STUDIES IN THE HYDANTOIN SERIES. II.

5-(3-PYRIDYL)HYDANTOIN AND ITS DERIVATIVES

APPROVED:

J. J. Hurlock
Major Professor

Price Truitt
Minor Professor

James L. Carrico
Director of the Department of Chemistry

Robert B. Toulouse
Dean of the Graduate School

STUDIES IN THE HYDANTOIN SERIES. II. 5-(3-PYRIDYL)HYDANTOIN AND ITS DERIVATIVES

THESIS

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By

Marion Calvin Banta, B. S.

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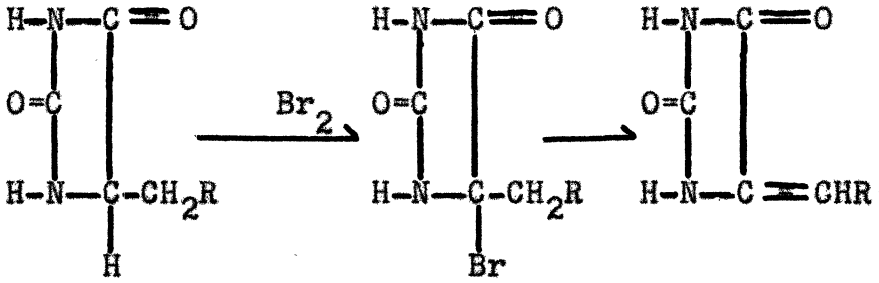
CHAPTER I

INTRODUCTION

Since 1861, when hydantoin was discovered by Baeyer,[1] a large amount of information has been accumulated on the compound and some of its derivatives.

One expects and finds that the chemical behavior of the hydantoin ring is affected by the nature of the substituent on it and its position on the ring. In the case of 5-substituted hydantoins, which are of interest because of their anticonvulsant properties, some differences in chemical behavior have been observed for substituents of aromatic as contrasted with aliphatic character.

Thus, when 5-alkylhydantoins are treated with an equivalent amount of bromine, a C-5 unsaturated derivative is formed.[2]



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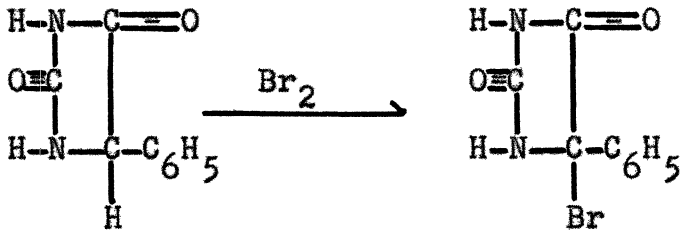
[1] Adolf Baeyer, "Vorlaufige Notiz uber das Hydantoin," Annalen der Chemie, CXVII (1861), 178-80.

[2] S. Gabriel, "Ueber die Einwirkung des Broms auf α-Lactylharnstoff und verwandte Verbindungen I," Annalen der Chemie, CCCXLVIII (1906), 50-90.

On the other hand, when 5-phenylhydantoin is treated with an equivalent amount of bromine in acetic acid, 5-bromo-5-phenylhydantoin, a fairly stable compound, is formed.[3]



The bromine is relatively reactive, being removed with hot water to produce 5-hydroxy-5-phenylhydantoin and reacting with aniline to give a 5-anilino derivative.[4] 5-bromo-5-phenylhydantoin reacts with alcohols or phenols to form 5-alkoxy[5] or 5-aryloxy-5-phenylhydantoins,[6] with primary or secondary amines to form 5-substituted-amino-5-phenylhydantoins,[7, 8]

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[3]S. Gabriel, "Ueber die Einwirkung des Broms auf ∝-Lactylharnstoff und verwandte Verbindungen II," Annalen der Chemie, CCCL (1906), 118-34.

[4]Ibid.

[5]J. R. Hoffman, "Hydantoins as Anticonvulsants, VI. 5-Substituted-Alkoxy Derivatives of 5-Phenylhydantoin," unpublished master's thesis, Department of Chemistry, North Texas State College, Denton, Texas, 1954.

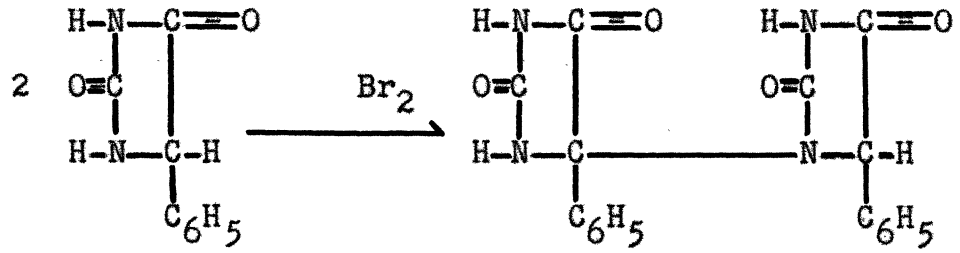
[6]M. O. Griffin, "Hydantoins as Anticonvulsants, VII. 5-Substituted-Aryloxy Derivatives of 5-Phenylhydantoin," unpublished master's thesis, Department of Chemistry, North Texas State College, Denton, Texas, 1953.

[7]W. G. Frazior, "Hydantoins as Anticonvulsants, II. 5-Substituted-Amino Derivatives of 5-Phenylhydantoin," unpublished master's thesis, Department of Chemistry, North Texas State College, Denton, Texas, 1950.

[8]D. P. Jeanes, "Hydantoins as Anticonvulsants, V. 5-Substituted-Amino Derivatives of 5-Phenylhydantoin," unpublished master's thesis, Department of Chemistry, North Texas State College, Denton, Texas, 1950.

and with mercaptans to form 5-alkylmercapto and 5-arylmercapto-5-phenylhydantoins.[9]

Gabriel was able to oxidize 5-phenylhydantoin using one-half mole of bromine to what he called diphenylhydantil.[10]



On the other hand hydantoin is oxidized to parabanic acid.[11] Holmberg[12] studied the oxidation of 5-phenylhydantoin using various oxidizing agents other than bromine. He found that potassium dichromate would oxidize 5-phenylhydantoin to 5-hydroxy-5-phenylhydantoin and diphenylhydantil, and that hydrogen peroxide would oxidize 5-phenylhydantoin to benzoylurea and benzoic acid. Baudisch and Davidson studied the catalytic oxidation of certain 5-alkyl and 5-aryl hydantoins[13]

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[9] H. A. Wiist, "Hydantions as Anticonvulsants, VI. 5-Substituted-Mercapto Derivatives of 5-Phenylhydantoins," unpublished master's thesis, Department of Chemistry, North Texas State College, Denton, Texas, 1951.

[10] S. Gabriel, "Ueber die Einwirkung des Broms auf α-Lactylharnstoff und verwandte Verbindungen II," Annalen der Chemie, CCCL (1906), 118-34.

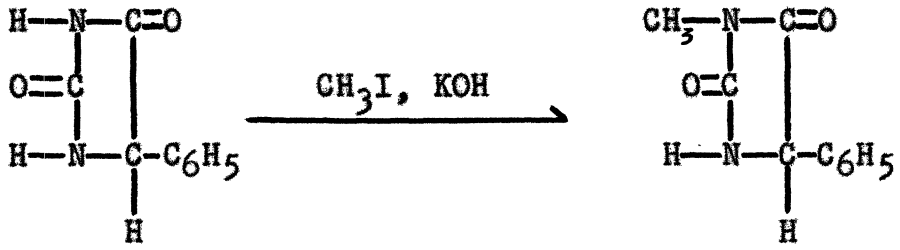
[11] L. Siemonson, "Ueber die Constitution des β-Methylallantoins," Annalen der Chemie, CCCXXXIII (1904), 101-41.

[12] G. Holmberg, "Oxidation of Phenyl-substituted-hydantoins," Acta Chem. Scand., IV (1950), 821-7 (cited in Chemical Abstracts, Vol. XLV 1951, ed. by E. J. Crane).

[13] O. Baudisch and D. Davidson, "The Catalytic Oxidation of Hydantoins," Journal of Biological Chemistry, LXXV (1927), 247-9.

and found that the rate of oxidation is a function of the nature of the substituted group. Arranged in descending order of their enhancing action on the oxidation rate, the groups are phenyl, hydrogen, methyl, and benzyl. They found that no substitution completely inhibited oxidation. Blitz found that diphenylhydantoin could be recrystalized from boiling nitric acid without being oxidized.[14]

Pinner found that hydantoins could be alkylated in the N-3 position by the action of methyl iodide on the salt of the 5-substituted-hydantoin in methanol.[15]



Dimethyl sulfate has also been used as an alkylating agent.[16] In general, it is difficult to introduce alkyl substituents in the N-1 position. Johnson and Bates concluded that in

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[14] H. Biltz, "Uber die Konstitution der Einwirkungsprodukte von substituierten Harnstoffen auf Benzil und uber einige neue Methoden zur Darstellung der 5,5-Diphenyl-hydantoine," Berichte der deutschen chemischen Gesellschaft, XLI (1908), 1379-93.

[15] A. Pinner, "Ueber Hydantoine," Berichte der deutschen chemischen Gesellschaft, XXI (1888), 2320-9.

[16] H. Biltz, op. cit.

[17] T. Johnson and T. Bates, "Researches on Hydantoins, XXX. Stereoisomeric Modifications of Benzalhydantoin," Journal of the American Chemical Society, XXXVII (1916), 383-5.

the case of hydantoin and its saturated methylene derivatives, the N-3 position is the point of attack. If an alkylidene group is attached at C-5, the N-1 position is activated,[18] and aromatic substitution produces the same effect.[19] Spurlock found that 3-alkyl-5-(2-thienyl) - hydantoins were soluble in 5 per cent sodium hydroxide and some were slightly soluble in 5 per cent sodium carbonate.[20] Thus, an increased acidity of the N-1 position is produced by the 2-thienyl group which may be related to the relative ease of N-1 methylation.

It is the purpose of this investigation to study the chemistry of 5-(3-pyridyl)hydantoin and to compare its properties with those of 5-phenylhydantoin. Teague and his coworkers[21, 22] prepared several 5-alkyl-5-pyridylhydantoins.

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[18] L. Pickett and M. McLean, "Dissociation of Hydantoins," Journal of the American Chemical Society, LXI (1939), 423-5.

[19] J. Klosa, "5-Phenylhydantoin," Archiv der Pharmazie und Berichte der deutschen pharmazeutischen Gesellschaft, CCLXXXV (1952), 274-80 (cited in Chemical Abstracts, XLVIII 1954 , ed. by E. W. Crane).

[20] J. J. Spurlock, "Hydantoins as Anticonvulsants. I. 5-R-5-(2-Thienyl)hydantoins," Journal of the American Chemical Society, LXXV (1953), 1115-7.

[21] P. Teague, A. Ballentine, and G. Rushton, "Some Pyridylhydantoins," Journal of the American Chemical Society, LXXV (1953), 3429-30.

[22] P. Teague, "Phenyl-pryidylhydantoin," Journal of the American Chemical Society, LXIL (1947), 714.

Henze and Knowles[23] also prepared several 5-alkyl-5-pyridylhydantoins. No work is reported in these studies on the chemical properties of 5-pyridylhydantoins.

It was pointed out by Mosher[24] that the 3-pyridyl group behaves as a typical "aromatic" group as phenyl. The 2-pyridyl and 4-pyridyl groups are "anomalous." Because the 3-pyridyl group is aromatic in character, it might be supposed that the chemical behavior of 5-(3-pyridyl)hydantoin would be similar to that of 5-phenylhydantoin. It must be noted, however, that the basic nature of the nitrogen atom in the pyridine ring could affect appreciably the behavior of 5-(3-pyridyl)hydantoin.

There is some interest in the possibility that 5-substituted-5-pyridylhydantoins may possess antoconvulsant activity. 5,5-diphenylhydantoin and 3-methyl-5-ethyl-5-phenylhydantoin have found clinical use as anticonvulsants. Other substituted phenylhydantoins show anticonvulsant activity. For example, 5-alkoxy[25] and 5-alkylmercaptophenylhydantoins[26] have shown high anticonvulsant activity. Thus

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[23]H. Henze and M. Knowles, "Synthesis of 5-(Pyridyl-Substituted)-Hydantoins," Journal of Organic Chemistry, XIX (1953), 1127-35.

