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The Synthesis of Potential Antitumor Compounds

Duane L. Aldous

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THE
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ANTITUMOR
COMPOUNDS

ALDOUS

THE SYNTHESIS OF POTENTIAL ANTITUMOR COMPOUNDS

By

Duane L. Aldous

A Dissertation
Submitted in Partial Fulfillment of the
Requirements for the Degree of
Doctor of Philosophy in Chemistry

The University of New Mexico
1961

This dissertation, directed and approved by the candidate's committee, has been accepted by the Graduate Committee of the University of New Mexico in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

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DEAN

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DATE

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ACKNOWLEDGMENT AND DEDICATION

The author wishes to express his gratitude to Dr. Raymond N. Castle and Dr. Jesse L. Riebsomer for their advice, understanding, and encouragement during the course of this investigation.

The financial assistance provided by the Los Alamos Scientific Laboratory, grant number SC-5, and the National Institutes of Health, grant number CY 2653 - C3, is gratefully acknowledged.

To my wife, Barbara, I wish to express my love and appreciation for her patience and cooperation. To her this work is dedicated.

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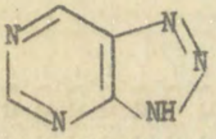
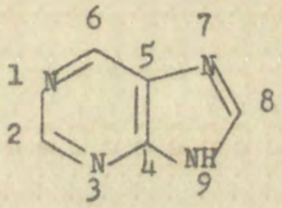
I. INTRODUCTION

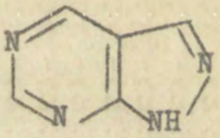
The antitumor activity found in such ring systems as the purine, pyrazolo[3,4-d]pyrimidine, and the 8-azapurine prompted the preparation of the imidazo[4,5-d]pyridazine ring system. Castle and Seese[1] were one of the first to study this ring system. 4-Aminoimidazo[4,5-d]-pyridazine possessed some antitumor activity. This antitumor activity suggested the preparation of the 4,7-disubstituted-aminoimidazo[4,5-d]-pyridazines reported here. The antileukemic activity reported for 6-purinethiol led to the synthesis of several 4- and/or 7-mono-and disubstitutedthioimidazo[4,5-d]pyridazines.



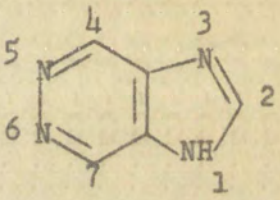
8-Azapurine



Purine



Pyrazolo[3,4-d]-
pyrimidine



Imidazo[4,5-d]-
pyridazine

Recently a number of oxazoles have been prepared as liquid scintillation solutes and as poikilothermic agents.[2] The synthesis of a number of oxazoles of possible physiological activity are reported.

---

1. R. N. Castle and W. S. Seese, *J. Org. Chem.*, 23, 1534 (1958)

2. D. G. Ott, F. N. Hayes, and V. N. Kerr, *J. Am. Chem. Soc.*, 78, 1941 (1956)

II. REVIEW OF THE LITERATURE

Karnofsky[3] defined cancer chemotherapy as "the use of any chemical substance administered systemically which, while relatively non toxic to the host, will interfer with, favorably modify, or destroy a neoplastic growth or alleviate its deleterious effects on the host." Karnofsky has listed eight possible avenues of chemotherapeutic attack on cancer. One of the eight possible avenues of chemotherapeutic attack on cancer is the inhibition of mitosis by chemical agents. This was the approach taken in this investigation. It has been observed by many investigators[3,4,5,6] that certain purines and purine-like compounds, the so-called purine antagonists, will inhibit the division of tumor cells.

One of the first purine antagonists to show activity was 2,6-diaminopurine.[5] This compound was promising in the treatment of leukemia in mice, but was not useful in clinical practice.[5]

The most important purine antagonist in use at the present time is 6-purinethiol. It was first synthesized by Hitchings, _et al_,[6] and is now known under the trade name Purinthol.

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[3]. D. A. Karnofsky, _Stanford M. Bull._, 6, 257-269 (1948)

[4]. M. M. Swann, _Cancer Research_, 17, 727-58 (1957)

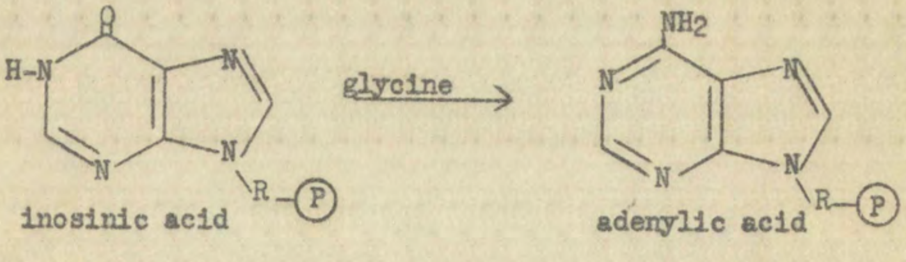
[5]. G. M. Timmis, _J. Pharm. Pharmacol._, 9, 81 (1957)

[6]. G. B. Elion, E. Burgi, and G. H. Hitchings, _J. Am. Chem. Soc._, 74, 411 (1952)

6-Purinethiol has been shown to inhibit the growth of Sarcoma 180 in mice, thereby increasing the survival time. In a significant number of animals, tumor regression was complete. These effects were observed when treatment was initiated either twenty-four or ninety-six hours after tumor implantation by either the oral or intraperitoneal route.[7]

6-Purinethiol has been extensively studied in different tumors and organisms in an effort to elucidate the mechanism of action.

At pharmacological concentration, 6-purinethiol inhibited the incorporation of hypoxanthine and glycine into adenine nucleotides in L 1210 leukemia *in vitro*. One possible explanation is offered by Davidson[8] as follows: "It is hypothesized that in L 1210 leukemia cells, 6-purinethiol is metabolized to its ribotide producing a metabolic block in the conversion of inosinic acid to adenylic acid; in resistant cells, 6-purinethiol is not converted to ribotides but competes with hypoxanthine in the process with insufficient 6-purinethiol ribotide formed to cause the critical block."



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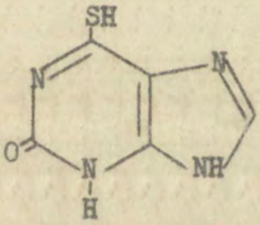
[7] D. A. Clarke, F. S. Philips, S. S. Sternberg, C. Chester Stock, G. B. Elion and G. H. Hitchings, *Cancer Res.* 13, 593-604 (1953)

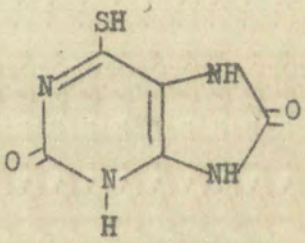
[8] J. D. Davidson, *Cancer Res.* 20, 225-232 (1960)

Brockman[9] obtained further evidence in support of Davidson's hypothesis when he observed that hypoxanthine-8-C^{14} and 6-purinethiol-S^{35} were metabolized into ribonucleotide derivatives by normal lines of leukemia L 1210. 6-Purinethiol resistant lines of L 1210 failed to form significant amounts of inosinic acid or of 6-purinethiol nucleotide *in vivo*.

Carey and Mandel[10] studied the action of 6-purinethiol on resting cells of *Bacillus cereus*, strain 569H. They found that 6-purinethiol was converted to the non inhibitory substances, 6-thioxanthine and 6-thiouric acid. When growing cells were used the drug was rapidly converted into normal purines which were then incorporated into nucleic acid (both RNA and DNA). No direct evidence was obtained to indicate that 6-purinethiol was incorporated as such into nucleic acids. 6-Purinethiol inhibited growth almost immediately upon administration. Inhibition of growth ceases when all the drug has been metabolized to other compounds. 6-Purinethiol ribonucleotide was found in the soluble fraction of cells. This supports the theory



6-thioxanthine



6-thiouric acid

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[9] R. W. Brockman, Cancer Res. 20, 643-653 (1960)

[10] N. H. Carey and H. G. Mandel, Biochem. Pharmacol. 5(1-2) 64-78 (1960)

that 6-purinethiol inhibits growth by interfering with cell metabolism at the nucleotide level. It is known that the inability to synthesize this ribonucleotide has resulted in resistance to 6-purinethiol. Cary and Mandel also noticed that increasing the concentration of 6-purinethiol did not increase the magnitude of growth-inhibition but only prolonged the duration of inhibitory action. Therefore, 6-purinethiol must tie up or saturate the enzyme system involved in purine exchange in DNA synthesis.

Similarities were observed[11] in the metabolism of 6-purinethiol and 6-purinethiol riboside when administered to a subline of Ehrlich ascites carcinoma resistant to 6-purinethiol. This would indicate extensive hydrolysis of the 6-purinethiol riboside *in vivo*.

Paterson[12], working with Ehrlich cells resistant to 6-purinethiol, found that these cells could not synthesize 6-purinethiol riboside-5'-monophosphate *in vivo*, while sensitive cells could.

Pecile, *et al*,[13] noted that mice carrying Ehrlich ascites cells after treatment with 6-purinethiol doubled the amount of cellular glycogen at a time when the drug had caused a 30% inhibition of tumor growth. They[13] suggest that 6-purinethiol reduces the rapid anaerobic glycolysis typical of neoplastic cells by inhibition of lactic

---

[11] A. R. P. Paterson, *Canad. J. Biochem.* 38(10) 1129-1135 (1960) (*Cancer Chemotherapy Abstracts*, 1, 827, 1960)

[12] A. R. P. Paterson, *Proc. Am. Assoc. Cancer Res.* 3, 141 (1960) (*Cancer Chemotherapy Abstracts*, 1, 139, 1960)

[13] A. L. Pecile, *Gior. Ital. Chemioter*, 5, 37-39 (1958) (*Cancer Chemotherapy Abstracts*, 1, 299, 1960)

dehydrogenase. Additional experiments[14] showed a marked decrease in the lactic dehydrogenase of Ehrlich ascites tumors which was not reversed by the addition of excess DPNH, suggesting that 6-purinethiol blocks protein synthesis and thus affects apoenzyme levels.

The ribonucleotide of 6-purinethiol was also found to be the active form which inhibits conversion of inosinate to adenylosuccinate and xanthylate in cell-free extracts of *Streptococcus faecalis* and pigeon liver respectively.[15]

When mouse fibroblasts were forced to utilize exogenous purines, it was shown that the resistant cell lines have a marked impairment of their ability to utilize hypoxanthine or inosine compared with the normal cell.[16]

Henderson and Junga[17] reported a potentiation of action when 6-purinethiol was used in combination with thioguanine on Ehrlichs ascites carcinoma. They used this evidence to support their claim for differences in the mechanism of action of the two drugs. A thioguanine resistant subline of Ehrlichs ascites carcinoma was found to be partially resistant to the tumor inhibiting action of 6-purinethiol.[17]

---

[14] T. Yamamoto, G. Riva and L. Tessari, *Gior Ital.* Chemioter, 5, 33-36 (1958) (*Cancer Chemotherapy Abstracts*, *295, 1960*)

[15] J. S. Salser, D. J. Hutchison and M. E. Balis, *J. Biol Chem.* 235, 429-432 (1960)

[16] S. Tomizawa, and L. Aronow, *J. Pharm. Exper. Ther.*, 128, 107-14 (1960)

[17] J. F. Henderson and I. G. Junga, *Biochem. Pharmacol.*, 5(1-2) 167-168, (1960)

Stone[18] studied the macromolecular properties of DNA isolated from Sarcoma 180. A decrease in molecular weight and a change in shape of the DNA molecules were observed after treatment with 6-purinethiol with either normal or 6-purinethiol-resistant strains of Sarcoma 180. Sulfur incorporation into the DNA molecule was not observed, and there was no evidence that the hydrogen bonded structure of the resultant DNA molecules was disturbed.

Mittler[19] found no change in the sex ratio of offspring of male mice given injection of 6-purinethiol or 8-azaguanine over many months.

Clinical studies indicate 6-purinethiol is effective in causing regression of acute leukemia in children.[20, 21, 22]

Among more than one hundred fifty patients with various malignancies other than acute leukemia and chronic myelogenous leukemia, 6-purinethiol treatment benefited a few with the following tumors: reticulum cell sarcoma, multiple myeloma, lymphosarcoma, melanosarcoma, Hodgkins disease, neuroblastoma, mycosis fungoides, and chronic myelosis.[23]

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[18] A. L. Stone, _Thesis_, Cornell Univ., 87, (1958) (_Cancer Chemotherapy Abstracts_, 1, 414, 1960)

[19] S. Mittler, _Genetics_ 45(8) 1000 (1960)

[20] J. H. Burcheal, R. R. Ellison, M. L. Murphy, D. A. Karnofsky, M. P. Sykes, T. C. Tan, A. C. Mermann, M. Yuceoglu, W. P. L. myers, K. Krakoff and N. Alberstadt, _Ann. N. Y. Acad. Sci._, 60, 259 (1954)

[21] I. D. J. Bross, _Ann. N. Y. Acad. Sci._, 60, 369 (1954)

[22] J. Bernard and M. Seligmann, _Ann. N. Y. Acad. Sci._, 60, 385 (1954)

[23] S. M. Sessoms, Editor, _Cancer Chemotherapy Reports_, 9, 144 (1960)

Toxic side effects have been reported with 6-purinethiol. These include oral lesions, damage to the bone marrow and intestinal epithelium, and some liver necrosis.[24, 25]

Ludwig and White[26] reported a case of pellagra in a woman suffering with myelogenous leukemia who had received up to 250 mg./day of 6-purinethiol for four years.

Upon administration of thioguanine-S^{35} to humans, an unidentified S^{35} containing compound rapidly appeared in the urine.[27] This was not thioguanine or thiouric acid. At later stages, most of the radioactivity was found in the form of sulfates.

Porter, *et. al.*,[28] isolated an antibiotic substance from *Streptomyces alboniger* which was named puromycin. Besides being able to inhibit both gram positive and gram negative bacteria and the protozoan *Trypanosoma equiperdum*[29, 30] it was found to have antimitotic properties.[30]

---

[24] F. S. Phillips, S. S. Sternberg, L. Hamilton and D. A. Clarke, *Ann. N. Y. Acad. Sci.*, 60, 283 (1954)

[25] S. Farber, R. Tock, E. M. Sears, and D. Pinkel, "Advances in Cancer Research", IV, Academic Press, Inc., New York, New York, 10-12 (1956)

[26] G. Ludwig and D. C. White, Clin. Res. 8, 212 (1960) (*Cancer Chemotherapy Abstracts*, 1, 417 1960)

[27] G. B. Elion, G. H. Hitchings, S. W. Callahan and R. W. Rundles, *Proc. Am. Assoc. Cancer Res.* 3, 109 (1960) (*Cancer Chemotherapy Abstracts* 1, 140, 1960)

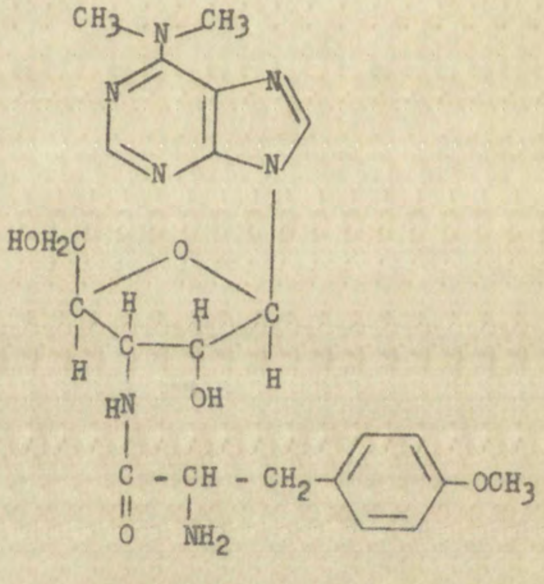
[28] J. N. Porter, R. I. Hewitt, C. W. Hesseltine, G. Krupka, J. A. Lowery, W. S. Wallace, N. Bohonas and J. H. Williams, *Antibiotics and Chemotherapy*, 2, 409 (1952)

[29] C. Waller, P. Fryth, B. Hutchings, and J. Williams, *J. Am. Chem. Soc.*, 75, 2025 (1953)

[30] *The Merck Index*, 7th Ed., Merck & Co., Inc., Rahway, N. J. (1960)

Leonardi[31] observed the destruction of nearly all the colonies of the Af strain (H. ep. 2) of human tumor cells when treated with 1-100 γ/ml of puromycin. When *Pseudomonas fluorescens* was incubated with puromycin (50 γ/ml), protein synthesis was completely abolished but RNA and DNA syntheses were much less affected.[32]

Baker, *et. al.*,[33] through a total synthesis were able to establish the structure of puromycin.



Puromycin

The presence of a 6-dimethylaminopurine moiety in puromycin prompted the preparation of the dialkylaminoimidazo [4,5-d] pyridazines.

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[31] A. Leonardi, *Gior. Ital. Chemioter*, 5, 297-301 (1958) (*Cancer Chemotherapy Abstracts*, 1, 286, 1960)

[32] Y. Takeda, S. Hayashi, H. Nakagawa and F. Suzuki, *J. Biochem.* (Japan) 48 (2) 169-177 (1960) (*Cancer Chemotherapy Abstracts*, 1, 828, 1960)

[33] B. R. Baker, R. E. Schaub, J. P. Joseph and J. H. Williams, *J. Am. Chem. Soc.*, 77, 12 (1955)

[illegible] observed the [illegible]

of [illegible] (9, 10, 11) [illegible]

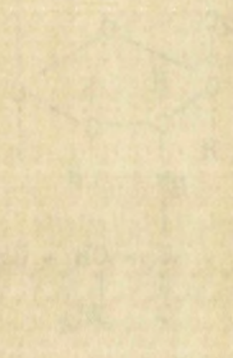
[illegible]. [illegible]

with puromycin (30, 31) [illegible]

that RNA and DNA [illegible] were [illegible].

[illegible] et al.,[33] [illegible]

the structure of puromycin.



Puromycin

The presence of [illegible]

prompted the preparation of the [illegible]

[illegible]

31. A. [illegible]

32. [illegible]

33. B. R. Baker, [illegible]

Remy[34] found that E. coli strains B, 15 T, and B-96 converted 6-methylaminopurine, to 6-dimethylaminopurine had no effect on 2-amino-6-methylaminopurine.

8-Azaguanine first synthesized by Roblin, et. al.,[35] possessed considerable antitumor activity.

This compound was found to be active in inhibiting transplantable adenocarcinomas of the breast in mice,[36] undifferentiated squamous cell carcinoma transplanted into a rabbit's eye,[37] and adenocarcinoma E o 771 in mice.[38, 39]

Mandel and Altman[40] observed in Bacillus cereus that the partial growth inhibition caused by 8-azaguanine was accompanied by a decrease in the incorporation of methione-S^{35} or cystine-S^{35}/unit of bacterial mass synthesized. This effect could be reversed by the addition of guanosine.

---

[34] C. N. Remy, Fed. Proc. 19, 313, (1960)

[35] R. O. Roblin, Jr., J. O. Lampen, J. P. English, Q. P. Cole and J. R. Vaughan, Jr., J. Am. Chem. Soc., 67, 290 (1945)

[36] K. Sugiura, G. H. Hitchings, L. F. Cavaliere, and C. C. Stock, Cancer Research, 10, 178 (1950)

[37] A. Gellhorn, M. Engelman, D. Shapiro, S. Graff, and H. Gillespie, Cancer Research, 10, 170 (1950)

[38] G. W. Kidder, V. C. Dewey, R. E. Parks, Jr., and G. L. Woodside, Science, 109, 511 (1949)

[39] J. Meyer and J. P. Weinmann, Cancer Research, 11, 914 (1951)

[40] H. G. Mandel and R. L. Altman, J. Biol. Chem., 235, 2029-2035 (1960)

Chantrenne and Devreux[41] also working with Bacillus cereus found that protein synthesis was strongly inhibited and the formation of penicillinase was completely abolished by 8-azaguanine. Concentrations were found that would block penicillinase, but not affect DNA synthesis.

Roodyn and Mandel[42] cultured Bacillus cereus cells in the presence of 8-azaguanine and radioactive protein precursors. They found that the cells so treated were able to incorporate radioactivity into the cell wall to a greater extent than the untreated cells. At the same time the formation of protoplasmic protein was sharply inhibited. It can be concluded from these data that the radioactive precursors were not utilized in the formation of DNA.

A cytological study of the effect of 8-azaguanine upon Yoshida sarcoma disclosed that shortened chromosomes appeared in 70% of all mitotic cells.[43]

Watanabe[44] reported that large doses of 8-azaguanine suppressed sexual cycle in the rat, and ovulation in the rabbit. Hypofunction of the pituitary and adrenals was also noted. These effects were not observed with 6-purinethiol.[44]

---

[41] H. Chantrenne and S. Devreux, Biochim. Biophys. Acta, 39, 486-499 (1960)

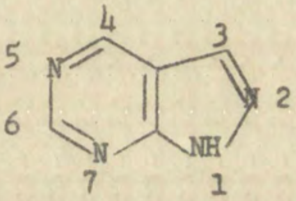
[42] D. B. Roodyn and H. G. Mandel, J. Biol. Chem., 235, 2036-2044 (1960)

[43] T. Yoshida and H. Hirumi, Jap. J. Cancer Clin. 6(5), 320 (1960) (Cancer Chemotherapy Abstracts, I, 933, 1960)

[44] K. Watanabe, Shikoku Acta Med. 13, 468-493 (1958) (Cancer Chemotherapy Abstracts, I, 617, 1960)

The effect of 8-azaguanine on viruses has been studied. The multiplication of T 4 (gamma) phase was inhibited by 8-azaguanine when E. coli R2 was the host.[45] The inhibition was reversed by guanine. The incorporation of 8-azaguanine into tobacco mosaic virus caused the loss of infectivity.[46]

Robins and coworkers have synthesized a tremendous number of potential purine antagonists. Of these the greatest activity was found in the pyrazolo[3,4-d]pyrimidines.



Pyrazolo[3,4-d] pyrimidine

Of a large number of pyrazolopyrimidines screened against adenocarcinoma 755 and Leukemia 5178 activity was limited to the 4-amino, the 4-monoalkylamino, and 4-dialkylaminopyrazolo[3,4-d]-pyrimidines, and the 1-alkyl derivatives of the compounds.[47] From these studies some generalizations concerning structure-activity relationships were made.[47]

---

[45] Y. Kiho, Y. Yamada and K. Hosokawa, <u>Virus</u>, 10, 1-5 (1960) (Cancer Chemotherapy Abstracts, 1, 311, 1960)

[46] Matthews, J. Gen. Microbiol., 10, 521, (1954)

[47] H. Skipper, R. Robins, J. Thomson, C. Cheng, R. Brockman, F. Schabel Jr., Cancer Research, 17, 579-96, (1957)

1. Any group in the 1-position except methyl or β -hydroxyethyl result in inactive compounds.

2. Phenyl or substituted phenyl groups at the 4-amino group destroys activity.

None of the pyrazolo[3,4-*d*] pyrimidines were as effective as 6-purinethiol as an antileukemic agent.[48] The 4-amino, 4-n-propyl, and 4-benzylaminopyrazolo[3,4-*d*]pyrimidines were assayed against adenocarcinoma 755. They inhibited growth, but none increased survival time at near toxic dose levels.[48]

Sixteen derivatives of the pyrazolo[3,4-*d*]pyrimidines were assayed *in vitro* on cultures of human epidermoid carcinomas. The most active compound was found to be the 4-amino derivative which destroyed all colonies in concentrations as low as 1 γ./ml and produced marked inhibition of growth at concentrations of 0.1 γ/ml. All substituents on the amino group or at the 1-position resulted in decreased antitumor activity.[49]

Krakoff and Karnofsky[50] used 4-aminopyrazolo[3,4-*d*]pyrimidine in three far-advanced cases of human carcinoma. There was one each of carcinoma of the cervix, breast, and urethra. The administration of 5mg/day for a total dosage of 50-127 mg. had no therapeutic effect

---

[48] J. M. Venditti, E. Frei III, A. Goldin, *Cancer*, 13, 959-966 (1960) (*Cancer Chemotherapy Abstracts*, 1, 709, 1960)

[49] A. Leonardi, *Gior. Ital. Chemioter*, 5, 41-48, (1958) (*Cancer Chemotherapy Abstracts*, 1, 286, 1960)

[50] I. H. Krakoff, and D. A. Karnofsky, *Proc. Am. Assoc. Cancer Res.*, 2, 223, (1957)

but did cause severe impairment of liver function. There was also histologic evidence of toxic hepatitis.

