

rical isomers although another type of space isomerism develops simultaneously with the reduction of the double bond.

SOUTH HADLEY, MASSACHUSETTS

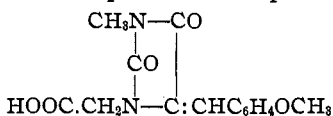
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF MOUNT HOLYOKE COLLEGE]
**ISOMERIZATION IN THE HYDANTOIN SERIES INDUCED BY
 THE ACTION OF HYDROGEN CHLORIDE**

BY DOROTHY A. HAHN AND ELIZABETH GILMAN

RECEIVED JUNE 15, 1925

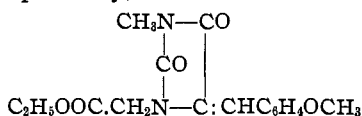
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In a recent paper¹ two cases of geometrical isomerism occurring among hydantoin derivatives were described. The substances consisted of two pairs of compounds corresponding, respectively, to Formulas I and II,



I

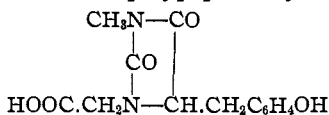
Two isomers; m. p., 167-167.5°
and 203-205°



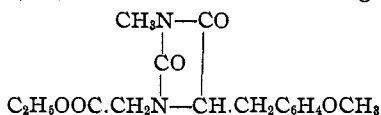
II

Two isomers; m. p., 107-108°
and 127-128°

and the conclusion that they represented pairs of geometrical isomers was based upon the fact that all four on treatment with hydrogen iodide gave the same polypeptide-hydantoin (III). Even more convincing evi-



III



IV

dence than the relationship between the two esters, m. p. 107-108° and 127-128°, is one of geometrical isomerism was furnished by the fact that both reduce to a single product (IV) when shaken in alcohol solution in the cold with hydrogen in the presence of colloidal palladium.²

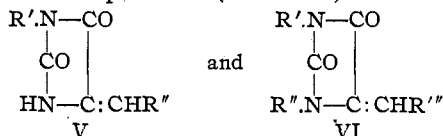
The further observation has now been made that isomerization of the lower into the higher-melting ester may be induced by suspending the former in alcohol and saturating the mixture with hydrogen chloride. The reaction is practically quantitative. It is usually attended by a change from a colorless to a colored solution (varying from pale yellow to deep red) and is complete in from eight to forty-eight hours. The product is pure and halogen free after two recrystallizations from alcohol.

Isomerization under these conditions took place so readily and was so complete that the possibility at once suggested itself that other similar hydantoin derivatives containing ethylene carbon atoms might be made to isomerize

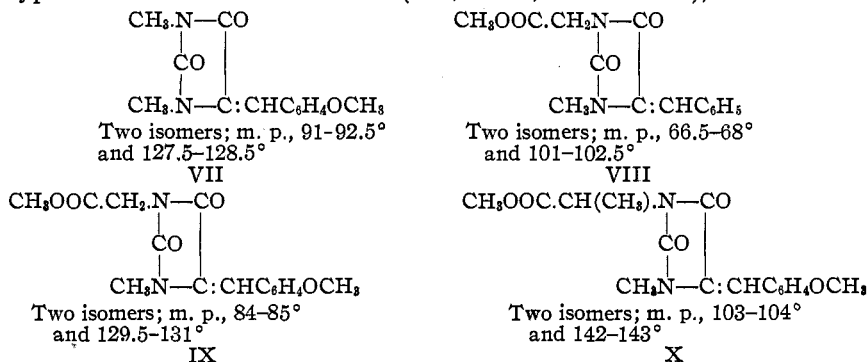
¹ Hahn and Renfrew, *THIS JOURNAL*, **47**, 147 (1925).

² Ref. 1, p. 157.

in the same way. It was thought that since many of the derivatives of anisalhydantoin and benzalhydantoin have been prepared in alkaline media, the primary product of the reaction might very well be a modification which was stable in neutral or alkaline solutions, but which in acid media would rearrange. Attempts to establish this hypothesis were limited to experiments with anisal- and benzalhydantoin and their N-1- and N-1-N-3-substitution products (V and VI). A comparative study of



the behavior of a fairly large number of substances which were investigated in this way led to the somewhat remarkable observation that while neither anisal- nor benzalhydantoin nor their respective N-1-substitution products showed any tendency to isomerize under the above conditions, the corresponding *disubstitution* products (N-1-N-3) isomerized with ease. In the case of four additional substances of the latter type which have been studied (VII, VIII, IX and X), well-defined