[24]H. S. Mosher, The Chemistry of Pyridines, Vol. I (4 vols.), Heterocyclic Compounds, edited by R. C. Elderfield (New York, 1950), p. 401.

[25]Hoffman, op. cit., p. 9.

[26]Wiist, op. cit., p. 9.

far only 5-phenyl-5-(pyridyl)hydantoin has shown appreciable anticonvulsant activity.[27, 28]

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[27] Henze and Knowles, op. cit., p. 1127.

[28] H. Henze, U. S. Patent 2,526,231 (1950), cited in Chemical Abstracts, XLV (1951), 2975.

CHAPTER II

EXPERIMENTAL

Method of Analysis

Infrared

Infrared spectra were run on a Perkin-Elmer Model 21B Infrared Spectrophotomater using a fairly wide slit program (980) and speeds of 20-30 seconds per micron since the amount of detail available in the solid phase was somewhat limited. The potassium bromide pellets which contained the compound to be analyzed were prepared by two methods:

Method A.--The sample (0.5-1.0 milligram) was ground with potassium bromide (300-325 milligrams) in an agate mortar in a slurry of spectroscopic grade acetone which was dried under an infrared heat lamp, reground without the use of acetone, and placed in a pellet press. The pressure employed was 20,000 pounds total load for 4-5 minutes.

Method B.--The same range of weights was used as is shown in the above paragraph. The sample and potassium bromide mixture was agitated in a Perkin-Elmer vibrator with six small stainless steel balls. The mixture was then pressed as before.

Nitrogen

Nitrogen determinations were done by the micro-Dumas method. The sample weights ranged from three to seven milligrams. The samples were introduced into the combustion tube in porcelain boats except for di-(3-pyridyl)hydantil in which case the sample was dry-washed into the combustion tube from a three inch test tube with finely ground copper oxide.

Sodium

A weighed sample was placed in a microcrucible which had been heated until a constant weight was obtained. Two drops of 50 per cent sulfuric acid was then added and the crucible heated over a small flame until the sulfuric acid had boiled away. The crucible was allowed to cool and two more drops of 50 per cent sulfuric acid was added. The crucible was again heated until it became dry. This procedure was repeated until no carbon deposits remained which usually took about three treatments. Then the crucible was heated over a Meker burner for about ten minutes, allowed to cool, and then weighed. The per cent sodium was calculated on the basis that the ignited residue was sodium sulfate. The sample weights ranged from 18.6 to 96.8 milligrams.

Melting Points

Melting points were determined in an electrically heated melting point block. Decomposition points of the compounds

which decomposed on melting were determined by heating the block very slowly until the compound decomposed. Another sample was then introduced and the temperature at which it decomposed recorded. Other fresh samples were introduced and the temperature at which they decomposed recorded until the sample decomposed within thirty seconds after being placed in the block. The temperature at which this occurred was corrected and recorded as the decomposition point of the compound. The thirty second time interval was determined with authentic samples of known melting points.

Halogen

Halogen analyses were done gravimetrically. The sample was weighed, dissolved in distilled water, acidified with nitric acid, and then an excess of 5 per cent silver nitrate was added. The precipitated silver halide was collected in a tared, sintered-glass crucible, dried for about one hour in an oven at 90°, and weighed. The per cent halogen was determined from the weight of the silver halide and the weight of the sample.

Preparations

Sodium Bisulfite Addition Product of Pyridine-3-carboxaldehyde

Ten grams (0.093 mole) of pyridine-3-carboxaldehyde was added to a solution containing 31.2 grams (0.3 mole) of sodium

bisulfite in 100 milliliters of water. Sulfur dioxide was then passed through the solution until precipitation ceased. A yield of 78 per cent was obtained which amounted to 15.4 grams (0.073 mole). This compound sublimed at 160°. It was found that cooling produced further precipitation, but the weight of the product thus produced was not recorded.

5-(3-Pyridyl)hydantoin [1]

Sixty grams (0.525 mole) of ammonium carbonate was placed in a 500 milliliter, two-necked, round-bottomed flask fitted with a large diameter air condenser. The flask was set in a water bath which was electrically heated and whose tenperature was controlled by a thermoregulator. To the flask was added 100 milliliters of 50 per cent methanol which contained 20 grams (0.31 mole) of potassium cyanide. The mixture thus produced was heated to 55-60°, then 30 grams (0.142 mole) of the sodium bisulfite addition product of pyridine-3-carboxaldehyde was added and the reaction mixture heated for about four hours at 55-60°. The contents of the flask was then placed in a steam-heated, vacuum evaporator which was evacuated with a water aspirator. After reducing the volume to about one fourth of the original, the solution was neutralized with acetic acid and cooled overnight. The crude dark yellow hydantoin which precipitated was dissolved in hot water,

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[1] Henze and Knowles, op. cit.

decolorized with norite, and cooled. After two or three recrystallizations and decolorizations, twelve grams of the white 5-(3-pyridyl)hydantoin was collected. This represents a yield of 48 per cent of the theoretical. The compound melted with decomposition at 226°.[2]

5-(3-Pyridyl)hydantoin reduced Tollen's reagent and also reduced a hot aqueous solution of cupric sulfate with formation of cuprous oxide and a small amount of metallic copper. 5-Phenylhydantoin, on the other hand, was found to give a negative test or perhaps only a trace of reduction with Tollen's reagent. Per cent nitrogen for $C_8H_7O_2N_3$: calculated, 23.72; found, 23.71.

The infrared spectrogram of 5-(3-pyridyl)hydantoin is shown in Figure 1 of the Appendix.

5-Bromo-5-(3-pyridyl)hydantoin

To a three-necked, 100 milliliter, round-bottomed reaction flask fitted with a mercury-sealed stirrer, a thermometer, and a condenser to which was attached a calcium chloride drying tube, was added 2.0 grams (0.00114 mole) of 5-(3-pyridyl)hydantoin and 50 milliliters of glacial acetic acid. The mixture was heated to 80° and then 2.0 grams (0.0013 mole) of bromine in 10 milliliters of glacial acetic acid was added as rapidly as possible. The solution

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[2] Ibid.

was refluxed for about one hour and was then sealed with ground glass stoppers and the contents frozen. The mixture was then allowed to melt and the 5-bromo-5-(3-pyridyl)hydantoin collected in a fritted glass funnel which was fitted with a calcium chloride drying tube. The yellow crude product was placed in a vacuum desiccator which contained potassium hydroxide as a desiccant and allow to remain in the desiccator several days in order to remove the acetic acid and unreacted bromine. The product became a light yellow in color and decomposed at 238°. It weighed 2.63 grams which represents a yield of 90 per cent of that theoretically obtainable. It was found to dissolve readily in water and it reacted with acidified potassium iodide to give a brown color. Per cent bromine in $C_8H_6O_2N_3Br$: calculated, 31.21: found 31.11. The infrared absopption spectrum for the product is given in the Appendix in Figure 2.

5-Hydroxy-5-(3-pyridyl)hydantoin

In a 125 milliliter Phillips beaker was placed 1.6 grams (0.0063 mole) of 5-bromo-5-(3-pyridyl)hydantoin and about 50 milliliters of water. The solution which resulted was heated on a steam bath for about one hour. Then sodium bicarbonate was added till the solution was neutral. The white precipitate which formed was separated by filtration and recrystallized from hot ethanol. One and twelve

hundredth grams of 5-hydroxy-5-(3-pyridyl)hydantoin which melted with decomposition at 217° was collected. This represents a yield of 92 per cent. Per cent nitrogen in $C_8H_7O_3N_3$: calculated, 21.75; found, 21.81. The infrared spectrogram for the product is shown in the Appendix in Figure 3.

5-n-Butoxy-5-(3-pyridyl)hydantoin

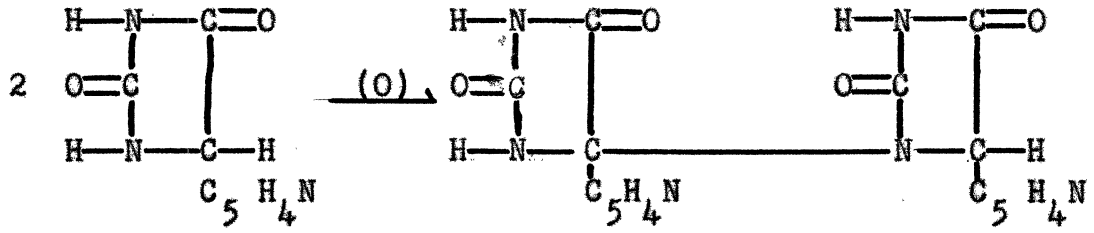
Into a dry 10 milliliter flask fitted with an air condenser and a calcium chloride drying tube was added 1.1 grams (0.0043 mole) of 5-bromo-5-(3-pyridyl)hydantoin, 0.5 gram (0.00636 mole) of pyridine (dried over KOH), and 2.5 grams (0.034 mole) of n-butanol. The n-butanol had been refluxed over calcium oxide for one hour and then distilled. The mixture was then heated on a steam bath for nine hours after which time 5.0 milliliters of dry dioxane was added. The dioxane had been dried by refluxing over sodium for one hour and then distilling. The mixture was heated in the same fashion for five more hours and then filtered. The precipitate melted with decomposition at 235° and contained reactive bromine. The precipitate was dissolved in water and neutralized with sodium bicarbonate. The white solid which formed melted with decomposition at 217° and was considered to be 5-hydroxy-5-(3-pyridyl)hydantoin. It weighed 0.18 gram (0.00093 mole).

From its melting point and reaction with water the above bromine compound was assumed to be unreacted 5-bromo-5-(3-pyridyl)hydantoin.

The filtrate from the reaction mixture was then evaporated to dryness with a stream of air. Water was added to the solid and the mixture filtered. That which did not dissolve in water was crystallized from hot ethanol. It melted with decomposition at 177°. Per cent nitrogen for 5-n-butoxy-5-(3-pyridyl)hydantoin, $C_{12}H_{15}O_3N_3$: calculated, 16.86; found, 17.11. The weight of this fraction was 0.12 gram (0.00048 mole). The infrared spectogram is shown in Figure 4 in the Appendix.

The combined filtrate and washings from the separation of the above fraction was then neutralized with sodium bicarbonate and a second fraction precipitated which melted with decomposition at 175° and which weighed 0.15 gram (0.0006 mole). The total yield of 5-n-butoxy-5-(3-pyridyl)-hydantoin was found to be 0.27 gram which was 25 per cent of the amount theoretically obtainable.

Di-(3-pyridyl)hydantil



Three hundredth gram (0.0017 mole of 5-(3-pyridyl)-hydantoin was dissolved in an excess of 5 per cent sodium hydroxide and air was passed through the solution for eleven

hours. The solution was then neutralized with carbon dioxide and the di-(3-pyridyl)hydantil separated by filtration. The product weighed 0.12 gram which is a yield of 40 per cent based on the number of moles of reactant introduced. Per cent nitrogen for $C_{16}H_{12}O_4N_6$: calculated, 23.86; found, 23.72. The product decomposed at 332°. The infrared absorption spectrum is given in the Appendix in Figure 5.

Diphenylhydantil

One gram (0.0029 mole) of 5-phenylhydantoin was dissolved in an excess of 5 per cent sodium hydroxide. Air was passed through the solution for thirteen hours. The solution was then acidified with hydrochloric acid, and the precipitate collected. This precipitate was boiled with 175 milliliters of water, and the insoluble solid collected and dried. It weighed 0.2 gram and decomposed at 335°. On the basis of its melting point and low water solubility, the product was assumed to be diphenylhydantil. The yield was 20 per cent of that theoretically obtainable. The infrared spectrum of this product is given in Figure 6 in the Appendix.

