STUDIES IN THE HYDANTOIN SERIES. I.

5-(4-PYRIDYL)HYDANTOIN AND ITS DERIVATIVES

APPROVED:

J. J. Sparkes

Major Professor

Carl T. York

Minor Professor

James L. Carrico

Director of the Department of Chemistry

Robert B. Toulouse

Dean of the Graduate School

STUDIES IN THE HYDANTOIN SERIES. I.
5-(4-PYRIDYL)HYDANTOIN AND ITS DETRIVATIVES

THESIS

Presented to the Graduate Council of the
North Texas State College in Partial
Fulfillment of the Requirements

For the Degree of

MASTER OF SCIENCE

By

Robert E. Crowe, B. S.

Denton, Texas

August, 1957

TABLE OF CONTENTS

LIST OF TABLES

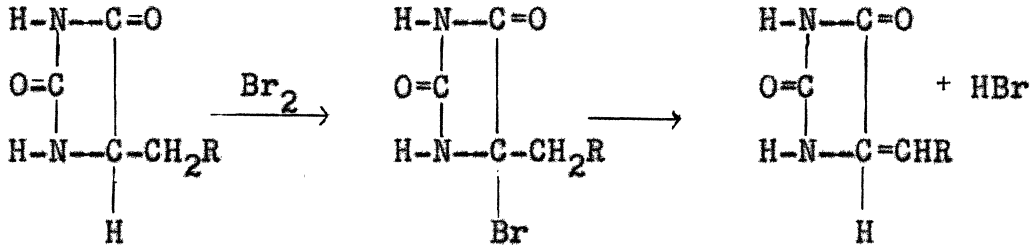
LIST OF ILLUSTRATIONS

CHAPTER I

INTRODUCTION

For some time research has been carried out concerning the chemical behavior of hydantoin, particularly as it is affected by substitution. It is of some interest to compare the chemical reactivities of 5-substituted hydantoins, since their chemical behavior varies somewhat depending on the nature of the substituent. This is particularly true when certain chemical properties of the 5-alkyl and 5-arylhydantoins are compared.

For example, bromination of 5-alkylhydantoins produces unstable bromine containing intermediates which lose hydrogen bromide to form unsaturated hydantoins as follows:[1]

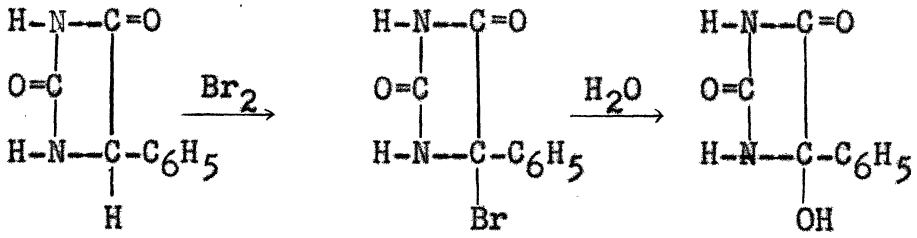


When one mole of 5-phenylhydantoin is treated with one mole of bromine in acetic acid, 5-bromo-5-phenylhydantoin is formed, which is fairly stable. This bromo derivative is

---

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

hydrolyzed with hot water to form 5-hydroxy-5-phenylhydantoin, and reacts with aniline to give a 5-anilino derivative.[2]



5-Bromo-5-phenylhydantoin has been shown in this laboratory to react with alcohols,[3] amines,[4, 5] phenols,[6] and mercaptans[7] to give derivatives of the general formula

---

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

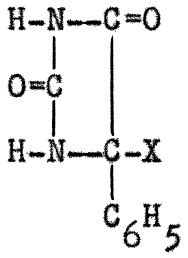
[3] J. R. Hoffman, "Hydantoins as Anticonvulsants, VI. 5-Substituted-Alkoxy Derivatives of 5-Phenylhydantoin," unpublished master's thesis, Department of Chemistry, North Texas State College, Denton, Texas, 1954.

[4] 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.

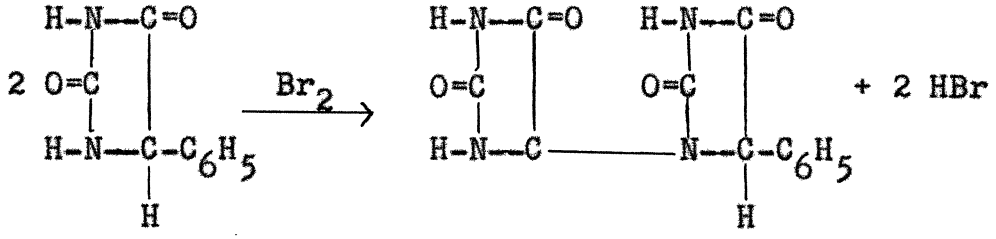
[5] W. G. Frazior, "Hydantoins as Anticonvulsants, II. 5-Substituted-Amino Derivatives of Phenylhydantoin," unpublished master's thesis, Department of Chemistry, North Texas State College, Denton, Texas, 1950.

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



where X represents a hetero-atom. When a half mole of bromine was used with one mole of 5-phenylhydantoin, the product formed was diphenylhydantil,[8] while oxidation of hydantoin gives parabanic acid.[9]



Research has been done by Baudisch and Davidson concerning the catalytic oxidation of certain 5-alkyl and 5-aryl-hydantoins.[10] They 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. It was also noted that disubstitution completely inhibited

---

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

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

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

oxidation. Holmberg[11] studied the oxidation of 5-phenylhydantoin using various oxidizing agents. The various products obtained were 5-hydroxy-5-phenylhydantoin, diphenlyhydantil, benzoylurea and benzoic acid.

Alkylation of 5-phenylhydantoin by heating 5-phenylhydantoin with methyl iodide in the presence of one equivalent of potassium hydroxide in methanol[12] form 3-methyl-5-phenylhydantoin. Dimethyl sulfate has also been used as the alkylating agent to produce the same result.[13] 5-Alkylhydantoins can be methylated in the N-3 position by the same method.[14] Methylation will not occur in the N-1 position unless a double bond exists between the alkyl group and C-5[15] or an aromatic group is substituted at position 5.[16] This behavior may be related to the increased acidity of the 1-NH

---

[11] G. Holmberg, "Oxidation of Phenyl-substituted-hydantoins," Acta Chem. Scand., IV (1950), 821-7; cited in Chemical Abstracts, LXV (1951), 2478.

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

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

[14] Ibid.

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

[16] J. Klosa, "5-Phenylhydantoin," Archiv der Pharmazie und Berichte der deutschen pharmazeutischen Gesellschaft, CCLXXV (1952), 274-80; cited in Chemical Abstracts, XLVIII (1954), 3266.

noted in the case of a 5-(2-thienyl) substituted hydantoin,[17] the thienyl group being of strongly aromatic character.

Due to the similarity in "aromatic character" existing between benzene and pyridine, it seems of interest to compare the properties of 5-pyridyl substituted hydantoins with those of phenylhydantoins. Several examples of 5-pyridyl substituted hydantoins have been reported.[18, 19, 20] However, these investigators did not study the chemical properties of the derivatives except hydantoic acid preparation attempted by Henze.[21] Concerning the similarity of benzene and pyridine as to "aromatic character", Mosher[22] has called attention to the typical "aromatic nature" of the 3-position in pyridine and to the anomalous nature of the 2- and 4-positions. It would seem of interest to look for the differences

---

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

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

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

[20] P. Teague, "Phenyl-pyridylhydantoin," Journal of the American Chemical Society, LXIX (1947), 714.

[21] Henze and Knowles, op. cit., p. 1133.

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

in properties between the 2- or 4- and 3-pyridyl substituted hydantoins. The weakly basic nature of pyridine might be expected to produce differences in solubility and chemical behavior.

Some interest would attach also to the anticonvulsant properties of 5-pyridyl derivatives, since several 5-phenylhydantoin derivatives are potent antoconvulsants. The most commonly used are 5,5-diphenylhydantoin and 3-methyl-5-ethyl-5-phenylhydantoin. Some of the 5-phenyl-5-hetero-substituted hydantoins prepared in this laboratory have shown to possess appreciable antoconvulsant activity.[23, 24] The 5-pyridylhydantoins thus far reported have had a high degree of activity.[25, 26]

The work presented in this investigation is concerned with the chemical properties of 5-(4-pyridyl)hydantoin as compared with 5-phenylhydantoin.

---

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

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

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

[26] H. Henze, "5-Phenyl-5pyridylhydantoin and Anticonvulsant Activity," U. S. Patent 2,526,231 (1950), cited in Chemical Abstracts, Vol. XLV (1951), edited by E. J. Crane.

CHAPTER II

EXPERIMENTAL

Methods of Analysis

Analyses for nitrogen were obtained using the micro-Dumas method. The amounts of sample varied from 2 to 5 mg.

Sodium was determined by igniting the sample with concentrated sulfuric acid and evaporating with sulfuric acid until a white residue was obtained. The percentage of sodium in the sample was then calculated from the amount of sodium sulfate formed. The weights of sample varied from 30 to 60 mg.

The total amount of bromine in a sample was determined by reducing the bromine with sodium bisulfite in an acidified solution of the sample, precipitating and weighing the bromine as silver bromide. The amounts of sample varied from 100 to 300 mg.

The infrared spectra were obtained using a Perkin-Elmer Model 21-B Infrared Spectromphotometer using a fairly wide slit program (980) and speeds of 20 to 30 sec. per micron since the amount of detail available in the solid phase spectra was somewhat limited. Samples for infrared analysis were prepared by either of two methods. A mixture of 0.3 to .9 mg. of compound with approximately 300 mg of spectroscopic grade potassium bromide (Harshaw Chemical Co.) was moistened

with reagent grade acetone and ground in an agate mortar until dry. The material was then scraped together and re-ground. Alternately the mixture of sample and potassium bromide was placed in a 1 ml. volumetric flask with six small stainless steel balls and vibrated for four to five minutes in a vibrator supplied by the Perkin-Elmer Company. The sample was placed in an evacuable die supplied by the same company and subjected under vacuum to a load of about 20,000 pounds for four to five minutes. The discs were occasionally cloudy but this apparently had little effect except to produce some scattering of light in the 2-3 micron region.

Melting points of the samples were obtained in an electrically heated metal block and are corrected values.

Decomposition points of compounds which decomposed on melting were determined by increasing the temperature at a uniform rate until the sample decomposed, at which time another sample was introduced into the block with the rate of temperature increase kept constant, and the time required for decomposition noted. This procedure repeated until the sample decomposed within 30 seconds of being placed in the block. This temperature was taken as the decomposition point.