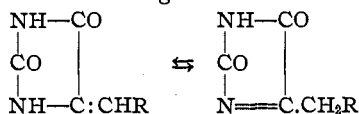
pairs of isomers have been separated. In each case the lower melting of the two esters was obtained by condensing the corresponding N-3-sodium compound with methyl iodide. The condensation products consisted principally of the low-melting esters and they alone were isolated under these conditions. It seems probable, however, that the higher-melting isomers were also present, since oils were obtained which, when dissolved in alcohol and repeatedly saturated with hydrogen chloride, gave good yields of the higher-melting isomers. The latter were always obtained in quantitative amounts by dissolving the lower-melting esters in alcohol and saturating the solutions with hydrogen chloride.

A study of these five pairs of isomers shows that the differences between the melting points of the low- and high-melting forms are numerically so close as to suggest something in the nature of a physical constant. That

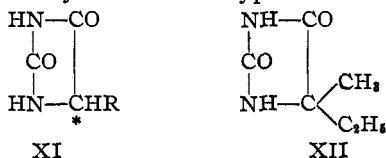
a perfectly definite parallelism exists seems apparent from the fact that the lower-melting form is invariably the one which is stable in neutral or alkaline solutions. It is also the more soluble and dissolves in all neutral solvents to give colorless solutions. The higher-melting modifications tend to impart a pale yellow color to their solutions and in two cases were separated in the form of yellow crystals. This parallelism is further borne out by a comparative study of the absorption spectra of the substances. This matter is at present under physicochemical investigation by Dr. Emma P. Carr of this Laboratory, but it may be said that the absorption curves of all five low-melting isomers are almost identical and that the differences between them and those for the corresponding high-melting forms are so nearly constant as to seem remarkable.

Attempts to accomplish the reverse reaction of transforming the high- into the low-melting isomer by heating it alone or in alcohol solution in the presence of alkali have been unsuccessful except in one case. Dimethyl-anisalhydantoin (VII), m. p. 127.5°–128.5°, yielded a small quantity of the isomer melting at 91–92.5° as the result of boiling an aqueous alcoholic solution (50%), containing 0.2 equivalent of sodium for a period of 22 hours. That negative results were obtained in all other cases may be due to the fact that favorable conditions for this transformation have not as yet been worked out and also to the fact that hydantoin is noticeably unstable in the presence of alkali, tending to decompose with the formation of mixtures.

The fact that neither anisalhydantoin nor benzalhydantoin, nor their respective N-1- substitution products show isomerism of this type is of some theoretical interest. The absence of isomeric forms in these cases may possibly be connected with the presence of labile hydrogen atoms which allow of tautomeric rearrangements in the sense

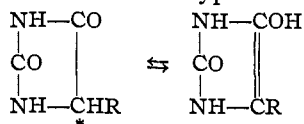


A tautomeric condition might in general be assumed to decrease the stability of the molecule and might be sufficient to prevent the existence of perfectly definite geometrical arrangements. It is to be noted that a somewhat similar hypothesis has been advanced by Dakin³ to account for the racemization of hydantoin of Type XI.



³ Dakin, *J. Chem. Soc.*, 107, 434 (1915).

In this case the instability of the optically active form was accounted for on the basis of a somewhat different type of tautomerism.



and the hypothesis was supported by the fact that the active form XII did not show a similar tendency to racemization. In general it would seem that the presence of a mobile hydrogen atom on the nitrogen or the methylene carbon atom in the hydantoin molecule tends to create a condition which is unfavorable to the existence of both optical and geometrical isomers.

In conclusion it may be added that while anisalhydantoin shows no tendency to isomerize it has been found to exist in two different crystalline modifications, a new pure white product of the same melting point as the common yellow form having been isolated. Similar yellow and white modifications of benzalhydantoin were also obtained. In neither case was the melting point lowered by mixing the two modifications.