α-(3-Pyridyl)hydantonic Acid

A solution which contained 0.300 gram (0.0131 mole) of sodium in five milliliters of methyl alcohol was added to twenty milliliters of water. The resulting solution was then placed in a three-necked flask which was fitted with: (1) a

gas inlet tube with stopcock, (2) an outlet tube leading to a water aspirator, and (3) a solid addition-tube which contained 2.00 grams (0.0113 mole) of 5-(3-pyridyl)hydantoin. In order to remove the air from the flask, nitrogen was passed through the solution for five minutes. Then the flask was evacuated and the solution boiled for five minutes, after which the flask was tilted in order to allow contact between the solution and the solid. The resulting solution was allowed to stand at room temperature for fifty-seven hours after which time it was saturated with carbon dioxide. Eighty-eight thousandths gram of a white solid was collected. The solid melted with decomposition at 326° and was assumed to be di-(3-pyridyl)hydantil on the basis of its decomposition point and water insolubility. The solution from which the di-(3-pyridyl)hydantil separated was evaporated at reduced pressure on a steam bath. The residue was heated with absolute ethyl alcohol and filtered. This filtrate was neutralized with hydrochloric acid and the white solid which was formed was separated by filtration. This solid melted with decomposition at 205°, and had greater water solubility than 5-(3-pyridyl)hydantoin. It was soluble in 5 per cent sodium bicarbonate, indicating the presence of a carboxyl group. The ∝-(3-pyridyl)hydantoic acid was analyzed for nitrogen. Per cent nitrogen for $C_8H_{10}O_3N_3$: calculated, 21.53; found, 21.65. This fraction weighed 0.24 gram. Further evaporation

of the filtrate from which the ∝-(3-pyridyl)hydantoic acid was taken gave an additional yield of ∝-(3-pyridyl)hydantoic acid, and 0.039 gram of a solid which melted at 227°. This compound was assumed to be 5-(3-pyridyl)hydantoin. The total yield of ∝-(3-pyridyl)hydantoic acid was 0.55 gram which represents a yield of 25 per cent of that theoretically obtainable. The infrared spectrum of ∝-(3-pyridyl)hydantoic acid is shown in Figure 7 in the Appendix.

Cyclization of ∝-(3-Pyridyl)hydantoic Acid

Two methods were used to effect cyclization of ∝-(3-pyridyl)hydantoic acid.

Method 1.--One gram (0.0051 mole) of ∝-(3-pyridyl)-hydantoic acid was dissolved in ten milliliters of 20 per cent hydrochloric acid in an 8-inch test tube and heated on a steam bath for two hours. During this heating period, a stream of nitrogen was passed over the solution to prevent contact of the solution with air. The solution was neutralized with sodium bicarbonate, cooled in the refrigerator, and the precipitate collected. It melted at 220° with decomposition, and was assumed to be 5-(3-pyridyl)hydantoin. The yield was 0.43 gram (0.0024 mole) or 48 per cent. No attempt was made to recover any 5-(3-pyridyl)hydantoin which remained in solution.

Method 2.--Eight-tenths gram (0.0041 mole) of ∝-(3-pyridyl)hydantoic acid was placed in an 8-inch test

tube fitted with a stopper and stopcock. To the solid was added eight milliliters of 20 per cent hydrochloric acid. The air was then removed by boiling the solution under reduced pressure without heating for five minutes. The solution stood at room temperature for thirty hours. It was neutralized with 10 per cent sodium hydroxide, and cooled in the refrigerator. The precipitate which was collected melted at 225° and weighed 0.4 gram. This is a yield of 55 per cent. The identity of the compound was based on its melting point which is that of authentic 5-(3-pyridyl)hydantoin. No attempt was made to recover any 5-(3-pyridyl)hydantoin which remained in solution.

Hydantoic Acid

Three grams (0.033 mole) of hydantoin was mixed with 15.0 grams (0.05 mole) of barium hydroxide in thirty-five milliliters of carbon dioxide free water. This mixture was refluxed for one hour in a one-necked, round-bottomed flask fitted with a condenser and soda lime drying tube. Sulfuric acid was then added until the solution was acidic. The mixture was heated to boiling and filtered through hy-flo supercell to remove the barium sulfate. After the filtrate had been cooled, crystals were formed and were collected by filtration. The hydantoic acid was recrystallized from water and dried in a vacuum desiccator. The product melted at 161-162°. The melting point has been reported at

160-161°[3]. A yield of about 20 per cent of that calculated on the basis of the amount of hydantoin introduced was obtained. The infrared spectrum on the product is shown in Figure 8 in the Appexdix.

Sodium Hydantoate

A solution which contained 0.08 gram (0.0035 mole) of sodium in five milliliters of absolute ethyl alcohol was added to 0.3728 gram (0.00315 mole) of hydantoic acid which had been dissolved in thirty milliliters of boiling absolute ethanol. A precipitate formed immediately. The solution was cooled and 0.38 gram (0.0027 mole of sodium hydantoate was separated by filtration. The yield was 86 per cent of the theoretical. The sodium hydantoate ($C_3H_5O_3N_2Na$) was analyzed for per cent sodium and the result was: calculated, 16.42; found, 16.24. The infrared spectrum for sodium hydantoate is given in the Appendix in Figure 9.

Sodium Hydantoinate

One gram (0.01 mole) of hydantoin was dissolved in a minimum amount of absolute ethanol. To this solution was added a solution of 0.3 gram (0.013 mole) of sodium in 8.0 milliliters of absolute athanol. The flask which contained the reactants was then placed in the refrigerator. The

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[3] T. L. Davis and K. C. Blanchard, "The Dearrangement of Nitrourea and Its Applications in Synthesis," Journal of the American Chemical Society, LI (1929), 1790-1801.

crystals which formed and which were separated by filtration weighed 1.38 grams. This was nearly a yield of 100 per cent based on the assumption that the product was $C_3H_3O_2N_2Na \cdot H_2O$. A small amount of this product was dissolved in water and neutralized with carbon dioxide. The crystals which separated melted at 218-220°. This is the same as the melting point of hydantoin.[4] The salt was analyzed for sodium and the results were: calculated, 16.53; found, 16.52. The product was dried at 130° at a pressure of 7.0 millimeters of mercury for several hours and analyzed for sodium on the basis of the formula $C_3H_3O_2N_2Na$: calculated, 18.84; found, 18.87. The infrared spectrum of the anhydrous sodium hydantoinate is shown in Figure 10 in the Appendix.

Sodium 5-(3-Pyridyl)hydantoinate

To a solution which contained 0.23 gram (0.01 mole) of sodium in about twenty milliliters of absolute methyl alcohol was added to 1.77 grams (0.01 mole) of 5-(3-pyridyl)hydantoin. The solution was allowed to stand for about twenty minutes in the absence of air and then filtered. The precipitate weighed 0.163 gram which represents a yiled of 8 per cent. No attempt was made to recover the remainder of the material. The infrared spectrum of sodium 5-(3-pyridyl)hydantoinate is given in Figure 11 in the Appendix.

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[4] Ibid.

Attempted Preparation of Sodium α-(3-Pyridyl)hydantoate

A solution containing 0.252 gram (0.003 mole) of sodium bicarbonate in twenty milliliters of water was added to 0.5 gram (0.00257 mole) of α-(3-pyridyl)hydantoic acid. The resulting mixture was filtered. Twenty-five hundredth gram of solid was collected and was found to contain only a trace of sodium. This was assumed to be undissolved α-(3-pyridyl)-hydantoic acid. The filtrate was evaporated under reduced pressure on a steam bath. The residue was heated for a short while with absolute ethyl alcohol and filtered. A precipitate was collected which contained sodium. It weighed 0.070 gram. The filtrate was then heated on a steam bath for about thirty minutes during which time 0.133 gram of a white solid was collected. A small amount of this solid was dissolved in water, neutralized with carbon dioxide, and filtered. The solid thus formed melted with decomposition at 324°. It was assumed that cyclization and subsequent oxidation had occurred, and that the product was sodium di-(3-pyridyl)hydantilate. Per cent sodium for $C_{16}H_{10}O_4N_4Na_2$: calculated, 11.61; found, 12.02.

Sodium Di-(3-pyridyl)hydantilate

To 0.1 gram (0.0025 mole) sodium hydroxide was added an excess of di-(3-pyridyl)hydantil in twenty milliliters of water. After about one hour the solution was filtered to

remove unreacted di-(3-pyridyl)hydantil. The filtrate was slowly evaporated by passing a stream of air over it and the crystals which were collected were dried in a vacuum desiccator.

In order to determine whether hydrolysis had taken place, a small amount of the sodium di-(3-pyridyl)hydantil was dissolved in water and then neutralized with carbon dioxide. A product which decomposed at 332° was precipitated and collected. This is the decomposition point of the starting material.

Sodium di-(3-pyridyl)hydantilate, $C_{16}H_{10}O_4N_6Na_2$, was analyzed for per cent sodium: calculated, 11.61; found, 11.48. The infrared spectrum of this compound was recorded and is given in Figure 12 in the Appendix.

Sodium Diphenylhydantilate

Two grams (0.0057 mole) of diphenylhydantil was dissolved in 10 per cent sodium hydroxide. Ethanol was added to the solution and the mixture placed in the refrigerator. The crystals were separated by filtration and washed with absolute ethanol. The product weighed 0.71 gram (0.002 mole) and represents a yield of 36 per cent based on the number of moles of diphenylhydantil used. An analysis for per cent sodium in sodium diphenylhydantilate ($C_{18}H_{12}N_4O_4Na_2$) was carried out and the result was: calculated, 16.66; found, 16.66. The infrared spectrum is shown in Figure 13 in the Appendix.

Preparation of 5-(3-Pyridyl)hydantion Hydrochloride

One gram (0.0057 mole) of 5-(3-pyridyl)hydantoin was dissolved in forty milliliters of hot absolute ethanol and heated on a steam bath. Dry hydrogen chloride was passed through the solution until three-fourths of the ethanol had evaporated. The crystals were separated by filtration and were then dried in a desiccator which contained potassium hydroxide as a desiccant. The product melted with decomposition at 245° and weighed 1.03 grams. This is a yield of 87 per cent based on the number of moles of 5-(3-pyridyl)-hydantoin used. The product $C_8H_8O_2N_3Cl$, was analyzed for chlorine: calculated, 16.60; found, 16.53. The infrared spectrum of 5-(3-pyridyl)hydantoin hydrochloride is shown in Figure 14 in the Appendix.

CHAPTER III

DISCUSSION

The preparation of 5-(3-pyridyl)hydantoin and the study of its chemical properties were complicated by the ease with which it was oxidized to di-(3-pyridyl)hydantil by oxygen from the air. In the preparation of 5-(3-pyridyl)hydantoin, it was found that the highest yields and the most easily purified crude products could be obtained by stopping the reaction when it became considerably darkened. This required from two to six hours. In one preparation a small sample of the reaction mixture was reacted with ammonical silver nitrate in an attempt to determine when the pyridine-3-carboxaldehyde had been consumed. After nine hours, only a very slight silver mirror was produced. This could have been due to reaction with 5-(3-pyridyl)hydantoin since it was found later that this compound would react with ammonical silver nitrate to give free silver.

Di-(3-pyridyl)hydantil does not reduce Tollen's reagent, so that the very slight test obtained after nine hours could be due in part to oxidation of the hydantoin to the hydantil derivative and in part to more profound decomposition leading to tars. At any rate, a shorter reaction time led to increased yields.

If the reaction mixture from the preparation of the hydantoin stood for several days in contact with the air the product consisted entirely of the hydantil derivative.

It was further noticed that in some preparations a considerable amount of α-(3-pyridyl)hydantoic acid was precipitated after allowing the filtrate from the initial precipitation to stand in the refrigerator. The pH of this solution, which varied from one to two units on either side of seven from one preparation to the next, was not definitely known. Thus it is not possible to state the pH of the solution from which α-(3-pyridyl)hydantoic acid was obtained. Presumably the solution was basic.

α-(3-Pyridyl)hydantoic acid was formed readily by allowing a slightly basic solution of the hydantoin to stand at room temperature in the absence of air. This is in contrast to the hydrolysis of 5-phenylhydantoin which is effected by boiling with barium hydroxide solution. α-(3-Pyridyl)-hydantoic acid was easily cyclized to the hydantoin by hydrochloride acid at room temperature. In this respect the behavior of the 3-pyridylhydantoin and hydantoic acid is comparable to that of the 4-pyridyl derivatives.[1]

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[1]Robert Edward Crowe, "Studies in the Hydantoin Series. I. 5-(4-Pyridyl)hydantoin and Its Derivatives," unpublished master's thesis, Department of Chemistry, North Texas State College, Denton, Texas, August, 1957.