4-Aminopyrazolo[3,4-d]pyrimidine was found to form a mononucleotide when used as a substrate for beef liver adenylic pyrophosphorylase.[51]

Bennett, _et_. _al_.,[52] observed that 4-aminopyrazolo[3,4-d]pyrimidine inhibited the uptake of formate and glycine into nucleic acids of Adenocarcinoma 755 _in vivo_. This provides additional evidence that this compound has a mode of action similar to 6-purinethiol.

---

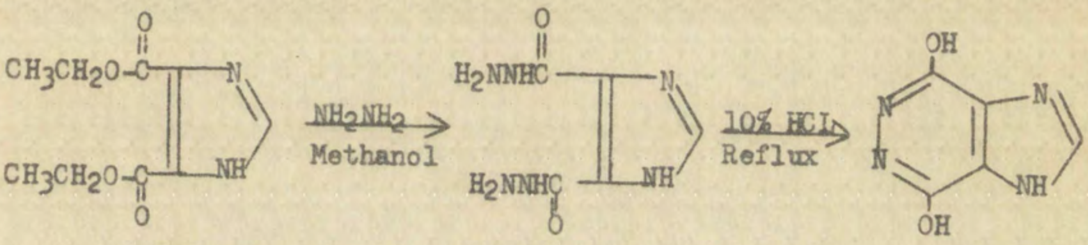
[51] J. K. Roy, C. A. Haavik, and R. E. Parks, Jr., Proc. Am. Assoc. Cancer Res., 3, 146, (1960) (_Cancer Chemotherapy Abstracts_, 1, 139, 1960)

[52] L. L. Bennett, Jr., R. W. Brockman, and D. Smithers, Proc. Am. Assoc. Cancer Res., 3, 94, (1960) (_Cancer Chemotherapy Abstracts_, 1, 135, 1960)

III. DISCUSSION

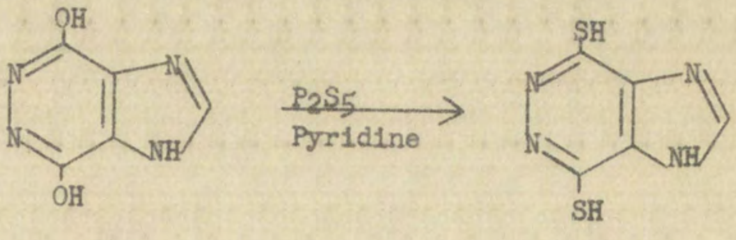
A. Synthesis and Reactions of the Substituted Imidazo[4,5-d]pyridazines

4,7-Dihydroxyimidazo[4,5-d]pyridazine (III) was prepared according to the procedure of Castle and Seese[1] outlined in the following scheme.



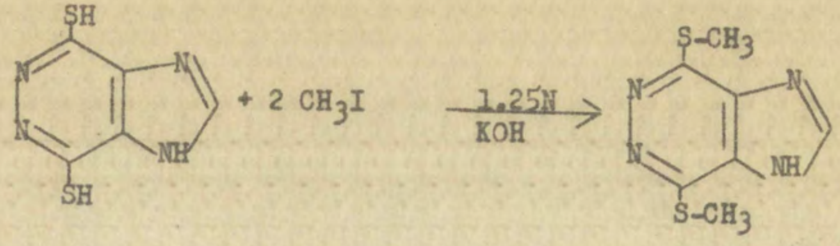
I II III

The next step in the synthetic sequence was the conversion of III into 4,7-dithioimidazo[4,5-d]pyridazine (IV). The procedure of Castle and Seese[1] for the preparation of the compound was modified to increase the yield (95%) and to facilitate the work up of the product.



III IV

Compound (IV) was converted to 4,7-bismethylthioimidazo-[4,5-d]pyridazine (V) by the action of methyl iodide on a basic solution of (IV).

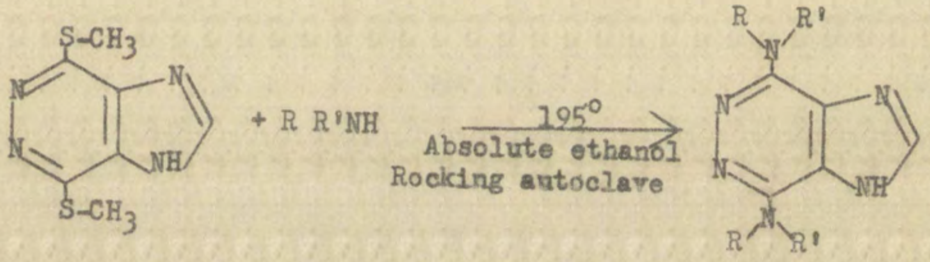


IV V

A number of 4,7-disubstitutedamino derivatives have been prepared by nucleophilic replacement of the methylthio group with the desired amine in a rocking stainless steel autoclave. These are listed in table I.

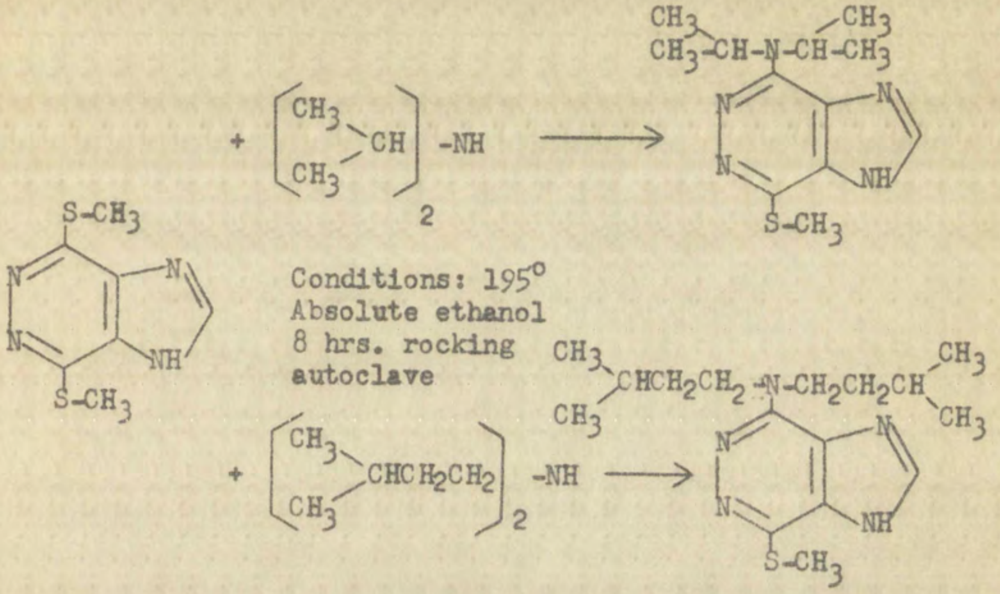
Table I

Preparation of 4,7-Bisaminoimidazo [4,5-d] pyridazines



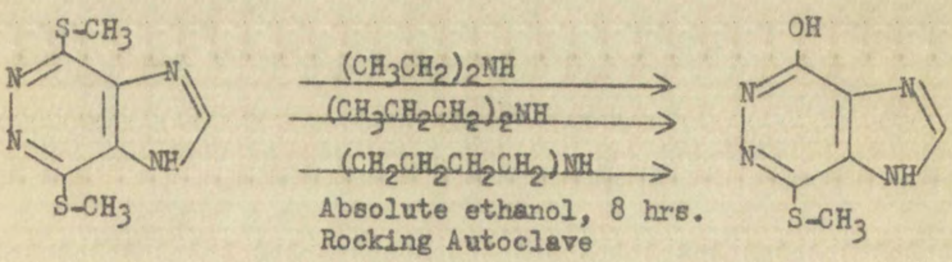
Amine Used	R	R'
CH_3NH_2	CH_3-	H-
$CH_3CH_2NH_2$	CH_3CH_2-	H-
$CH_3CH_2CH_2CH_2NH_2$	$CH_3CH_2CH_2CH_2$-	H-
$HOCH_2CH_2NH_2$	$HOCH_2CH_2$-	H-
$(CH_3)_2N-CH_2CH_2CH_2NH_2$	$(CH_3)_2N-CH_2CH_2CH_2$-	H-
$(C_2H_5)_2N-CH_2CH_2CH_2NH_2$	$(C_2H_5)_2N-CH_2CH_2CH_2$-	H-
$(CH_3)_2$ NH	CH_3-	CH_3-

Primary amines with one exception nucleophilically displaced both the methylthio groups. Secondary branched-chain amines replaced only one of the methylthio groups. This is shown below.



Conditions: 195°
Absolute ethanol
8 hrs. rocking
autoclave

In the instance where secondary straight chain amines were used, only one product, 4(7)-hydroxy-7(4)-methylthioimidazo[4,5-d]pyridazine, was obtained. This may be illustrated by the following reaction.



Absolute ethanol, 8 hrs.
Rocking Autoclave

In the purine ring system Noell and Robins[53] were able to exchange a methylthio group for a chlorine atom.

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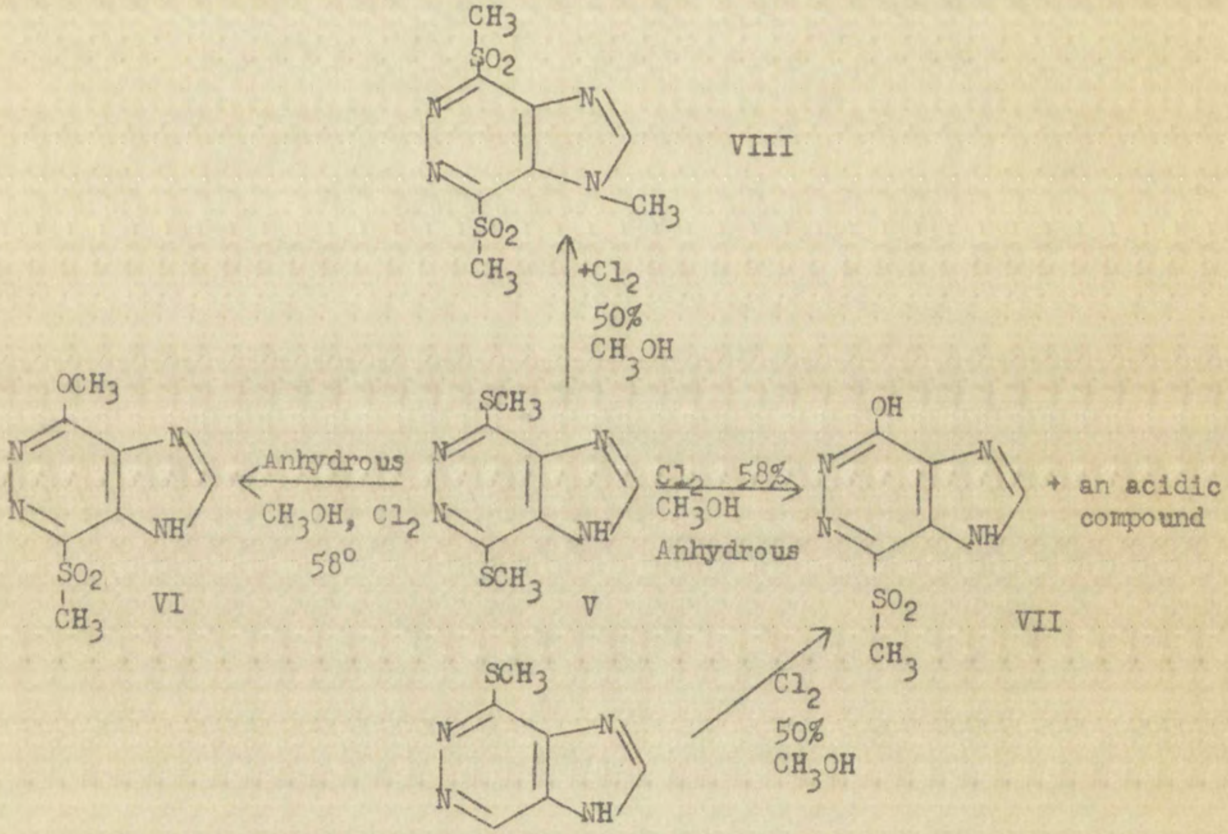
[53] C. W. Noell and R. K. Robins, J. Am. Chem. Soc., 81, 5997 (1959)

Because of the previous difficulties of Castle and Seese[1] in introducing chlorine atoms at positions 4 and 7, this new method seemed appropriate. After a number of attempts to displace a methylthio group with a chlorine atom under various experimental conditions, no chloro compounds were obtained. However, five compounds were isolated, three of which have been identified. This is shown in the following scheme:



In some instances Noell and Robins[53] also obtained the methylsulfonyl, and the hydroxyl groups upon treatment of 2,6,8-trimethylthiopurine with chlorine gas in anhydrous and in aqueous methanol.

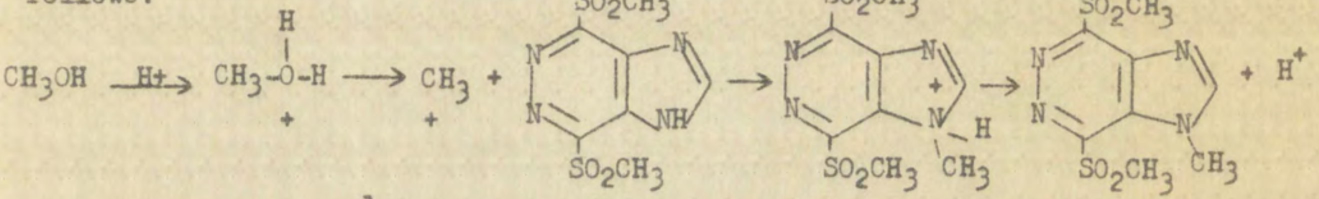
The assignment of structure for Compound VIII was based on the following observations:

(1) the insolubility of the compound in both acid and alkali;

(2) carbon, hydrogen, nitrogen and sulfur analyses;

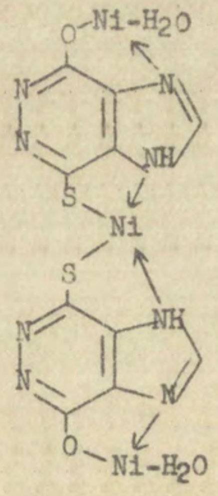
(3) infra red and ultraviolet absorption spectra.

A possible mechanism for the formation VIII may be illustrated as follows:



Castle and Seese[1] were unable to dethiate (IV) with Raney nickel to obtain the parent imidazo [4,5-d] pyridazine ring system.

Upon reinvestigation of the work, using solid sodium hydroxide in absolute ethanol, the product isolated was found to be a green nickel complex. It contained water of hydration. Preparation of an analytical sample was difficult because of decrepitation.

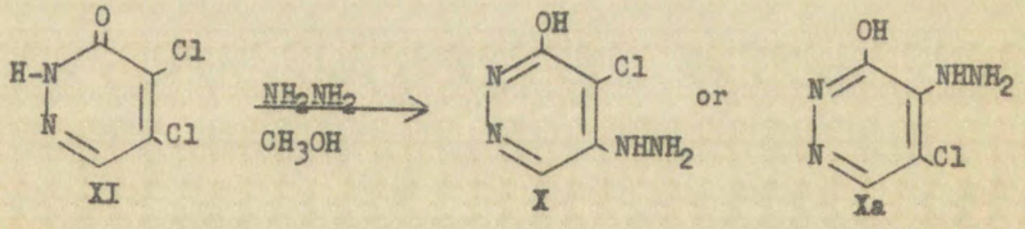


IX

The structure (IX) agrees with the analytical data.

4(5)-Chloro-5(4)-hydrazino-3-hydroxypyridazine (X) was prepared accidently when it was found that dimethyl imidazole-4,5-dicarboxylate had been contaminated with 4,5-dichloro-3-pyridazone (XI). Originally it was thought that a separation of the two compounds could be accomplished by treatment of the mixture with hydrazine. Castle and Seese[1] found it necessary to treat 4,5-dichloro-3-pyridazone with liquid ammonia in a stainless steel autoclave at high temperatures in order to replace the 5-chlorine atom with an amino group. Compound (X) or (Xa) precipitated from a solution of (XI) when it was allowed to react on a steam bath for six minutes.

In an effort to determine the position of attachment of the chlorine atom and the hydrazino group (X) or (Xa) was refluxed with an excess of formaldehyde to give (XII), (XIIa) or (XIIb). The product isolated was found to possess the structure (XII) or (XIIb). Another attempt to cyclize (X) or (Xa) to (XIII) with benzoyl chloride according to the procedure of Kuraishi[54] failed. An unequivocal assignment of structure has not been made but structure (X) is favored based upon analogy with 5-amino-4-chloro-3-pyridazone whose structure has recently been established by Castle and Kaji[55].



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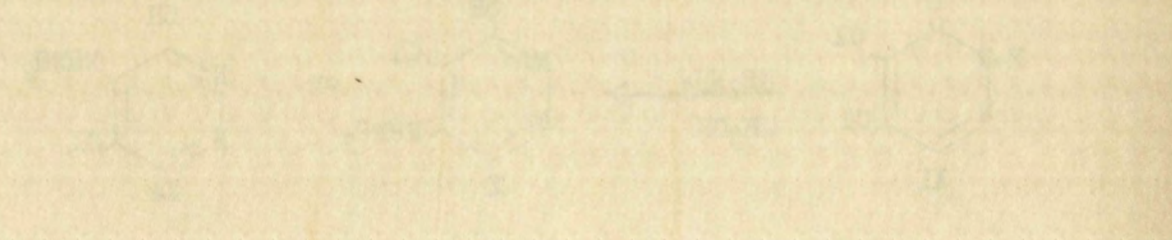
[54] T. Kuraishi, Chem. & Pharm. Bulletin, 6, 331 (1958)

[55] R. N. Castle and K. Kaji, unpublished work.

[illegible] compound (I) [illegible] compound [illegible] was found that [illegible] the same [illegible] (III) [illegible]. It was thought that a preparation of the (V) [illegible] would be accomplished by treatment of the [illegible] with [illegible] and [illegible] in a [illegible] to [illegible] (II) [illegible] (II or (Ia) [illegible] from a [illegible] of (II) [illegible] was given [illegible].

In an effort to [illegible] the [illegible] of [illegible] of the chlorine atom and the [illegible] group (I) or (Ia) was [illegible] with an excess of [illegible] to give (XII), (XIIa) or (XIIb). The product obtained was found to be [illegible] the [illegible] (XII) or (XIIa). Another attempt to [illegible] (I) or (Ia) to (XIII) with [illegible] of the [illegible] at [illegible] of [illegible] (I) [illegible] based upon [illegible] with [illegible] and [illegible] has recently been established by [illegible] and [illegible].[8]



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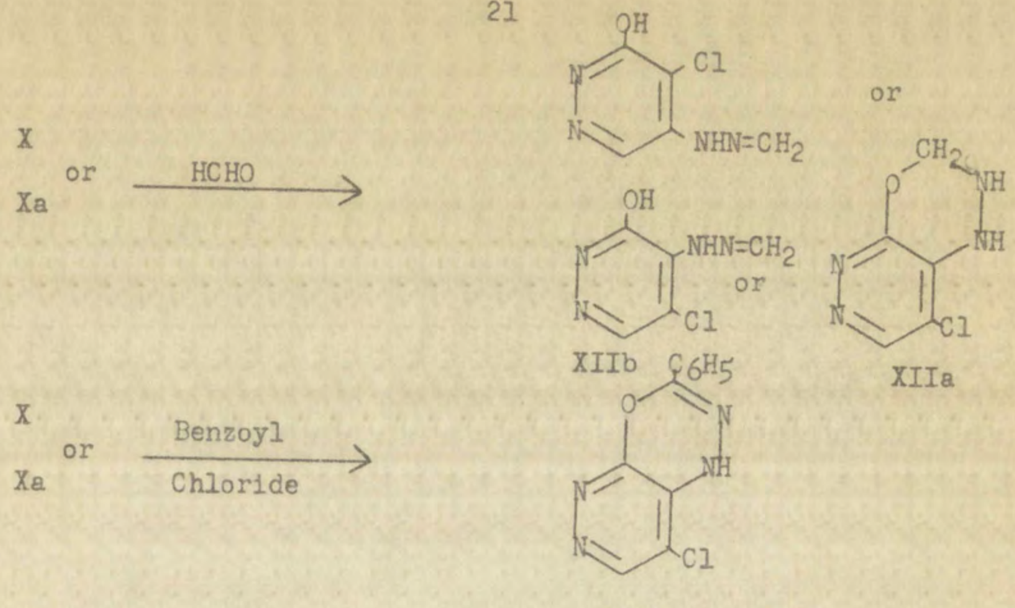
[8] [illegible]

[illegible]



XIIb

XIIa

XIII

Castle and Seese[1] reported the following substituted thioimidazo-[4,5-d]pyridazines: 4(7)-methylthio-7(4)-thio-, 4(7)-ethylthio-7(4)-thio-, 4,7-bismethylthio-, 1-ethyl-4,7-bisethylthio, and the hydrogen iodide salt of the last mentioned compound.

Their attempts to prepare any of the higher homologs were unsuccessful when alkyl bromides were used. The higher alkylthio and substituted benzylthio compounds were successfully prepared from imidazo[4,5-d]pyridazine-4,7-dithiol and the corresponding iodo compounds in alkali. The general procedure A of Daub and Castle[56] was used to prepare the substituted benzyl iodides.

The disubstituted compounds were difficult to purify. Many separated from the reaction mixture as tars. With persistence, these were crystallized from various solvents.

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[56] G. H. Daub and R. N. Castle, J. Org. Chem., 19, 1571 (1954)

[illegible]

[illegible] each of the [illegible] [illegible].

These schedules [illegible] [illegible] [illegible]

[illegible] in the [illegible]. The [illegible]

[illegible] used to prepare the [illegible] [illegible]

The [illegible] [illegible] [illegible]

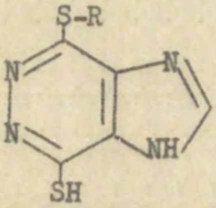
[illegible]

Some of the monosubstituted thio derivatives were prepared from the iodides in alkali and others were prepared from other halides by the method of Robins, et. al.[57] The latter method was much more successful, however in some instances more than one product was obtained.

The monothiosubstituted derivatives are listed in Table II.