Experimental Part

Ethyl N-1-Methyl-4-anisalhydantoin-N-3-acetate was prepared according to the method described by Hahn and Renfrew.¹

Fifty-four g. of ester, m. p. 107–108°, was suspended in 600 cc. of 95% alcohol and the mixture saturated with hydrogen chloride under cooling just sufficient to keep the alcohol from boiling. After two hours the substance had almost completely dissolved and the solution which was originally colorless had changed to a pale yellow. The mixture was then heated on the water-bath with a return condenser for two hours. On cooling, a crystalline precipitate separated which, when examined, was found to represent a mixture. The solution was, therefore, again saturated with hydrogen chloride and the process described above repeated. After being treated alternately in this way for a period of about a week, a homogeneous crystalline precipitate was obtained which melted at 126–127°. This melting point was raised to 127–128° on one recrystallization from alcohol. The original precipitate consisted of 47 g., but additional amounts sufficient to make the yield quantitative were obtained by concentrating the filtrate. The substance was identified as the same as the ester previously described⁴ but even when perfectly pure and absolutely colorless it imparts a yellow color to its alcoholic solutions.

N-1-Methyl-N-3-methyl-4-anisalhydantoin was prepared from anisalhydantoin according to the method described by Johnson and Nicolet.⁵ The separation of the reaction product was, however, varied somewhat.

Twenty g. of anisalhydantoin and 2.2 equivalents of potassium hydroxide were dissolved in 12 parts of 50% alcohol, methyl iodide (2.3 molecular equivalents) was added and the solution heated on a steam-bath for three hours. The product consisted of a clear, pale yellow solution which was neutral to litmus and which, when evaporated on a steam-bath to a volume of 250 cc. and cooled, precipitated an oil. The supernatant

⁴ Ref. 1, p. 154.

⁵ Johnson and Nicolet, *Am. Chem. J.*, **47**, 468 (1912).

liquid was decanted and the oil washed with small quantities of hot water during vigorous shaking. The heavy, yellow oil was then covered with the smallest possible amount of ether and stirred, when an immediate transformation into a heavy, white, granular precipitate took place. Upon filtering and washing the substance with cold alcohol 11 to 12 g., m. p. 83–88°, was obtained which after two recrystallizations from alcohol melted at 91–92.5°. The alcohol-ether filtrate gave additional small quantities on seeding but after these were separated an oil was precipitated which showed no tendency to crystallize. Alcoholic solutions of this oil when saturated with dry hydrogen chloride gave good yields of crystalline material; m. p., 120–124°.

1,3-Dimethyl-4-anisalhydantoin, m. p. 91–92.5°, was also prepared from *N*-1-methyl-4-anisalhydantoin by using 1.2 equivalents of potassium hydroxide and a corresponding amount of methyl iodide.

In this case, as in the preceding, the crude product of the reaction was an ester; m. p., 83–88°. The substance is very soluble in boiling alcohol (25 g. in 100 cc.) from which it separates in large, transparent, colorless prisms. It is soluble in ether but appears to isomerize in ether solutions, giving oily precipitates. Analyses of this substance showed that it was the same as that described by Johnson and Nicolet although their melting point is somewhat lower.

A second isomeric modification of 1,3-dimethyl-anisalhydantoin (VII), m. p. 127.5–128.5°, was obtained⁶ by dissolving the product melting at 91–92.5° in alcohol and saturating the solution with hydrogen chloride. The process is the same as that described for ethyl *N*-1-methyl-4-anisalhydantoin-*N*-3-acetate⁷ except that in this case it was easier to follow the transformation because of the fact that the low-melting isomer (91–92.5°) is very soluble in hot alcohol and separates in prisms on the bottom of the container while the high-melting form is very much less soluble and separates in long needles which fill the entire space occupied by the solution. The reaction requires about a week for the complete conversion of 20 g. of ester. The product consists of about 18 g., m. p. 127.5–128.5°, which is pure and halogen-free after one recrystallization from alcohol.

Anal. Calcd. for $C_{13}H_{14}O_3N_2$: N, 11.38. Found: 11.39, 11.25.

The higher-melting isomer is fairly soluble in boiling alcohol (14.7 g. in 100 cc.) from which it usually separates in long, transparent, colorless needles. When the substance is allowed to crystallize very slowly a second crystalline modification appears which consists of large, transparent, yellow prisms. Both modifications melt at the same temperature, which is not lowered by mixing. The yellow prisms are readily transformed into the colorless needles when recrystallized from alcohol saturated with hydrogen chloride. Both are halogen-free.

The low-melting (91–92.5°) and the high-melting (127.5–128.5°) isomers are both readily reduced when their alcoholic solutions are shaken with hydrogen in the presence of colloidal palladium. The product is the same in both cases and consists of 1,3-dimethyl-4-anisylhydantoin. Efforts to isomerize one modification into the other as the result of heating were not successful at the temperature at which the experiment was conducted. However, Table I shows the results obtained when 1 g. of each isomer was put into a small tube and heated in an oil-bath.