5-(3-Pyridyl)hydantoin is more easily oxidized than 5-phenylhydantoin which in turn is more easily oxidized than 5-(4-pyridyl)hydantoin.[2] 5-(4-Pyridyl)hydantoin is oxidized with difficulty by permanganate ion to the hydroxy compound.

The bromination of 5-(3-pyridyl)hydantoin is comparable to that of 5-phenylhydantoin. However, there seemed to be no hydantil formation as is the case in the bromination of 5-phenylhydantoin. The bromo compounds show similar reactivity toward water and alcohols. 5-Bromo-5-(4-pyridyl)hydantoin[3] on the other hand, is a considerably better oxidizing agent than either of these and is reduced to the original hydantoin by alcohols and amines.

Attempts at methylation of 5-(3-pyridyl)hydantoin results in profound decomposition or in formation of what apparently was a hydantil derivative.

The carbonyl bands for 5-(3-pyridyl)hydantoin, Figure 1, are at slightly longer wavelengths than the other hydantoins examined in this laboratory. In solution, however, these bands shift to more nearly normal wavelengths.

The band at 2.91 microns in the spectrum of 5-n-butoxy-5-(pyridyl)hydantoin, Figure 4, is difficult to explain as an NH band of the hydantoin ring, at so short a wavelength. In most of the hydantoins examined the NH band is found at

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[2] Ibid. [3] Ibid.

3.1 to 3.2 microns. The questionable band actually falls in the region of free NH_2 absorptions.

In comparing the spectra of hydantoic acid, Figure 8, and ∝-(3-pyridyl)hydantoic acid, Figure 7, it is seen that the general nature of the curves between 3 and 6.5 microns is similar but with fairly large variations in wavelength. Sodium hydantoate, Figure 9, shows the typical shift from a carboxyl absorption at 5.8 microns to bands at 6.25 and 7.05 microns characteristic of carboxylate ions.[4]

Substitution at carbon-5 of the hydantoin ring might be expected to affect the 4-carbonyl frequency in the same way that ketone carbonyls are affected by ∝-substitution.[5] Thus, substitution of an electron attracting group such as bromine ∝- to a carbonyl causes a shift to shorter wavelengths due to an increase in double bond character. The normal 4-carbonyl in hydantoin appears to absorb generally at about 5.6 microns. The observed 4-carbonyl absorption for certain of the 5-(-3-pyridyl)hydantoins are as follows: 5-bromo, 5.57; 5-hydroxy, 5.55; 5-n-butoxy, 5.56. There may be a slight effect due to negative substitution. Examination of the compounds in solution would give more reliable results but is made difficult by lack of suitable solvents.

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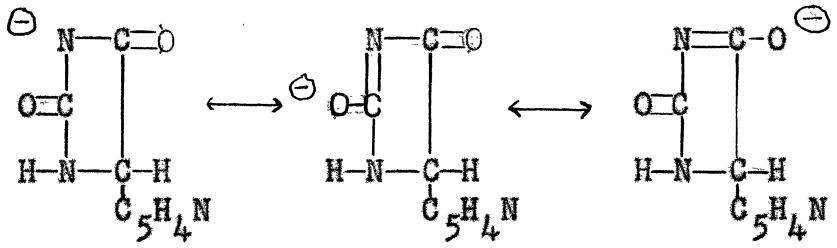
[4] L. J. Bellamy, The Infrared Spectra of Complex Molecules (New York, 1954), p. 140.

[5] Ibid., p. 120.

The infrared spectra of the sodium salts of the hydantoins which have been examined are very characteristic. The 4-carbonyl band at 5.6 and the 2-carbonyl band at 5.8 microns in the hydantoin are replaced by strong bands at 5.82 and 6.25 microns. These bands in the salts are related to each other in the same way as the two bands in the free hydantoin. That is, the band of shorter wavelength is somewhat weaker and not so broad as the one of longer wavelength.

These bands in the salts could be quite easily explained as the 4- and 2-carbonyl absorptions with less double bond character and therefore lower frequency due to contributions by the following structures:



The salts examined included sodium hydantoinate, Figure 10; sodium 5-phenylhydantoinate[6]; sodium 5-(3-pyridyl)hydantoinate, Figure 11, sodium di-(3-pyridyl)hydantilate, and sodium diphenylhydantilate, Figure 12.

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[6] Crowe, op. cit.

APPENDIX

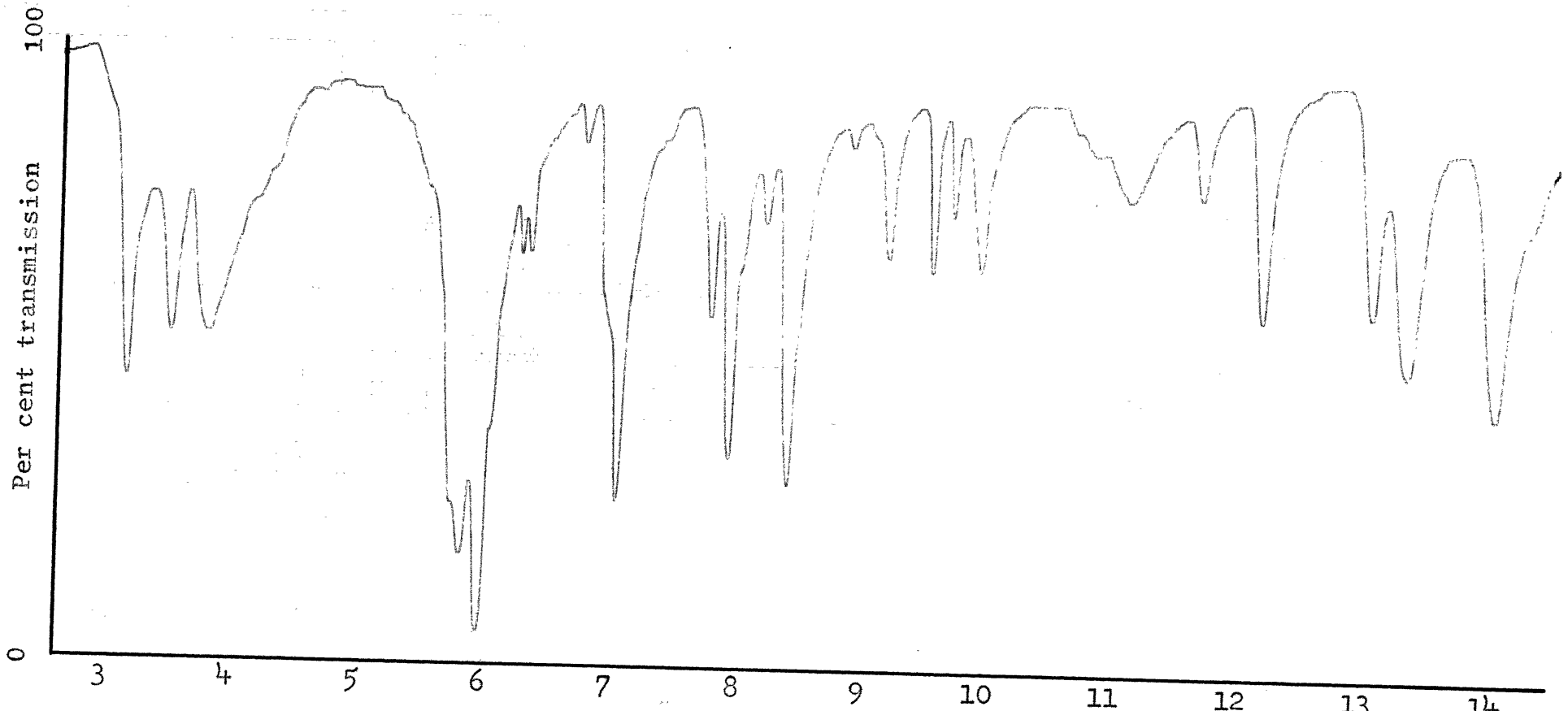

Fig. 1--5-(3-Pyridyl)hydantoin. Acetone preparation, 0.6 mg./310 mg. KBr.

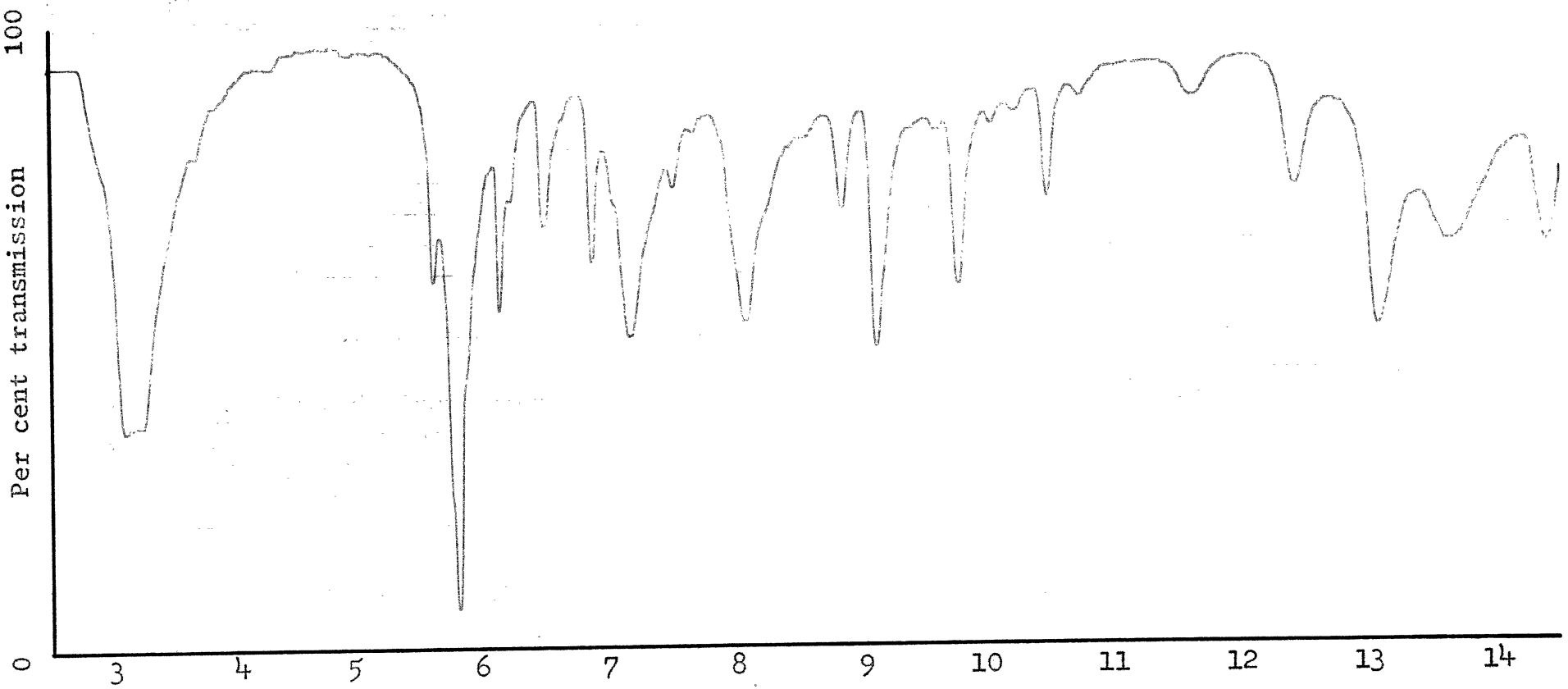

Fig. 2--5-Bromo-5-(3-pyridyl)hydantoin. Vibrator preparation, 0.6 mg./308 mg. KBr.