Table II

4(7)-Substitutedthioimidazo [4,5-d] pyridazine-7(4)-thiols

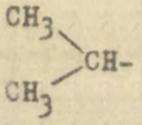


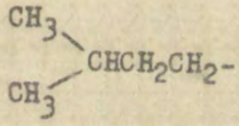
R =

$CH_3CH_2CH_2-$

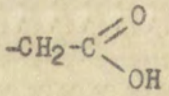
$CH_3CH_2CH_2CH_2-$

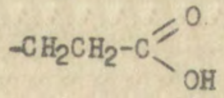
$CH_2=CH-CH_2-$

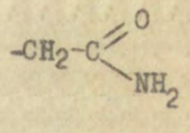

$(CH_3)_2CH-$

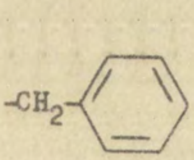

$(CH_3)_2CHCH_2CH_2-$

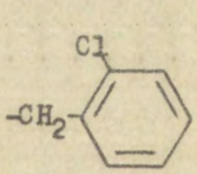
$HO-CH_2CH_2-$

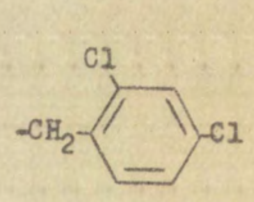

$-CH_2-C(=O)OH$

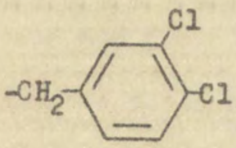

$-CH_2CH_2-C(=O)OH$

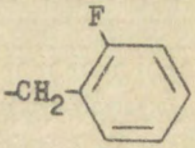

$-CH_2-C(=O)NH_2$

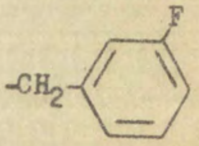


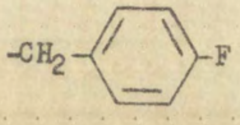


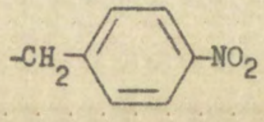


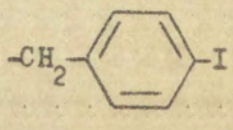












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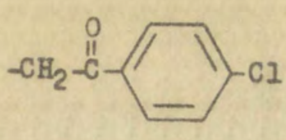
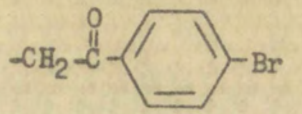
[57] G. D. Daves, Jr., C. W. Noell, R. K. Robins, H. C. Koppel, and A. G. Beaman, J. Am. Chem. Soc., 82, 2633 (1960)

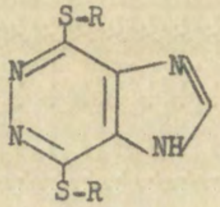




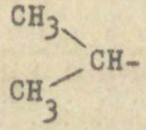
The 4,7-Dithiosubstituted derivatives are listed in Table III.

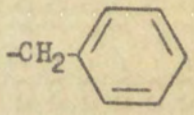
Table III

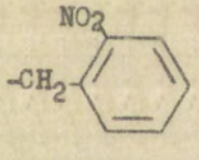
4,7-Dithiosubstitutedimidazo[4,5-d]pyridazines

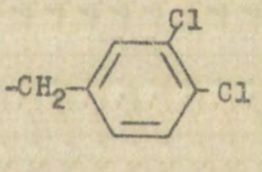


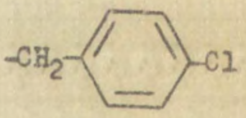
R= $CH_3CH_2CH_2$-

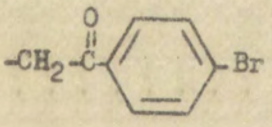


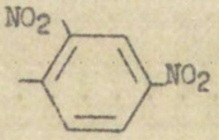












B. Synthesis and Reactions of Diaryloxazoles.

The general method for the preparation of these oxazoles was suggested by the work of Davidson, Weiss, and Jelling[58] and by

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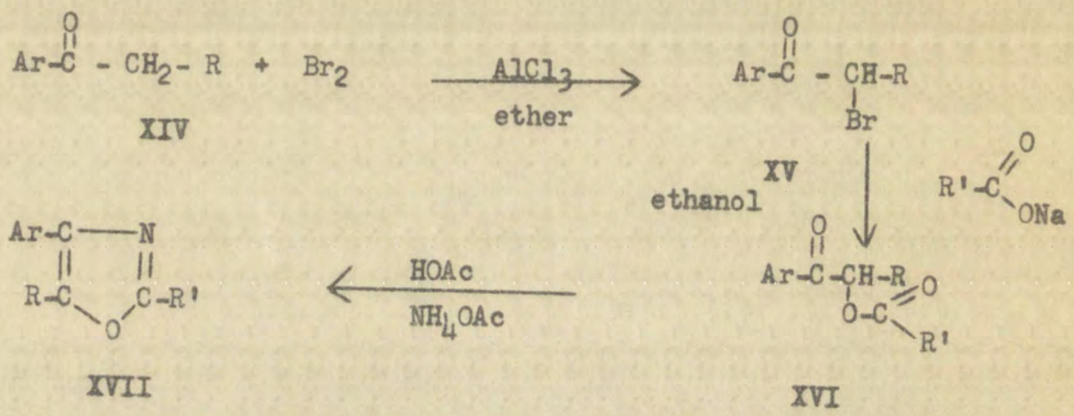
58. D. Davidson, M. Weiss, and M. Jelling, J. Org. Chem., 2, 328 (1937)

Dornow and Eichholtz[59]. An aryl ketone (XIV) was converted to the α-bromoketone (XV) which was allowed to react with the sodium salt of an acid to produce the ester (XVI). Ring closure to form the oxazole (XVII) was accomplished by refluxing the ester with ammonium acetate in a solution of acetic acid.



In table XVII is presented a series of esters of type XVI which were prepared by this method in which (XIV) was propiophenone. Table XVIII lists a series of oxazoles (XVII) which were prepared from the esters in Table XVII. It was not possible to cyclize all the esters listed in Table XVII into oxazoles.

The position of the methyl group in 2-methyl-4,5-diphenyloxazole situated on a carbon atom adjacent to two electronegative atoms suggested that the hydrogen atoms of the methyl group might be relatively active. Four styryloxazoles (XIX) were prepared by refluxing 2-methyl-4,5-diphenyloxazole (XVIII) with an excess of the desired aldehyde in the presence of anhydrous zinc chloride.

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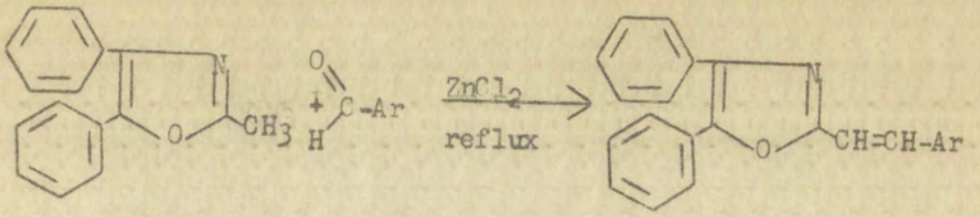
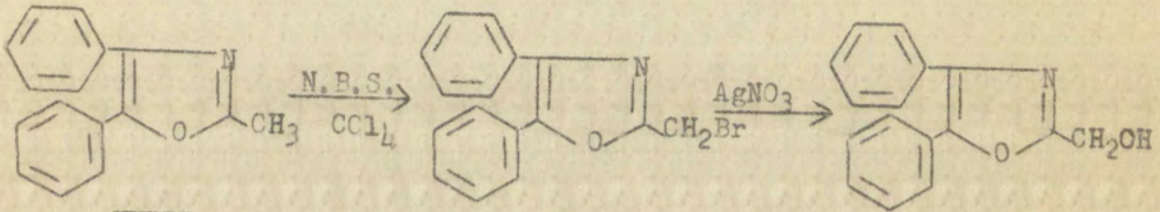
[59] A. Dornow and H. Eichholtz, Ber., 86, 384 (1953)



XVIII

XIX

In an effort to introduce a functional group into the 2-position, 2-bromomethyl-4,5-diphenyloxazole (XX) was prepared. This was accomplished by the bromination of 2-methyl-4,5-diphenyloxazole with N-bromosuccinimide. 4,5-Diphenyl-2-hydroxymethyloxazole was produced in good yield by hydrolysis of the 2-bromomethyl-4,5-diphenyloxazole in an aqueous alcohol solution of silver nitrate.



XVIII

XX

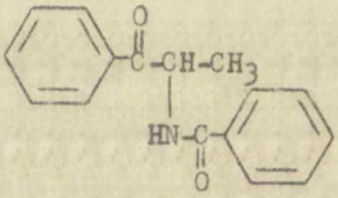
XXI

An attempt to oxidize the 2-hydroxymethyl derivative with alkaline potassium permanganate to a carboxylic acid was unsuccessful. The odor of ammonia was observed during the course of the reaction and the only products isolated were benzil and benzoic acid.

In order to introduce a carboxyl group into the 5-position of the oxazole ring, ethyl benzoylacetate was brominated as in (XIV). The bromocompound was converted to ethyl α -benzoyloxybenzoylacetate, which in turn was cyclized with ammonium acetate and acetic acid to ethyl 2,4-diphenylimidazole-5-carboxylate. This imidazole upon

refluxing in aqueous potassium hydroxide solution was converted to 2,4-diphenyloxazole-5-carboxylic acid. This acid was further characterized by converting it into the N,N-dimethylaminopropyl amide.

In three instances when ring closures of esters of type (XVI) were attempted, side products other than the expected oxazoles were formed. When 2-benzoyloxy-1-phenyl-1-propanone was refluxed with ammonium acetate in acetic acid, not only was the expected oxazole (m.p. 74-75°) produced in good yield but another solid (m.p. 108-109°) was formed whose properties seem to coincide with those expected of 2-benzoylamido-1-phenyl-1-propanone (XXII). The structure of (XXII) was established from the infrared spectrum and from the preparation of a semicarbazone derivative.



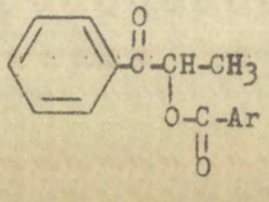
XXII

Similar observations were made when the starting esters were 1-phenyl-2-(6-quinolinecarboxoyloxy)-1-propanone and di-α-benzoylethyl pyridine-2,6-dicarboxylate.

C. Ultraviolet Absorption Spectra.

1. Oxazoles and Related Compounds.

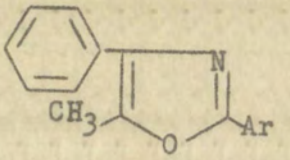
Among the β-keto esters represented by the following structure (XXIII), the esters of the pyridine carboxylic acids absorb at 245mμ.



XXIII

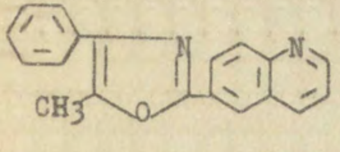
This represents a bathochromic shift compared with the quinoline carboxylic acids which absorb at 241 mμ.

In the 2-substituted-5-methyl-4-phenyloxazoles (XXIV) a shift

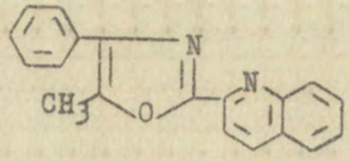


XXIV

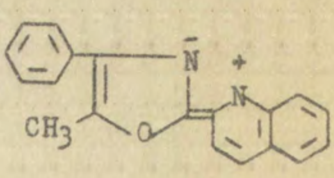
to the longer wavelengths was observed beginning with an absorption of 220.5 mμ when Ar = phenyl. When the α-naphthyl and the β-naphthyl groups were present in the 2-position, absorption was observed at 232 mμ and 233.5 mμ respectively. This is in accord with the observation that increased conjugation produces a shift to the longer wavelengths. It was also observed that the 2-(6-quinolyl) derivative (XXV) absorbed at 236.5 mμ and the 2-(2-quinolyl)derivative (XXVI) absorbed at 244 mμ. This can be accounted for by the increased conjugation possible in the 2-quinolyl structures (XXVIa) and (XXVIb). The same degree of conjugation is not possible in (XXV).



XXV



XXVIa



XXVIb

The spectra of 2-bromomethyl-and 2-hydroxymethyl-4,5-diphenyloxazole are similar. Gillam and Stern[60] report that simple alcohols

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[60] A. E. Gillam and E. S. Stern, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry", Edward Arnold (Publishers) LTD., p. 58

and ethers are transparent within the range of quartz spectrograph.

2. Imidazo [4,5-d] pyridazines.

Among the 4(7)-alkylthioimidazo [4,5-d] pyridazine-7(4)-thiol compounds very little difference in absorption spectra was noted. Castle and Seese[1] reported absorption maxima of 250, 270, 326-330 mμ for 4(7)-methylthioimidazo [4,5-d] pyridazine-7(4)-thiol and 252, 272, 330 mμ for 4(7)-ethylthioimidazo [4,5-d] pyridazine-7(4)-thiol. The results reported here are consistant with those reported above. Lengthening the alkyl side chain produced a very slight shift to the longer wave length. For example the maxima observed for 4(7)-(3-methylbutylthio)imidazo [4,5-d] pyridazine-7(4)-thiol were 252, 274, and 334.5 mμ respectively. The introduction of functional groups at the terminal position of the side chain resulted in slight to moderate hypsochromic shifts as compared with the n-propyl derivative. Examples are shown in the following table.

Table IV

Ultraviolet Absorption Spectra of 4(7)-Alkylthioimidazo [4,5-d] - pyridazine-7(4)-thiols

Alkyl	λ Max mμ	ϵ x10^{-3}	λ Max mμ	ϵ x10^{-3}	λ Max mμ	ϵ x10^{-3}
n-propyl	252	11.1	274	11.9	332	12.7
allyl	251.5	11.8	272	11.7	332	13.1
hydroxyethyl	252	11.8	271	12.1	330.5	12.9
carboxyethyl	251	11.3	270	10.9	332	12.9
carboxymethyl	250	11.6	266.5	10.9	332.5	13.2
carboxamidomethyl	251	10.4	264.5	9.75	330	10.6

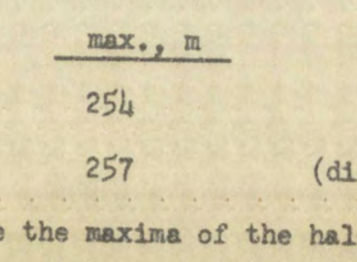
When the spectra of these compounds were determined in 0.5 N sodium hydroxide solution a definite hypsochromic shift occurred. The maxima at about 272-274 mμ shifted to 251-253 mμ, while the maxima at 332 mμ shifted to the neighborhood of 305 mμ. This would indicate the shift of the thione structure in ethanol to the thiol structure in base.

The absorption spectra of 4(7)-benzylthioimidazo [4,5-d] pyridazine-7(4)-thiol and their halo-substituted derivatives were similar to the alkylthio series in both absolute ethanol and in 0.5 N sodium hydroxide solution.

The spectra of the p-halophenylsubstitutedimidazo [4,5-d] pyridazine derivatives were not similar to the aliphatic or substituted benzyl derivatives. A slight bathochromic shift was noted. This is shown in the following table as the atomic weight of X increased.

Table V

Ultraviolet Absorption Spectra of 4(7)-Phenacylthioimidazo [4,5-d]-pyridazine-7(4)-thiols.



X	max., m	max., m
Cl	254	332
Br	257	(diff. sh.) 324

In 0.5 N sodium hydroxide the maxima of the halogenated derivatives

in the region of 332 mμ was shifted to approximately 288 mμ in each instance.

The spectra of the 4,7-bisalkylthioimidazo[4,5-d]pyridazines are in good agreement with that of 4,7-bismethylthioimidazo[4,5-d]-pyridazine reported by Castle and Seese.[1] These data are illustrated in the following table:

Table VI

Ultraviolet Spectra of 4,7-Bisalkylthioimidazo[4,5-d]pyridazines

Alkylthio group	λ max., mμ	λ max., mμ
$S-CH_3$ [1]	246 [1]	282-4 [1]
$S-CH_2CH_2CH_3$	245.5	288
$S-CH(CH_3)_2$	242	290
$S-C_6H_5$	242.5	290

In 0.5 N sodium hydroxide solution these compounds failed to show the dramatic hypsochromic shift of the monosubstituted compounds. This indicates that both thio groups are substituted and therefore cannot undergo the thiol-thione tautomerism. These spectra also establish that one of the alkyl groups could not be attached to one the imidazole nitrogen atoms.

The spectra of the 4,7-disubstitutedaminoimidazo[4,5-d]pyridazines show four maxima in ethanol. There is very little change in the absorption spectra with variation of the alkyl substituents. In 0.5 N sodium hydroxide solution a strong ~~maxima~~ was observed at 229 mμ and a weak maxima was observed at 274 mμ. In 0.1 N hydrochloric

acid solution, two maxima were also observed. One maximum of medium intensity was observed at 204.5 mμ and one maximum of strong intensity was observed at 242 mμ. The 4(7)-Dialkylamino-7(4)-alkylthioimidazo-[4,5-d]pyridazines possess strong maxima at 206 mμ and at 245 mμ with shoulders at 228.5 mμ and 240 mμ respectively in ethanol solution. These compounds in 0.1 N acid solution possessed strong maxima at 206.5 mμ, 246 mμ and 273 mμ. In 0.1 N sodium hydroxide solution a strong absorption maximum at 228 mμ was observed. In addition a shoulder at 240 mμ was observed. These spectra were not too different from those of the bisalkylamino derivatives.

The spectra of 4(7)-hydroxy-7(4)-methylsulfonylimidazo[4,5-d]-pyridazine and 4(7)-methoxy-7(4)-methylsulfonylimidazo[4,5-d]pyridazine were similar. In both instances a moderate bathochromic shift was observed when recorded in 0.5 N sodium hydroxide solution. Our spectral data are consistant with those reported by Noel and Robins[53] for 2-methylsulfonyl-6-hydroxypurine. The spectrum of 1-methyl-4,7-bismethylsulfonylimidazo[4,5-d]pyridazine in ethanol was different from that of the preceeding two compounds. The insolubility of this compound in alkali precluded the measurement of the spectrum in this solvent.

The spectrum of 4(5)-chloro-5(4)-hydrazino-3-hydroxypyridazine was recorded in neutral, acidic, and basic media. The absence of a shift in base coupled with the strong hydrogen bonding exhibited in the infrared spectrum, indicates that this compound exists in the enol rather than the keto form.

The spectrum of 4(5)-chloro-5(4)-methylenehydrazino-3-pyridazone was obtained in neutral, acidic, and basic media. The spectrum determined in base produced a definite hypsochromic shift indicating this compound exists in neutral solution in the keto amide form.

D. Infrared Absorption Spectra

1. Oxazoles and Related Compounds.

4,5-Diphenyl-2-styryloxazole and three substituted styryl derivatives show the characteristic CH out of plane deformation vibration of a -CH=CH- (trans) group at 10.3μ and the C-C stretching vibration at 6.2 - 6.25μ.

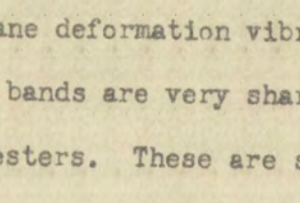
The arylalkyl ether band at 7.9 - 8.0μ was clearly evident in the case of 4,5-diphenyl-2-p-methoxystyryloxazole and 4,5-diphenyl-2-(3,4-methylenedioxystyryl)oxazole.

The absorption bands characteristic of a carboxylic acid were observed for 2,4-diphenyloxazole-5-carboxylic acid. These are the C=O stretching vibration at 5.9μ; C-O stretching or OH deformation at 7.9μ, and OH out of plane deformation vibration at 10.9μ.

The ester and ketone bands are very sharp and distinct for the following type of β keto esters. These are shown in Table VII.

Table VII

Infrared Absorption Spectra of β-Ketoesters



R	Ester Band (μ)	Ketone Band (μ)
phenyl	5.74	5.85
phenyl*	5.76	5.88
α naphthyl	----	5.92
β naphthyl	5.78	5.89
2-quinolyl	5.70	5.89
6-quinolyl	5.78	5.86
2-pyridyl	5.69	5.85
3-pyridyl	5.74	5.84
4-pyridyl	5.72	5.85
2,6-dipyridyl	5.67	5.87

*Hexanophenone was the ketone used instead of propiophenone.

Infrared spectra were of the greatest importance in assigning the proper structure to three side products obtained from the cyclization of the β keto ester to the corresponding oxazoles. The following bands shown in Table VIII provided the basis for our assignment of structure of these compounds as β-keto amides.

Table VIII

Infrared Absorption Spectra of β Keto Amides

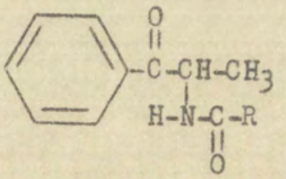


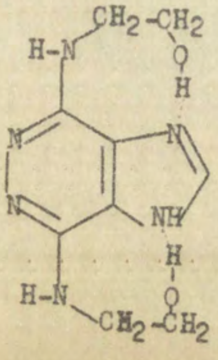
Table VIII Continued

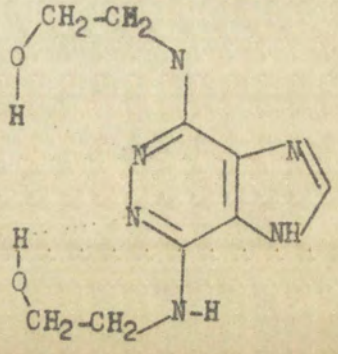
R	NH Stretching Sec. Amide (μ)	Ketone Carboxyl Vibration μ	Amide I (μ) CO Absorption	Amide II (μ) Sec. noncyclic Amide
phenyl	2.91	5.82	6.03	6.59
6 quinolyl	2.89	5.80	6.03	6.57
2,6-dipyridyl	2.88	5.84	5.97	6.60

2. Imidazo[4,5-d]pyridazines.

In the 4,7-disubstitutedamino compounds the NH stretching band at 2.85-3.03 μ is readily discernable in the secondary amines, but lacking as would be expected in the tertiary amines. The N-H deformation bands for these compounds are difficult to assign. All of the primary and secondary amines possessed an absorption band in the range of 5.97-6.08 μ. Because this band was lacking in the tertiary amine one might assign this to NH deformation even though the range for NH deformation in secondary amines is 6.05-6.45 μ.

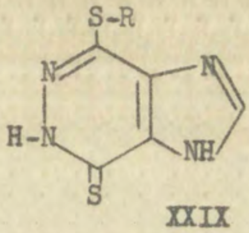
4,7-Bis-β-hydroxyethylaminoimidazo[4,5-d]pyridazine is interesting in that the free OH stretching band is absent but there is strong hydrogen bonding in the 3.5-4.0 μ region. This could be accounted for by the following structures or combinations of these structures, XXVII and XXVIII.


XXVII


XXVIII

This hydrogen bonding phenomena has been observed in many instances involving a hydroxyl group and a heterocyclic nitrogen atom.[61] The CO stretching band is tentatively assigned to a band at 9.27μ and the OH deformation at 7.48μ.

Among compounds possessing the following structure, an NH stretching

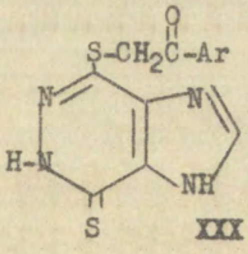


XXIX

band was observed in the 3.0-3.1μ region. Another strong band (6.64-6.77μ) was observed in this group of compounds. Bellamy[62] listed the absorption of the -N-C=S group at 6.66-6.8μ and for this reason the assignment of the 6.64-6.72μ band to this structure seemed reasonable.