Preparation of 5-(4-Pyridyl)hydantoin

Into a three-necked, 1-l. reaction flask fitted with a large-diameter air condenser and thermometer, was placed 86.4 g. (0.90 mole) of ammonium carbonate and 2.94 g. (0.45

mole) of potassium cyanide dissolved in 250 ml. of water. The resulting mixture was heated to 50°, then 31.8 gms (0.30 mole) 4-pryidinecarboxaldehyde dissolved in 250 ml. of ethanol was added to the mixture dropwise from a separatory funnel over a period of one hour. The resulting mixture was heated for three hours at 50°-55°. At the end of this time the reaction mixture was transferred to a 1-l. beaker and the alcohol evaporated on a steam bath. The mixture was cooled and the pH was adjusted to 7-8 using concentrated hydrochloric acid. The brown precipitate was removed by filtration. This crude product weighed 30 gms. The spectrum of this material is recorded in Fig. 1 of the Appendix. The product was then dissolved in a minimum amount of 5 per cent aqueous sodium hydroxide. The sodium hydroxide solution was then allowed to stand until precipitation of the mixed sodium salts of 5-(4-pyridyl)hydantoin and α-(4-pyridly)hydantoic acid was complete. A few ml. of saturated aqueous solution of sodium chloride was added to decrease the solubility of the salts. After the precipitated salts had been removed, the filtrate was saturated with carbon dioxide to obtain any hydantoin or hydantoic acid which did not salt out. The precipitate recovered from the saturated carbon dioxide solution was dissolved in a minimum amount of sodium hydroxide and allowed to precipitate as the sodium salt. The combined sodium salt mixture was then dissolved in water and decolorized

with norite. The aqueous solution was saturated with carbon dioxide and the precipitate was removed by filtration, dissolved in 10 per cent hydrochloric acid and allowed to stand approximately ten hours at room temperature. The solution was then diluted with an equal volume of water and neutralized with solid sodium bicarbonate. The precipitated hydantoin was removed by filtration, washed thoroughly with water to remove any sodium bicarbonate, and dried in vacuo. Fourteen grams of light cream-colored product was obtained. This represents a yield of 26 per cent of the theoretical. The decomposition point was found to be 331° as compared to 305°C reported by Henze and Knowles.[1] The infrared spectrum is recorded in Fig 2 of the Appendix. Per cent nitrogen calculated for $C_7H_8O_2N_3$ = 23.72; found: 23.76.

Preparation of ∝-(4-Pyridyl)hydantoic Acid

Five milliliters (0.00625 mole) of 5 per cent aqueous sodium hydroxide was added to one gram (0.00565 mole) of 5-(4-pyridyl)hydantoin. Water was added until all solid was dissolved and the solution was heated on a steam bath for five minutes. The solution was cooled, saturated with carbon dioxide, filtered and the precipitate was washed with water and dried in vacuo. One gram (0.00513 mole) of ∝-(4-pyridyl)-hydantoic acid representing 91 per cent of the theoretical

---

[1]Henze and Knowles, op. cit.

yield was obtained. The product was soluble in 5 per cent sodium bicarbonate solution and decomposed at 360-363° without melting but with some sublimation. The infrared spectrum is recorded in Fig. 3 of the Appendix. Per cent nitrogen calculated for $C_8H_9O_3N_3$:21.53; found: 21.54.

Conversion of α-(4-Pyridyl)hydantoic Acid to 5-(4-Pyridyl)hydantoin

Five ml. of 10 per cent hydrochloric acid (0.0139 mole) was added to one gram (0.00513 mole) of α-(4-pyridyl)-hydantoic acid. The mixture was allowed to stand at room temperature for ten hours. An equal volume of water was then added and the solution saturated with sodium bicarbonate. The product was filtered, washed with water, and dried in vacuo. The weight of the product was 0.85 g. (0.0048 mole) representing a yield of 93 per cent. The product had the same melting point as the 5-(4-pyridyl)hydantoin and a mixed melting point showed no lowering.

Reaction of 5-(4-Pyridyl)hydantoin with Hot Hydrochloric Acid

One gram (0.00565 mole) of 5-(4-pyridyl)hydantoin was heated with ten milliliters of 20 per cent hydrochloric acid on a steam bath for one hour. At this point no solid remained. The solution was saturated with sodium bicarbonate, filtered and the precipitate washed with water and dried in vacuo. The product (compound A) was dark yellow in color and

weighed 0.76 g. The melting point of the product was 283-285° (dec.). When recrystallized from dimethylformamide 5-(4-pyridyl)hydantoin was recovered. Recrystallization from methanol also gave 5-(4-pyridyl)hydantoin.[2] Compound A is soluble in acetic acid and after recovery from the acetic acid solution by dilution and neutralization with sodium bicarbonate the melting point is unchanged. An attempted methylation of A was carried out using 0.46 g. of compound suspended in a mixture of 0.92 g. (0.0065 mole) of methyl iodide in five milliliters of pyridine, and heating under pressure in a Carius tube at 120° for two hours. The only material recovered consisted of 0.39 g. (0.0022 mole) of 5-(4-pyridyl)hydantoin.

Compound A was also formed when α-(4-pyridyl)hydantoic acid was heated with hydrochloric acid in the same manner as described above.

Attempts to prepare a silver salt of A resulted in products of indefinite composition. Compound A was too insoluble in camphor to permit a molecular weight determination. The infrared spectrum of this material is shown in Fig. 4 of the Appendix, the sample being prepared with the vibrator, and in Fig.5, Appendix, as prepared by grinding with acetone. When the process of heating with hydrochloric acid was continued for another hour a product decomposing at 289° was

---

[2] Ibid.

obtained. The infrared spectrum of this material is shown in Fig. 6, Appendix. It is seen to be essentially the same as the spectrum of the crude product from the hydantoin preparation, Fig. 1, Appendix.

Compound A gave no test for halogen and contained 22.80 per cent nitrogen.

Bromination of 5-(4-Pyridyl)hydantoin

Four grams (0.0226 mole) of 5-(4-pyridyl)hydantoin was placed in a 100 milliliter, three-necked, round-bottomed flask fitted with a mercury-sealed stirer, thermometer, and a water-cooled condenser fitted with a calcium chloride drying tube. Fifty milliliters of anhydrous glacial acetic acid was added and the resulting suspension was heated to 70° with stirring. Four grams (0.025 mole) of bromine in ten milliliters of anhydrous glacial acetic acid was added to the hot mixture. The mixture was heated at 70-80° for eight hours, then cooled. The precipitate was removed by filtration using a calcium chloride drying tube in the funnel to protect the product from moisture in the air. The precipitate was washed with ten milliliters of glacial acetic acid followed by twenty milliliters of anhydrous ether. Four grams (0.016 mole) of light yellow product, representing 71 per cent of the theoretical yield of 5-bromo-5-(4-pyridyl)hydantoin was obtained. The decomposition point was 275-277°C (dec.). The product liberated iodine from an acidified aqueous solution

of potassium iodide. When the product was treated with 5 per cent sodium hydroxide 5-(4-pyridyl)hydantoin and α-(4-pyridyl)hydantoic acid were obtained. Hydrolysis with hot water gave a hydroxy derivative as described in the following experiment. The infrared spectrum of the bromo derivative is shown in Fig. 7, Appendix. Per cent bromine calculated for $C_8H_6O_2N_3Br$: 31.21; found: 30.90.

Preparation of 5-Hydroxy-5-(4-pyridyl)hydantoin

One gram (0.0039 mole) of 5-bromo-5-(4-pyridyl)hydantoin was added to ten milliliters of boiling water and heating was continued for a few minutes. The pH of the solution was adjusted to six with sodium bicarbonate and the resulting precipitate removed by filtration. Six-tenths gram of product melting at 134° with gas evolution but no coloration was obtained. The infrared spectrum of this compound is shown in Fig. 8, Appendix. This material was recrystallized from hot ethanol and gave 0.45 g. (0.00233 mole) of 5-hydroxy-5-(4-pyridyl)hydantoin. This represents a yield of 60 per cent of the theoretical. The melting point was 225° (dec.). The infrared spectrum is recorded in Fig. 9, Appendix. Per cent nitrogen calculated for $C_8H_7O_3N_3$: 21.75; found: 21.90 per cent.

Preparation of 5-(4-Pyridyl)hydantoin Perbromide

One gram (0.00565 mole) of 5-(4-pyridyl)hydantoin was added to ten milliliters of cold water. To the suspension

was added one gram (0.00625 mole) of bromine. The resultant mixture was stirred at room temperature until the color of the bromine had disappeared. The precipitate was removed by filtration and dried in vacuo. The product had an odor of bromine at room temperature. The yield was 1.75 g. (0.0052 mole) which represents 92 per cent of the theoretical. The decomposition point was 298-300° with liberation of bromine gas. The filtrate from the reaction mixture contained very little bromine as was evidenced by a test with silver nitrate. Heating the perbromo compound in water liberated some bromine gas and formed 5-hydroxy-5-(4-pyridyl)hydantoin. The infrared spectrum of the perbromo compound is shown in Fig. 10, Appendix.

Reaction of 5-Bromo-5-(4-pyridyl)hydantoin with Aniline

Two milliliters of dioxane was added to 0.5 g. (0.00195 mole) of 5-bromo-5-(4-pyridyl)hydantoin, and then 0.32 g. (0.0039 mole) of aniline was added to the mixture. The mixture was than heated on a steam bath for two hours and filtered. The precipitate was washed with dioxane, dried in vacuo, and weighed. The weight of product was 0.30 g. The melting point was the same as that of the hydantoin and a mixed melting point showed it to be 5-(4-pyridyl)hydantoin. No appreciable amount of material was obtained from the filtrate.

Reaction of 5-Bromo-5-(4-Pyridyl)hydantoin with Ammonia

Two milliliters of dioxane was added to 0.5 g. (0.00195 mole) of 5-bromo-5-(4-pyridyl)hydantoin. Ammonia gas was passed into the mixture for three hours. At this time all of the dioxane had evaporated and a white precipitate remained. This precipitate was suspended in water and filtered immediately. The precipitated product was shown to be 5-(4-pyridyl)hydantoin.

Reaction of 5-Bromo-5-(4-pyridyl)hydantoin with n-Butyl Alcohol

To 0.5 g. (0.00195 mole) of 5-bromo-5-(4-pyridyl)-hydantoin was added 3 ml. of pyridine. To this mixture 0.15 g. (0.002 mole) of n-butyl alcohol was added. The mixture was heated on a steam bath for thirty minutes. The reaction mixture was then filtered and there was obtained 0.25 g. (0.0141 mole) of 5-(4-pyridyl)hydantoin. The filtrate gave a negative Tollens test. From the filtrate 0.04 g. (0.00023 mole) of 5-(4-pyridyl)hydantoin was obtained.

Reaction of 5-Bromo-5-(4-pyridyl)hydantoin with t-Butyl Alcohol

Five milliliters of pyridine was added to 1 g. (0.0039 mole) of 5-bromo-5-(4-pyridyl)hydantoin. To this mixture was added 0.3 g. (0.0041 mole) of t-butyl alcohol. The mixture was then heated on a steam bath for thirty minutes. The reaction mixture was evaporated to dryness on a steam bath

and the residue was suspended in water and filtered. There was obtained in this manner 0.63 g. (0.00356 mole) of 5-(4-pyridyl)hydantoin.

Attempted Methylation of 5-(4-Pyridyl)hydantoin

Dimethyl sulfate in methanol.--One gram (0.00565 mole) of 5-(4-pyridyl)hydantoin was suspended in 20 ml. of methanol. Twenty-six hundreths gram (0.0113 mole) of sodium metal was added to the suspension and the hydantoin partially dissolved. Dimethyl sulfate, 1.43 g. (0.0113 mole), was added to the suspension and the mixture was heated at 55° until it began to darken in color. The reaction mixture was allowed to cool for one hour during which time some additional precipitation took place. The precipitate was removed by filtration and was found to consist of 0.72 g. (0.00405 mole) of 5-(4-pyridyl)hydantoin. From the filtrate an additional 0.20 g. (0.00113 mole) of the unchanged hydantoin was recovered.