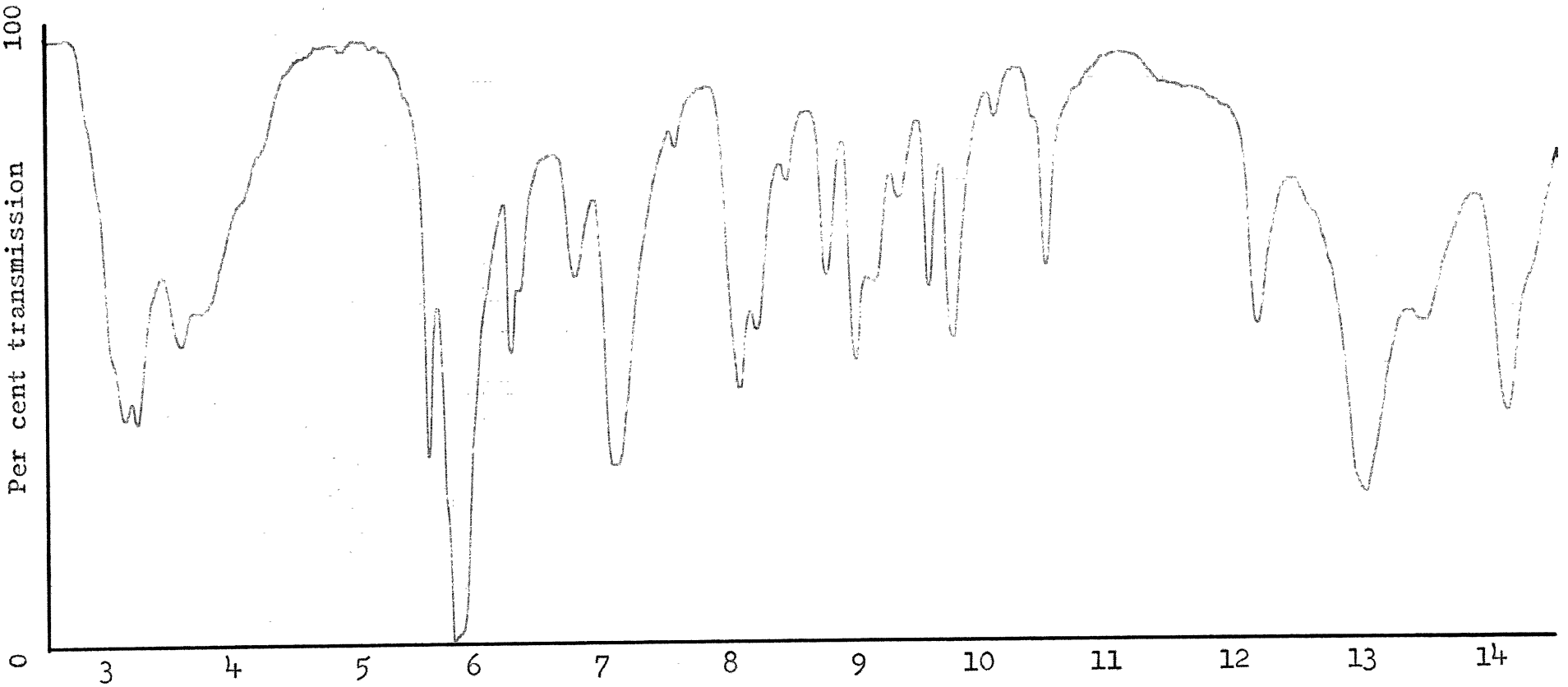

Fig. 3--5-Hydroxy-5-(3-pyridyl)hydantoin. Acetone preparation, 0.8 mg./316 mg. KBr.

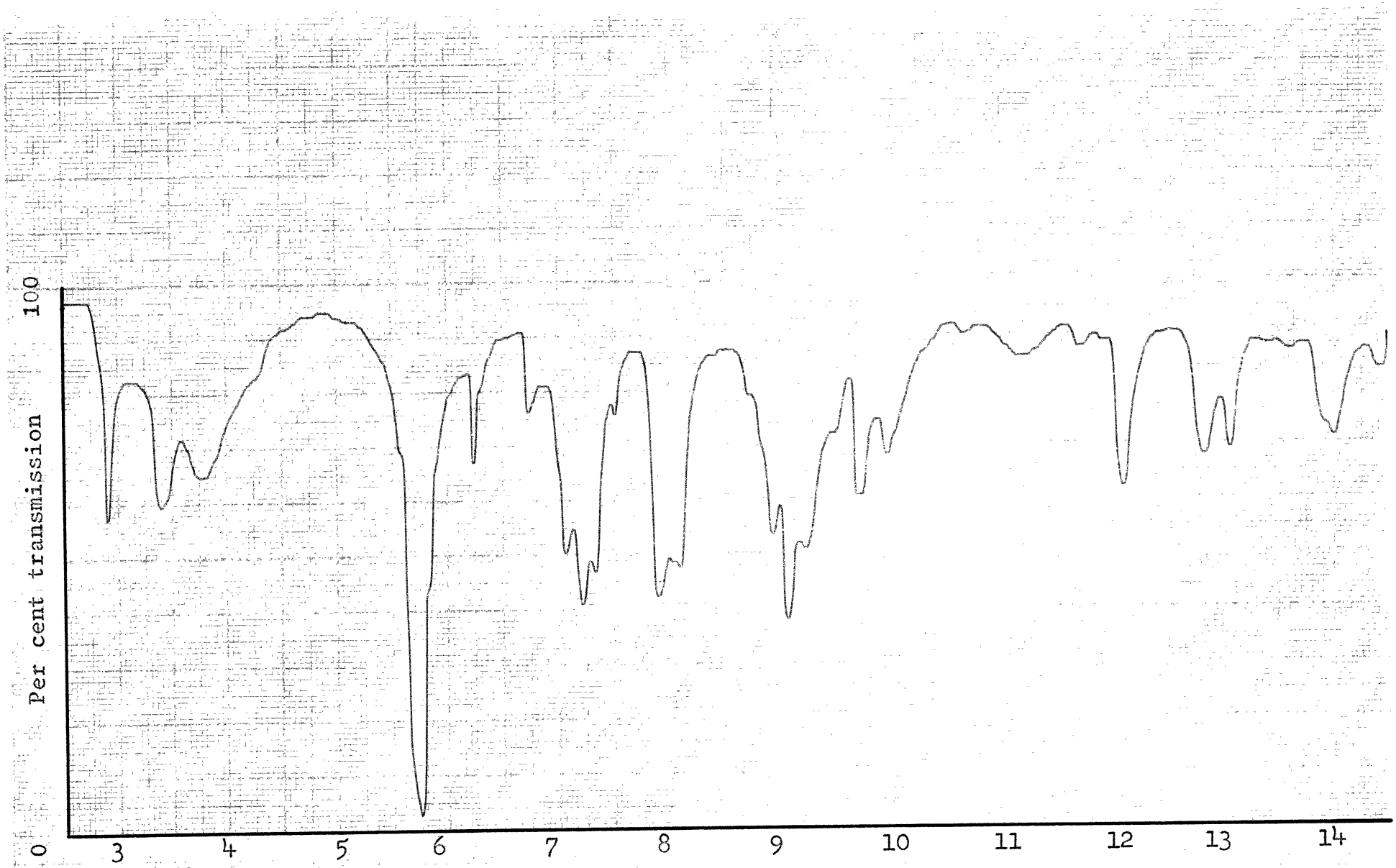

Fig. 4--5-Butoxy-5-(3-pyridyl)hydantoin. Vibrator preparation, 0.6 mg./317 mg. KBr.

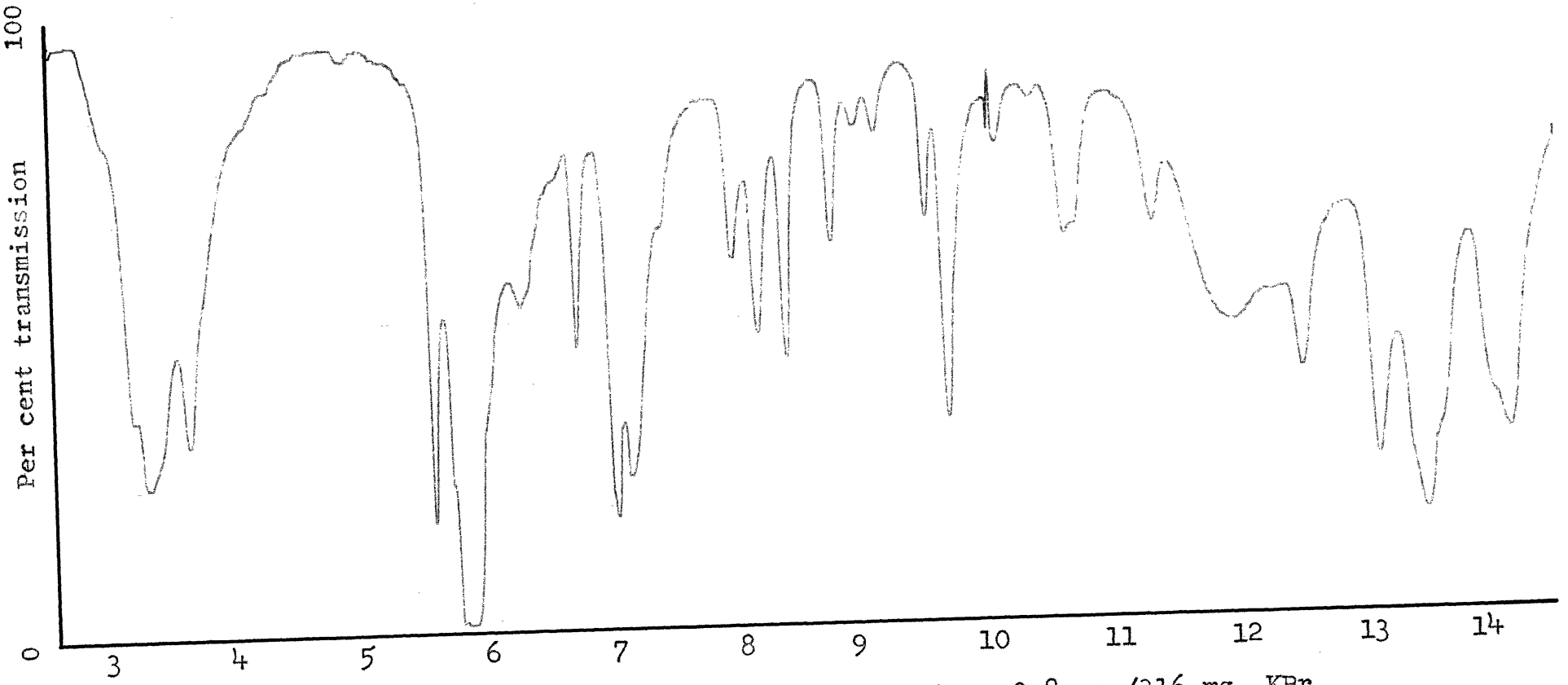

Fig. 5--Di-(3-pyridyl)hydantil. Vibrator preparation, 0.8 mg./316 mg. KBr.