After observing approximately thirty compounds of structure XXIX, it was noted that very intense sharp bands occurred in the region of 8μ. From one to three bands were observed, the most intense one, falling within the range 7.9-8.15μ. It is proposed that these absorption bands are due to the C-S stretching vibration.

In two compounds of structure XXX a strong absorption band



XXX

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[61] L. J. Bellamy, "The Infra Red Spectra of Complex Molecules", Methuen & Co. Ltd., London, 2nd Edition, 1958, p. 105

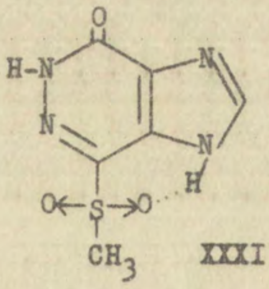
[62] Ibid., p. 357

at 5.9μ was observed indicative of the carbonyl group in addition to those mentioned above.

In four compounds having aryl nitro groups present an intense band at 7.4μ was observed. According to Bellamy[63] these are the valence vibrations of $C-NO_2$ group.

Considerable hydrogen bonding and the lack of an OH stretching band were observed in the spectrum of 4(7)-β-hydroxyethylthioimidazo-[4,5-d]pyridazine-7(4)-thiol.

A number of interesting compounds were obtained by chlorination of 4,7-bismethylthioimidazo[4,5-d]pyridazine either in absolute or aqueous methanol. The structures of these compounds were assigned on the basis of analytical data, infrared spectra and certain qualitative tests. The spectra of 4(7)-hydroxy-7(4)-methylsulfonylimidazo[4,5-d]pyridazine possessed a band at 3.1μ indicating NH stretching. A considerable amount of hydrogen bonding was noted which might be accounted for by the following structure (XXXI). A



XXXI

strong ∨ shape at 5.9μ was present which represents the Amide I Band (C-O stretching). The sulfone bands ($8.62-8.77\mu$ and $7.41-7.68\mu$)[64]

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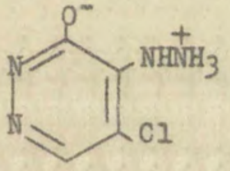
[63] Ibid., p. 298

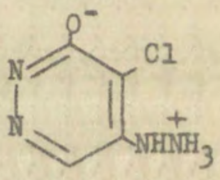
[64] Ibid., p. 350

were readily observed at 8.75-8.85μ and 7.57μ respectively. The methoxyl group of 4(7)-methoxy-7(4)-methylsulfonylimidazo[4,5-d]-pyridazine was observed as a strong band at 8.1μ. One of the products of chlorination was assigned the structure 1-methyl-4,7-bismethylsulfonylimidazo[4,5-d]pyridazine on the basis of the analytical data and the base insolubility together with the lack of both an NH stretching vibration and an amide absorption band in the infrared region of the spectrum.

The ultraviolet absorption spectra of 4(5)-chloro-5(4)-hydrazino-3-hydroxypyridazine did not undergo a marked shift in absorption maxima from neutral to basic solution. Thus the ultraviolet spectra indicate the possible structures (XXXII) and (XXXIII). An examination of the infrared spectrum eliminates (XXXII) and (XXXIII) on the basis that the NH stretching bands at 2.94μ and 3.06μ were present. This is not possible for a protonated amine structure.[65] Strong hydrogen bonding was observed in the infrared. The dimeric structure (XXXIV) is consistent with the ultraviolet and infrared absorption spectra as well as with the chemical and physical properties of the compound. Another alternative structure would be a linear hydrogen-bonded polymer, (XXXV).



XXXII



XXXIII

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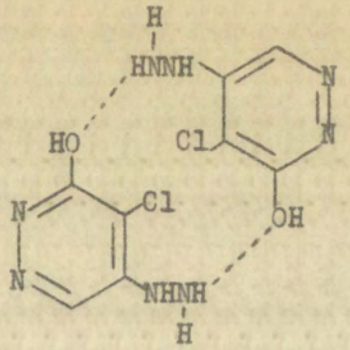
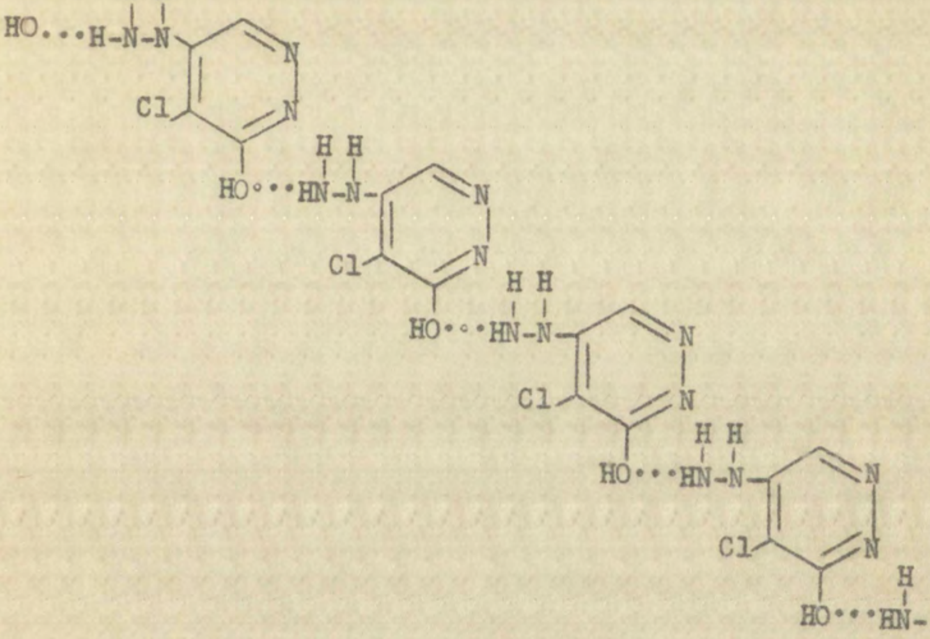
[65] Ibid., p. 237



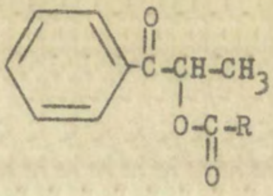
XXXIV



XXXV

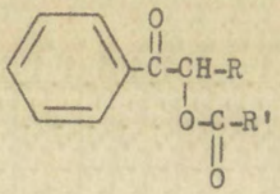
Table IX

Ultraviolet Absorption Spectra of β Keto Esters in Ethanol



R	λ Max.	ϵ x10^{-3}	λ Min.	ϵ x10^{-3}
α-naphthyl	211.5	44.0	216	42.0
	217.5	42.5	231	29.8
	236.5	30.8	266.5	3.8
	293.5	8.0		
β-naphthyl	Sh 205.5	30	213.5	27.5
	241.5	71	265	8.6
	Sh 272.5	9.4		
	281	10.9		
	Sh 290	7.5		
2-quinolyl	206	53.7	220	31.0
	241	67.8	271	9.8
	Diff. Sh 284	10.0		
6-quinolyl	209.5	36.5	202.5	31.7
	241	59.2	221	28.3
	Sh 272.5	6.9		
2-pyridyl	206	16.6	216.5	11.2
	219.5	11.3	231	10.7
	245	14.5		
3-pyridyl	205	18.6	216	11.8
	Sh 225.5	12.5		
	244.5	17.0		
4-pyridyl	206	19.9	221	7.5
	245	15.9		
	Sh 273	4.25		

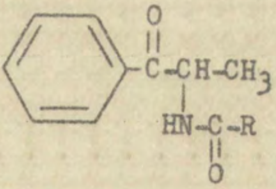
Table IX Continued



R	R'	λ Max.	$\epsilon \times 10^{-3}$	λ Min.	$\epsilon \times 10^{-3}$
n-butyl	phenyl	204	21.0	215	7.88
		240	22.8		
		Sh 272.5	2.38		
		Sh 280	2.13		
carboethoxy	phenyl	204	19.6	217	8.38
		239.5	20.0		
		Sh 281.5	2.63		
Di-α-benzoylethyl 2,6-dicarboxylate	pyridine-	206.5	17.5	219	5.7
		244.5	11.8		
		Sh 270	3.10		
		Sh 278.5	2.40		

Table X

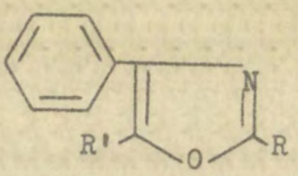
Ultraviolet Absorption Spectra of Aryloylamido-1-phenyl-1-propanones in Absolute Ethanol



R	Max.	$\times 10^{-3}$	Min.	$\times 10^{-3}$
phenyl	204	18.3	215	14.1
	222.5	15.3		
6-quinolyl	212	52	202	34
	236	59.5	223	43.2
N,N'-Bis (α-benzoylethyl) pyridine-2,6-dicarboxamide	207	31.3	272.5	6.50
	Sh 266	6.83		
	276	6.6		
	Sh 283.5	4.9		

Table XI

Ultraviolet Absorption Spectra of Oxazoles in Absolute Ethanol



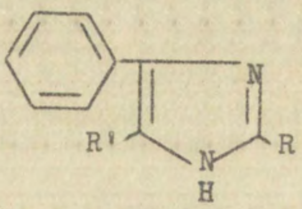
R	R'	λ Max.	ϵ x10^{-3}	λ Min.	ϵ x10^{-3}
phenyl	methyl	205.5	22.3	212	19.8
		220.5	21.0	244	9.75
		Sh 266.5	14.9		
		282	17.0		
		Sh 289	16.5		
α-naphthyl	methyl	207	39.8	216	32.0
		232	45.3	292	11.8
		Diff.Sh 251	17.0		
		318.5	15.2		
β-naphthyl	methyl	233.5	48.8	203.5	25.3
		255	26.3	252.5	26.0
		268.5	24.8	261.5	24.0
		Sh 276.5	22.5	289.5	13.5
		314	23.0		
2-quinolyl	methyl	212	33.5	202	22.5
		244	36.6	229.5	22.3
		Sh 280.5	11.6	296	9.5
		Sh 324	13.5		
		Sh 338.5	16.0		
		348	17.0		
6-quinolyl	methyl	219	36.0	201.5	28.3
		236.5	38.7	224.5	35.1
		255	26.8	251.5	26.6
		Sh 309	16.0	293.5	11.9
		319.5	18.8		
		Sh 341	12.2		
bromomethyl	phenyl	206.5	20.4	215	16.4
		225.5	18.0	244	8.60
		272	10.5		

Table XI Continued

R	R'	λ Max.	∊ x10^{-3}	λ Min.	∊ x10^{-3}
hydroxymethyl	phenyl	206	18.6	214	15.1
		226	17.4	243	8.40
		264.5	10.3	268	10.1
		274	10.3		
phenyl	carboxylic acid	203.5	28.8	229.5	10.9
		255	32.2	280	21.0
		285	21.5		
		Sh 290	21.2		
phenyl	N,N-dimethylaminopropylcarboxamide	207.5	29.8	214	25.5
		220.5	26.8	241	6.10
		300.5	33.1		
styryl	phenyl	205.5	27.9	216.5	18.1
		228.5	20.3	249	10.3
		Sh 232	20.0	295	15.3
		274.5	21.2		
		340	25.6		
o-hydroxystyryl	phenyl	207.5	31.5	253	11.7
		Diff.Sh 225	23.0	291	15.5
		275	18.5	326	15.4
		305	16.4		
		347	16.9		

Table XII

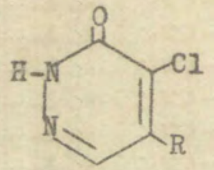
Ultraviolet Absorption Spectra of Imidazoles in Absolute Ethanol



R	R'	λ Max.	∊ x10^{-3}	λ Min.	∊ x10^{-3}
phenyl	ethyl carboxylate	208	23.4	233	12.0
		281	24.4		
4-pyridyl	methyl	206	15.7	248.5	7.85
		Sh 235.5	9.63	278.5	7.65
		263.5	9.15		
		329	21.2		

Table XIII

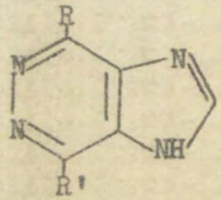
Ultraviolet Absorption Spectra of Pyridazines



R	Neutral				Base				Acid			
	λMax	∊ x10^{-3}	λMin	∊ x10^{-3}	λMax	∊ x10^{-3}	λMin	∊ x10^{-3}	λMax	∊ x10^{-3}	λMin	∊ x10^{-3}
hydrazino	227 300	9.5 2.2	252.5	0.75	225.5 294	14.8 5.0	251	9.17	221.5 290	24.6 5.25	245	1.88
methylene hydrazino	219 253.5 294	14.8 19.8 10.6	233 274.5	7.0 8.6	231 280.5	14.2 9.42	221 269	9.25 8.83	220.5 250.5 299	21.4 9.88 8.25	235 265.5	6.88 6.13

Table XIV

Ultraviolet Absorption Spectra of 4 and/or 7 Amino Imidazo [4,5-d] pyridazines



R and R'	Neutral				Base				Acid			
	λ Max	∊ x10^{-3}	λ Min	∊ x10^{-3}	λ Max	∊ x10^{-3}	λ Min	∊ x10^{-3}	λ Max	∊ x10^{-3}	λ Min	∊ x10^{-3}
R diisopropylamino R' methylthio	205 245.5 277	17.5 20.0 9.38	224 265.5	13.5 8.75	226 239*	26.3 21.5			206.5 247 274	16.3 14.8 15.3	231.5 259	12.5 11.9

*Sh

Table XIV Continued

R and R'	Neutral				Base				Acid			
	λ Max	ϵ x10^{-3}	λ Min	ϵ x10^{-3}	λ Max	ϵ x10^{-3}	λ Min	ϵ x10^{-3}	λ Max	ϵ x10^{-3}	λ Min	ϵ x10^{-3}
R diisoamylamino	206.5	26.3	216	20.2	228	31.7			206.5	21.6	231.5	16.5
R' methylthio	Sh 230	22.3			Sh 240	27.8			246	19.8	260.5	13.6
	Sh 240	26.3			*275	9.3			273	15.5		
	245	28.2										
R hydrazino	222		251.5		224	8.5	242.5	5.9	226	19.5	250.5	7.13
R' hydrazino	263.5				257.5	6.2			231	20.4		
					*290	4.95			261	7.5		
R methylamino	213	22.0	202.5	13.5								
R' methylamino	232	20.5	221.5	17.3	229.5	25.8	251	5.83	204.5	15.0	201	13.6
	241	23.6	233.5	20.3	273	7.0			Sh 229	15.8	213.5	12.0
	246	23.8	243	23.3					242	22.1		
	Sh 261.5	7.3										
R ethylamino	213	26.3	202.5	14.0	230.5	25.5	258.5	5.17	203	16.0	212.5	11.9
R' ethylamino	232.5	21.5	222.5	17.8					Sh 230	15.9		
	Sh 242	27.7	234	21.3					243.5	24.0		
	247	28.5										
	Sh 263	8.5										
R ethanolamino	214	22.0	203	11.8	230	27.0	258	6.17	204	15.0	212.5	12.0
R' ethanolamino	Sh 233	19.7	223	16.6	275	6.67			Sh 222.5	13.9		
	Sh 243	25.3							Sh 229	15.5		
	247.5	25.8							243	23.6		
	*263.5	7.67							*275	6.63		

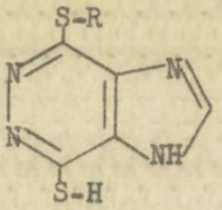
* Diff. Sh.

Table XIV Continued

R and R'	Neutral				Base				Acid			
	λ Max	ϵ x10^{-3}	λ Min	ϵ x10^{-3}	λ Max	ϵ x10^{-3}	λ Min	ϵ x10^{-3}	λ Max	ϵ x10^{-3}	λ Min	ϵ x10^{-3}
R butylamino	213.5	23.0	202.5	13.0	231.5	25.2	258	4.83	205	14.2	201.5	13.1
R' butylamino	Sh 234	20.7	222.5	16.8	277.5	6.50			Sh 225	13.3	213.5	11.3
	Sh 243.5	26.8							Sh 230	15.3		
	247.5	27.5							244.5	23.1		
	Diff.Sh 263	8.33							Diff.Sh 275	6.33		
R dimethylamino-	213.5	25.0	202.5	16.1	232.5	25.2	221	9.67	204	14.8	212.5	11.6
propylamino	232.5	21.6	222.5	18.6	276	6.67	260	5.5	Sh 222.5	13.6		
R' dimethylamino-	243	27.0	234.5	21.5					Sh 229	15.6		
propylamino	248	27.2	245	26.6					243	24.2		
	Diff.Sh 263.5	8.67							Diff.Sh 275	6.62		
R diethylamino-	214	26.0	203	16.3	232	28.1	259	5.50				
propylamino	233.5	22.6	224	19.8	276.5	7.0						
R' diethylamino-	Sh 245	28.1	235.5	22.5								
propylamino	248	28.7										
	Diff.Sh 265	9.0										
R dimethylamino	222	18.8	206.5	13.1	235	21.1	266.5	6.70	210.5	11.3	222.5	9.90
R'dimethylamino	Sh 235	16.5			282	8.25			Sh 230	15.2		
	259	23.9							258	18.9		
									Sh 262	18.4		

Table XV

Ultraviolet Absorption Spectra of 4(7)-Thiosubstitutedimidazo[4,5-d]-Pyridazine-7(4)-thiols



	Neutral				Base			
R	λ Max	ϵ x10^{-3}	λ Min	ϵ x10^{-3}	λ Max	ϵ x10^{-3}	λ Min	ϵ x10^{-3}
n-propyl	212.5 252 274 332	11.2 11.2 11.9 12.7	234.5 259.5 291	6.46 10.1 5.67	253 305	18 13.2	222 278	7.74 7.12
isopropyl	211 252.5 275 332	9.16 8.67 9.74 10.6	235 259 291	4.83 7.83 4.50	251 307.5	13.9 10.8	222 278	7.25 5.75
allyl	208.5 251.5 272 332	13.2 11.8 11.7 13.1	234 259 289.5	7.67 10.8 5.50	222 251 305.5	14.6 19.0 13.9	230 277.5	13.5 8.25
n-butyl	211 252.5 274 331	8.15 8.35 9.0 9.25	235.5 249 291.5	4.75 7.65 4.45	226.5 253.5 304.5	9.50 13.7 10.0	221 230 278	8.75 9.33 6.08
isoamyl	210 252 274 334.5	10.0 10.3 11.0 11.5	235 259 292	5.81 9.68 5.56	228.5 257.5 308.5	11.8 16.3 12.1	224 234.5 282	11.1 11.5 7.49
β-hydroxy-ethyl	210 252 271 330.5	12.1 11.8 12.1 12.9	235 259 289.5	7.25 11.0 5.42	*229 252 304	12.4 19.4 13.6	221 278	10.6 7.88
carboxymethyl	211 250 266.5 332.5	11.8 11.6 10.9 13.2	232 257.5 287	7.07 10.5 4.71	221.5 251.5 301.5	14.0 20.4 13.8	228.5 271	12.9 8.63

* Sh

Table XV Continued

	Neutral				Base			
R	λMax	ε x10^{-3}	λMin	ε x10^{-3}	λMax	ε x10^{-3}	λMin	ε x10^{-3}
β-carboxyethyl	210.5	11.2	232.5	6.42	222.5	14.1	230	13.6
	251	11.3	258.5	10.2	252.5	19.4	278.5	9.38
	270	10.9	289	5.08	304.5	14.2		
	332	12.9						
carboxamidomethyl	206	10.3	232	6.31	221	8.13	277	6.88
	251	10.4	261.5	9.56	Sh 230.5	11.1		
	Sh 256.5	9.81	288	3.75	251.5	18.0		
	264.5	9.75			303	11.6		
	330	10.6						
benzyl	208	20.3	235	9.13	227	15.5	221.5	13.8
	252	13.1	261	12.0	251.5	19.4	233	14.9
	272	12.5	290	6.0	307	14.0	280	8.25
	330	14.1						
o-chlorobenzyl	207	21.9	231.5	8.75	223.5	19.1	234.5	15.9
	251.5	12.6	262.5	11.3	250	19.5	279	8.75
	272	11.5	291	5.50	307	13.6		
	330	13.4						
3,4-dichlorobenzyl	307.5	32.3	243	10.3	226.5	22.9		
	Sh 221	22.0	258	9.5	*291	8.0		
	247.5	10.5	300	5.5				
	273	10.8						
	330	7.17						
2,4-dichlorobenzyl	206.5	32.0	259.5	8.83	228	21.1	288	8.13
	Sh 221	19.7	304	5.66	304	8.75		
	Sh 247	10.3						
	273	9.53						
	327	6.17						
o-fluorobenzyl	209.5	18.3	234.5	7.75	222.5	17.4	233	14.4
	251	11.9	260	11.1	250	18.6	280	8.25
	Sh 267	11.6	290	5.13	306	13.0		
	272	11.8						
	330	12.9						
m-fluorobenzyl	210.5	19.5	235	8.38	223.5	17.1	232	15.0
	251	12.8	260	11.8	250.5	19.8	280	8.88
	Sh 268.5	12.3	290	5.50	306	14.0		
	272.5	12.4						
	331	13.9						

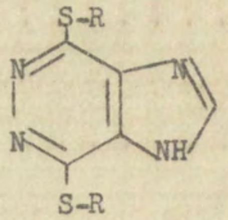
* Diff. Sh

Table XV Continued

	Neutral				Base			
R	λ Max	ϵ x10^{-3}	λ Min	ϵ x10^{-3}	λ Max	ϵ x10^{-3}	λ Min	ϵ x10^{-3}
p-fluoro benzyl	208.5	19.9	235.5	9.38	224	17.1	231.5	15.3
	251.5	13.0	261	11.9	251	19.6	279.5	8.75
	267.5	12.5	270	12.3	306.5	14.1		
	272.5	12.5	290	5.75				
	331	13.8						
p-iodobenzyl	206	26.5	221.5	17.0	241	27.8	221	17.2
	237.5	22.2	291	5.83	307	13.7	282	9.50
Diff.Sh	267	13.2						
	332	14.0						
p-nitrobenzyl	207.5	20.4	232.5	9.50	222.5	18.8	232.5	16.4
	269	21.4	299	11.4	256	21.5	274.5	17.9
	330.5	15.1			298.5	20.4		
p-chloro-phenacyl	208	25.0	227.5	10.3	236.5	23.4	221	15.5
	254	29.5	291.5	6.33	288	16.1	278	15.8
	332	13.2						
p-bromo-phenacyl	207	25.4	228.5	13.9	239	25.5	220.5	12.0
	257	24.3			286	17.3	276	17.2
Diff.Sh	324	6.75						

Table XVI

Ultraviolet Absorption Spectra of 4,7-Disubstitutedthioimidazo [4,5-d]-pyridazines



	Neutral				Base			
R	λ Max	ϵ x10^{-3}	λ Min	ϵ x10^{-3}	λ Max	ϵ x10^{-3}	λ Min	ϵ x10^{-3}
n-propyl	206	10.3	22.5	7.31	248	17.7	221	8.87
	245.5	12.3	263.5	7.43	290	9.87	274	8.87
	288	11.8						