Dimethyl sulfate in pyridine.--Twenty milliliters of pyridine and 1.43 g. (0.0113 mole) of dimethyl sulfate were added to one gram (0.00565 mole) of 5-(4-pyridyl)hydantoin. The mixture was heated on a steam bath for one hour and then evaporated to dryness by air. The residue was dissolved in a minimum amount of 5 per cent sodium hydroxide and acidified immediately with carbon dioxide and filtered. The precipitate consisted of 0.88 g. (0.00497 mole) of unchanged 5-(4-pyridyl)-hydantoin.

Methyl iodide pyridine.--One gram (0.00565 mole) of 5-(4-pyridyl)hydantoin, 2.0 g. (0.0141 mole) of methyl iodide, and ten milliliters of pyridine were mixed in a Carius tube, which was sealed and heated in a furnace at 120-130° for thirteen hours. The mixture was removed from the tube by washing with ether, and evaporated to dryness on a steam bath. The residue was suspended in water and filtered. The precipitate was found to be unchanged hydantoin, as shown by a mixed melting point. The recovery amounted to 0.98 g. (0.0055 mole).

Methyl iodide in dioxane.--One g. (0.00565 mole) of 5-(4-pyridyl)hydantoin, ten milliliters of dioxane, and 20 g. (0.0146 mole) of methyl iodide were mixed in a Carius tube, and the tube was sealed and heated at 120° for six hours. The mixture was washed out of the tube with ether, evaporated to dryness by steam, suspended in water and filtered. The product was found to be 0.99 g. (0.0056 mole) of 5-(4-pyridyl)-hydantoin by mixed melting point.

Reaction of 5-(4-Pyridyl)hydantoin with One-half Mole of Bromine in Acetic Acid

One gram (0.0056 mole) of 5-(4-pyridyl)hydantoin was added to 30 ml. of acetic acid containing 0.48 g. (0.003 mole) of bromine. The mixture was refluxed for one hour, cooled and the remaining precipitate separated by filtration. The weight of this precipitate was 1.0 g. The precipitate

was heated with water for 15-20 minutes and the mixture filtered. The precipitate weighed 0.42 g. (0.0024 mole) and was found to be 5-(4-pyridyl)hydantoin. The aqueous filtrate was evaporated to about one-third of its original volume and the pH adjusted to 6 with sodium bicarbonate. The precipitate which formed was filtered and recrystallized from ethanol. There was obtained 0.25 g. (0.0013 mole) of 5-hydroxy-5-(4-pyridyl)hydantoin. From the acetic acid filtrate of the initial reaction mixture an additional 0.05 g. (0.0003 mole) of 5-(4-pyridyl)hydantoin was recovered.

Reaction of 5-(4-Pyridyl)hydantoin with One-half Mole of Bromine in Water

Five-tenths gram (0.0028 mole) of 5-(4-pyridyl)hydantoin was suspended in ten milliliters of water and 0.24 g. (0.0015 mole) of bromine was added. The mixture was stirred at room temperature until the bromine color disappeared and then heated on a steam bath for fifteen minutes. The mixture was cooled and the precipitate was filtered, dried, and weighed. It consisted of 0.23 g. (0.0013 mole) of 5-(4-pyridyl)-hydantoin as shown by a mixed melting point. The pH of the filtrate was raised to 6 by adding sodium bicarbonate and the solution allowed to stand in the refrigerator. The precipitate was filtered and found to have a melting point of 132-134°C which corresponds to the hydrated form of 5-hydroxy-5-(4-pyridyl)hydantoin. This precipitate was recrystallized

from ethanol and 0.15 g. (0.008 mole) of 5-hydroxy-5-(4-pyridyl)hydantoin was obtained.

Reaction of 5-(4-Pyridyl)hydantoin with 5-Bromo-5-(4-pyridyl)hydantoin

Five-tenths gram (0.0028 mole) of 5-(4-pyridyl)hydantoin and 0.72 g. (0.0028 mole) of 5-bromo-5-(4-pyridyl)hydantoin were mixed in fifty milliliters of glacial acetic acid and refluxed for two hours. The reaction mixture was cooled and filtered, resulting in 1.1 g. of precipitate. The precipitate was then heated with water on a steam bath for fifteen minutes, and filtered. There was obtained 0.33 g. (0.0019 mole) of 5-(4-pyridyl)hydantoin. The pH of the aqueous filtrate was adjusted to 6 with sodium bicarbonate and the solution allowed to crystallize. The precipitate was filtered and recrystallized from ethanol giving 0.31 g. (0.0016 mole) of 5-hydroxy-5-(4-pyridyl)hydantoin. From the acetic acid filtrate from the initial reaction mixture 0.15 g. (0.00085 mole) of 5-(4-pyridyl)hydantoin was recovered.

Reaction of 5-(4-Pyridyl)hydantoin with Potassium Permanganate

Five-tenths gram (0.0028 mole) of 5-(4-pyridyl)hydantoin was suspended in about 25ml. of water and dissolved by the addition of dilute sulfuric acid. Then 0.188 g. (0.0012 mole) of potassium permanganate dissolved in a minimum amount of water was added to the solution of the hydantoin. The mixture was stirred at room temperature for fifteen minutes,

after which time the color was lighter, and then was heated on a steam bath for thirty minutes and filtered. The precipitate was inorganic in nature. The filtrate was cooled and sodium bicarbonate was added to adjust the pH to 6-7 at which point precipitation occurred. This material consisted of 0.12 g. (0.00068 mole) of 5-(4-pyridyl)hydantoin. The mixture was filtered immediately and the filtrate evaporated to about one-third its volume and chilled in the refrigerator. The crystals thus obtained were 5-hydroxy-5-(4-pyridyl)-hydantoin hydrate. After recrystallization from ethanol 0.24 g. (0.00125 mole) of 5-hydroxy-5-(4-pyridyl)hydantoin was obtained.

Reaction of 5-(4-Pyridyl)hydantoin with Sodium Hypochlorite

Five-tenths gram (0.0028 mole) of 5-(4-pyridyl)hydantoin was suspended in water, and 0.23 g. (0.0031 mole) of sodium hypochlorite (as "Purex" solution) was added to the water suspension. The solution which resulted was stirred for ten minutes, a white precipitate appearing during this time. The mixture was cooled and the solid removed by filtration, washed with water and dried. The precipitate gave a negative Beilstein test for halogen and had a decomposition point of about 355°. A mixed melting point with α-4-pyridylhydantoic acid showed no depression. A total of 0.5 g. (0.00256 mole) of α-(4-pyridyl)hydantoic acid was recovered.

Reaction of 5-(4-Pyridyl)hydantoin with Chlorine in Water

Twenty-five hundredth gram (0.0014 mole) of 5-(4-pyridyl)hydantoin was suspended in water and chlorine gas was passed through the mixture for one hour. At the end of this time a precipitate remained which weighed 0.15 g. and which gave a positive Beilstein test for halogen. From this precipitate after further washing there was recovered some 5-(4-pyridyl)hydantoin and some 5-hydroxy-5-(4-pyridyl)-hydantoin. The weights of products obtained were not available due to breakage of the centrifuge tube.

Reaction of 5-(4-Pyridyl)hydantoin with Chlorine in Acetic Acid

Thirty milliliters of acetic acid was added to 1.0 g. (0.00565 mole) of 5-(4-pyridyl)hydantoin. Chlorine gas was passed through this solution for four hours at room temperature. The mixture was filtered and the precipitate washed with anhydrous ether and dried. It consisted of 0.97 g. (0.00548 mole) of 5-(4-pyridyl)hydantoin.

Preparation of Sodium α-(4-Pyridyl)hydantoate

A slight excess of 5 per cent sodium hydroxide was added to approximately 0.5 g. of α-(4-pyridyl)hydantoic acid. The sodium salt precipitated immediately and was filtered and pressed dry between filter papers. The infrared spectrum of the salt is shown in Fig. 11, Appendix. Per cent sodium calculated for $C_8H_8O_3N_3Na$: 10.60; found 10.38 per cent.

Preparation of 5-(4-Pyridyl)hydantoin Hydrochloride

About 0.5 g. of 5-(4-pyridyl)hydantoin was suspended in a small amount of water and concentrated hydrochloric acid was added until the hydantoin just dissolved. Then an excess of concentrated hydrochloric acid was added until precipitation of the hydrochloride took place. The mixture was allowed to stand in the refrigerator for several hours until precipitation of the hydrochloride was complete. The product was filtered and pressed dry on filter paper. The infrared spectrum is shown in Fig. 12, Appendix.

Preparation of Sodium 5-Phenylhydantoinate

About 0.5 gram of 5-phenylhydantoin was suspended in water and 5 per cent sodium hydroxide was added until the solid just dissolved. Saturated sodium chloride solution was then added to the solution and the precipitated sodium salt was filtered and pressed dry between filter paper. The infrared spectrum of the salt is shown in Fig. 13, Appendix. Per cent sodium calculated for $C_9H_7O_2N_2Na$: 11.63; found 11.48.

The pK_a of 5-phenylhydantoin was determined by a potentiometric titration of the sodium salt with hydrochloric acid. Nitrogen gas was bubbled through the salt solution to exclude carbon dioxide. The titration curve is shown in Fig. 14, Appendix. The pK_a as estimated from the half-equivalence point is 8.1.

CHAPTER III

DISCUSSION

The nature of the crude product (compound A) from the preparation of 5-(4-puridyl)hydantoin is unknown. It is interconvertible with the hydantoin:

$$\text{Compound A} \underset{H_3O^+}{\overset{\bar{O}H}{\rightleftharpoons}} \text{5-(4-pyridyl)hydantoin}$$

In addition it is apparently converted to the hydantoin in the process of recrystallization from certain solvents. The increased color as compared with the hydantoin suggests enhanced resonance, and the shifts to longer wave-lengths of the NH and CO absorptions suggests involvement of these groups. Reliable elementary analyses are not available for compound A at present and little can be done toward proving its structure until accurate analyses are ontained.

5-(4-Pyridyl)hydantoin undergoes the reversible change to the hydantoic acid with great ease even at room temperature.

$$\text{5-(4-pyridyl)hydantoin} + H_2O \underset{H_3O^+}{\overset{\bar{O}H}{\rightleftharpoons}} \alpha\text{-(4-pyridyl)-}$$

hydantoic acid. In fact it is difficult to form the salt of the hydantoin. This change takes place much more readily than in the case of 5-phenylhydantoin. Failure of the

hydantoin to form a methyl derivative in water solution with dimethyl sulfate and alkali could be related to this fact. However, the compound was not alkylated in non-aqueous media either. This failure of the hydantoin to form a methyl derivative is difficult to understand.

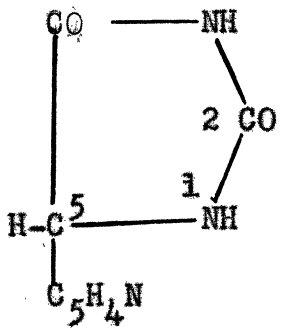
Efforts to produce a di-(4-pyridyl)hydantil analogous to diphenylhydantil by oxidation with half-molar quantities of bromine in water or acetic acid resulted only in partial oxidation to the 5-hydroxy derivative. Oxidation with $KMnO_4$ solution likewise resulted in formation of the hydroxy compound. This is in contrast to the behavior of 5-(3-pyridyl)-hydantoin which is oxidized in alkaline solution by oxygen from the air to the hydantil derivative.[1]

Bromination of 5-(4-pyridyl)hydantoin at room temperature formed a compound with analysis and properties suggesting a perbromide. On the other hand, bromination in hot acetic acid formed a monobromo derivative.

