosphorus at temperatures ranging between 130° and 140° for periods of from one to two hours. The reagent served to hydrolyze, reduce and demethylate as the case required.

Thus, for example, 10 g. of ethyl N-1-methyl-anisal-hydantoin-3-acetate was treated with 30 cc. of hydrogen iodide and 1 g. of red phosphorus. The mixture was connected with a return condenser and heated on a metal bath at 130–140° for one hour.

The flask was then connected with an ordinary condenser and as much liquid distilled as could be separated by keeping the bath at a temperature of 140–145°. The residue in the flask was then treated with 50 cc. of boiling water and filtered in order to remove the red phosphorus. The filtrate obtained in this way was evaporated almost to dryness on the water-bath in order to remove hydrogen iodide as completely as possible. It was then dissolved in about 30 cc. of boiling water. This solution on cooling deposited the polypeptide-hydantoin in the form of well-defined, hard, compact prisms that melted at 167–167.5° and grouped themselves in characteristic roset forms. Usually about 7 g. of material separated in this way, and additional quantities up to a total of about 85% of the calculated yield were obtained from the filtrates. The crude material always was slightly pink and the color was difficult to remove by recrystallization of the substance from water.

The polypeptide-hydantoin (IX) was also obtained from its ester by hydrolysis with hydrochloric acid. This transformation was brought about very readily by heating the substance in a dilute aqueous solution of the mineral acid. For example, 10 g. of ester melting at 145–146° was dissolved in 40 cc. of 10% hydrochloric acid and the solution evaporated on a water-bath to a volume of 20 cc. As it cooled, the pure polypeptide-hydantoin melting at 167–167.5° crystallized in an amount that was found to be approximately quantitative. This method represents the best way of preparing what seems to be an absolutely pure substance and one which is at the same time perfectly colorless.

Anal. Calcd. for $C_{13}H_{14}O_5N_2$: N, 10.07. Found: 9.62, 9.58.

N-1-Methyl-4-hydroxy-benzyl-hydantoin-3-acetic acid is very soluble in hot and fairly soluble in cold water. For example, 10 g. dissolves in 40 cc. of boiling water to give about 8 g. as the solution cools, additional quantities being obtained when the filtrates are concentrated. The substance is very soluble in hot and cold alcohol so that small quantities of material cannot be purified profitably by recrystallizing from this solvent. When the substance is dissolved in 95% alcohol and treated with dry hydrogen chloride, it passes smoothly and quantitatively into the corresponding ester melting at 145–146° (X).

When an aqueous solution of the hydantoin which was acid to litmus paper was treated with Millon's reagent, a white precipitate was formed which promptly changed in color to a dark red. The solution showed the peculiar red coloration which is usually described as a characteristic of tyrosine.

Ethyl N-1-Methyl-4-hydroxy-benzyl-hydantoin-3-acetate (X), m. p. 145–146°, like the corresponding acid, was obtained in a variety of ways, such as by starting with either of the isomeric acids, VI or VII, or with their corresponding esters, III and IV.

The procedure was the same as in the case of N-1-methyl-4-hydroxy-benzyl-hydantoin-3-acetic acid up to the point where the aqueous solution containing hydriodic acid was filtered to remove the red phosphorus. If at this point the filtrate was evaporated almost to dryness, the residue dissolved in 95% alcohol, this solution again evaporated, and the process repeated several times, the product is found to consist of an ester melting at 145–146°. Such a procedure is more convenient than the one employed to prepare the polypeptide-hydantoin itself, since it affords a means for removing the hydrogen iodide in the form of ethyl iodide and gives better percentage yields of the product. According to this method quantities approximating 90% of those calculated may be obtained. The substance is readily purified by three or four recrystallizations from hot alcohol from which it separates on cooling in the form of well-defined, glistening, white leaflets.

Anal. Calcd. for $C_{15}H_{18}O_5N_2$: N, 9.15. Found: 8.84, 8.84.

Ethyl N-1-Methyl-4-hydroxy-benzyl-hydantoin-3-acetate was also prepared by esterifying the corresponding polypeptide-hydantoin by dissolving it in alcohol and saturating the solution with hydrogen chloride.