Table XVI Continued

	Neutral				Base			
R	λ Max	ϵ x10^{-3}	λ Min	ϵ x10^{-3}	λ Max	ϵ x10^{-3}	λ Min	ϵ x10^{-3}
isopropyl	208	10.4	223.5	8.18				
	242	10.9	264.5	6.75				
	290	11.0						
benzyl	208	25.8	231	12.8	*235	17.0	277	7.13
	242.5	21.2	264.5	8.5	293.5	8.38		
	290	12.8						
p-chloro-benzyl	206	30.3	212	28.5				
	223.5	32.2	265	11.5				
	286.5	14.5						
3,4-dichloro-benzyl	207	40						
	Sh 217	31.3						
	Sh 246	15.5						
o-nitrobenzyl	208.5	34.5	230	20.6	229	26.6	220	19.6
	243	24.9						
	*275	17.7						
2,4-dinitro-phenyl	216	50.5	239	22.5	225.5	47.3	313	16.0
	249	23.5	288.5	12.7	*270.5	21.5		
	317.5	16.6			340.5	17.6		
p-bromo-phenacyl	206	33.3	200.5	23.8				
	Sh 254	41.5	226	18.0				
	257	42.0						

* Diff. Sh

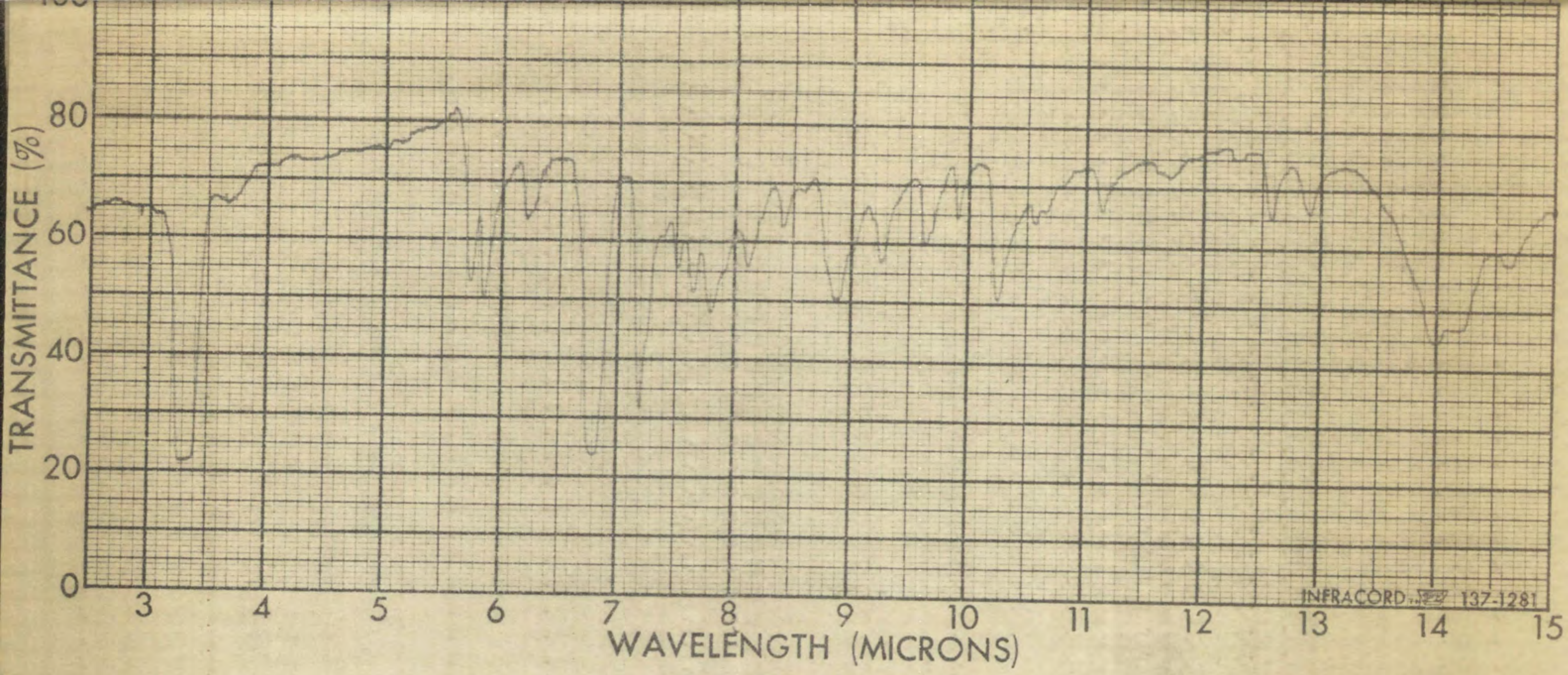
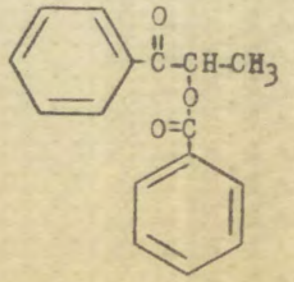


Plate I: Infrared Spectrum of 2-Benzoyloxy-1-phenyl-1-propanone



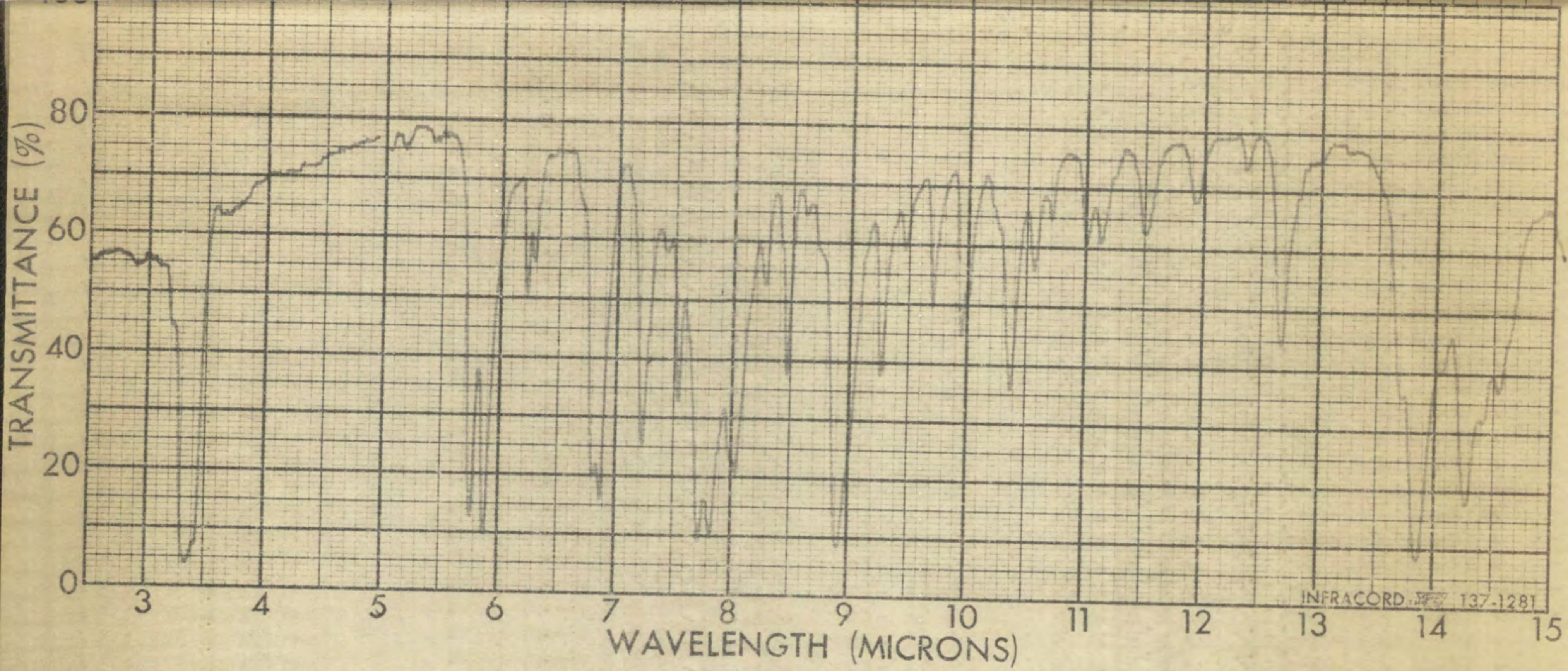
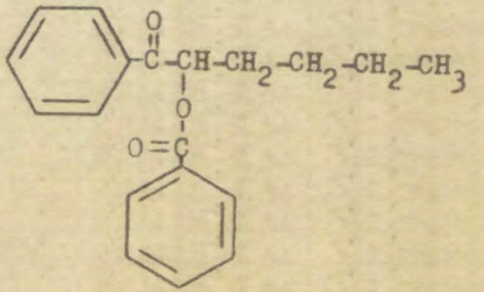


Plate II: Infrared Spectrum of 2-Benzoyloxy-1-phenyl-1-hexanone



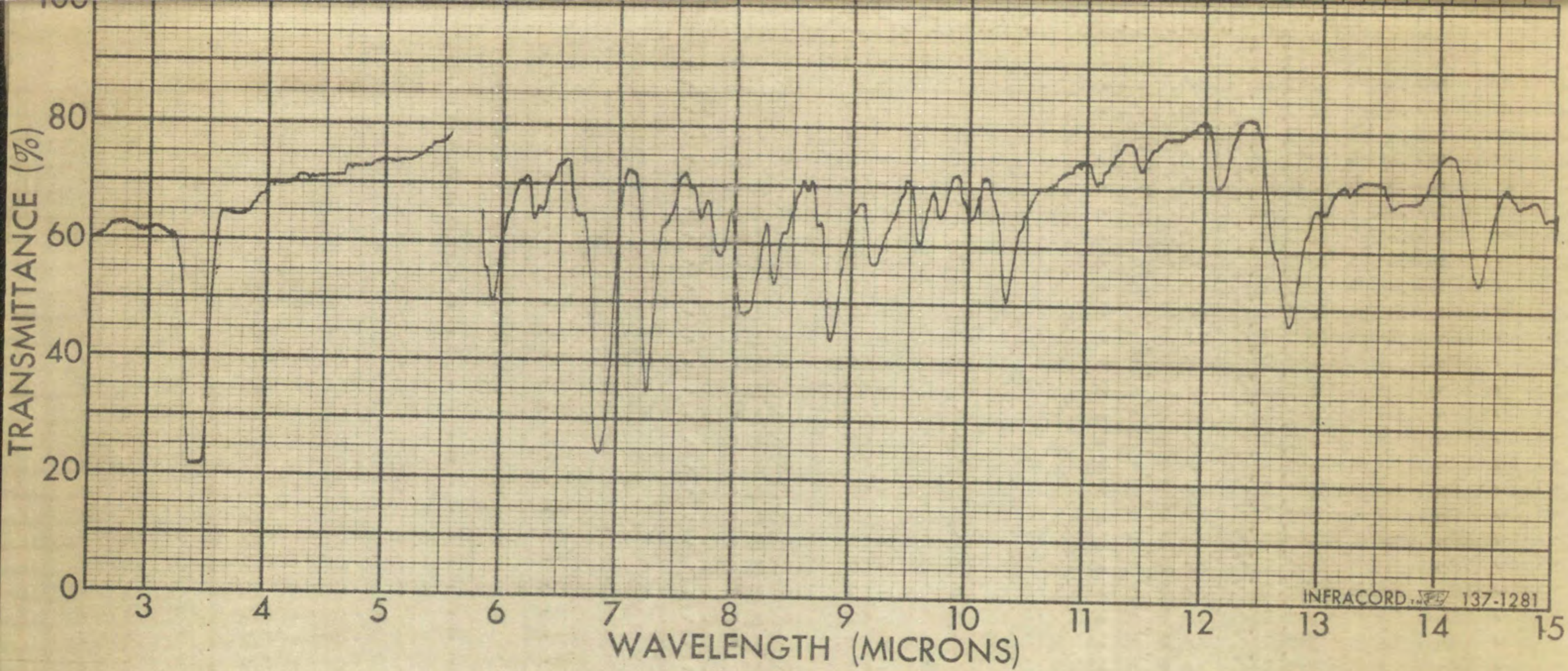
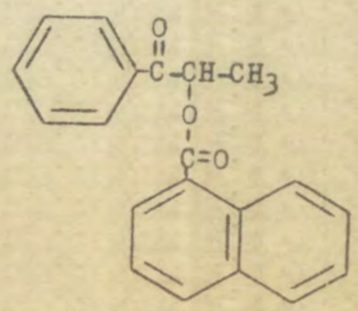


Plate III: Infrared Spectrum of 2-(1-Naphthoyloxy)-1-phenyl-1-propanone



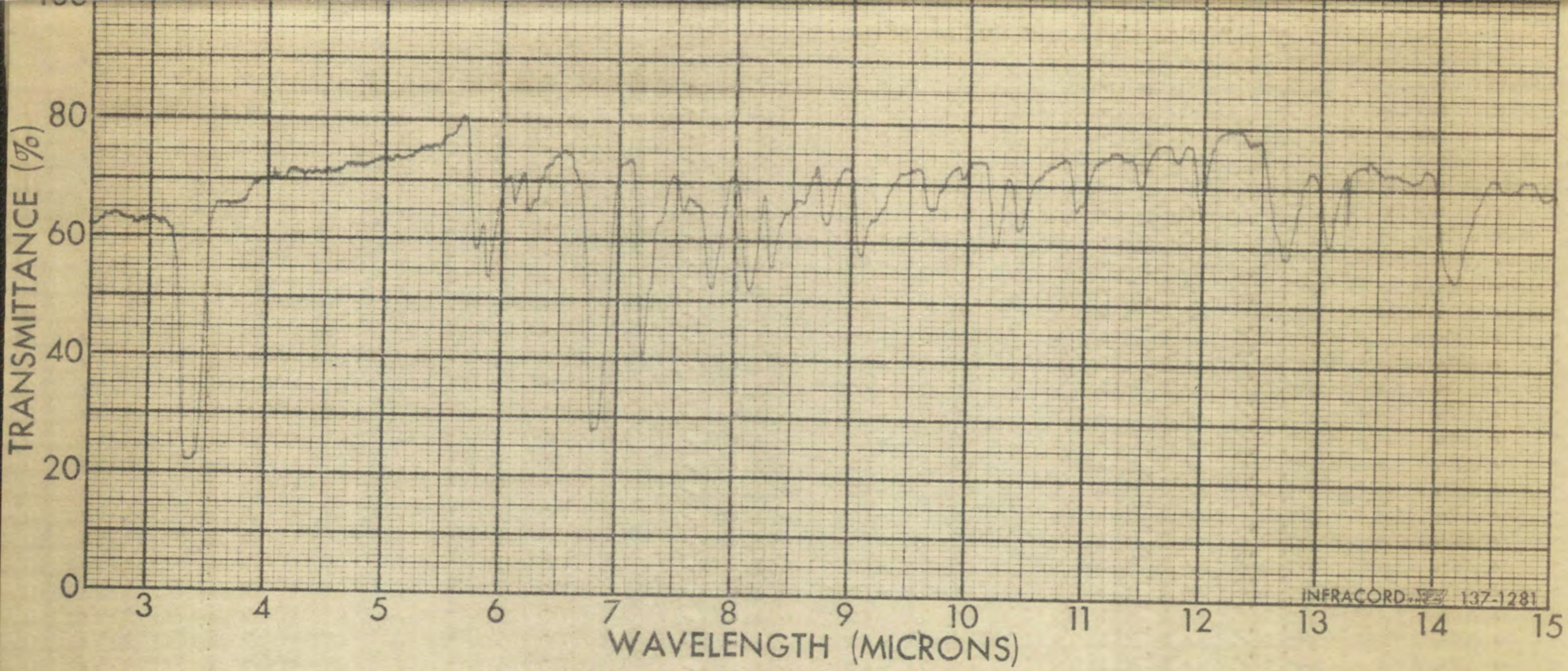
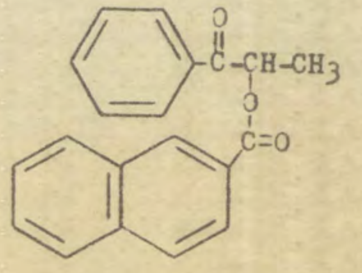


Plate IV: Infrared Spectrum of 2-(2-Naphthoyloxy)-1-phenyl-1-propanone



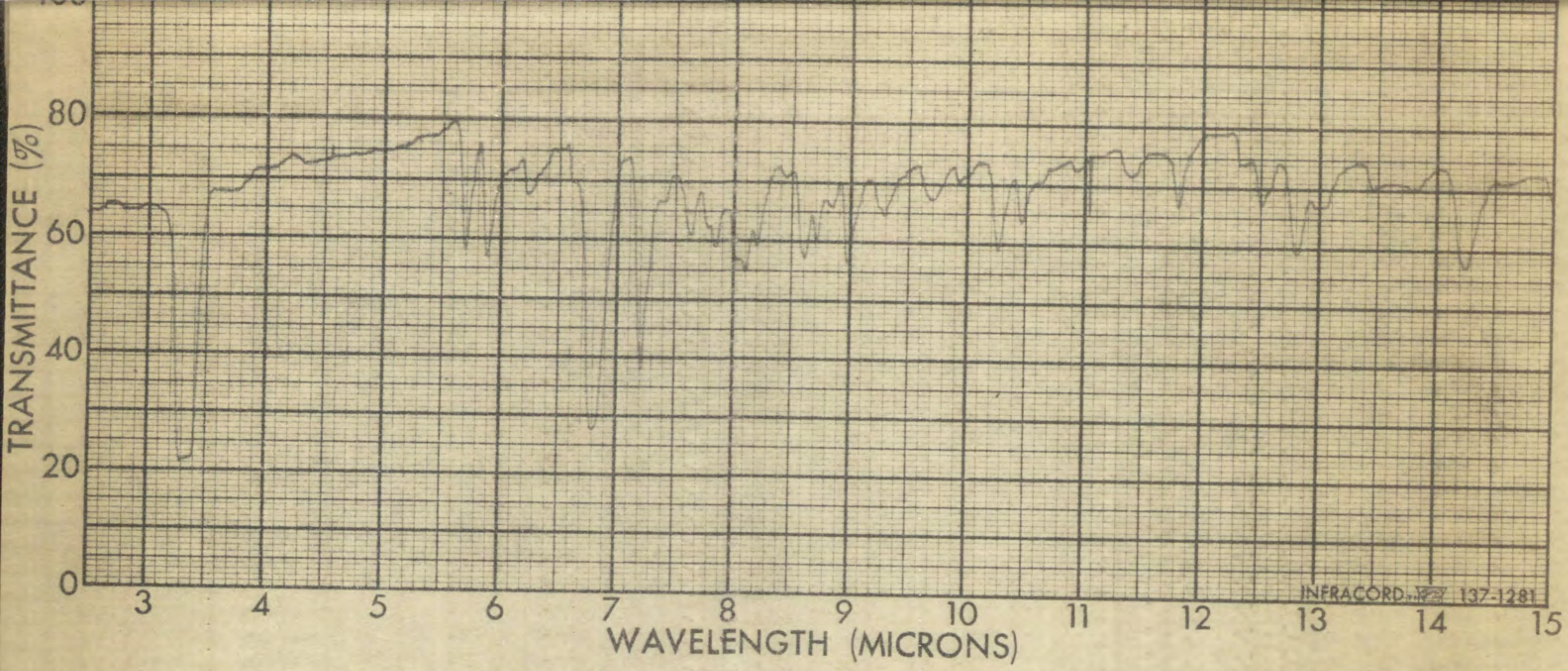
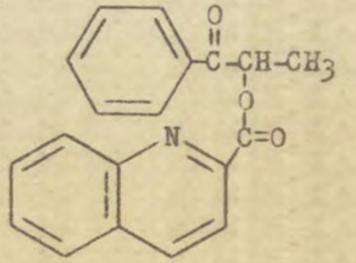


Plate V: Infrared Spectrum of 1-Phenyl-2-(2-quinoline-carboxyloxy)-1-propanone



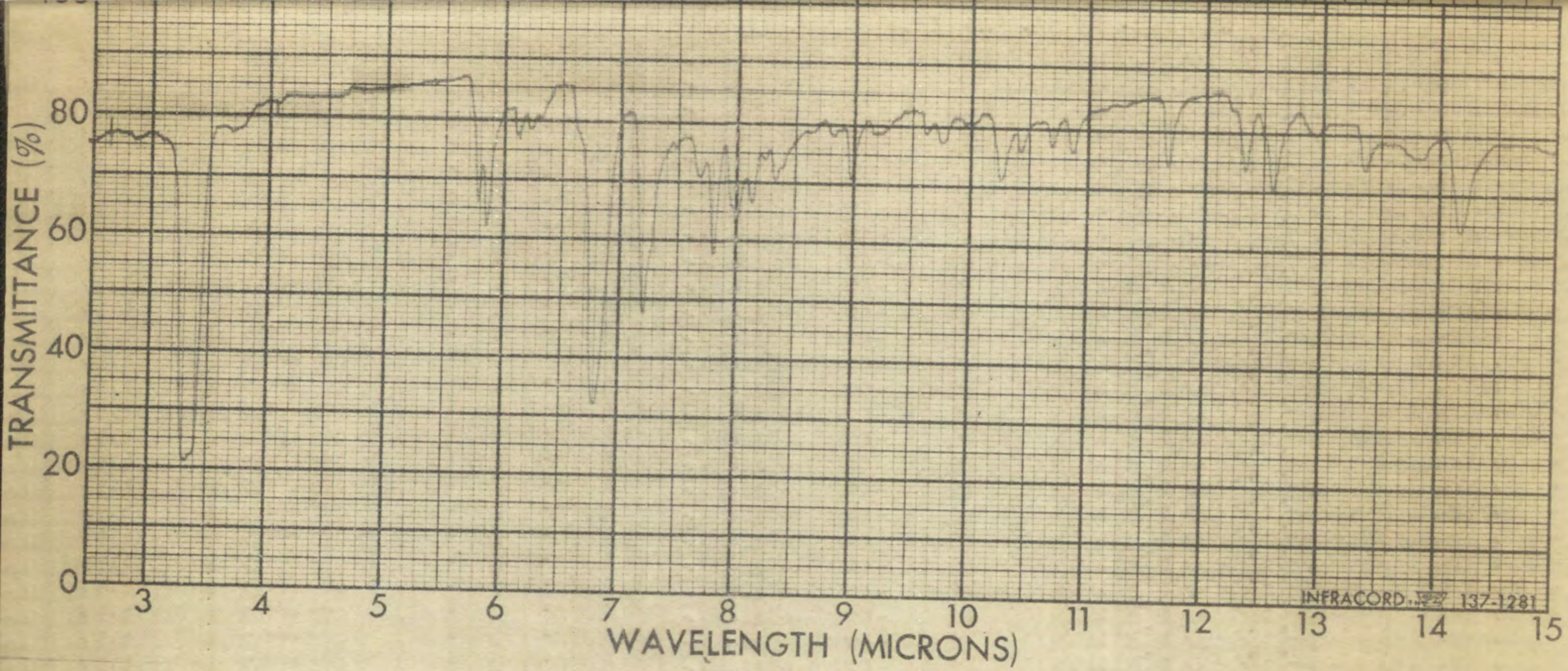
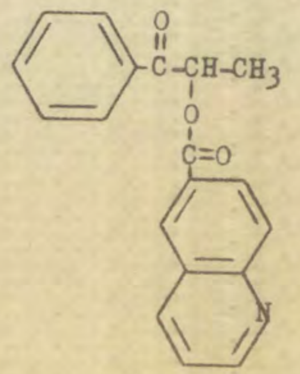