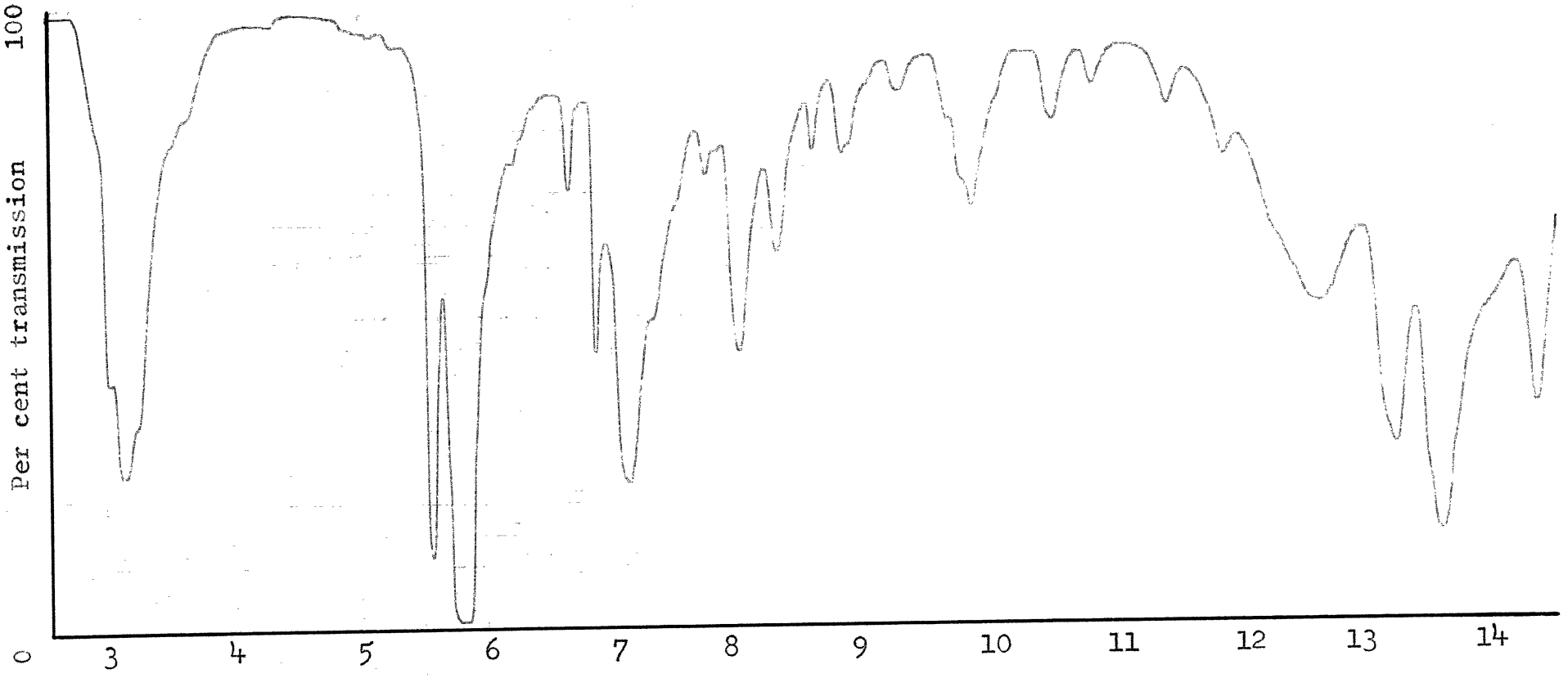

Fig. 6--Diphenylhydantil. Vibrator preparation, 0.6 mg./326 mg. KBr.

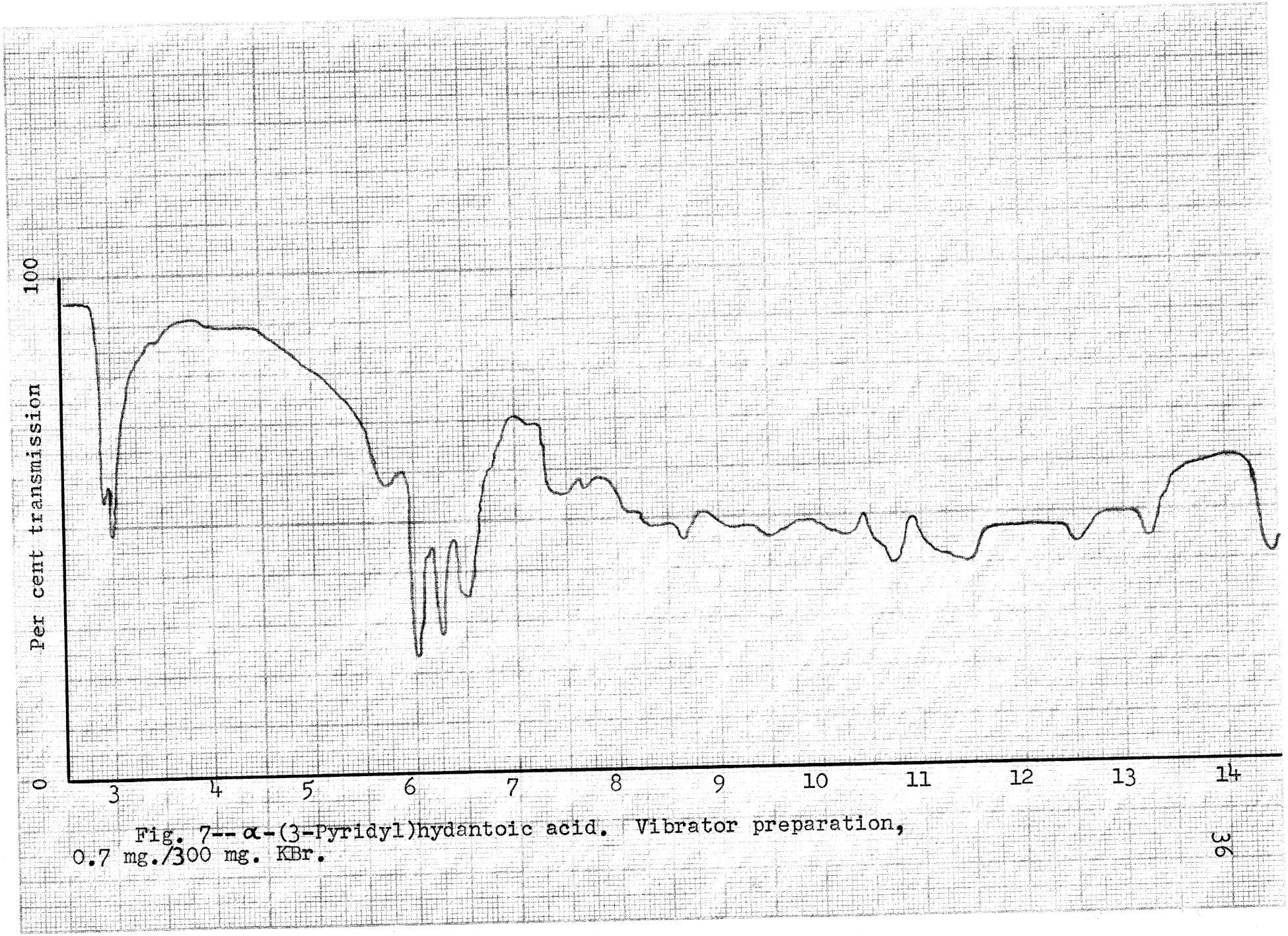

Fig. 7-- α-(3-Pyridyl)hydantoic acid. Vibrator preparation, 0.7 mg./300 mg. KBr.

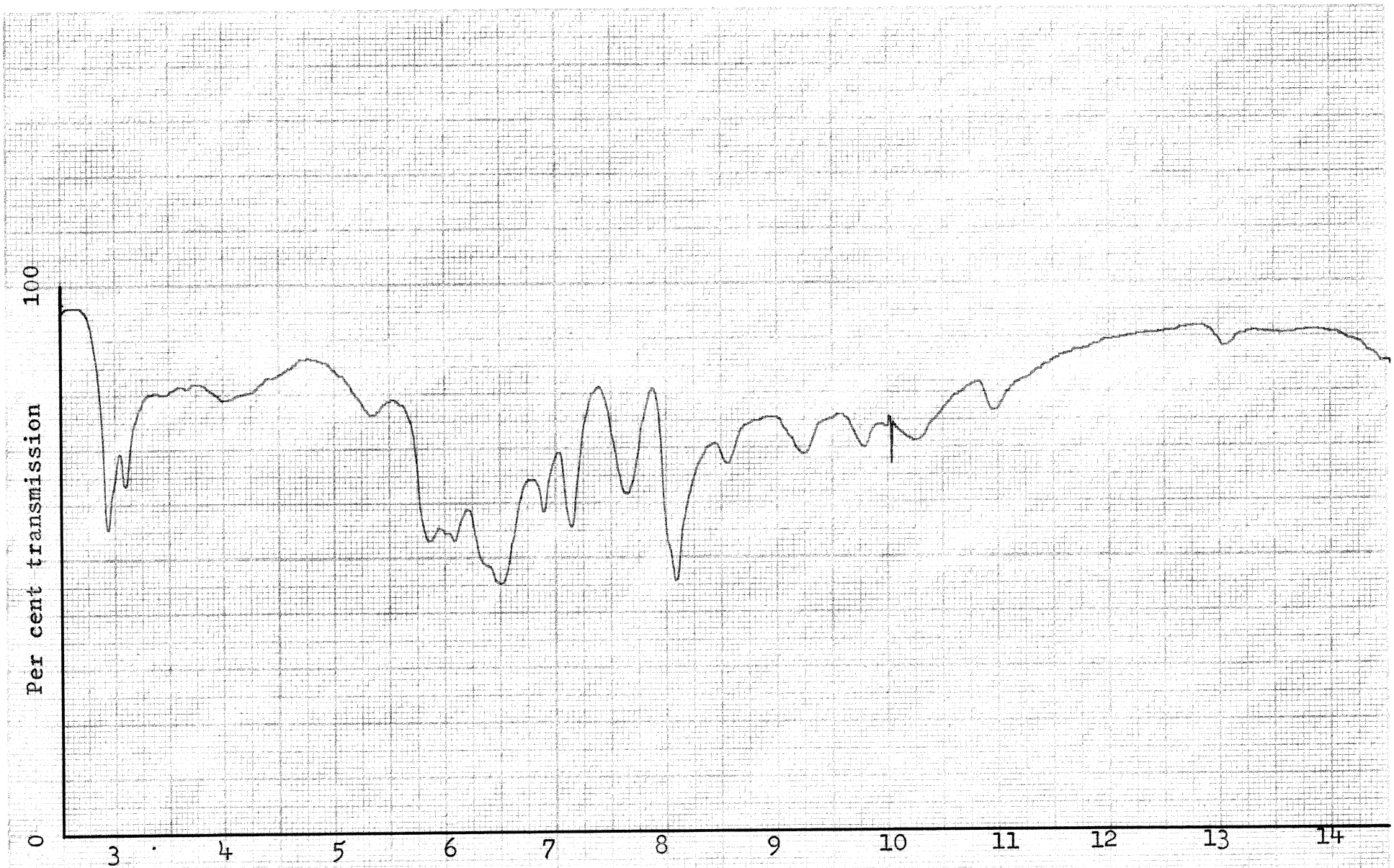

Fig. 8--Hydantoic acid. Vibrator preparation, 0.8 mg./306 mg. KBr.

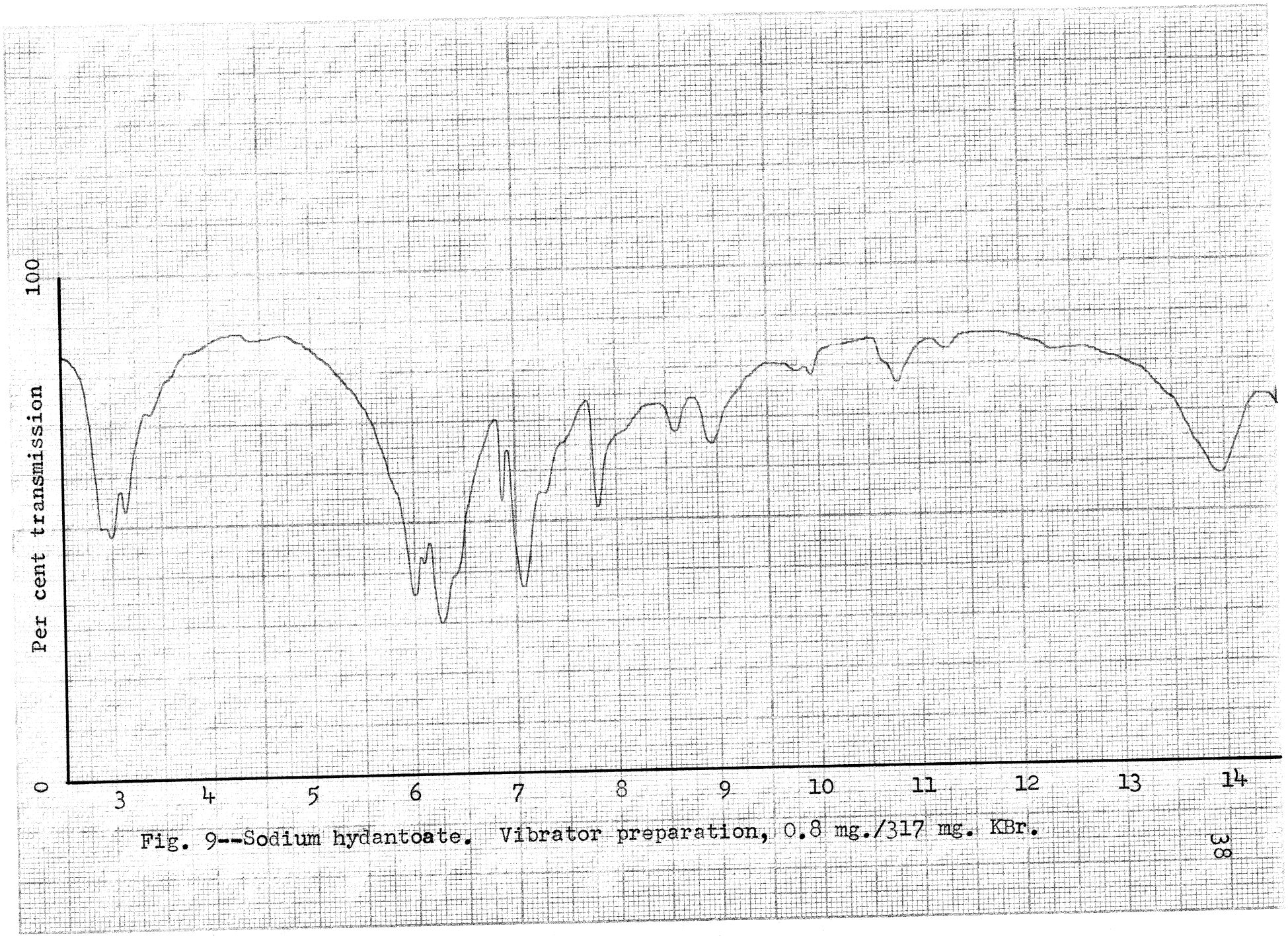

Fig. 9--Sodium hydantoate. Vibrator preparation, 0.8 mg./317 mg. KBr.