In whatever manner it was prepared the ester was found to separate from its reaction mixture in a remarkably pure condition and gave a very sharp melting point after two or three recrystallizations. The ester is quite soluble in hot alcohol from which it separates in good yields as the solution cools. For example, 10 g. in 40 cc. of boiling 95% alcohol thus gave 8 g. Practically all of the original substance was recovered by adding water to the alcohol filtrates. The compound is not very soluble in boiling water, dissolving in the proportion of about one to 50 of the solvent. It crystallizes in good yield as the liquid cools but the melting point does not improve so rapidly and the method is not so convenient as that of recrystallization from alcohol.

When boiled with 25% hydrochloric acid the ester passes quantitatively into the corresponding acid.

Hydrolysis of the Polypeptide-hydantoin N-1-Methyl-4-hydroxy-benzyl-hydantoin-3-acetic Acid.—The first attempts to hydrolyze this substance were undertaken in acid solutions and the results were entirely negative in character.

(a) Two g. of polypeptide-hydantoin, m. p. 167–167.5°, was treated with 10 cc. of concd. hydrochloric acid and the mixture was heated in a bomb tube at 190–200° for eight hours. At the end of this time the tube was allowed to cool. When it was opened no gaseous pressure was observed and the contents consisted of a colorless liquid in which a white, crystalline solid was suspended. The latter when filtered and washed was found to consist of unaltered polypeptidehy-dantoin. The entire quantity of material used in this experiment was recovered by evaporation of the hydrochloric acid filtrate.

(b) Two g. of polypeptide-hydantoin, m. p. 167–167.5°, was treated with 15 cc. of hydriodic acid and 0.5 g. of red phosphorus and the mixture was then heated in a bomb tube at 180° for six hours. On opening the tube no pressure of gas was observed and the contents consisted of a slightly brownish liquid in which the red phosphorus was suspended. The mixture was diluted with water and filtered. The filtrate on evaporation gave unaltered material in practically the amount used in the experiment.

(c) When the preceding experiment (b) was repeated at a temperature of about 200°, the same results were obtained. So far as could be observed, working with such a small quantity of material, no change whatever had occurred as a result of the heating.

Hydrolysis in alkaline solution was found, on the other hand, to take place readily and under these conditions the hydantoin readily decomposed with the evolution of methyl amine and carbon dioxide. Solid barium hydroxide was used as the reagent in this experiment, and the same general method of procedure was followed that has been described by Johnson and Nicolet[8] and by Wheeler, Hoffman and Johnson,[9] the only difference being that the corresponding ethyl ester (X) was used in place of the free hydantoin (IX) and the amount of solid barium hydroxide was slightly decreased.

Fifteen g. of ethyl N-1-methyl-4-hydroxy-benzyl-hydantoin-3-acetate was suspended in 100 cc. of water to which 55 g. of solid barium hydroxide was then added. The

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[8] Ref. 7, p. 471.

[9] Wheeler, Hoffman and Johnson, *J. Biol. Chem.*, **10**, **147** (1911–1912).

mixture was connected with a return condenser and placed on a water-bath. In order to follow the course of the reaction the top of the condenser was connected with a glass tube, the other end of which was immersed under alcohol that had previously been saturated with hydrogen chloride. An evolution of gas was observed immediately upon heating and continued over a period of four days. The heating was discontinued at the end of this period and the contents of the flask were examined and found to consist of a cake of barium carbonate and barium hydroxide covered by a clear, slightly pinkish solution which gave off strong fumes of methylamine. The gas showed a basic reaction to moist litmus paper and fumed strongly in the presence of hydrogen chloride but was not evolved in sufficient quantity during the four days of heating to allow its identification as methylamine hydrochloride. The mixture in the flask was therefore diluted with water up to a volume of 400 cc., heated to boiling, filtered hot and the precipitate washed with a small quantity of hot water. This precipitate when examined by heating on platinum was found to consist exclusively of inorganic material and was therefore discarded. The filtrate and aqueous washings from the precipitate were combined and since the mixture gave off heavy alkaline fumes when heated, it was placed in a flask and heated on an oil-bath at 120° in a current of air in order to remove any free volatile base that might be present. Under these conditions about 150 cc. of an alkaline distillate was given off, and following this an aqueous distillate that was neutral to litmus. The distillate was collected in a flask which was closed except for one outlet that passed under the surface of an aqueous solution of hydrochloric acid contained in an adjoining receptacle. At the end of the operation, the hydrochloric acid solution was added to the alkaline distillate and the mixture, which was then acid to litmus, was evaporated to small volume on a steam-bath and then to dryness by warming at about 50° on a hot-plate. A crystalline solid in the form of long, fine, white needles was obtained in this way. After being purified by recrystallization from absolute alcohol, the product consisted of 1.5 g., which melted at 228° and was fully identified as methyl-amine hydrochloride.