Plate VI: Infrared Spectrum of 1-Phenyl-2-(6-quinolinecarboxyloxy)-1-propanone



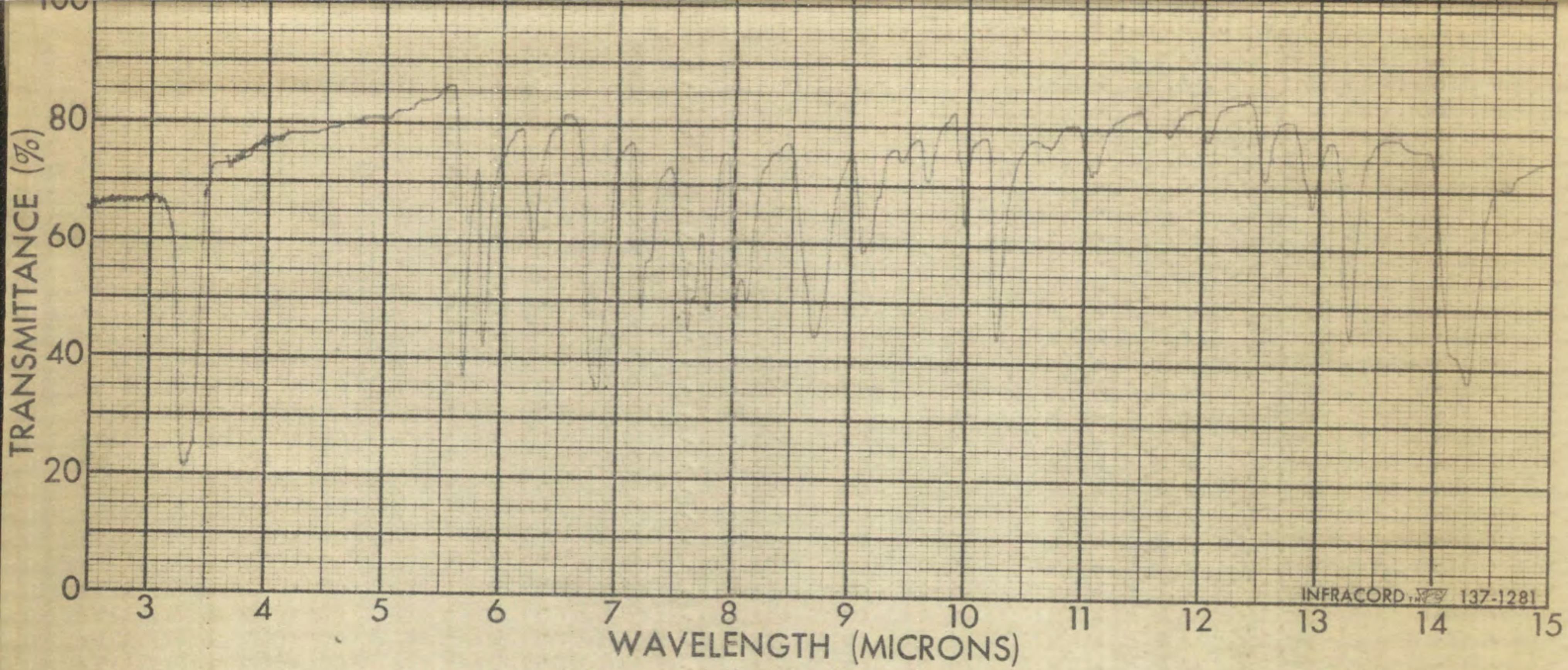
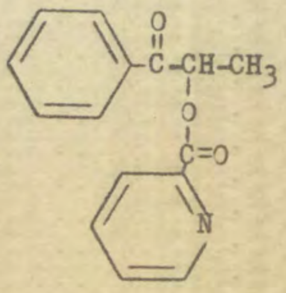


Plate VII: Infrared Spectrum of 1-Phenyl-2-picolinoyloxy-1-propanone



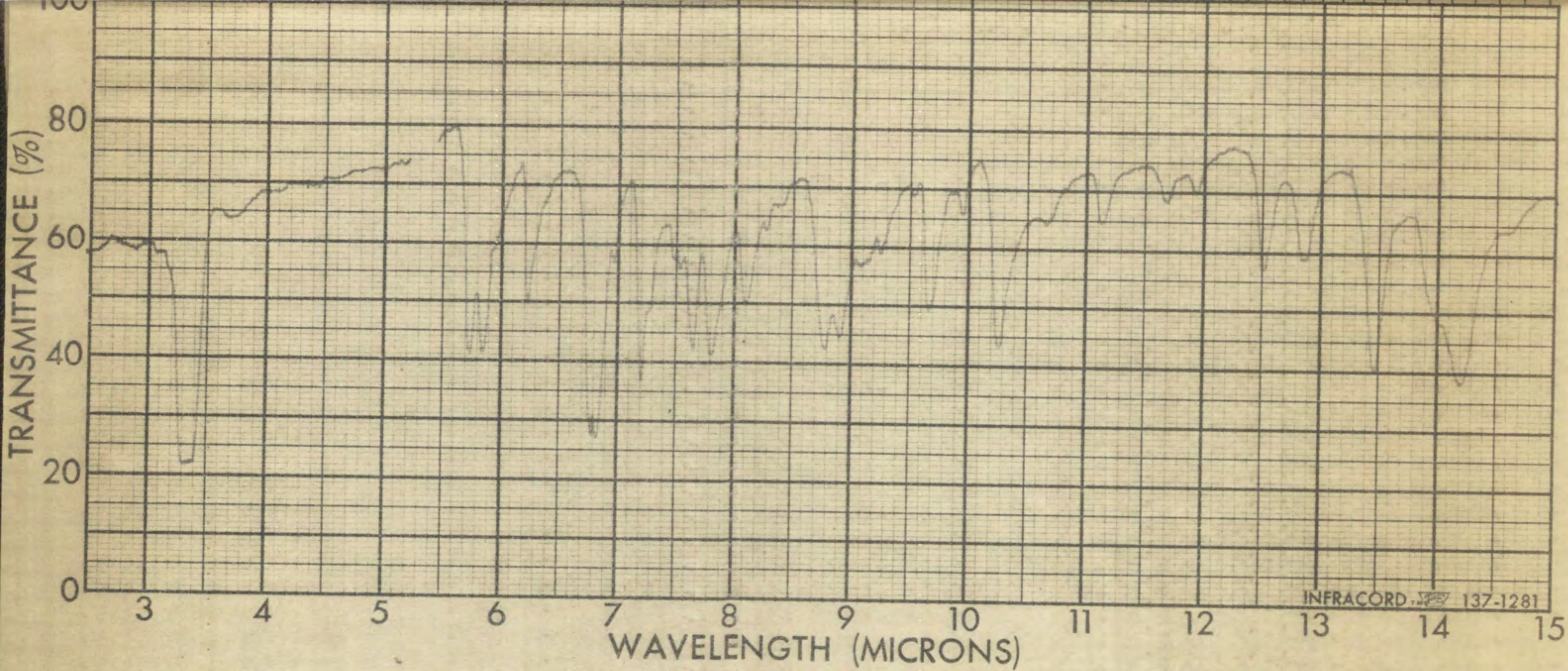
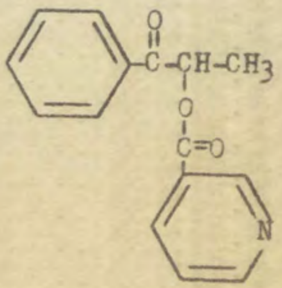


Plate VIII: Infrared Spectrum of 2-Nicotinoyloxy-1-phenyl-1-propanone



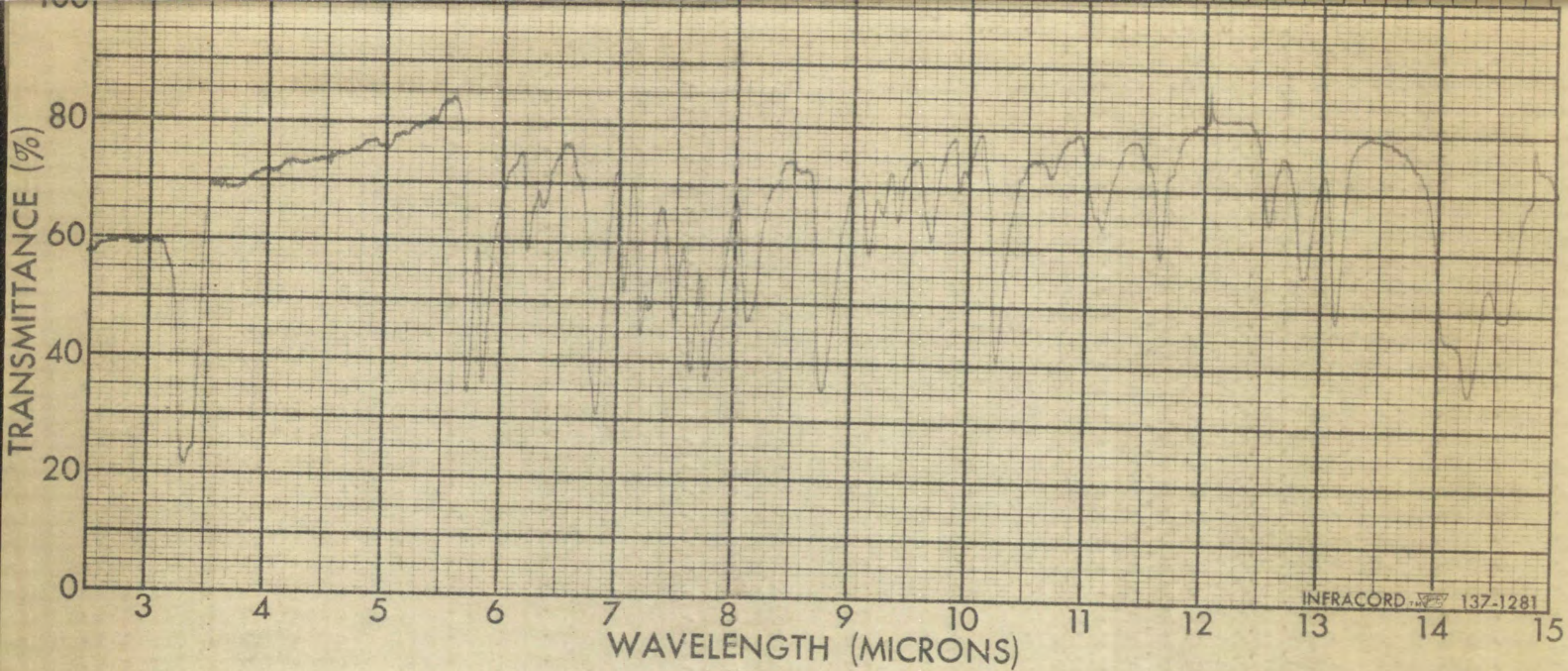
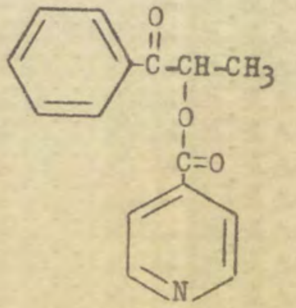


Plate IX: Infrared Spectrum of 2-Isonicotinoyloxy-1-phenyl-1-propanone



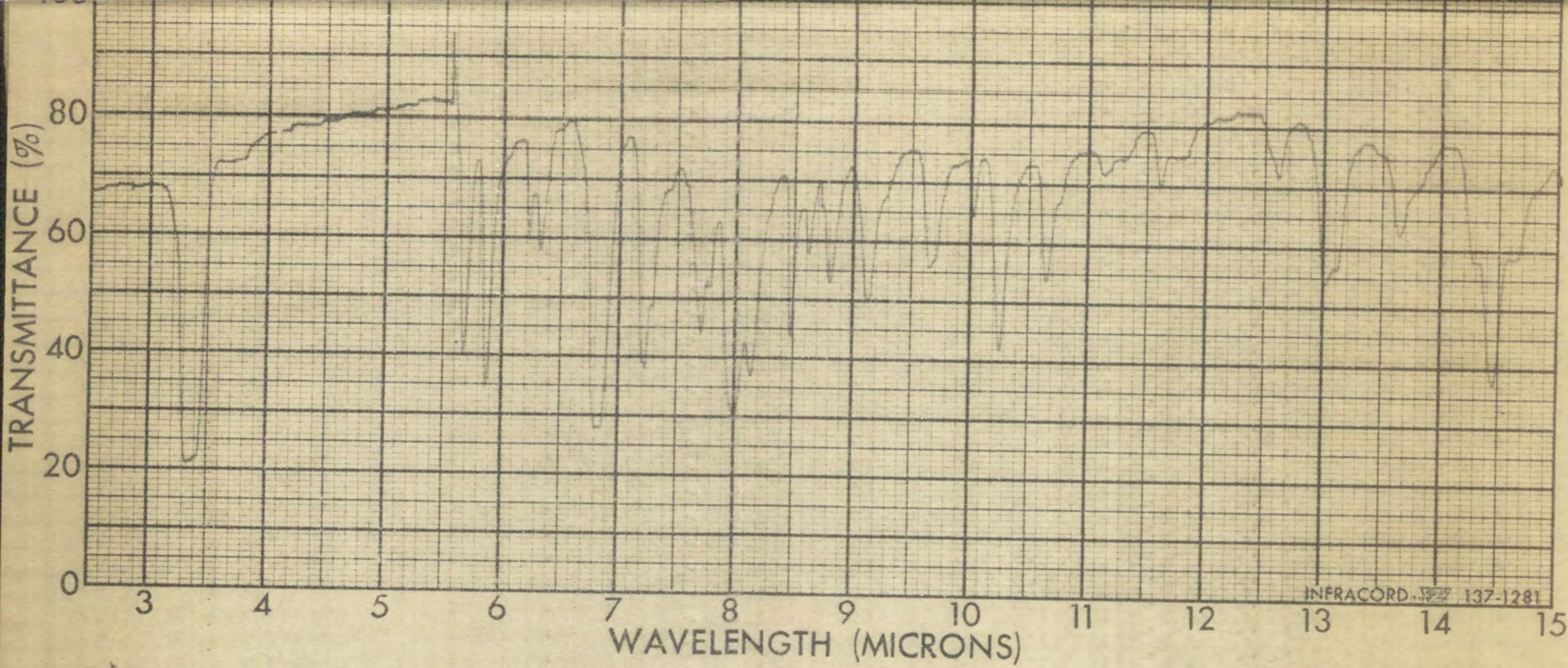
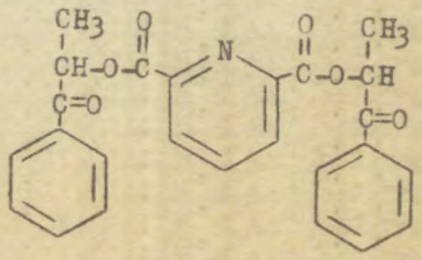


Plate X: Infrared Spectrum of Di-α-benzoylethyl-pyridine-2,6-dicarboxylate



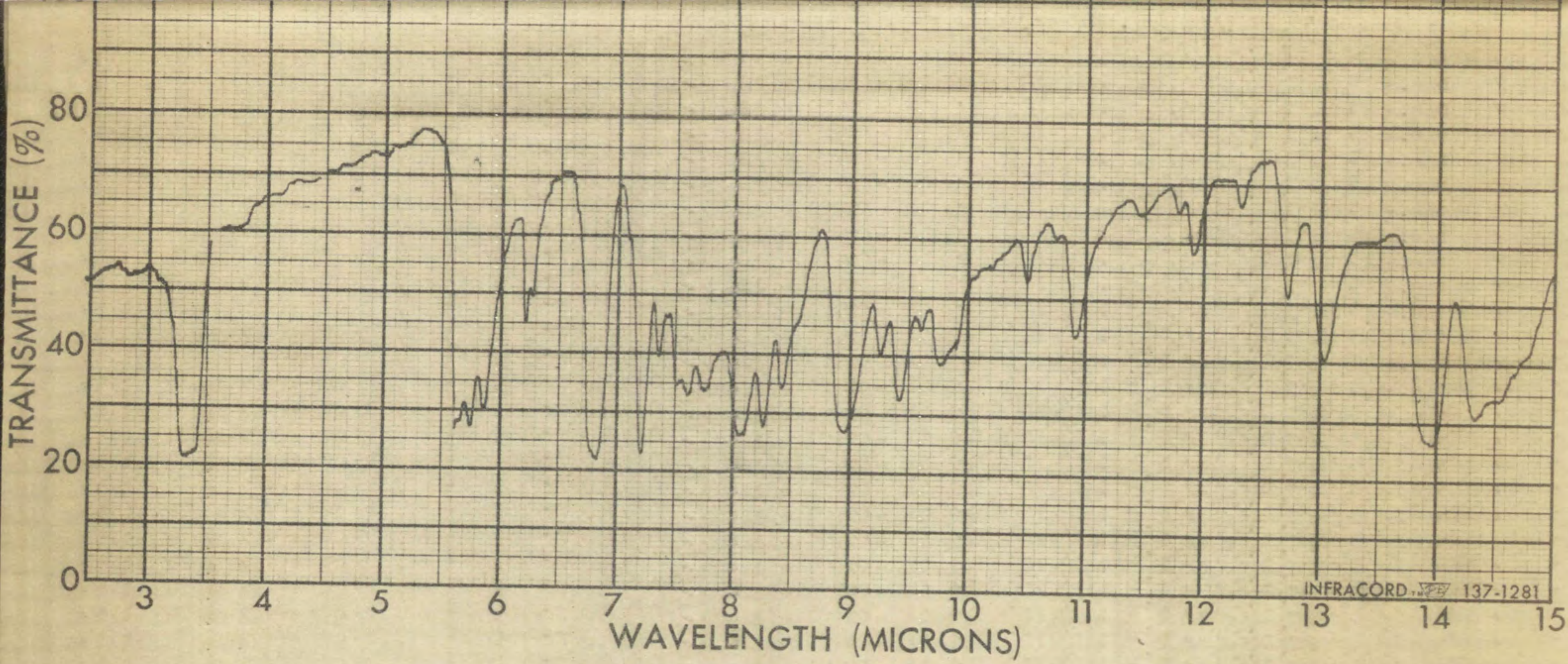
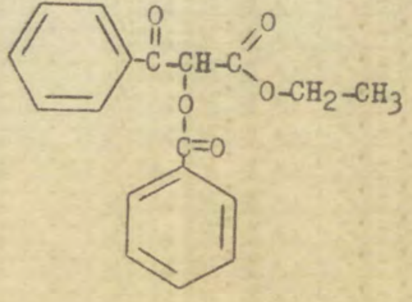


Plate XI: Infrared Spectrum of Ethyl α-benzoyloxybenzoylacetate



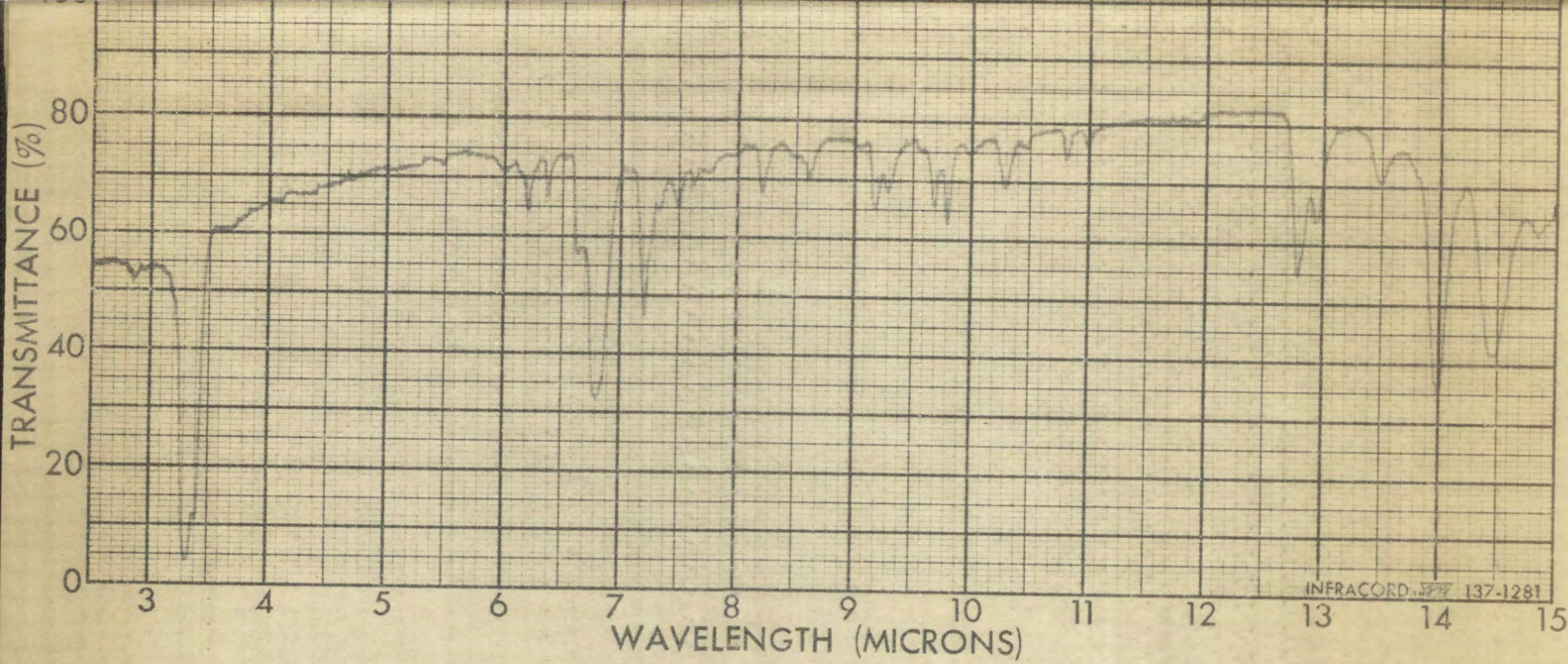
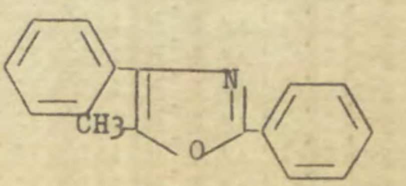