Substitution of halogen α- to a carbonyl group has been shown by many investigators to produce a shift to higher frequencies of the carbonyl band, presumably by an inductive effect. Substitution of halogen or other electronegative group in position 5 of the hydantoin ring might be expected

---

[1] Calvin Banta, "Studies in the Hydantoin Series. II, 5-(3-Pyridyl)hydantoin and Its Derivatives," unpublished master's thesis, Department of Chemistry, North Texas State College, Denton, Texas, August, 1957.



to produce a high-frequency shift for the 4-CO band, and to a much lesser extent for the 2-CO. Similarly, substitution in position 1 should affect the 2-CO while substitution in position 3 should affect both carbonyl absorptions.

In the case of the bromo derivatives substitution in positions 1 and 3 is ruled out by the fact that the NH absorption at about 3.1 μ shows no decrease in intensity as compared with the unsubstituted hydantoin. The 4-CO absorptions as shown in the following table are consistant with the structures assigned. 5-(4-Pyridyl)hydantoin dibromide of unknown structure is included also.

TABLE I

INFRARED ABSORPTION OF HYDANTOIN DERIVATIVES

Compound	Wavelength, microns	
	4-CO	2-CO
5-(4-Pyridyl)hydantoin	5.62	5.84
5-Bromo-5-(4-pyridyl)hydantoin	5.55	5.87
5-Hydroxy-5-(4-pyridyl)hydantoin	5.51	5.75
5-(4-Pyridyl)hydantoin dibromide	5.56	5.82

The monobromo compound gives a hydroxy derivative on hydrolysis with hot water. The hydroxy compound shows a decided shift in both CO bands as shown in Table I. In view of all these facts the bromine atom in the monobromo derivative is assigned to position 5.

The dibromo derivative has essentially the same spectrum as the monobromo. The NH band has about the same position and intensity and the shift in the 4-CO band is comparable. The 2-CO band is shifted by very small amounts in opposite directions in the two compounds.

The structure of the dibromide must be left open for the present.

Attempts to form 5-amino or alkoxy derivatives by reaction of 5-bromo-5-(4-pyridyl)hydantoin with ammonia, aniline, n-butyl alcohol, and t-butyl alcohol all resulted in reduction of the bromo compound to 5-(4-pyridyl)hydantoin. Thus the bromo compound has a strong tendency to form Br^+ rather than Br^-. While 5-bromo-5-phenylhydantoin like 5-bromo-5-(4-pyridyl)hydantoin liberates iodine from acidified I^- solution, yet it has a greater tendency to form Br^- and gives a variety of 5-hetero derivatives (see footnotes 3-7). 5-Bromo-5-(3-pyridyl)hydantoin seems to be intermediate between these two.[2]

---

[2] Ibid.

The determination of pK_a and pK_b for 5-(4-pyridyl)-hydantoin did not give reliable results due to precipitation of the hydantoin during titration of the salts. However, pK_a for 5-phenylhydantoin was determined and was found to be 8.1 as compared with hydantoin, 9.12. Thus the phenyl group would appear to exert a definite inductive effect on the hydantoin ring. In contrast Zief and Edsall[3] have shown the pK_a of 5,5-dimethylhydantoin, 9.19, to be essentially the same as that of hydantoin.

---

[3]Norris Zief and John T. Edsall, "The Dissociation Constants of Some Amino Derivatives," Journal of American Chemical Society, LIX (1937), 2246.

APPENDIX

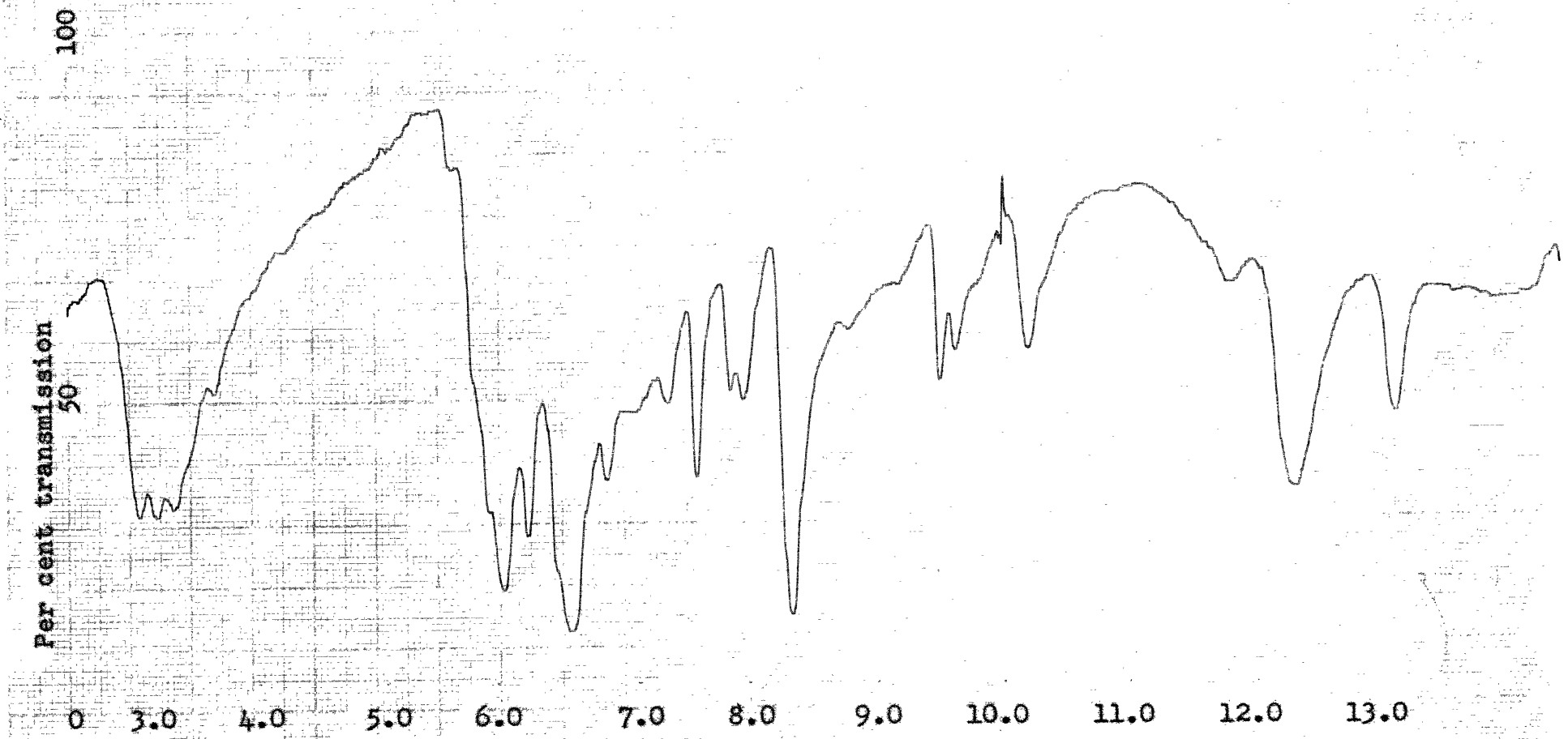


Fig. 1--Crude product from preparation of 5-(4-pyridyl)hydantoin. 0.4 mg. in 319 mg. KBr. Acetone preparation.

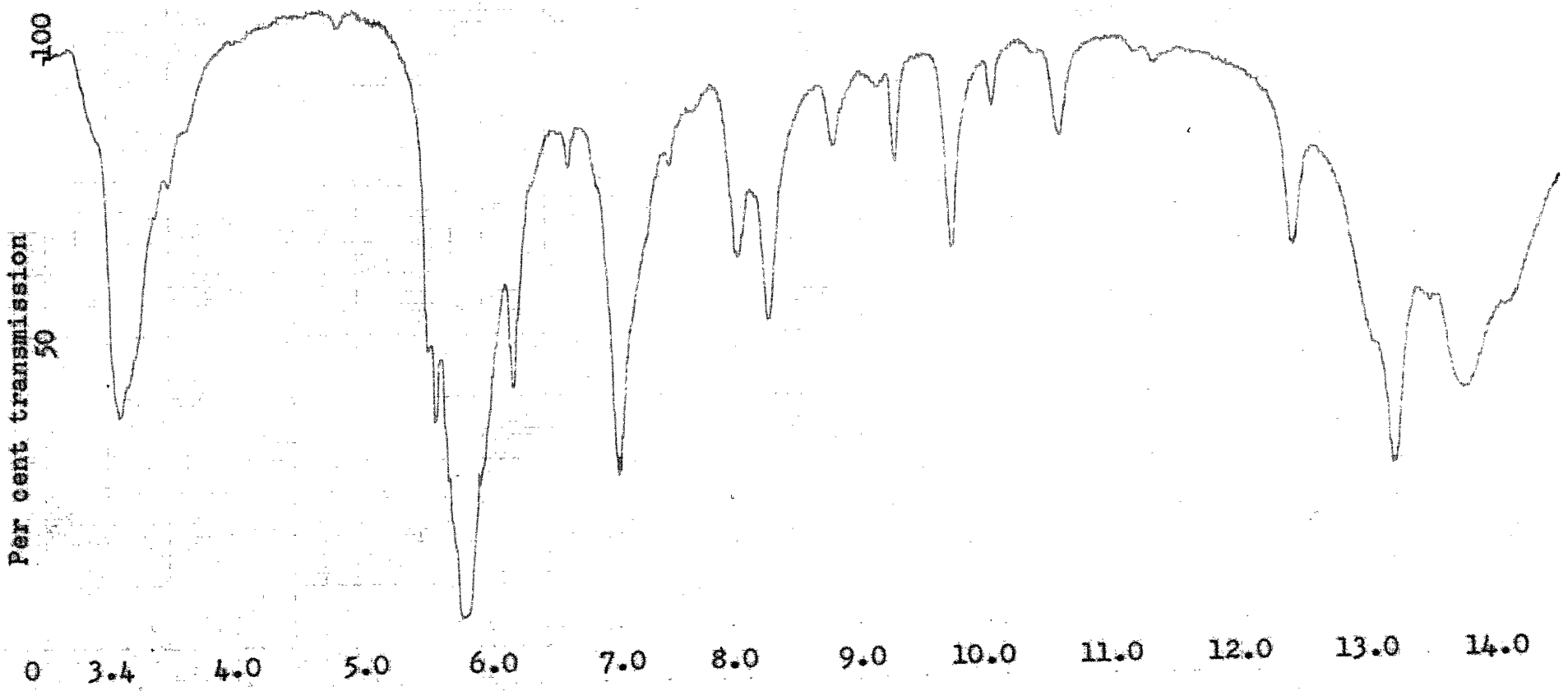


Fig. 2--5-(4-Pyridyl)hydantoin. 0.7 mg. in 300 mg. KBr. Vibrator preparation.