The aqueous solution left in the flask after the distillation of methylamine was again diluted with water to 400 cc. and saturated with carbon dioxide in order to remove excess of barium in the form of barium carbonate. After the mixture had been repeatedly filtered and the filtrate resaturated with carbon dioxide until no more barium carbonate was precipitated, the solution was evaporated to 60 cc. and acidified with acetic acid. It was hoped that in this way the free imino dibasic acid might be obtained. The substance which finally separated from the solution under these conditions was not, however, the free acid but what appeared from analyses to be an acid barium salt corresponding to one of the two formulas: $CH_2(COOH)NH.CH(COOBa/_2)CH_2C_6H_4OH$ or $CH_2(COOBa/_2)NH.CHCH_2C_6H_4OH$. The composition of this substance remained unchanged after several recrystallizations from aqueous 10% acetic acid and efforts to obtain the free imino acid by precipitation with acetic acid were therefore abandoned.

The salt (XI) which was formed in this way from 15 g. of ester was obtained in amounts averaging from 8 to 9 g. In winter when the temperature of the laboratory was about 21–25° this salt separated from its aqueous solutions with what appeared to be approximately three molecules of water of crystallization. Under these conditions it was observed to melt in its water of crystallization at 110°. Above this temperature it resolidified and melted again at about 250–260° with decomposition. In summer when the temperature of the laboratory was about 20–35° an anhydrous form of what appeared to be the same salt was obtained.

Anal. Calcd. for $C_{11}H_{12}O_5NBa/_2$: N, 4.57. Found: 4.53, 4.54.
Calcd. for $C_{11}H_{12}O_5N.Ba/_2$: Ba, 22.22. Found: 20.80, 20.92.
Calcd. for $C_{11}H_{12}O_5N.Ba/_2.3H_2O$: H_2O, 15. Found: 16.1.

The substance is very soluble in hot water, 5 g. dissolving in 20 cc. to give on cooling a 2.4 g. of a crystalline precipitate. It separates slowly from its aqueous solutions (sometimes requiring from 10 to 12 hours) in characteristic round clumps which consist of long, fine, soft needles that form about a central point in roset fashion. When dissolved in water and treated with Millon's reagent the salt gave a heavy, white precipitate which immediately changed to red, while the solution gradually assumed the peculiar red coloration which is so characteristic of tyrosine.

In a series of subsequent experiments in which N-1-methyl-tyrosyl-hydantoin-3-acetic acid (X) was decomposed by boiling with barium hydroxide, the attempt was made to separate a barium salt without the introduction of acetic acid into the solution. Under these conditions the composition of the salt was observed to vary greatly depending apparently upon the concentration of the solutions and possibly upon other factors. For example, a specimen was obtained which resembled the acid salt which has just been described in general appearance and properties but which after two recrystallizations from water analyzed quite differently, containing 5.70%, 5.84% of nitrogen and 16.44%, 16.68% of barium. Another specimen was separated from such neutral solutions which was quite different from the other two, forming very small, glistening plates; m. p., 280–290°. This salt on analysis was found to correspond fairly closely to the formula

$$CH_2(COO\overline{Ba)NHCH(COO})CH_2C_6H_4OH \qquad (XII)$$

Anal. Calcd. for $C_{11}H_{11}O_5NBa$: Ba, 36.63. Found: Ba, 40.33, 40.38.

It may be noted that in no case did the aqueous solution of any one of these salts give the slightest evolution of gas when treated with hydrochloric acid, from which it may be concluded that no trace of barium carbonate was present as an impurity. All three gave the same diethyl ester when esterified.