Plate XII: Infrared Spectrum of 2,4-Diphenyl-5-methyloxazole



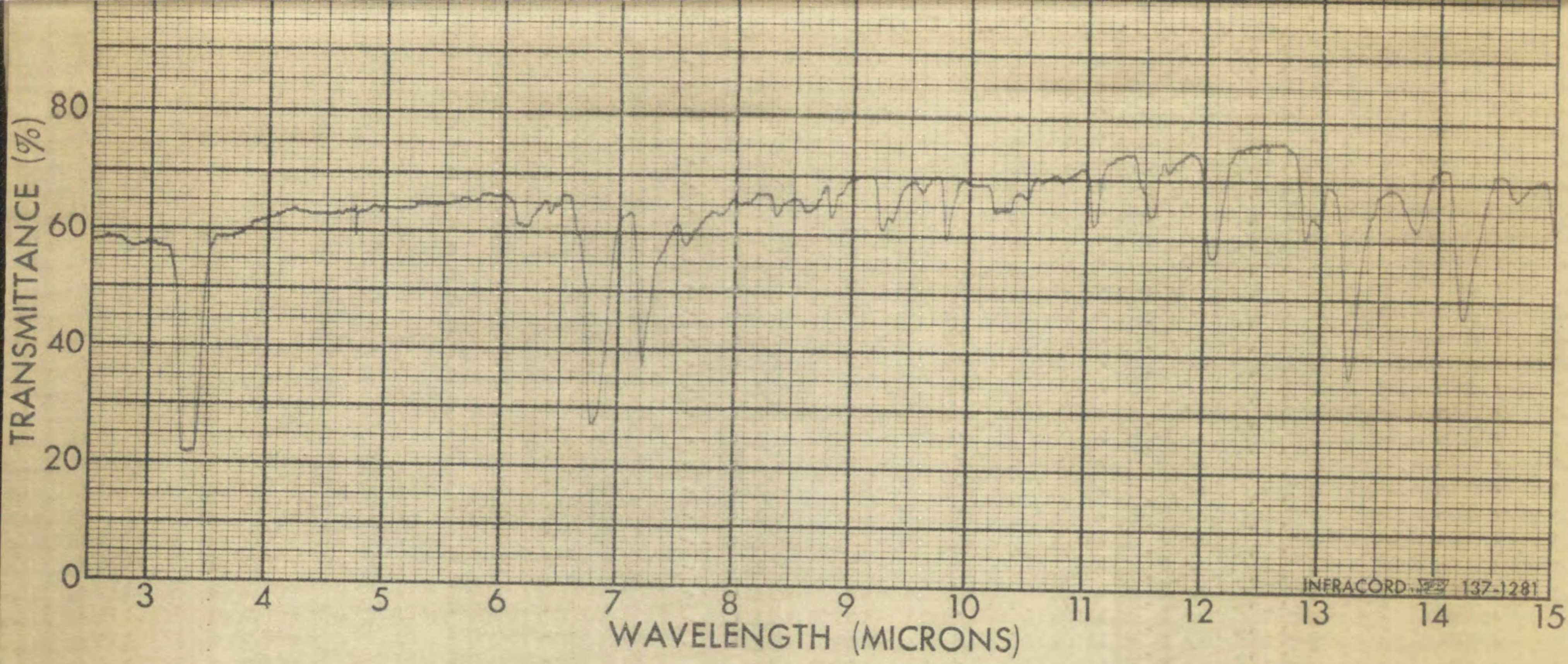
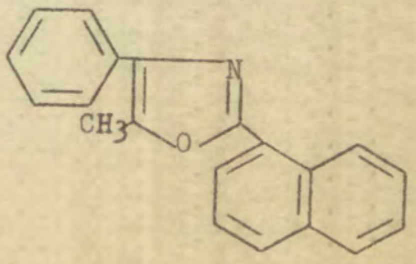


Plate XIII: Infrared Spectrum of 5-Methyl-2(1-naphthyl)-4-phenyloxazole



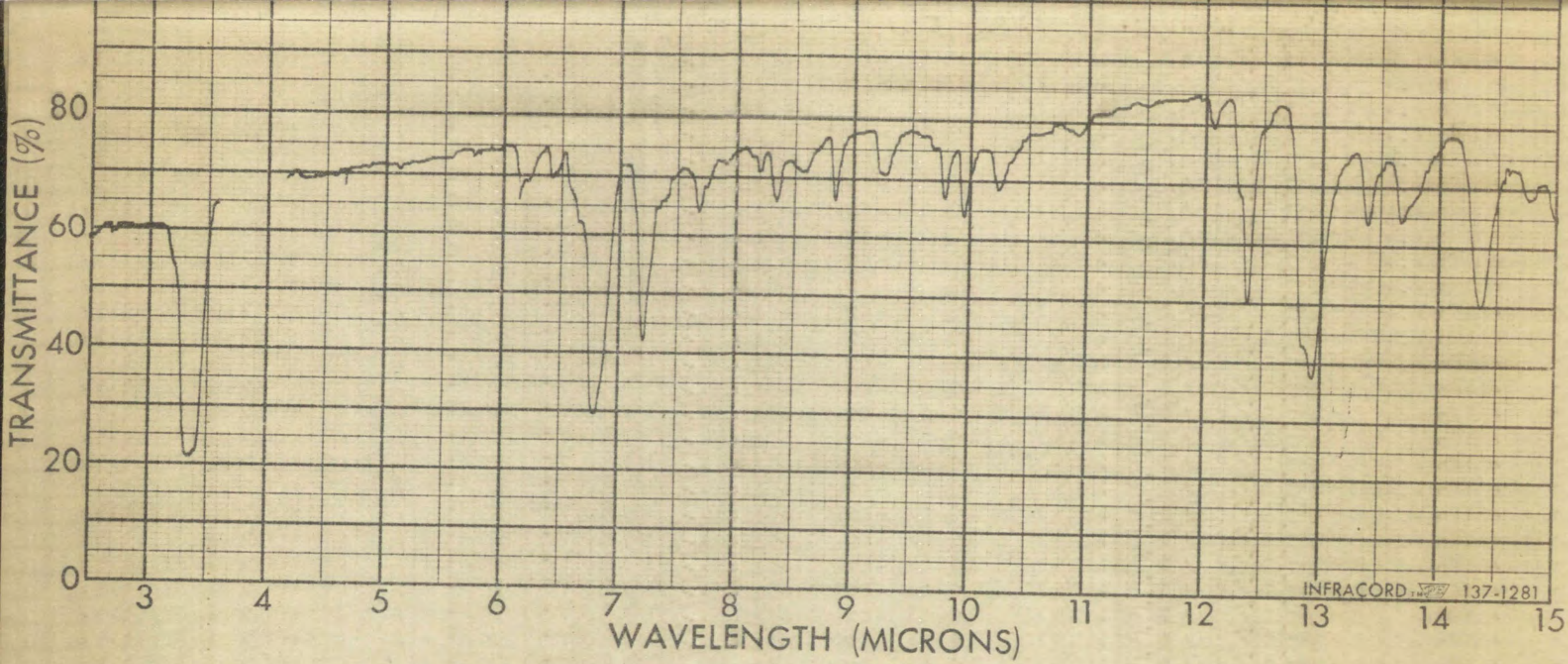
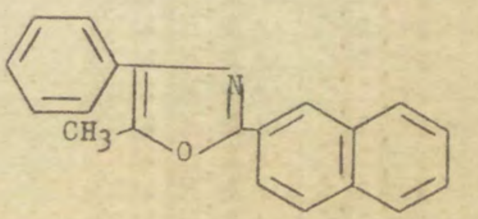


Plate XIV: Infrared Spectrum of 5-Methyl-2-(2-naphthyl)-4-phenyloxazole



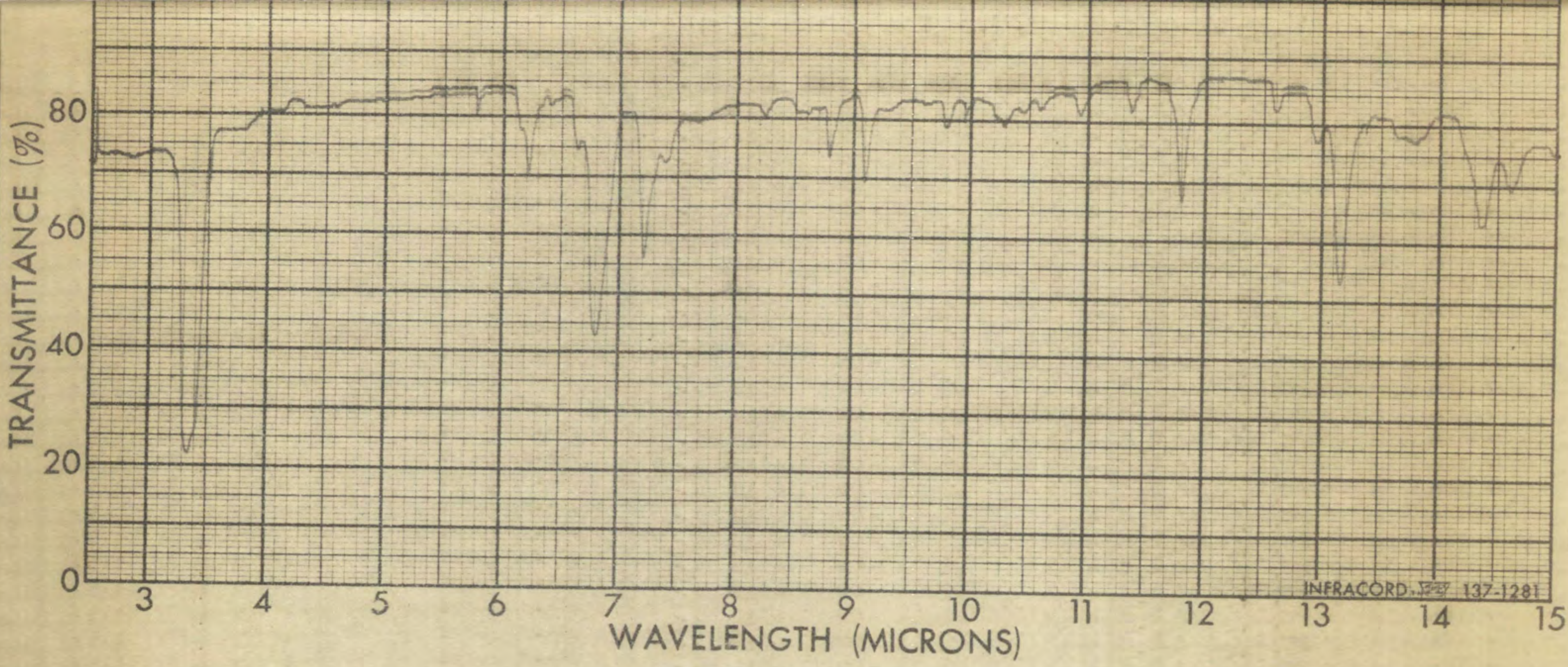
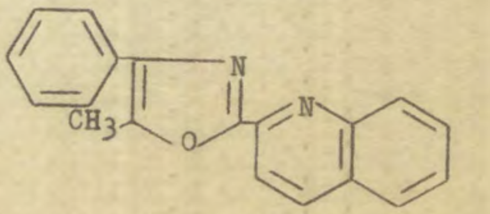


Plate XV: Infrared Spectrum of 5-Methyl-4-phenyl-2-(2-quinolyl)oxazole



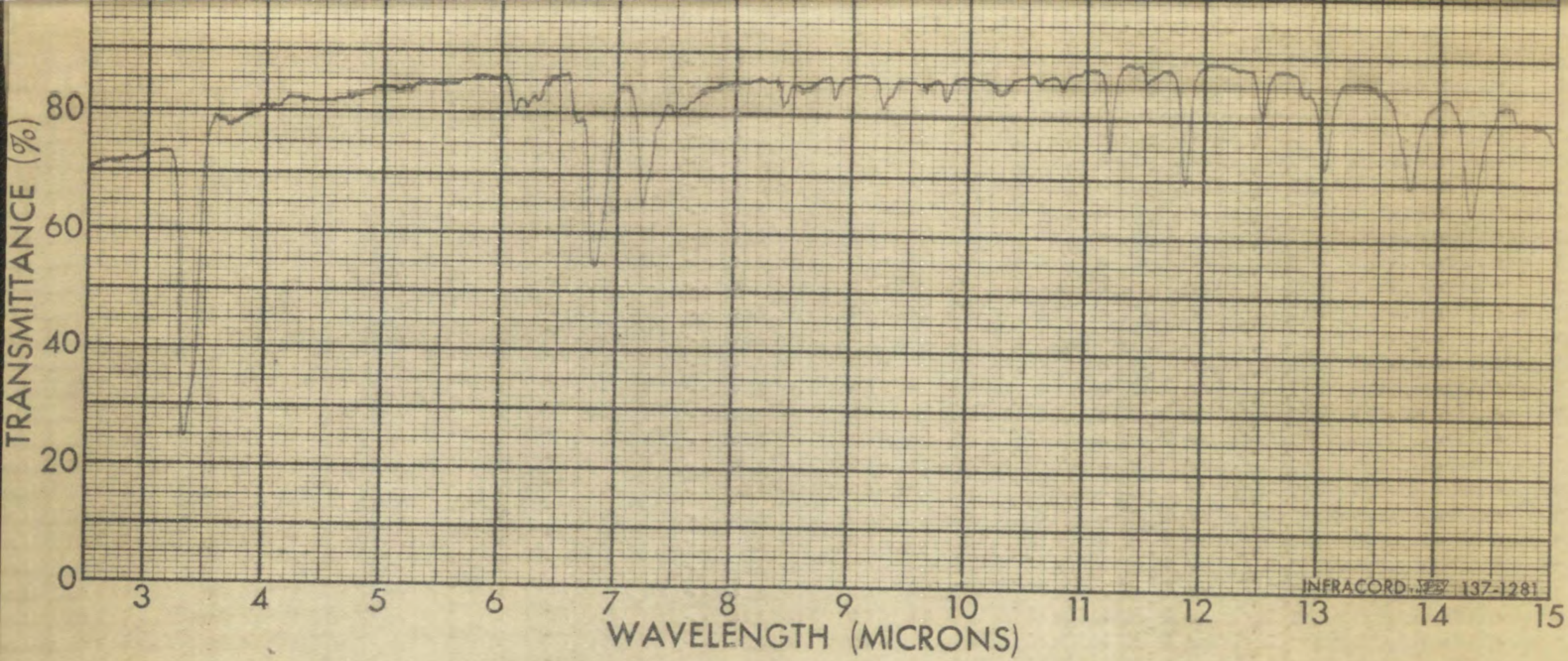
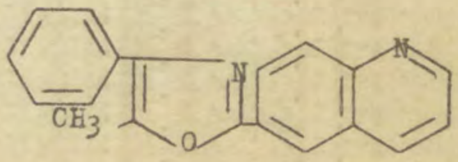


Plate XVI: Infrared Spectrum of 5-Methyl-4-phenyl-2-(6-quinolyl)oxazole



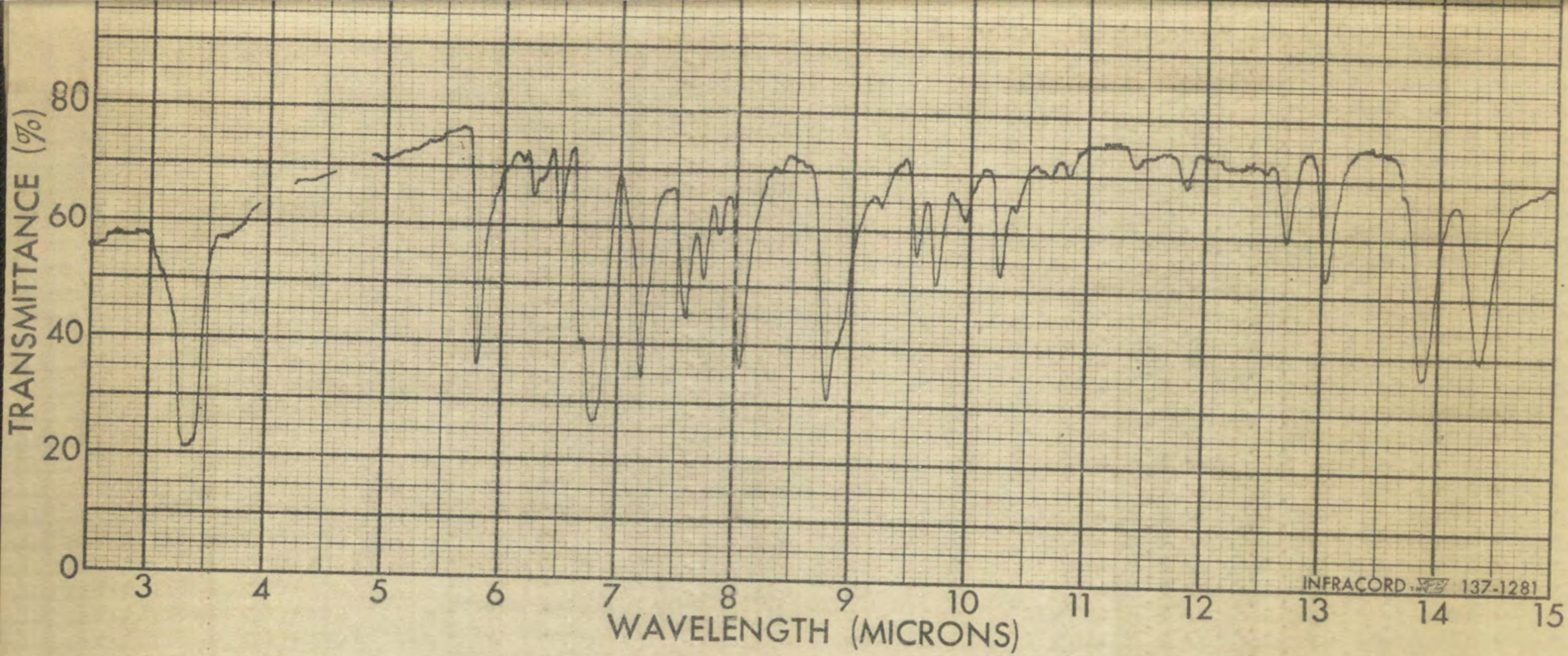
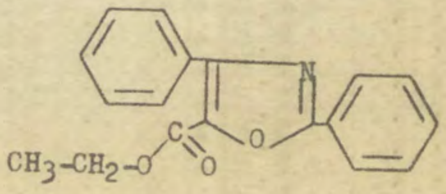


Plate XVII: Infrared Spectrum of Ethyl 2,4-diphenyloxazole-5-carboxylate



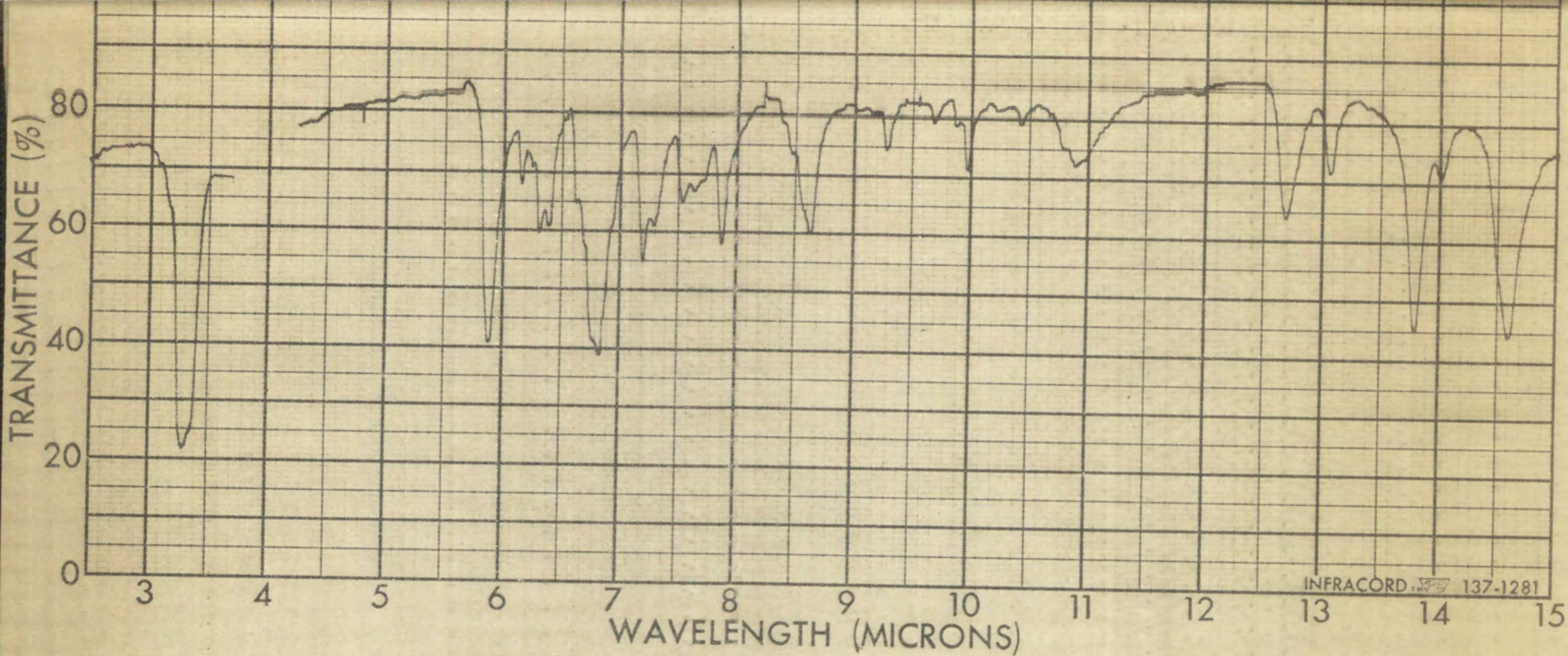
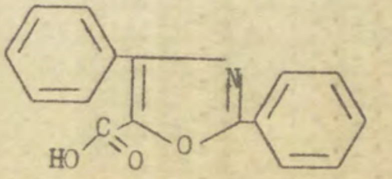


Plate XVIII: Infrared Spectrum of 2,4-Diphenyloxazole-5-carboxylic acid



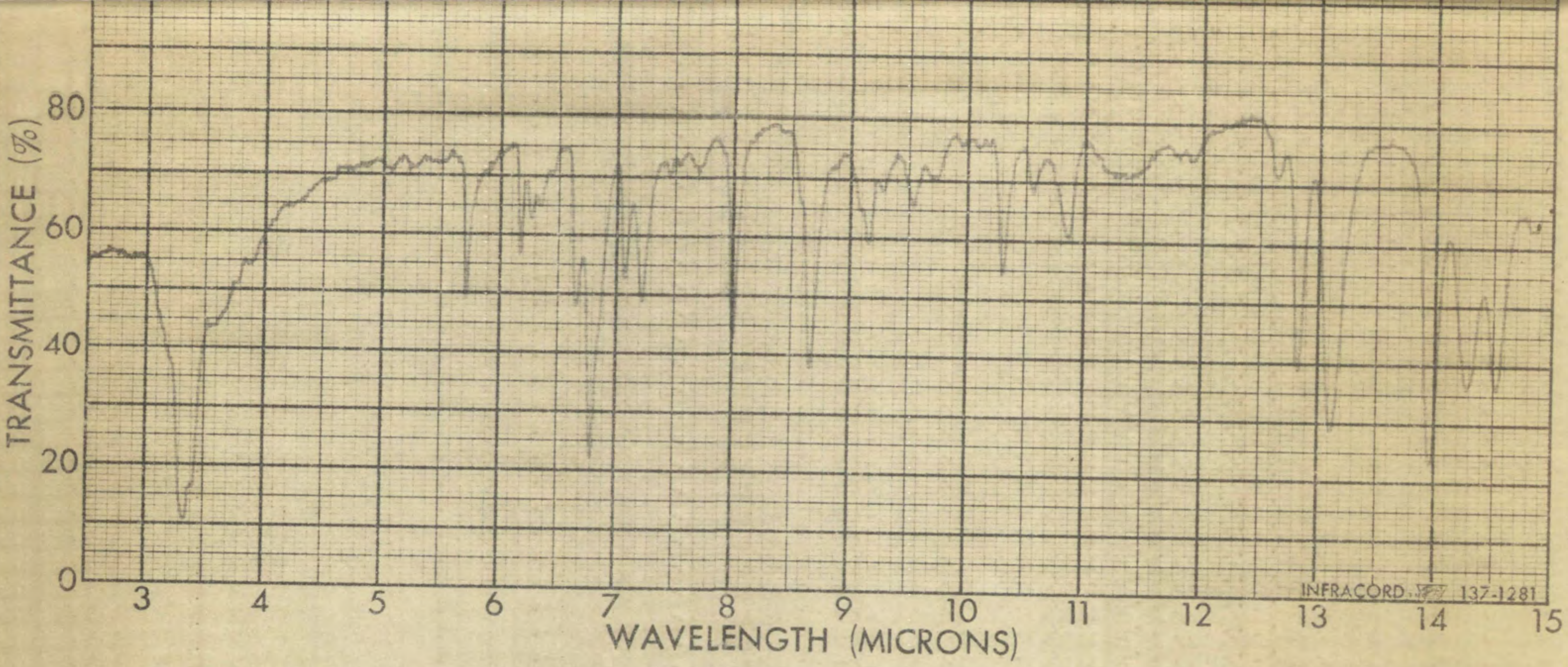
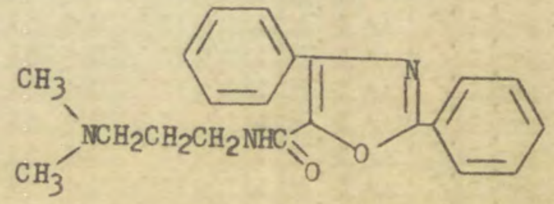