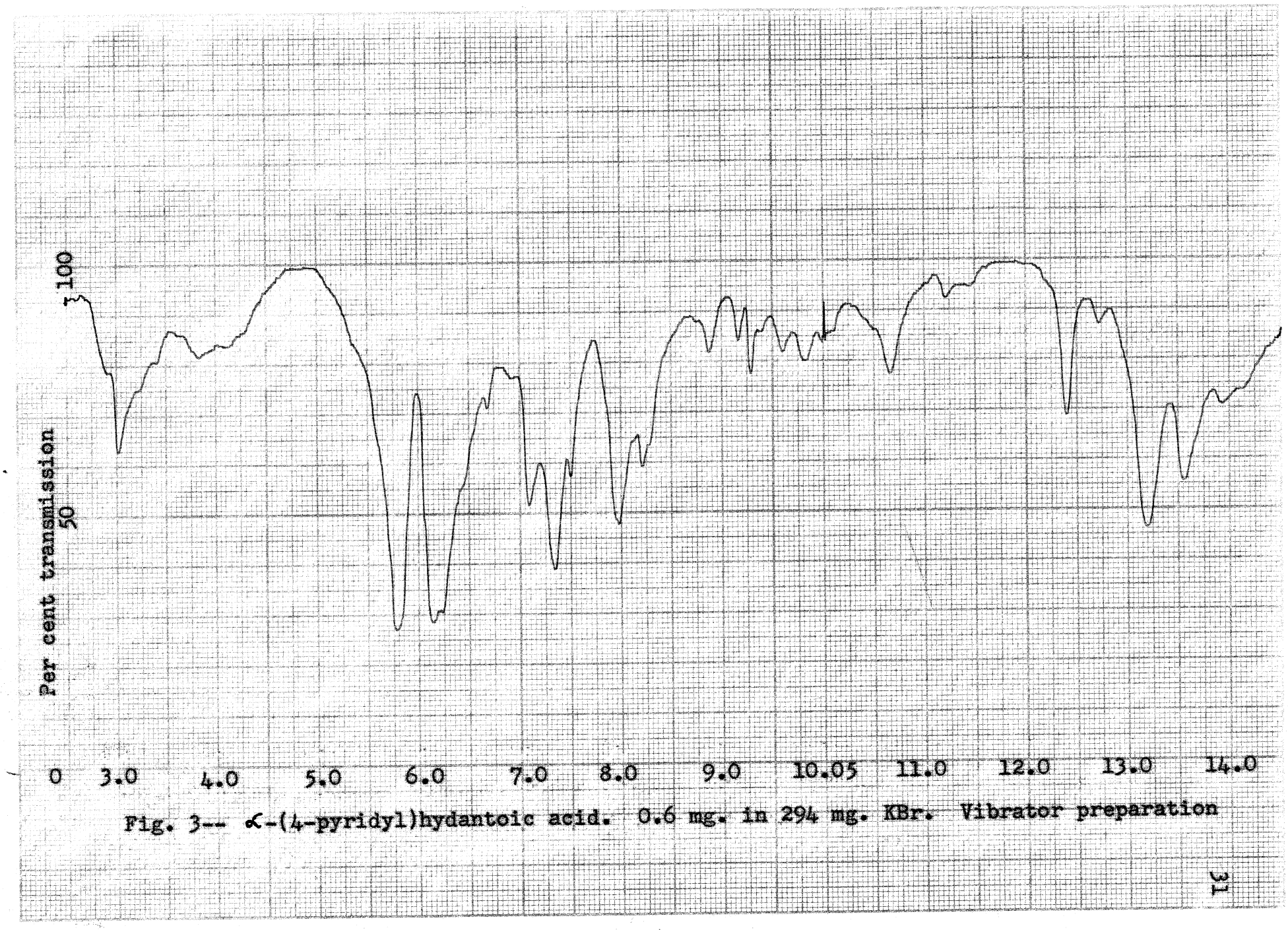


Fig. 3-- ∝-(4-pyridyl)hydantoic acid. 0.6 mg. in 294 mg. KBr. Vibrator preparation

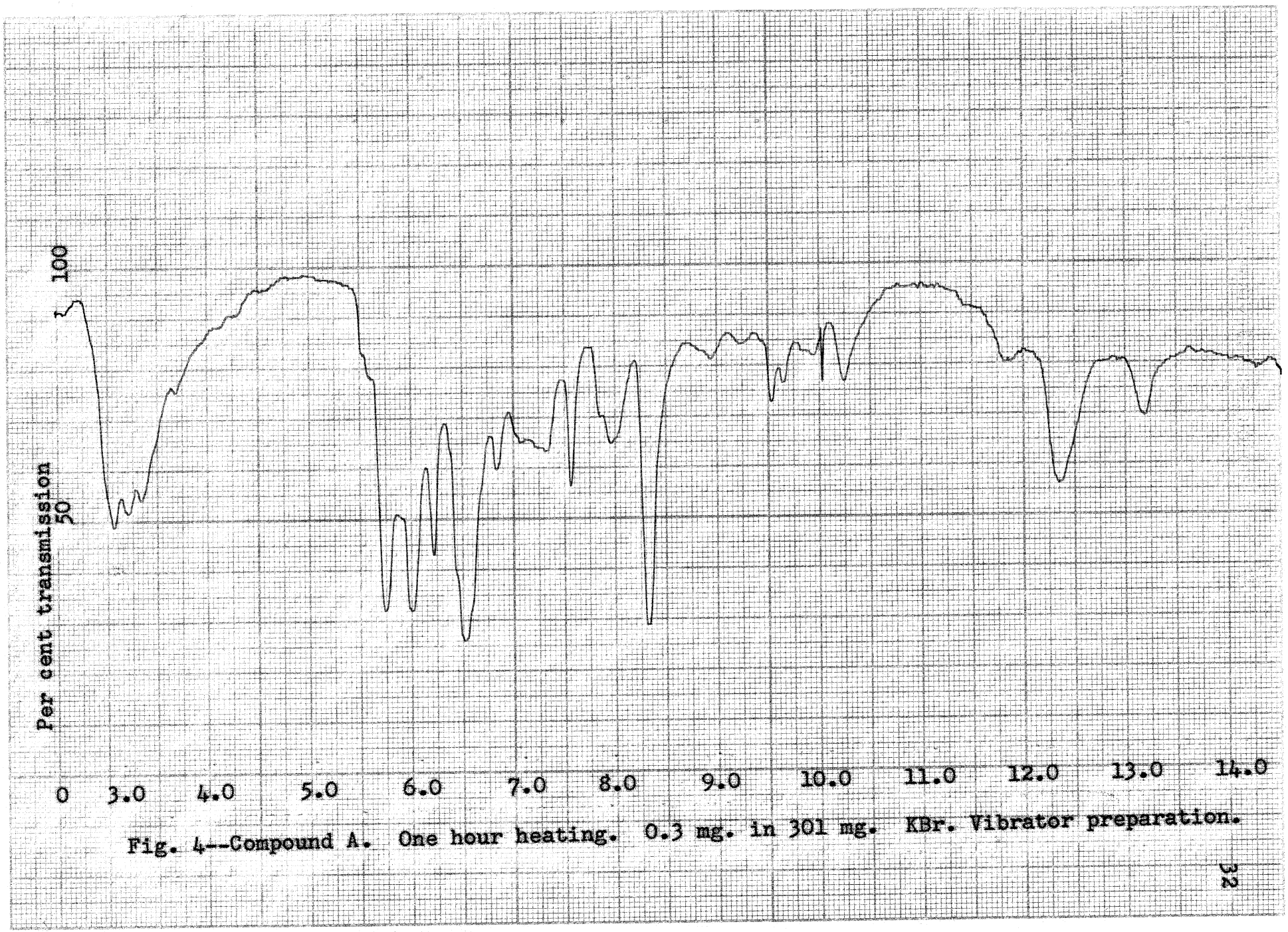


Fig. 4--Compound A. One hour heating. 0.3 mg. in 301 mg. KBr. Vibrator preparation.

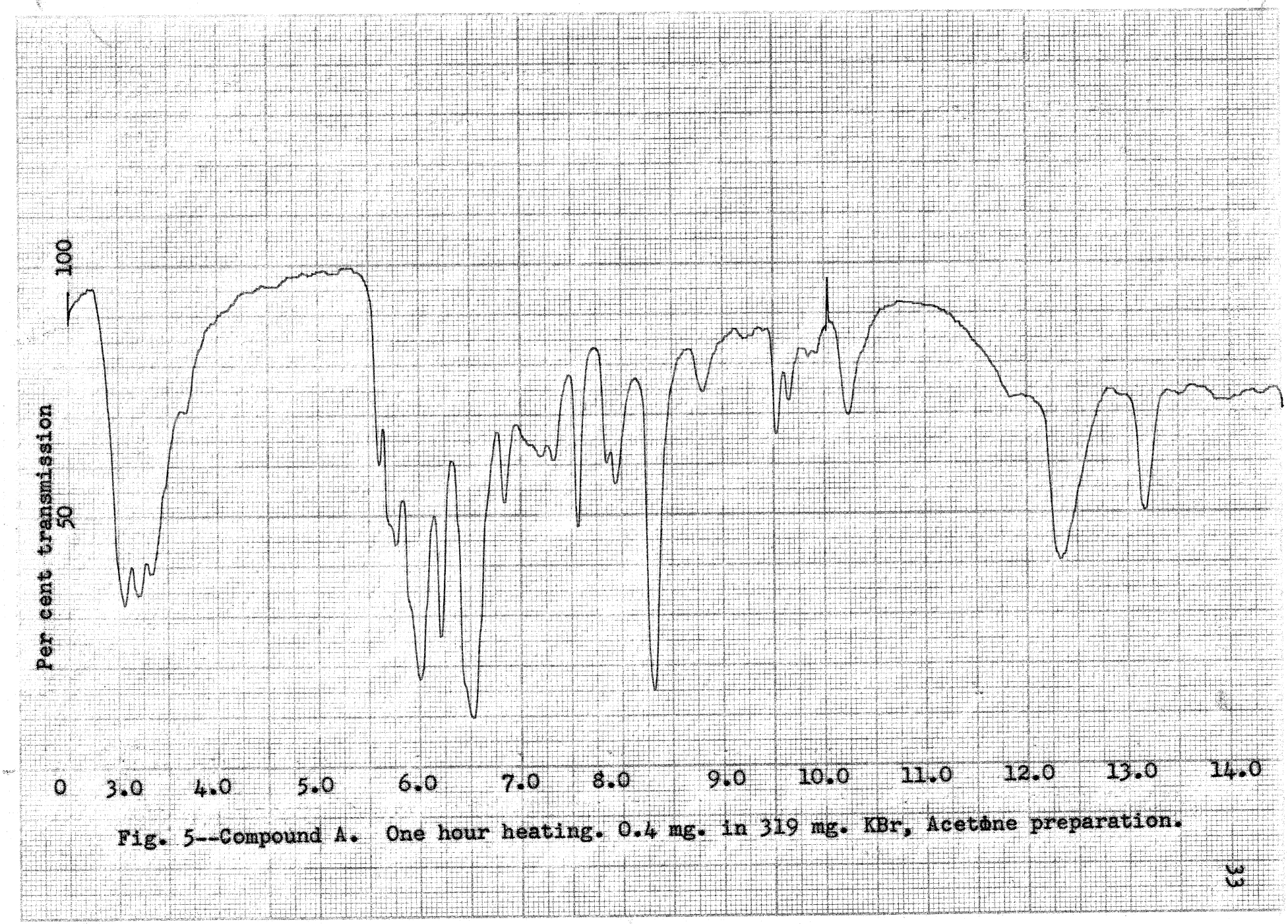


Fig. 5--Compound A. One hour heating. 0.4 mg. in 319 mg. KBr, Acetone preparation.