A series of experiments was undertaken with a view to transforming the higher- into the lower-melting isomer by prolonged heating in alkali.

⁶ Acknowledgment is made to Miss Marion Maclean and Miss Elizabeth Sherman for their assistance in preparing this substance.

⁷ See p. 2956 of this article.

TABLE I
RESULTS OF HEATING AT 135° TO 150°

Time, hrs.	2	2.75	16	21.75
Isomer, m. p. 91-92.5°	M. p., 86-92°	Softening, 75°; m. p., 77-90°	Very gummy	A gum
m. p. 127.5-128.5°	Grad. softening before orig. m. p. reached	M. p. sl. lower	M. p. 110-115°	A gum

line solutions. Ten-g. portions of the ester melting at 127-128° were dissolved in 150cc. portions of aqueous alcohol (50%) containing various amounts of sodium (dissolved as metal), and heated on a steam-bath with return condensers. The product consisted in all cases of unchanged ester and an oil. In a single case where 0.2 equivalent of sodium was used and the mixture boiled for 22 hours, a small quantity of the lower-melting ester (0.4 g.) was separated and identified by means of a mixed-melting-point determination.

1,3-Dimethyl-4-anisylhydantoin was prepared by catalytic reduction with hydrogen (a) of dimethyl-anisalhydantoin, m. p. 91-92.5°, and (b) of the corresponding isomer, m. p. 127.5-128.5°.

The procedure was the same in both cases, namely, 0.42 g. of colloidal palladium was mixed with water and introduced into the reaction chamber, a small quantity of 95% alcohol added and the mixture shaken with hydrogen for a few minutes. A solution of 10 g. of ester in 200 cc. of boiling alcohol was then added, when absorption of hydrogen began immediately. The reaction was allowed to proceed in the cold during constant shaking for about 10 hours or until hydrogen was no longer absorbed.

After the palladium had been precipitated the solution was filtered and concentrated to 75 cc. when a white crystalline product, melting at 75-77°, separated. The yield was practically quantitative and after two recrystallizations from alcohol an ester which melted sharply at 78.5° was obtained. The identity of the products obtained in the two experiments was established by mixed-melting-point determinations.

Anal. Calcd. for $C_{13}H_{16}O_3N_2$: N, 11.29. Found: 11.21, 11.07.

Dimethyl-anisylhydantoin is very soluble in boiling alcohol (5 g. in 10 cc.) from which it separates in large, transparent, colorless prisms. It is almost insoluble in cold but is slightly soluble in boiling water. It may be recrystallized conveniently from alcohol-water mixtures. The constitution of the substance was established by transforming it into 1,3-dimethyl-4-*p*-hydroxy-benzylhydantoin (7.5 g. of ester, m. p. 78.5°, yielding 5 g. of the hydantoin, m. p. 149-150°) which was identified by comparison with a specimen of the same substance prepared according to the method described by Johnson and Nicolet.⁸

Methylation in the N-3 position of derivatives of anisalhydantoin which contain acid groups in the N-1 position presents certain difficulties which were not encountered in the case of alkyl derivatives such as N-1-methyl-anisalhydantoin. It was found, for example, that esters such as ethyl 4-anisalhydantoin-N-1-acetate, ethyl 4-anisalhydantoin-N-1-propionate and ethyl 4-benzalhydantoin-N-1-acetate, all show in varying degrees a tendency to undergo partial hydrolysis to the corresponding sodium salts when warmed with alcohol to which (with a view to sub-

⁸ Ref. 5, p. 470.

sequent condensation with methyl iodide) one equivalent of metallic sodium has been added. This is true even when absolute alcohol is used in the operation. The product of the condensation, therefore, consists of a mixture of sodium salts corresponding to the original ester and its N-3-methyl derivative. Both substances are soluble in cold water and can be separated readily from their esters which are also present in the reaction product; but the mixture of esters even after purification in this way usually consists of an oil which is resolved into its solid constituents only partially and with the greatest difficulty. It seemed possible that the difficulty which was experienced in this separation might be due in part to the presence of a mixture of methyl and ethyl esters since partial alkylation on the carboxyl group might have taken place under the conditions outlined above and it was therefore decided to start with the methyl instead of ethyl ester in all reactions which involved condensation of esters with methyl iodide. In the case of methyl 4-anisalhydantoin-N-1-acetate and the corresponding propionate this change in the procedure was justified since much better results were obtained. The tendency to salt formation was also largely overcome in the case of the two substances mentioned above by means of slight modifications in the conditions of the experiments. These will be described later in this paper.