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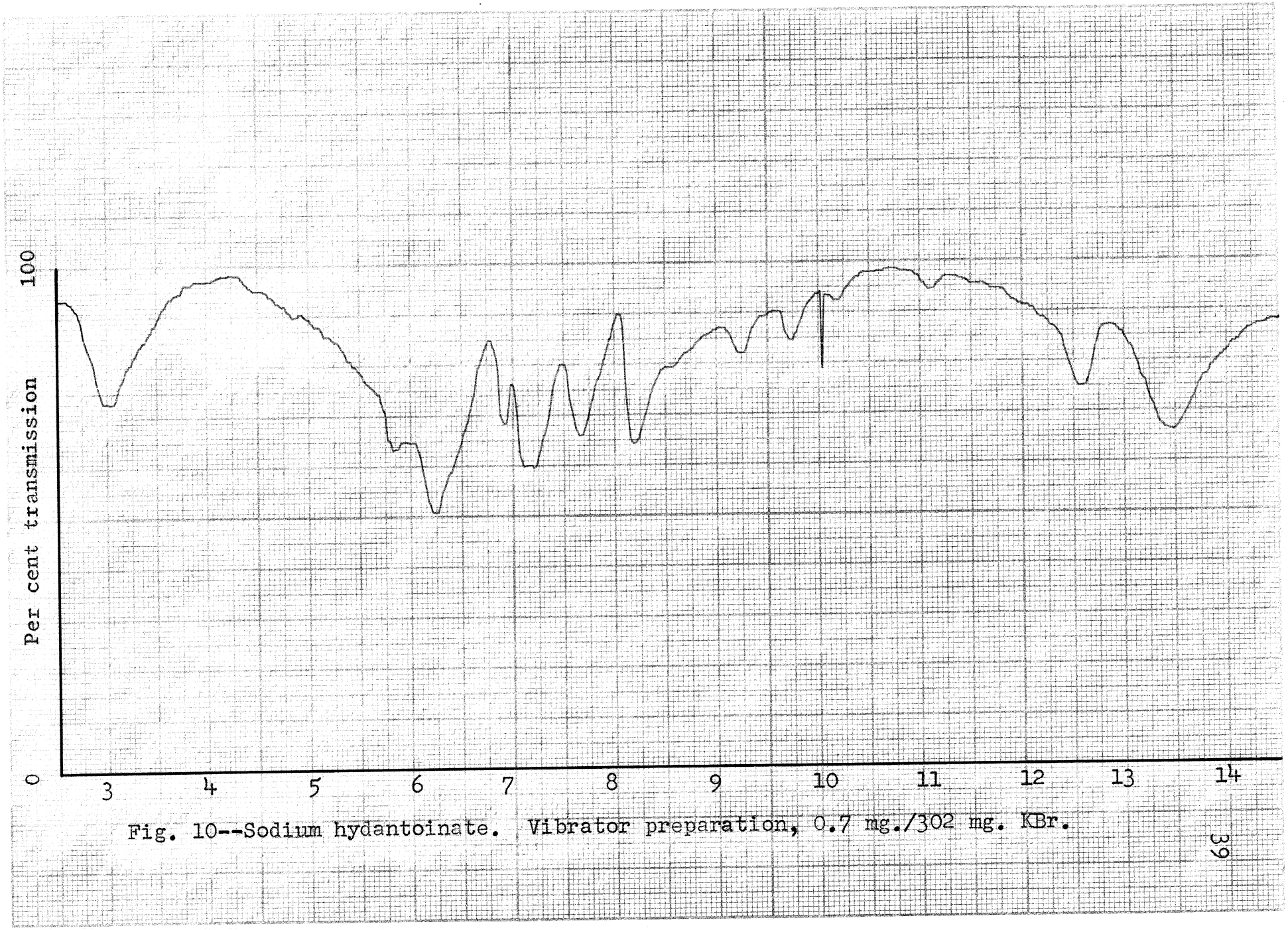

Fig. 10--Sodium hydantoinate. Vibrator preparation, 0.7 mg./302 mg. KBr.

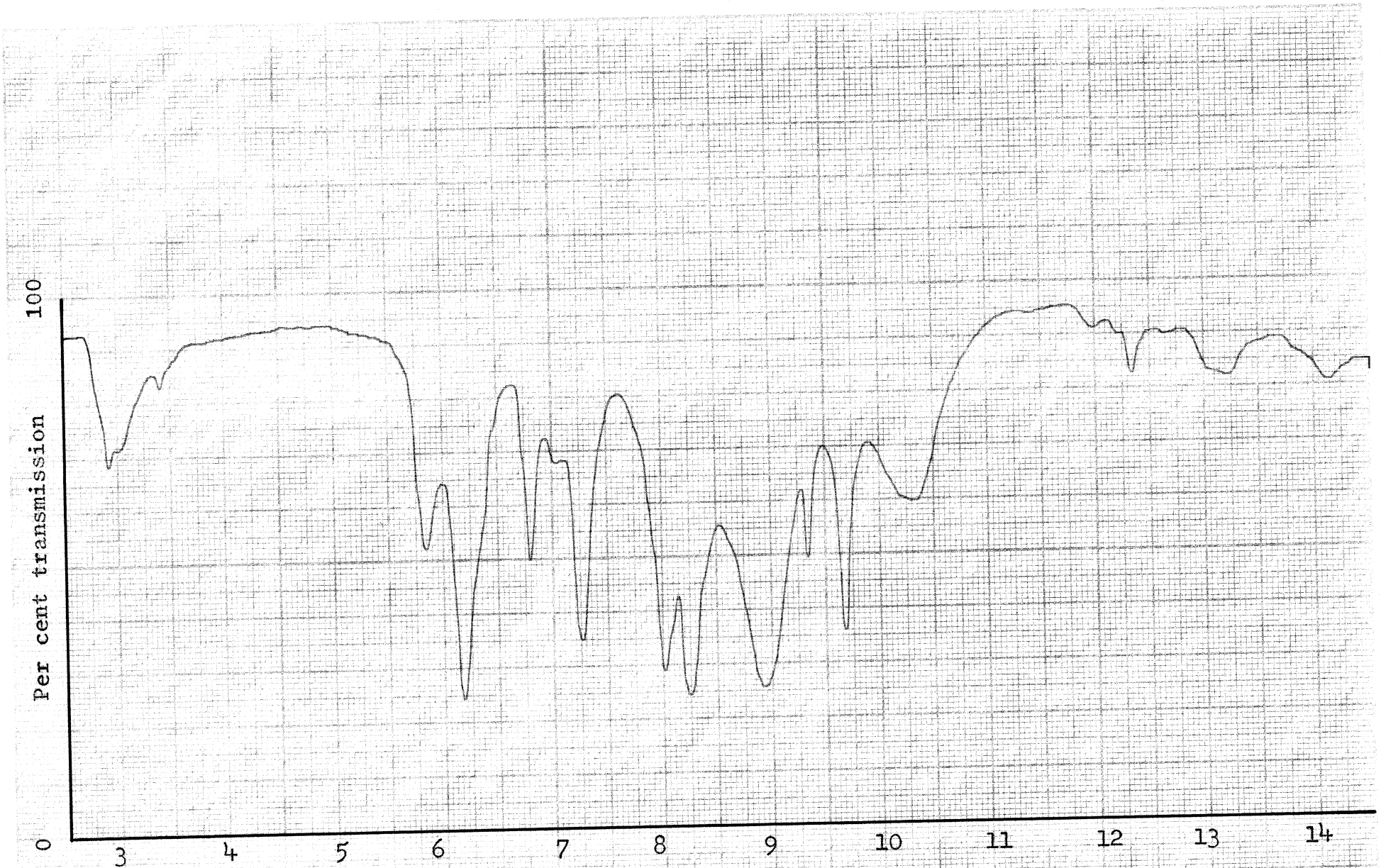

Fig. 11--Sodium 5-(3-pyridyl)hydantoinate. Vibrator preparation, 0.8 mg./325 mg. KBr.

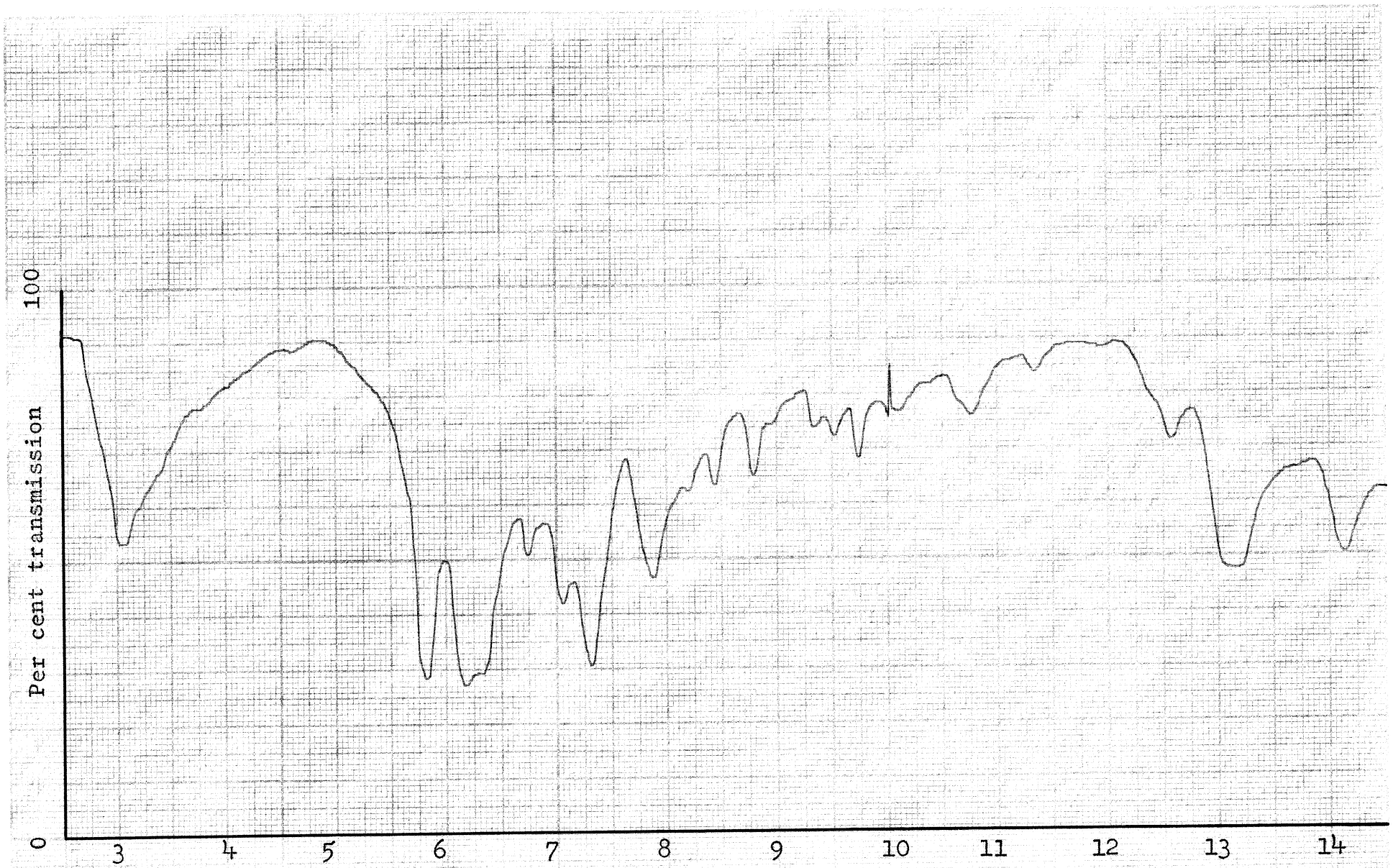

Fig. 12--Sodium di-(3-pyridyl)hydantilate. Vibrator preparation, 0.8 mg./325 mg. KBr.