The esterification of the barium salt was readily accomplished by suspending it in absolute alcohol and saturating the mixture with dry hydrogen chloride. Under these conditions the barium was completely precipitated as barium chloride. The latter was filtered and washed with alcohol and was found to be entirely free from traces of organic material. The filtrate on cooling deposited a small quantity of solid material in the form of white, glistening plates. This substance was very soluble in water and alcohol and was obtained only in very small amounts. Its aqueous solution showed an acid reaction and gave a precipitate with silver nitrate and it was, therefore, assumed to represent the hydrochloride of the corresponding ester. In order to obtain the free ester, the alcohol solutions obtained after filtering the barium chloride were evaporated to dryness and the residue was dissolved in a small quantity of water. The aqueous solution was introduced into a separatory funnel together with about twice its volume of alcohol-free ether and while being constantly shaken was treated with small quantities of solid sodium carbonate. The ether was finally decanted from the semi-solid mass containing the carbonate, washed with a small amount of water and dried. The ether on evaporation deposited an oil but this after solution in 95% alcohol separated in the form of large, transparent prisms; m. p., 84–85.5°. Thus, 3 g. of acid barium salt in 100 cc. of absolute alcohol yielded 1.5 g. of ester.

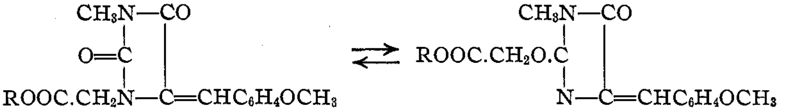
Anal. Calcd. for $C_{15}H_{21}O_5N$: N, 4.75. Found: 4.83, 4.75, 4.65.

The ester (XIII) is very soluble in hot alcohol; 8 g. dissolved in 12 cc. to give 4.4 g. when the solution had cooled. Because of its relatively great solubility in alcohol, the substance may be conveniently recrystallized from a mixture of alcohol and water.

Summary

The synthesis of the polypeptide-hydantoin N-1-methyl-tyrosyl-hydantoin-3-acetic acid has led to the discovery of what appear to be two well-

defined pairs of geometrical isomers. Isomerism of this type is particularly interesting among hydantoin derivatives. Incidentally the observation has been made that ethyl N-1-methyl-anisal-hydantoin-3-acetate seems to split off an acetic acid residue during the course of some of its transformations. This fact deserves attention since a hydrocarbon residue in union with nitrogen is commonly assumed to be present in a compound in a very stable form of combination. If, however, the assumption is admissible that the ester, m. p. 107–108°, is tautomeric in the sense



$$\begin{array}{l} \quad CH_3N—CO \\ \quad O{=}C \quad | \\ ROOC.CH_2N—C{=}CHC_6H_4OCH_3 \end{array} \rightleftarrows \begin{array}{l} \qquad\qquad\quad CH_3N—CO \\ ROOC.CH_2O.C \quad | \\ \qquad\qquad\quad N—C{=}CHC_6H_4OCH_3 \end{array}$$

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and that alkali favors the enolic modification, the splitting off of the acetate group could readily be understood because of the fact that compounds of this type have been studied and have been found to be unstable.

The intense hydrolysis of the polypeptide-hydantoin has resulted in its decomposition with the formation of the mixed aliphatic-aromatic imidodibasic acid

$$\begin{array}{ll} CH_2NH.CH & CH_2C_6H_4OH \\ | & | \\ COOH & COOH \end{array}$$

The barium salts and ethyl ester are described in this paper, but a detailed description of the free acid and its other derivatives is being reserved for a later publication.

SOUTH HADLEY, MASSACHUSETTS

[CONTRIBUTION FROM MELLON INSTITUTE OF INDUSTRIAL RESEARCH AND THE COLLEGE OF PHARMACY, UNIVERSITY OF PITTSBURGH]

SYNTHESES WITH β,β'-DICHLORO-DIETHYL ETHER

BY LEONARD H. CRETCHER[1] AND W. H. PITTENGER[2]

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Introduction

β,β'-Dichloro-diethyl ether is a by-product formed during the manufacture of ethylene chlorohydrin and, as such, is available in comparatively large amounts. So far, no use has been made of this substance and its reactions have been little studied. It was first described by Kamm and Waldo,[3] who established its constitution on the basis of the fact that, on boiling with aniline and 10% aqueous sodium hydroxide, it formed 4-phenyl-morpholine.

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[1] Senior Fellow of Pure Research, Mellon Institute of Industrial Research.

[2] Veterans' Bureau Student, College of Pharmacy, University of Pittsburgh.

[3] Kamm and Waldo, THIS JOURNAL, **43**, 2223 (1921).