The N-3-methyl derivative of methyl 4-benzalhydantoin-N-1-acetate (VIII) could not be obtained in satisfactory yields by direct methylation of the ester and a wholly different method of procedure had to be worked out. This will be described fully in a later paper.⁹ The simple statement may be made, however, that two isomeric esters, m. p. 66.5–68° and 101–102.5°, have been obtained¹⁰ and that the lower-melting form isomerizes readily into the higher- in alcoholic solution under the action of hydrogen chloride.

N-3-Methyl 4-Anisalhydantoin-N-1-acetate was prepared by dissolving 29 g. of ethyl anisalhydantoin-N-1-acetate¹¹ in a solution of 10.7 g. of potassium hydroxide in 200 cc. of 50% aqueous alcohol and boiling the mixture for one hour. The clear solution when acidified precipitated the corresponding acid¹² which was converted into the ester by suspending it in methyl alcohol and saturating with hydrogen chloride. The crude product melted at 180–182° and the yield was practically quantitative. After recrystallization from chloroform-methyl alcohol mixtures a pure substance which melted at 183–184° was obtained.

Anal. Calcd. for $C_{14}H_{14}O_5N_2$: N, 9.65. Found: 9.66, 9.67.

This ester resembles the ethyl ester in its solubility in different solvents¹³ but differs in that it exists in two different crystalline modifications. Thus, it separates from hot alcoholic solutions in a meshwork of long, fine, white needles which completely fill the space occupied by the solution, but on standing in contact with the solution these are gradually transformed into compact, transparent, colorless prisms which collect on the

⁹ Hahn and Evans, unpublished results.

¹⁰ Compare p. 2954 of this article.

¹¹ Johnson and Hahn, *THIS JOURNAL*, 39, 1260 (1917).

¹² Ref. 11, p. 1262.

¹³ Ref. 11, p. 1261.

bottom of the containing vessel, leaving the supernatant solution perfectly clear. Both modifications have the same melting point, which is not lowered by mixing.

Methyl N-3-Methyl-4-anisalhydantoin-N-1-acetate (IX).—Two isomeric esters, m. p. 84–85° and 129.5–131°, were obtained which correspond to Formula IX. The lower-melting substance was formed exclusively when 5 g. of methyl 4-anisalhydantoin-N-1-acetate was dissolved in a solution of 1.25 g. of potassium hydroxide (1.3 equivalents) in 100 cc. of 95% alcohol to which 4 g. of methyl iodide was then added. After heating for 45 minutes on a steam-bath the solution was neutral and was evaporated to 50 cc. As the liquid cooled a small quantity of the original ester, m. p. 180–182°, separated and was filtered off. The addition of water to the filtrate precipitated further small quantities of this substance mixed with the condensation product; m. p. 84–105°. This after recrystallization from methyl alcohol gave 1.5 g. of ester, m. p. 84–85°. The aqueous alcohol filtrate (which yielded no further precipitate on the addition of water) was evaporated to dryness. The residue was completely soluble in a very small quantity of cold water and consisted largely of potassium N-3-methyl-4-anisalhydantoin-N-1-acetate. The latter represented about one-half of the reaction product. It was purified and used for the preparation of the higher-melting ester.

Anal. Calcd. for $C_{15}H_{18}O_5N_2$: N, 9.21. Found: 9.17, 9.21.

The ester melting at 84–85° is very soluble in boiling alcohol (2 g. in 20 cc.) and separates from its solutions on cooling in clusters of transparent colorless needles or plates.

The higher-melting modification of methyl N-3-methyl-4-anisalhydantoin-N-1-acetate, m. p. 129.5–131°, was obtained by dissolving the lower-melting modification in methyl alcohol and saturating the solution with hydrogen chloride. It was also conveniently prepared from potassium N-3-methyl-4-anisalhydantoin-N-1-acetate by the same general method. The crude product consisted of a yellow crystalline precipitate, m. p. 120–123°, which on recrystallization from methyl alcohol melted at 129.5–131°.

Anal. Calcd. for $C_{15}H_{18}O_5N_2$: N, 9.21. Found: 9.12, 9.16.