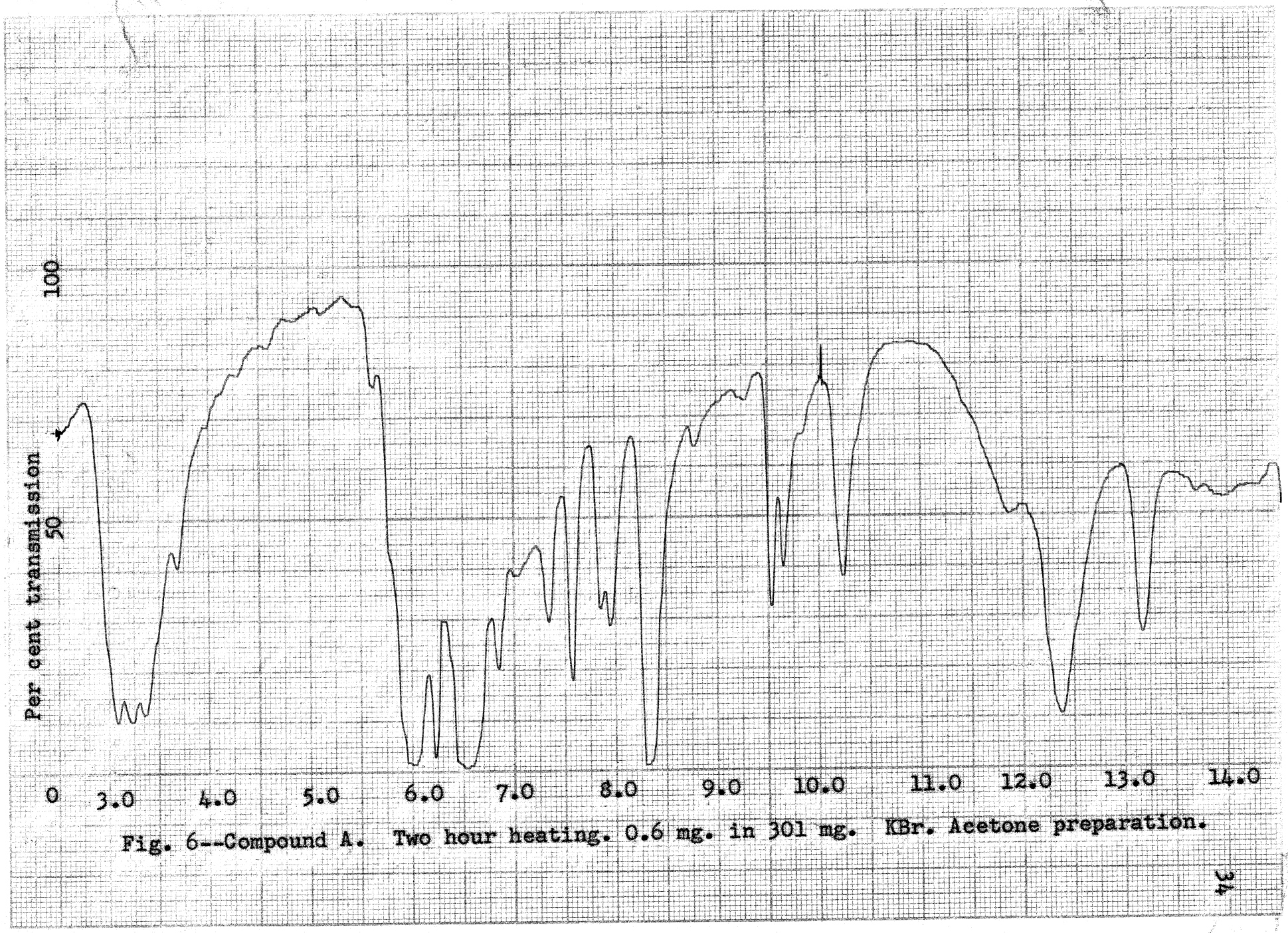


Fig. 6--Compound A. Two hour heating. 0.6 mg. in 301 mg. KBr. Acetone preparation.

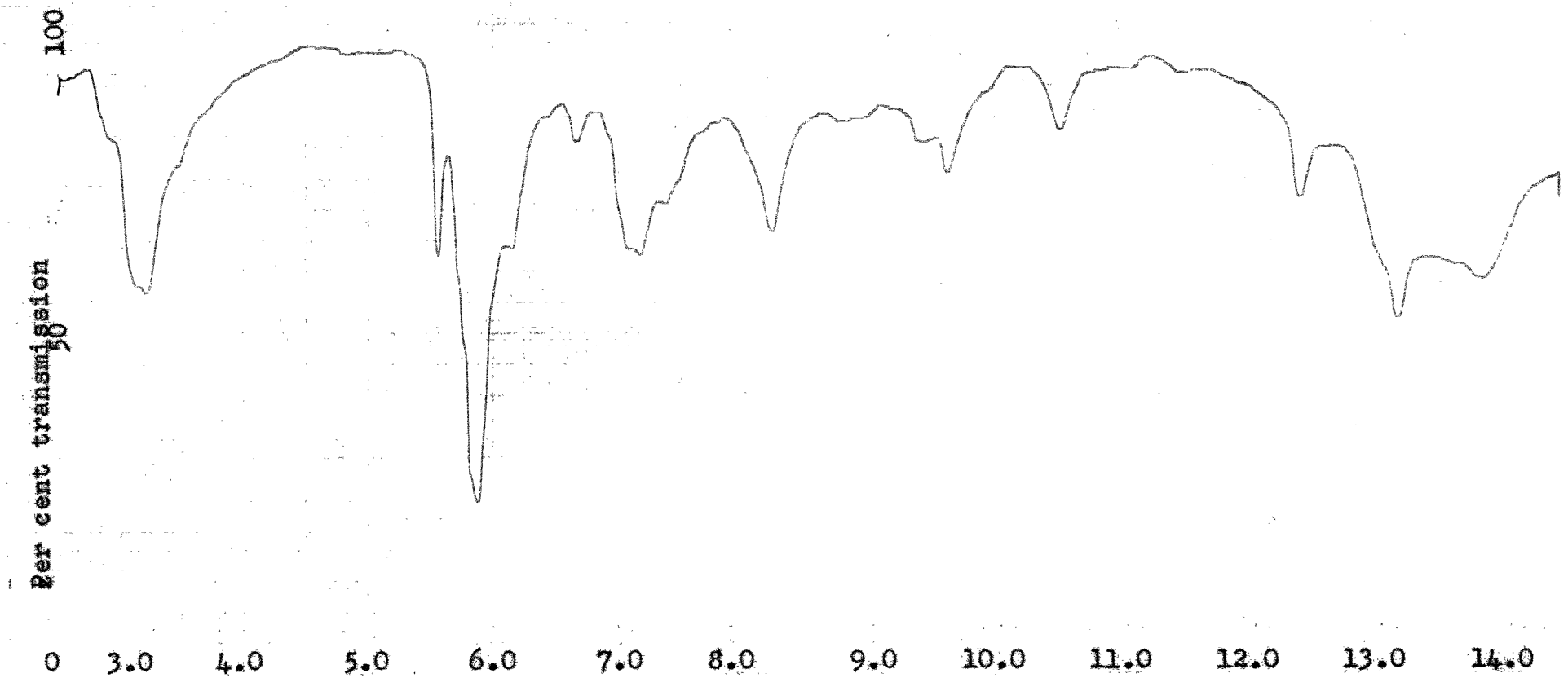


Fig. 7--5-Bromo-5-(4-pyridyl)hydantoin. 0.7 mg. in 305 mg. KBr. Vibrator preparation.

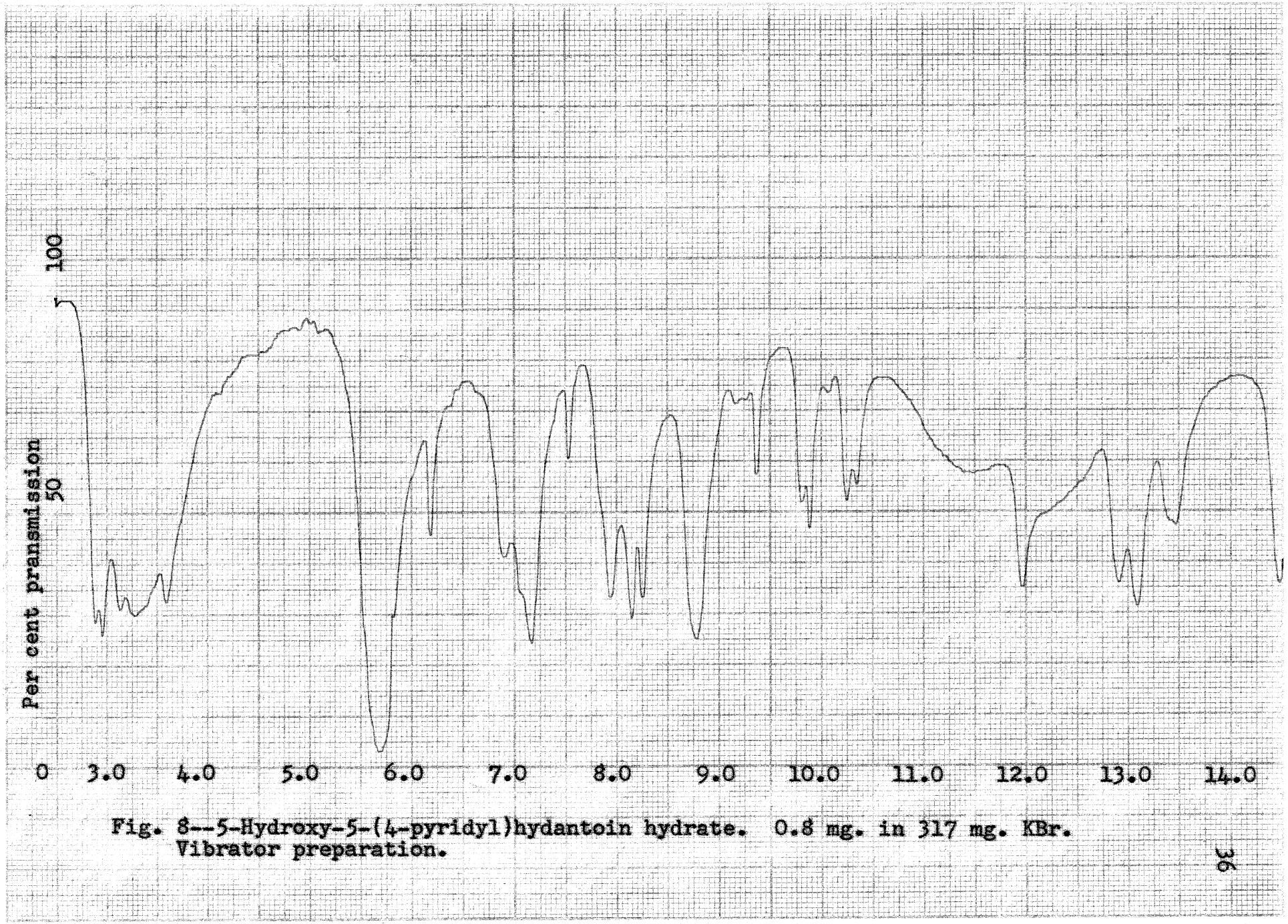


Fig. 8--5-Hydroxy-5-(4-pyridyl)hydantoin hydrate. 0.8 mg. in 317 mg. KBr. Vibrator preparation.