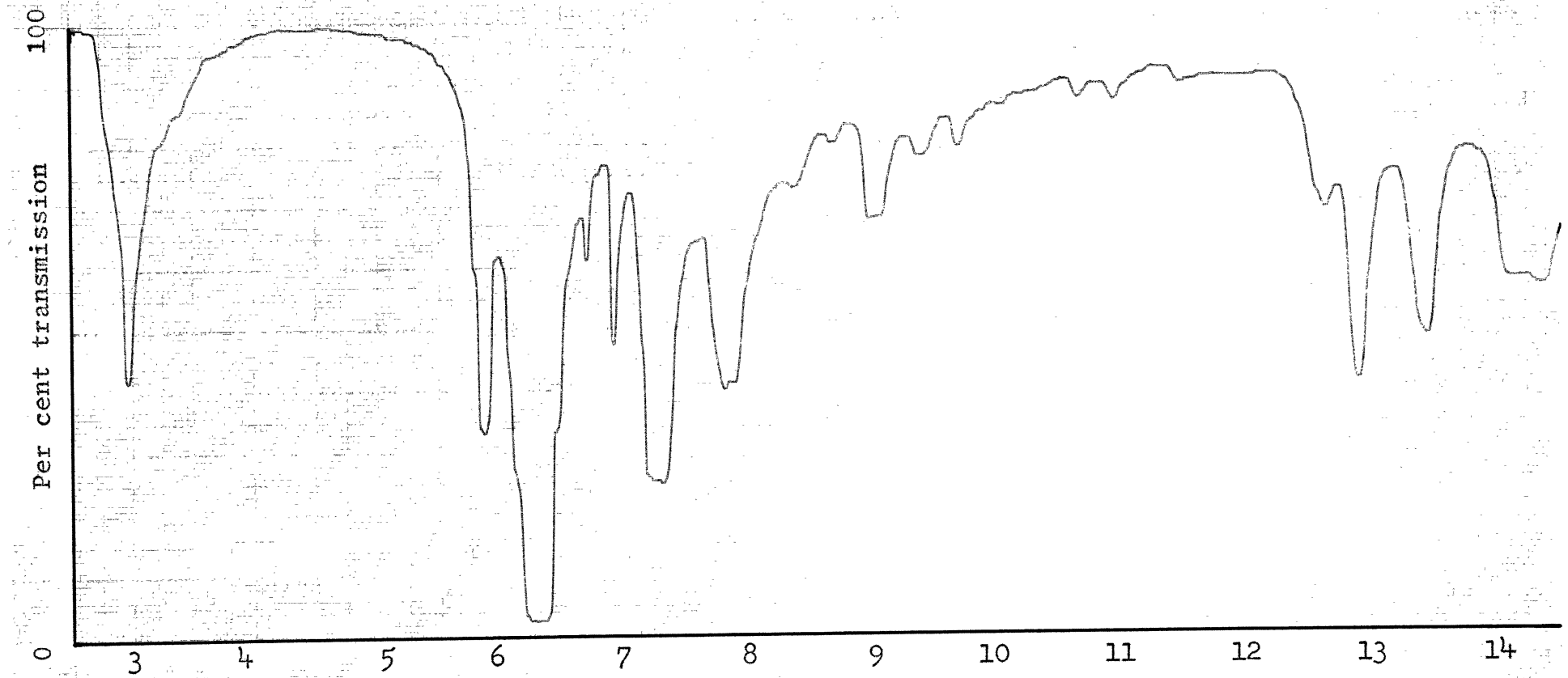

Fig. 13--Sodium diphenylhydantilate. Vibrator preparation, 0.7 mg./300 mg. KBr.

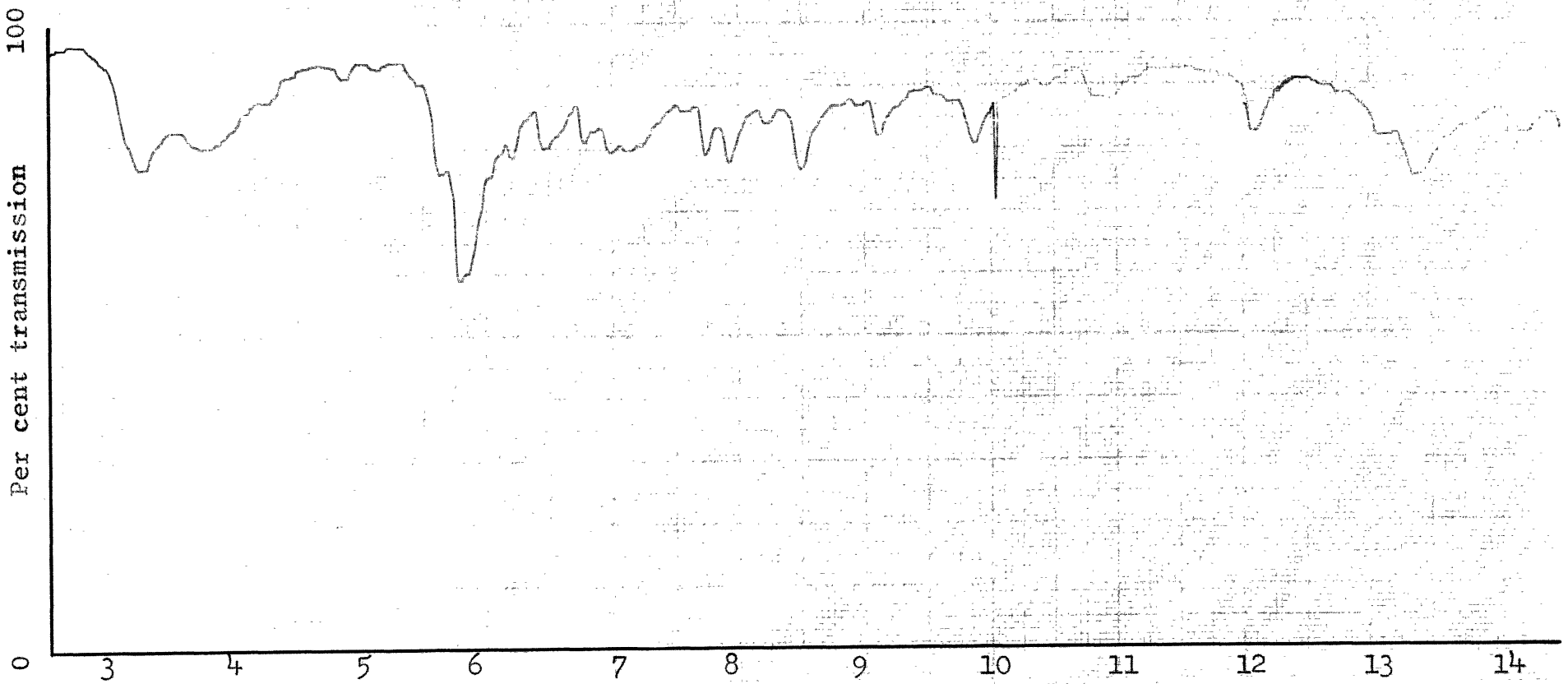

Fig. 14--5-(3-Pyridyl)hydantoin hydrochloride. Vibrator preparation, 0.8 mg./303 mg. KBr.

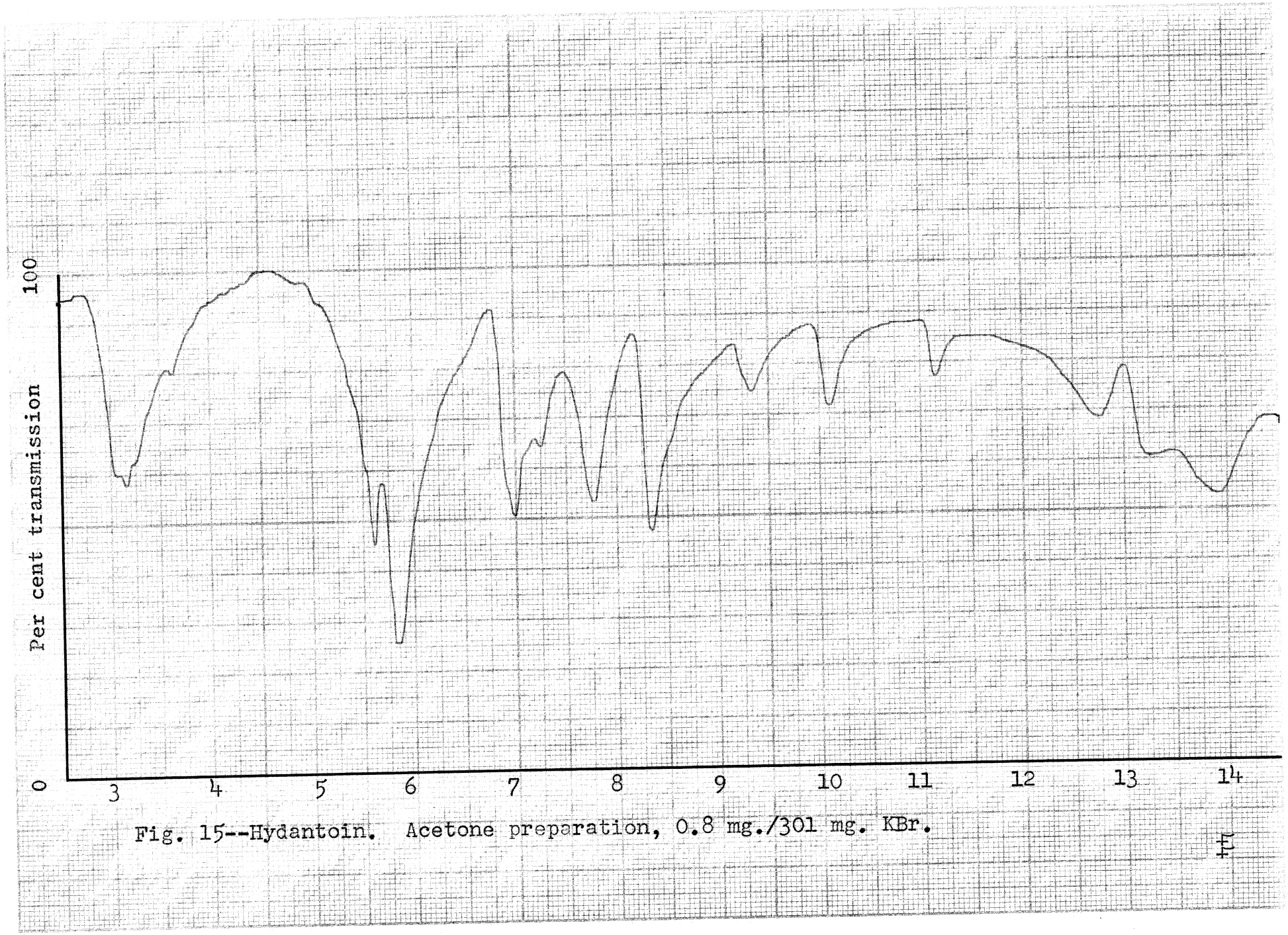

Fig. 15--Hydantoin. Acetone preparation, 0.8 mg./301 mg. KBr.

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