The ester melting at 129.5–131° is less soluble in boiling alcohol (2 g. in 40 cc.) than the lower-melting isomer. It separates from its solutions on cooling in the form of small, transparent, greenish-yellow prisms, and imparts a yellow color to all of its solutions.

Methyl 4-Anisalhydantoin-N-1-propionate.—This substance was prepared from the corresponding ethyl ester.¹⁴ The procedure was the same as that which has just been described in the case of the corresponding acetate and, as in that case, the transformations were accomplished without noticeable loss of material. When the new ester was purified by recrystallization from chloroform-alcohol mixtures it melted at 163–164°.

Anal. Calcd. for $C_{15}H_{18}O_5N_2$: N, 9.21. Found: 9.16, 9.24.

The methyl ester closely resembles the corresponding ethyl ester in its relative solubilities, 20 g. requiring approximately 60 cc. of boiling chloroform, 250 cc. of boiling acetone and 660 cc. of boiling methyl alcohol. It separates from its solutions in clusters of fine, feathery, white needles.

Methyl N-3-Methyl-4-anisalhydantoin-N-1-propionate (X) has been obtained in two isomeric modifications, m. p. 103–104° and 142–143°. The lower-melting modification was formed exclusively when 10 g. of methyl 4-anisalhydantoin-N-1-propionate, m. p. 163–164°, was dissolved in a solution of 2.5 g. of potassium hydroxide (1.3 equivalents) in 100 cc. of methyl alcohol to which 7 g. of methyl iodide was then added. The solution was neutral after warming on a steam-bath for one and three-quarters hours. After it had been concentrated to 100 cc. small quantities of water were added succes-

¹⁴ Hahn and Gilman, *THIS JOURNAL*, 47, 2947 (1925).

sively until no more precipitate appeared. The crystalline product, when filtered off, washed with aqueous alcohol and dried, weighed between 9 and 10 g.; m. p., 92–130°. This precipitate was washed with hot water, in order to remove any traces of salt, and recrystallized from boiling alcohol. After four recrystallizations 5 g. of ester, m. p. 103–104°, was obtained.

Anal. Calcd. for $C_{16}H_{18}O_6N_2$: N, 8.80. Found: 8.85, 8.76.

This ester is very soluble in boiling methyl alcohol (10 g. in 50 cc.) from which it separates in the form of a meshwork of fine, white needles which tend to turn yellow on the surface when exposed to air containing traces of hydrogen chloride.

The higher-melting modification of methyl N-3-methyl-4-anisalhydantoin-N-1-propionate, m. p. 142–143°, was obtained by dissolving the lower-melting isomer in methyl alcohol and saturating the solution with hydrogen chloride. The transformation was complete in the course of a few hours and was noticeably much more rapid than the corresponding change in the case of 1,3-dimethyl-anisalhydantoin. The crude product which separates from the acid solution melts at 141–143°. After one recrystallization from methyl alcohol the substance melts at 142–143° and is halogen-free.

Anal. Calcd. for $C_{16}H_{18}O_6N_2$: N, 8.80. Found: 8.84, 8.90.

This ester is less soluble than the lower-melting modification in boiling methyl alcohol (4 g. in 50 cc.) from which it separates in large, well-defined, slightly yellow needles or prisms. It imparts a yellow color to all of its solutions.

Summary

Hydantoin compounds which contain unsaturated ethylene linkages of the type $\begin{array}{c} | \\ -C=CHR \end{array}$ seem to show geometrical isomerism only when the hydrogen atoms in both the N-1- and N-3- positions have been substituted.

In the case of the five esters studied the lower-melting forms are all very similar in physical properties and the differences between them and their higher-melting isomers are almost constant. The former may all be transformed into the latter by saturating their alcoholic solutions with hydrogen chloride.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF MOUNT HOLYOKE COLLEGE]

THE ABSORPTION SPECTRA OF SOME DERIVATIVES OF ANISALHYDANTOIN

BY EMMA P. CARR AND MARIE A. DOBBROW

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A study of the ultraviolet absorption spectra of some derivatives of anisalhydantoin has been of particular interest in its relation to the structure of these compounds and has necessitated a revision of the conclusions based on earlier evidence.¹

The substances under investigation were the propionate derivatives of anisalhydantoin, which had been prepared and studied by Dr. Hahn and her collaborators in this Laboratory. The results led to the conclusion

¹ Hahn, Kelley and Schaeffer, *THIS JOURNAL*, **45**, 843 (1923).