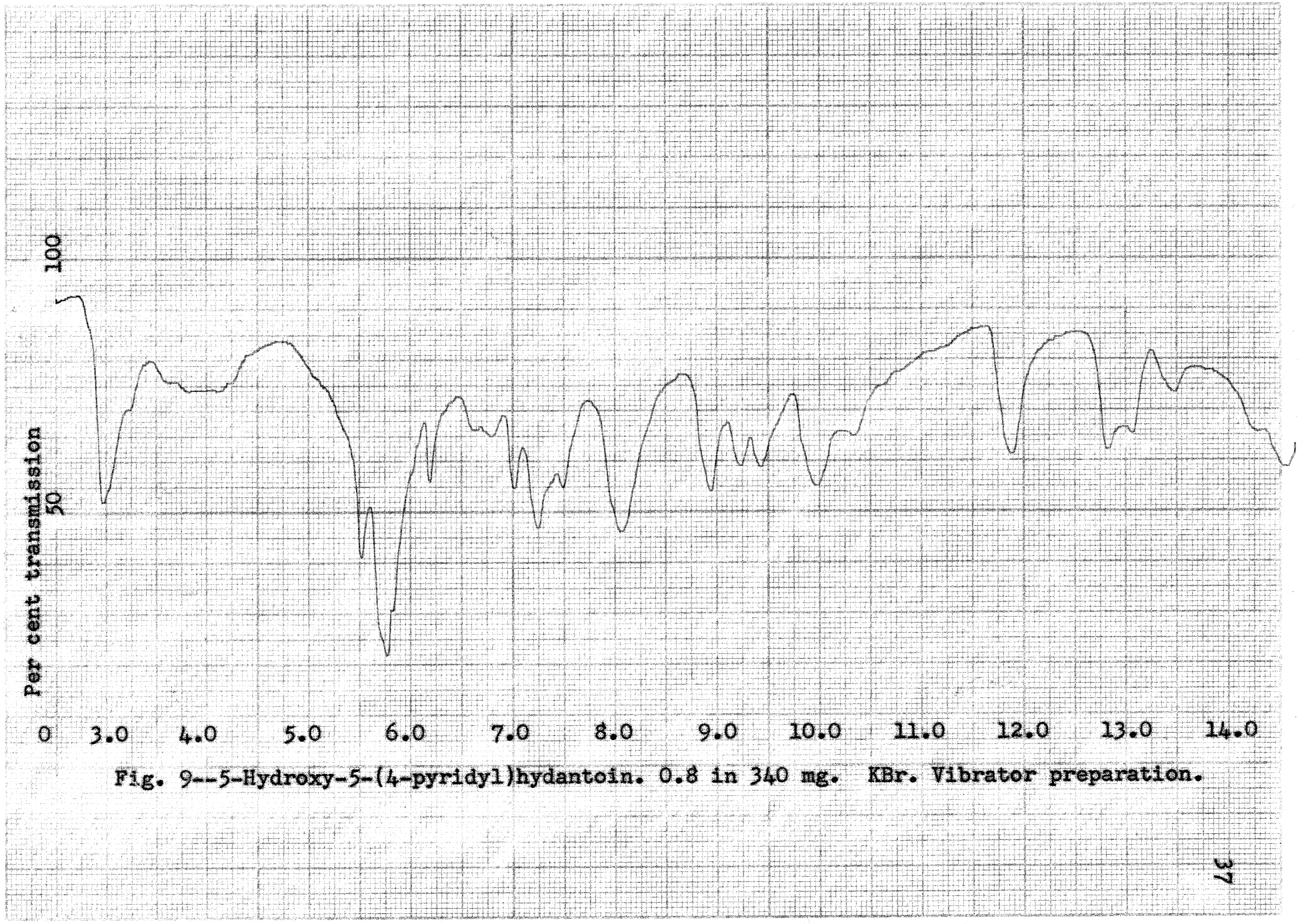


Fig. 9--5-Hydroxy-5-(4-pyridyl)hydantoin. 0.8 in 340 mg. KBr. Vibrator preparation.

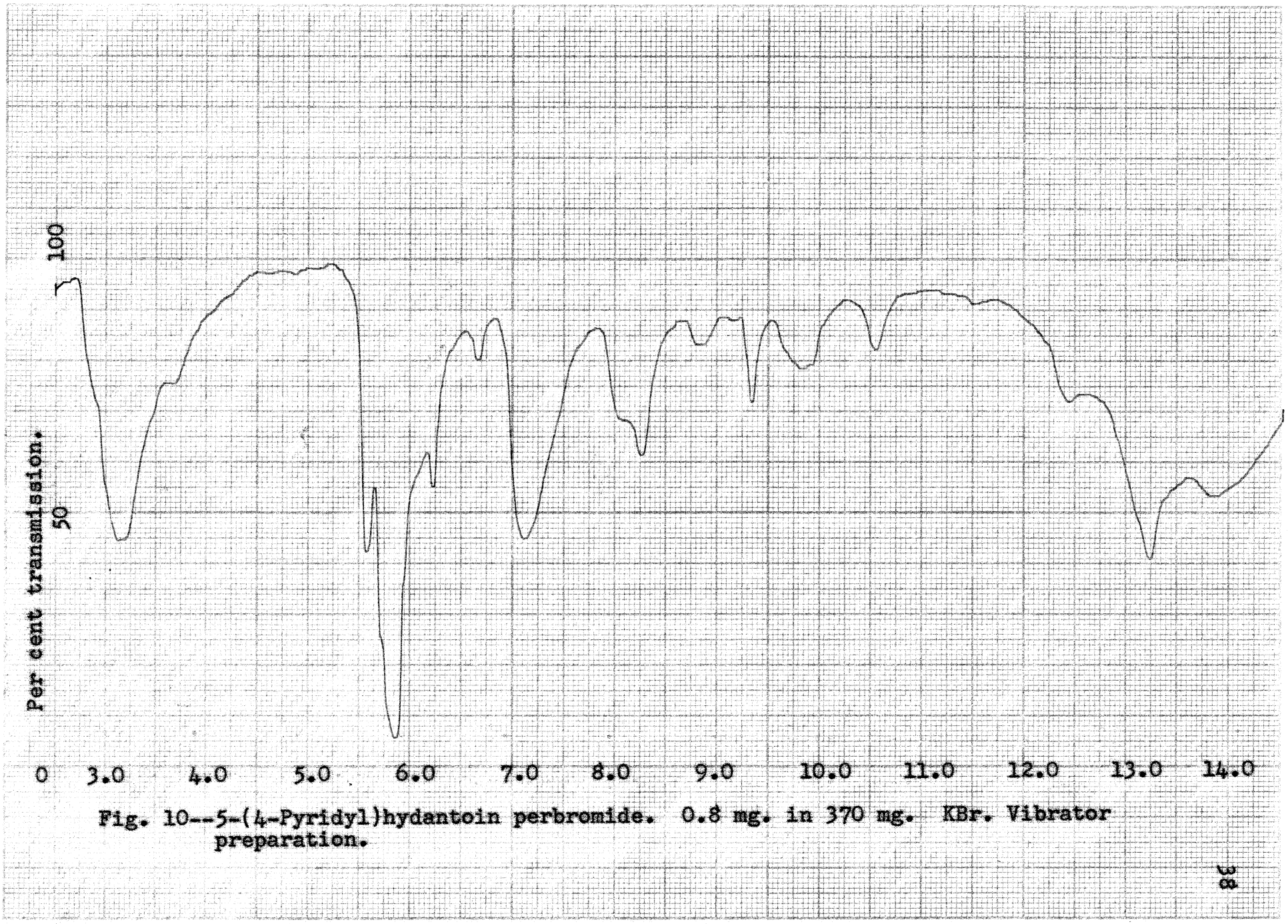


Fig. 10--5-(4-Pyridyl)hydantoin perbromide. 0.8 mg. in 370 mg. KBr. Vibrator preparation.

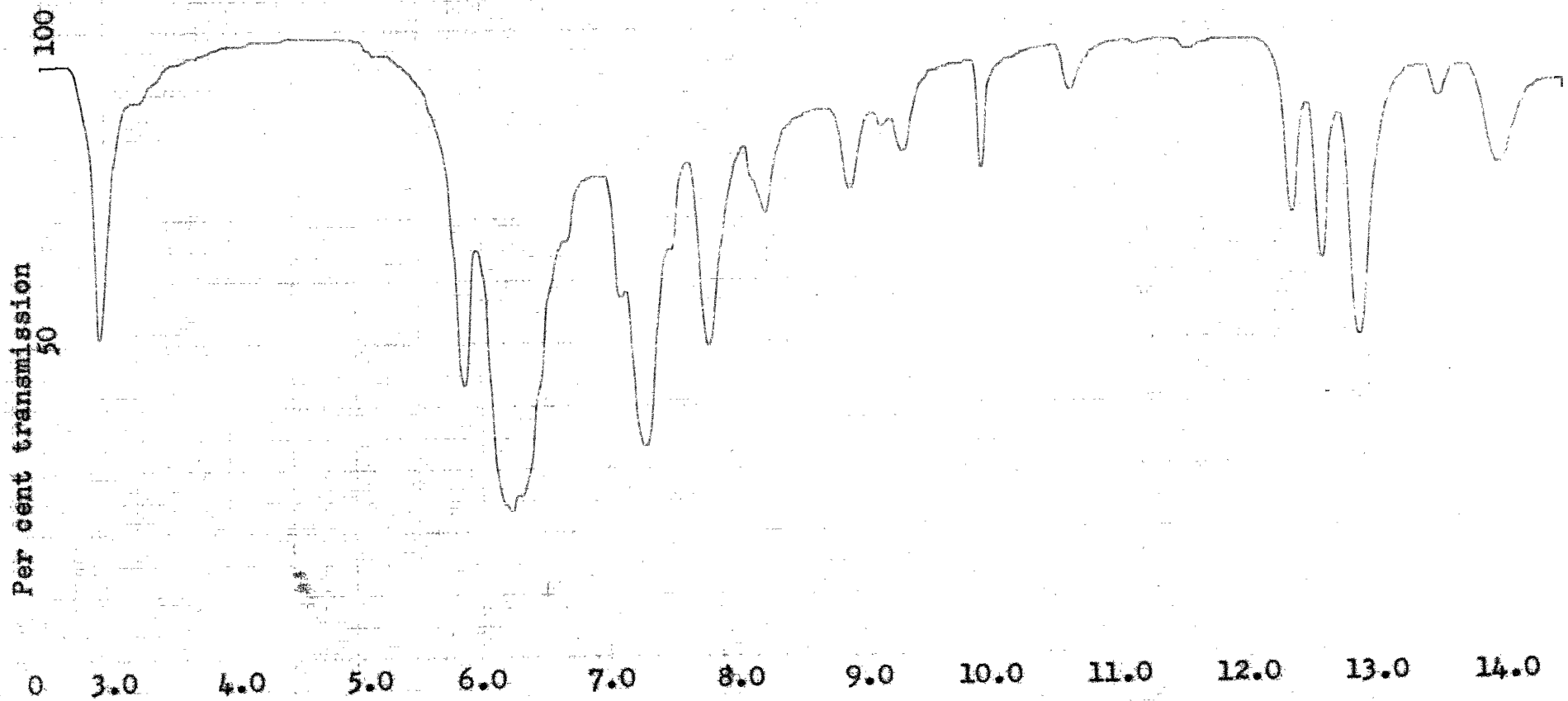


Fig. 11--Sodium ∝-(4-pyridyl)hydantoate. 0.0 mg. in 307 mg. KBr.
Vibrator preparation.

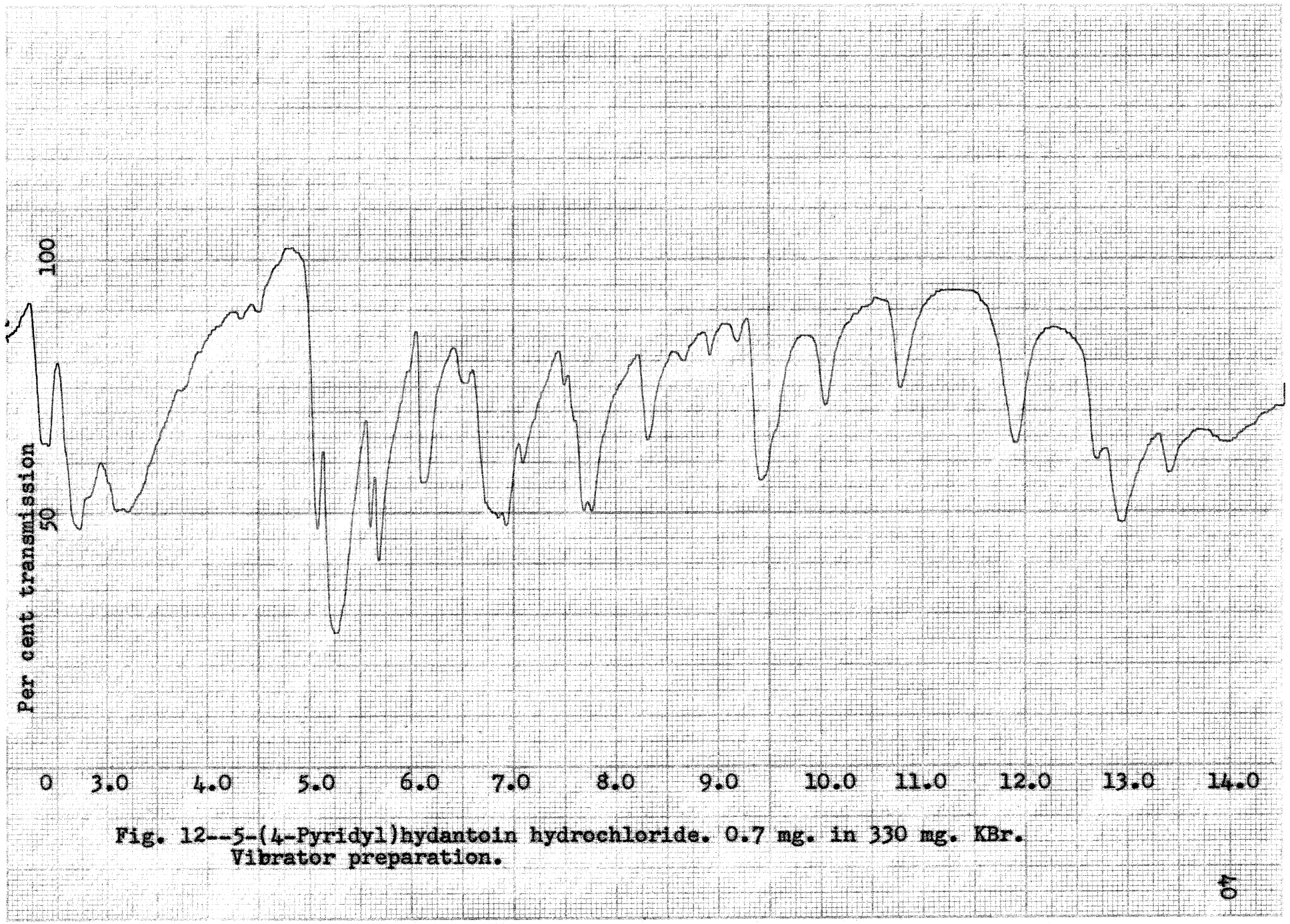


Fig. 12--5-(4-Pyridyl)hydantoin hydrochloride. 0.7 mg. in 330 mg. KBr. Vibrator preparation.

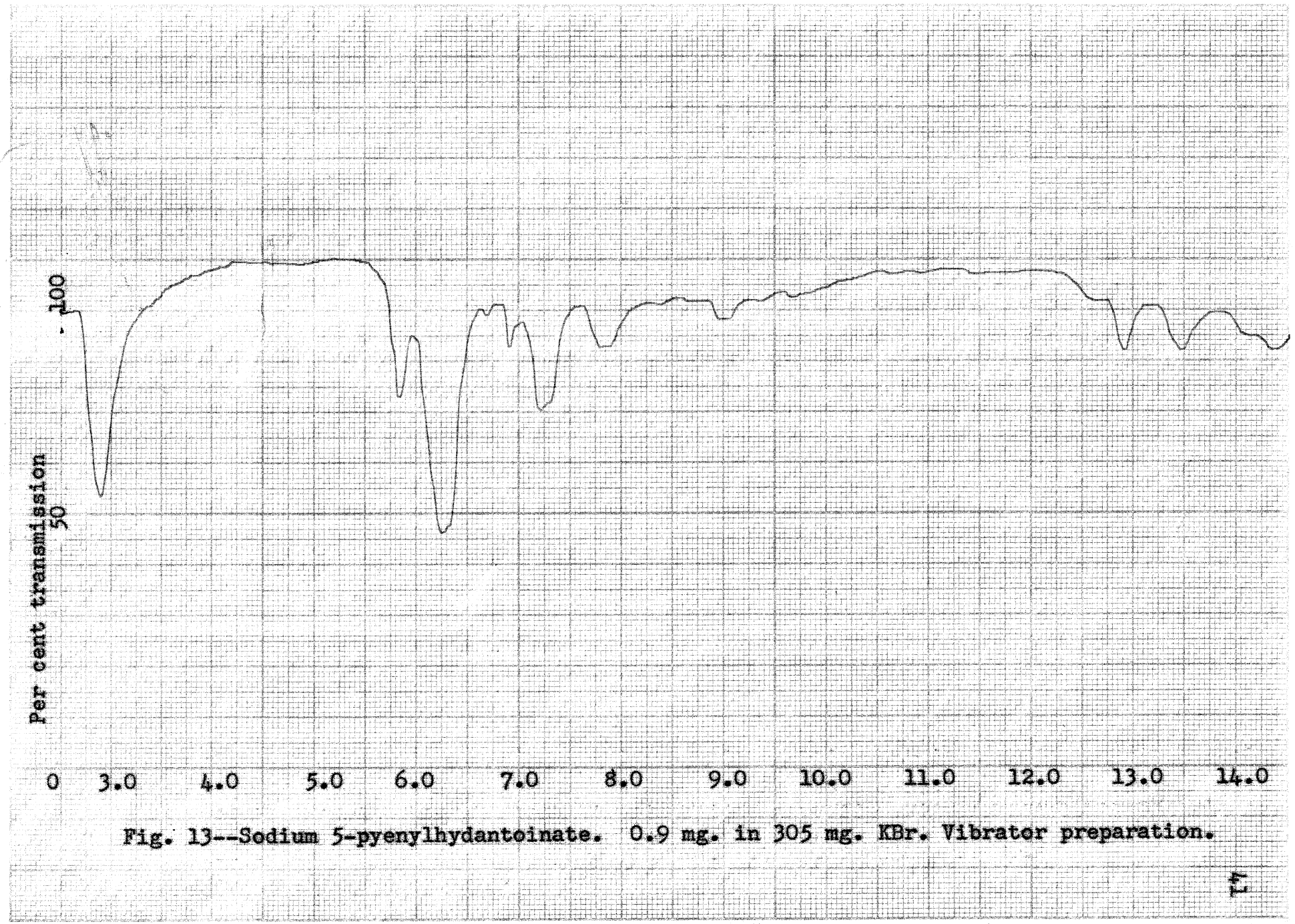


Fig. 13--Sodium 5-pyenylhydantoinate. 0.9 mg. in 305 mg. KBr. Vibrator preparation.

Fig. 14.—Titration of sodium 5-phenylhydantoinate.
C.00 67g. sample using approximately .05 N_1 Hcl.

BIBLIOGRAPHY

Books

Mosher, H. S., and others, Three-, Four-, Five-, and Six-Membered Monocyclic Compounds Containing One O, N, and S Atom, Vol. I of Heterocyclic Compounds, edited by Elderfield, R. C. (4 volumes), New York, John Wiley and Sons, Inc., 1950.

Zief, Norris, and Edsall, John T., "The Dissociation Constants of Some Amino Derivatives," Journal of the American Chemical Society, LIX (1937), 2246.

Articles

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

Bates, J., and Johnson, T., "Researches on Hydantoins, XXX. Stereoisomeric Modifications of Benzalhydantoin," Journal of the American Chemical Society, XXXVII (1916), 383-85.

Baudisch, O., and Davidson, D., "The Catalytic Oxidation of Hydantoins," Journal of Biological Chemistry, LXXV (1927), 247-49.

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

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

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

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

Henze, H., and Knowles, M., "Synthesis of 5-(Pyridyl-Substituted)-Hydantoins," Journal of Organic Chemistry, XIX (1954), 1127-35.

Holmberg, G., "Oxidation of Phenyl-substituted-hydantoins," Acta Chemica Scandinavica, IV (1950), 821-27, cited in Chemical Abstracts, XLV (1951), 2478.

Klosa, J., "5-Phenylhydantoin," Archiv der Pharmazie und Berichte der deutschen pharmazeutischen Gesellschaft, CCLXXXV (1952), 274-80, cited in Chemical Abstracts, XLVIII (1954), 3266.

Pickett, L., and McLean, M., "Dissociation of Hydantoins," Journal of the American Chemical Society, LXI (1939), 423-25.

Pinner, A., "Ueber Hydantoine," Berichte der deutschen chemischen Gesellschaft, XXI (1888), 2320-29.

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

Spurlock, J. J., "Hydantoins as Anticonvulsants. I. 5-R-5-(2-Thienyl)hydantoins," Journal of the American Chemical Society, LXXV (1953), 1115-17.

Teague, P., "Phenyl-pyridylhydantoin," Journal of the American Chemical Society, LXIX (1947), 714.

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

Unpublished Materials

Banta, Calvin, "Studies in the Hydantoin Series. II. 5-(3-Pyridyl)hydantoin and Its Derivatives," unpublished master's thesis, Department of Chemistry, North Texas State College, Denton, Texas, August, 1957.

Frazior, W. G., "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.

Griffin, M. O., "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.

Hoffman, J. R., "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.

Jeanes, D. J., "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.

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

Patent

Henze, H., "5-Phenyl-5-pyridylhydantoin," U. S. Patent 2,526,231, 1950, cited in Chemical Abstracts, XLV (1951), 2975.