Plate XIX: Infrared Spectrum of N,N-Dimethylaminopropyl-2,4-diphenyloxazole-5-carboxamide



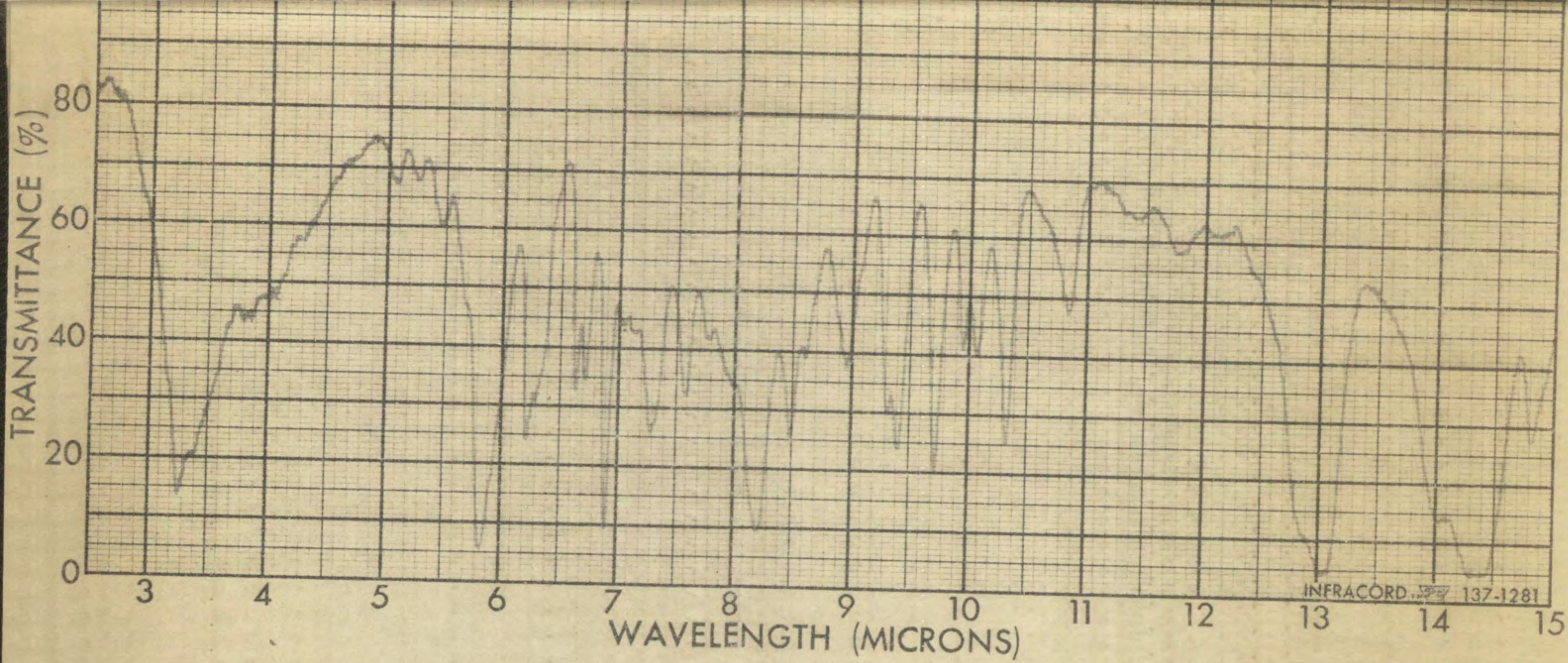
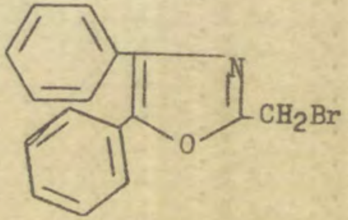


Plate XX: Infrared Spectrum of 2-Bromomethyl-4,5-diphenyloxazole



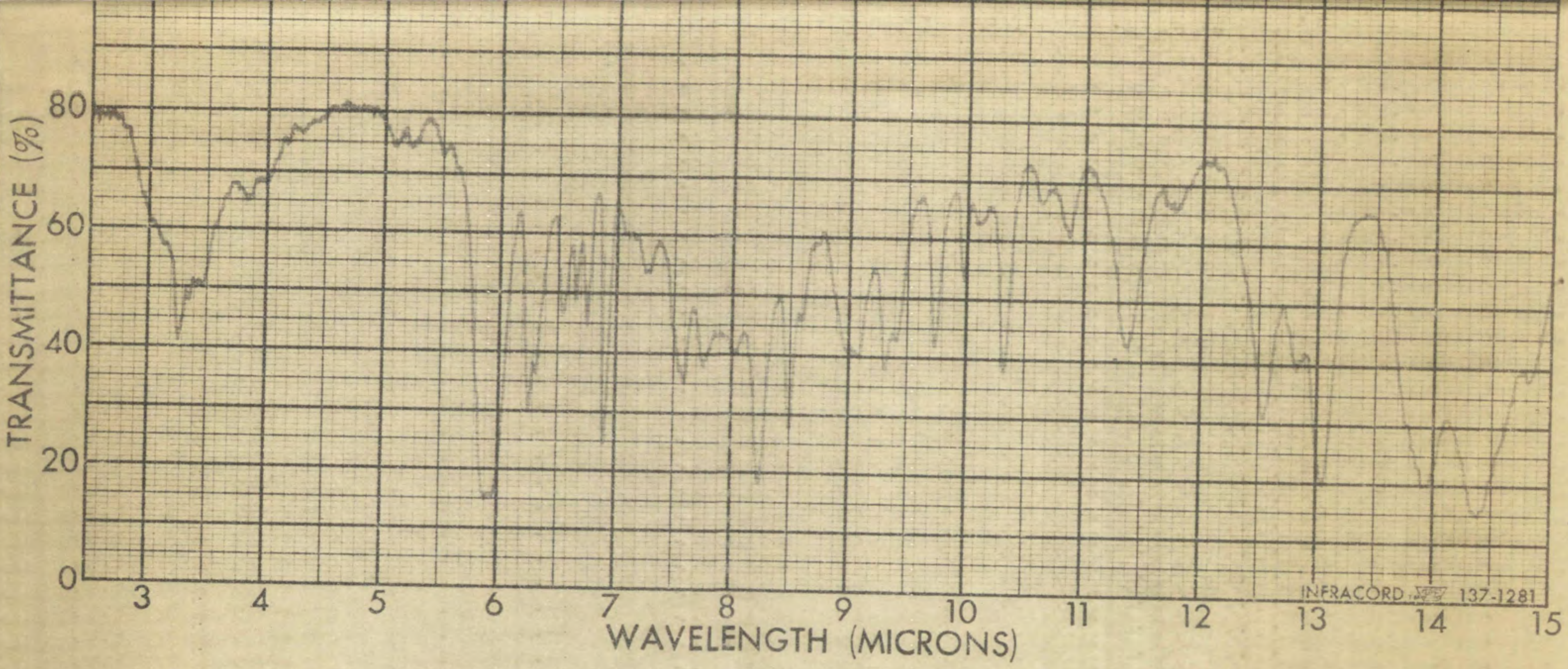
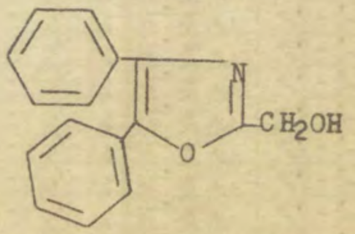


Plate XXI: Infrared Spectrum of 4,5-Diphenyl-2-hydroxymethyloxazole



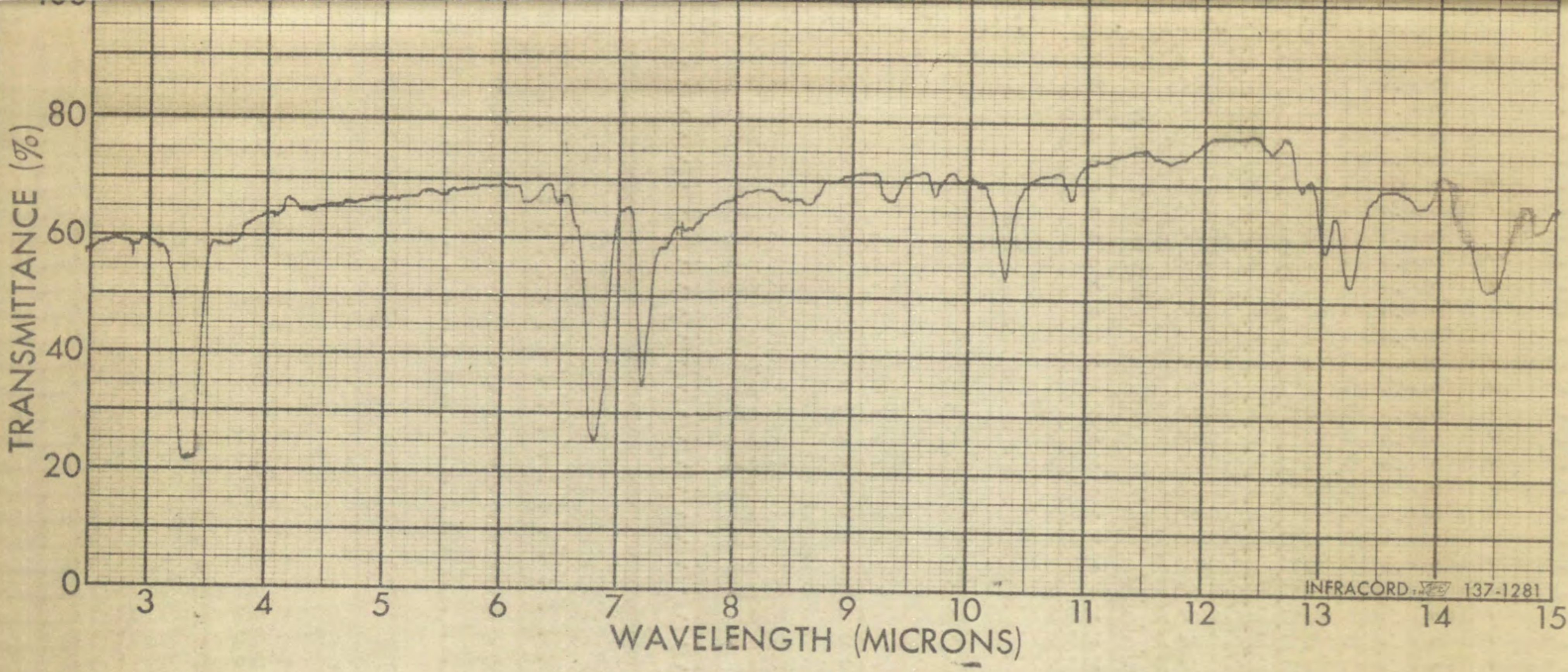
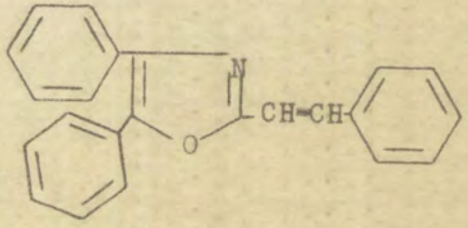


Plate XXII: Infrared Spectrum of 5,4-Diphenyl-2-styryloxazole



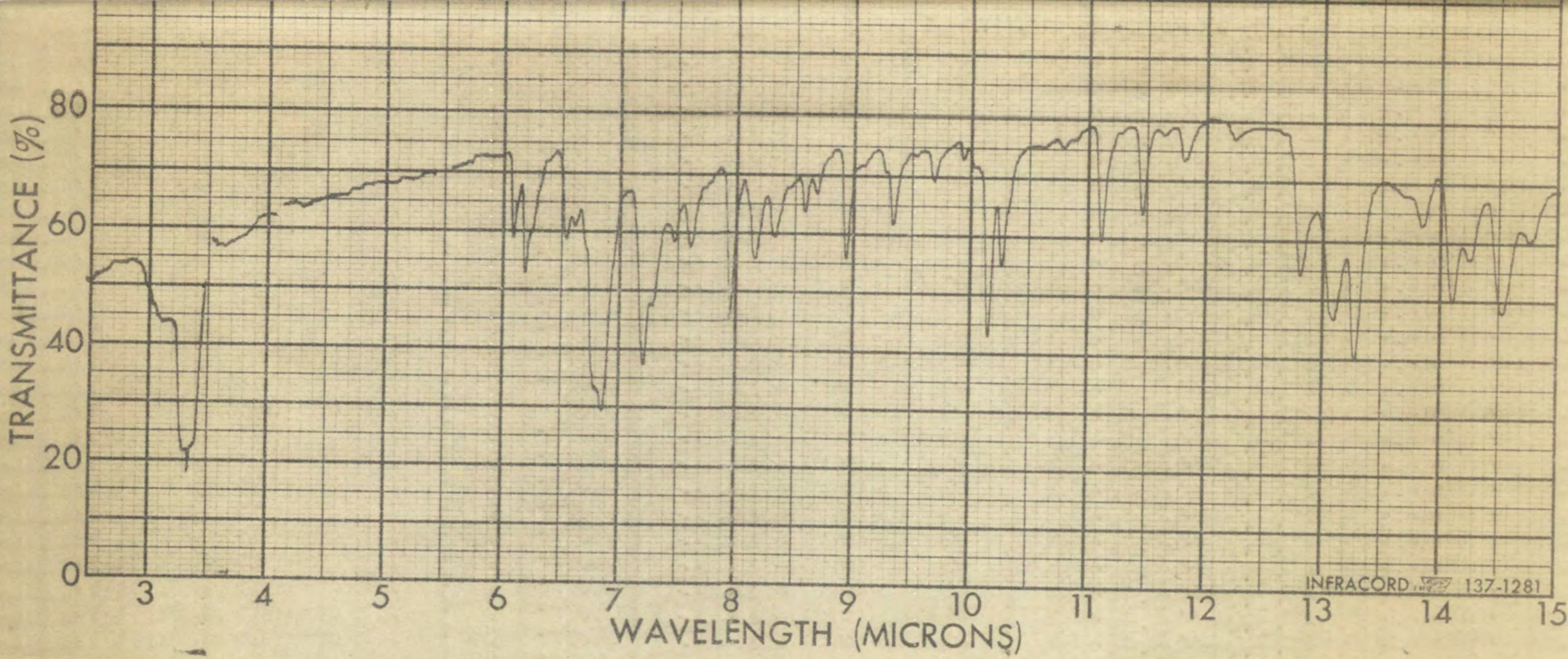
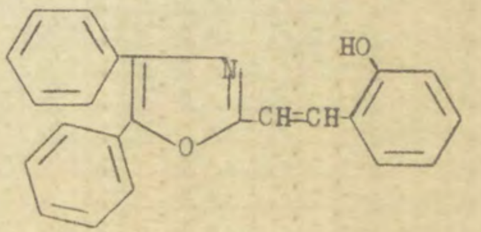


Plate XXIII: Infrared Spectrum of 5,4-Diphenyl-2-(2-hydroxystyryl)oxazole



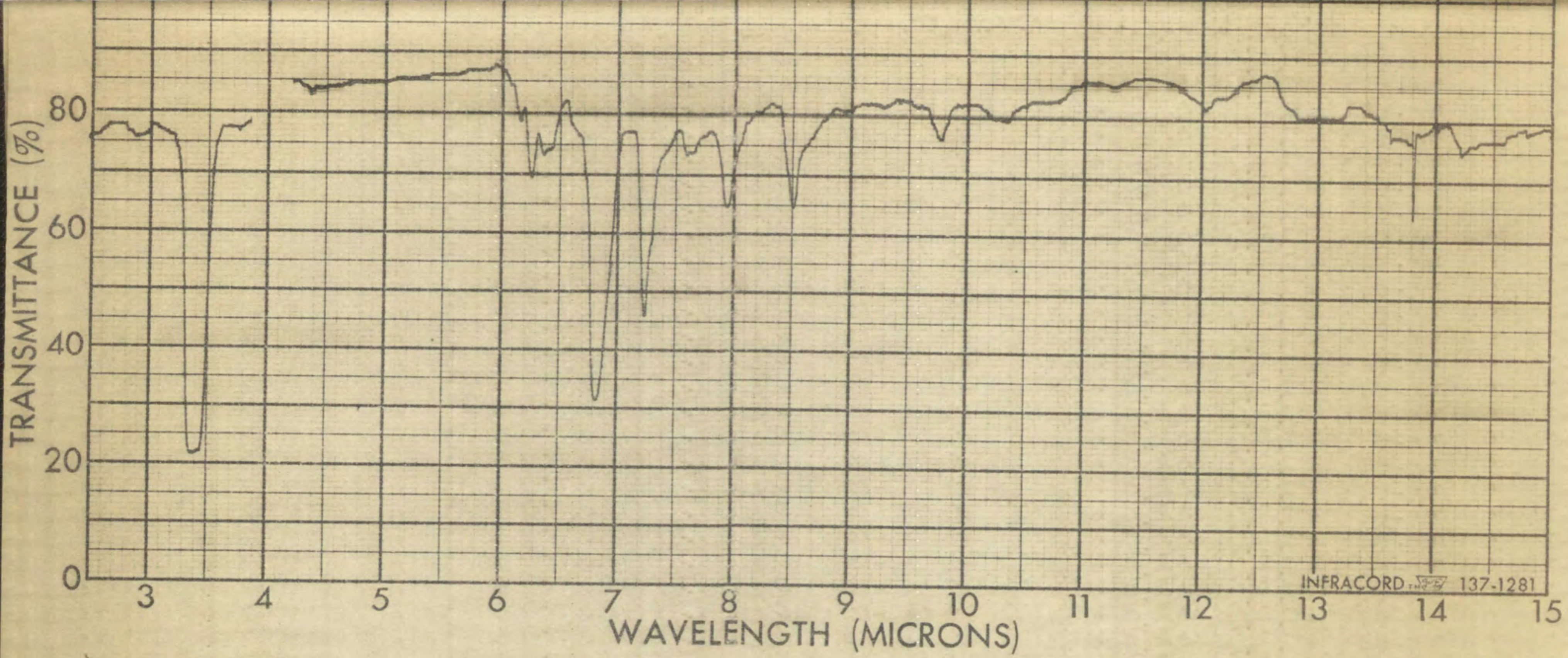
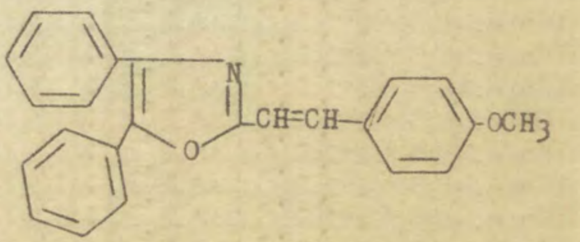


Plate XXIV: Infrared Spectrum of 5,4-Diphenyl-2-(4-methoxystyryl)oxazole



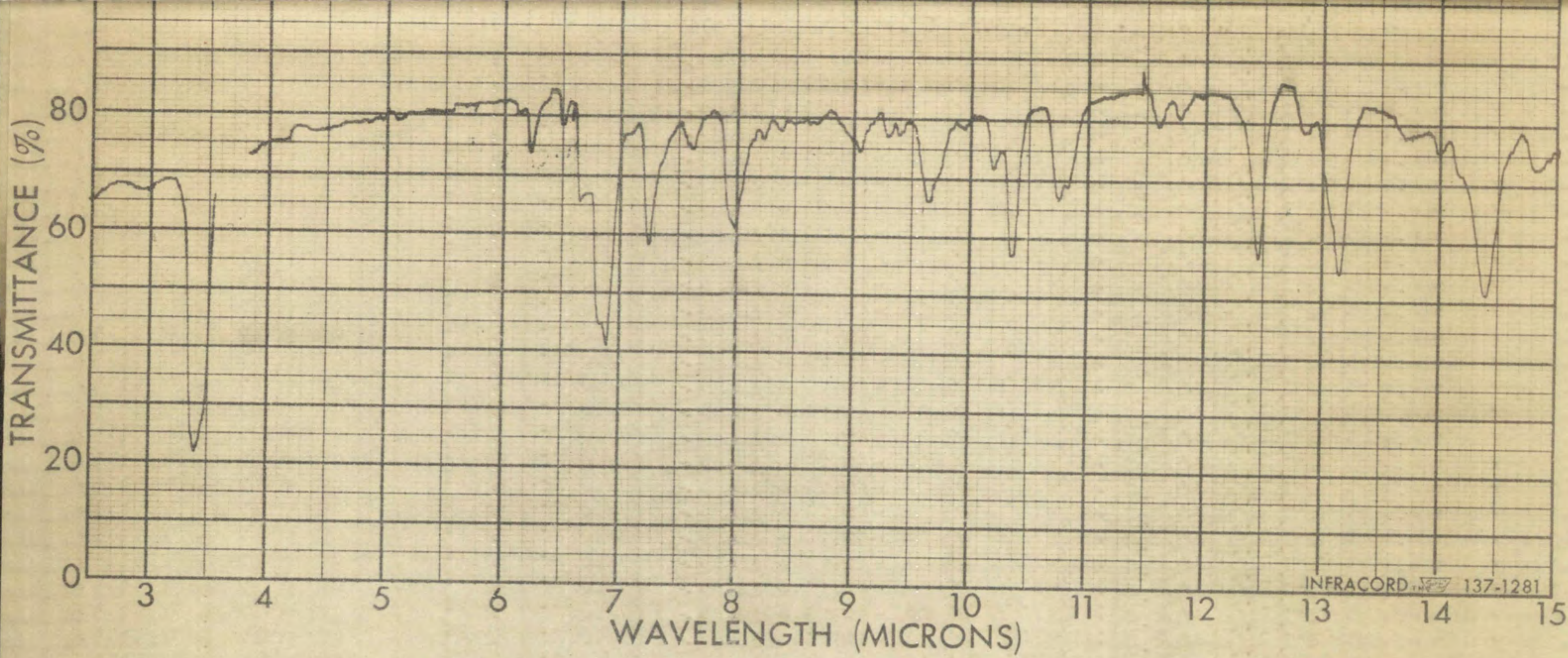
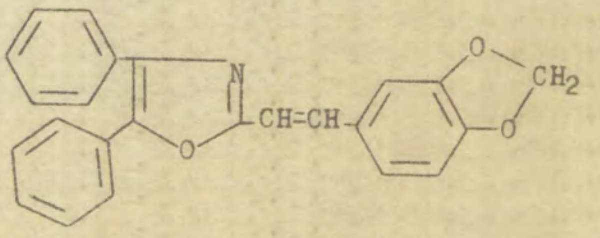


Plate XXV: Infrared Spectrum of 5,4-Diphenyl-2-(3,4-methylenedioxystyryl)oxazole



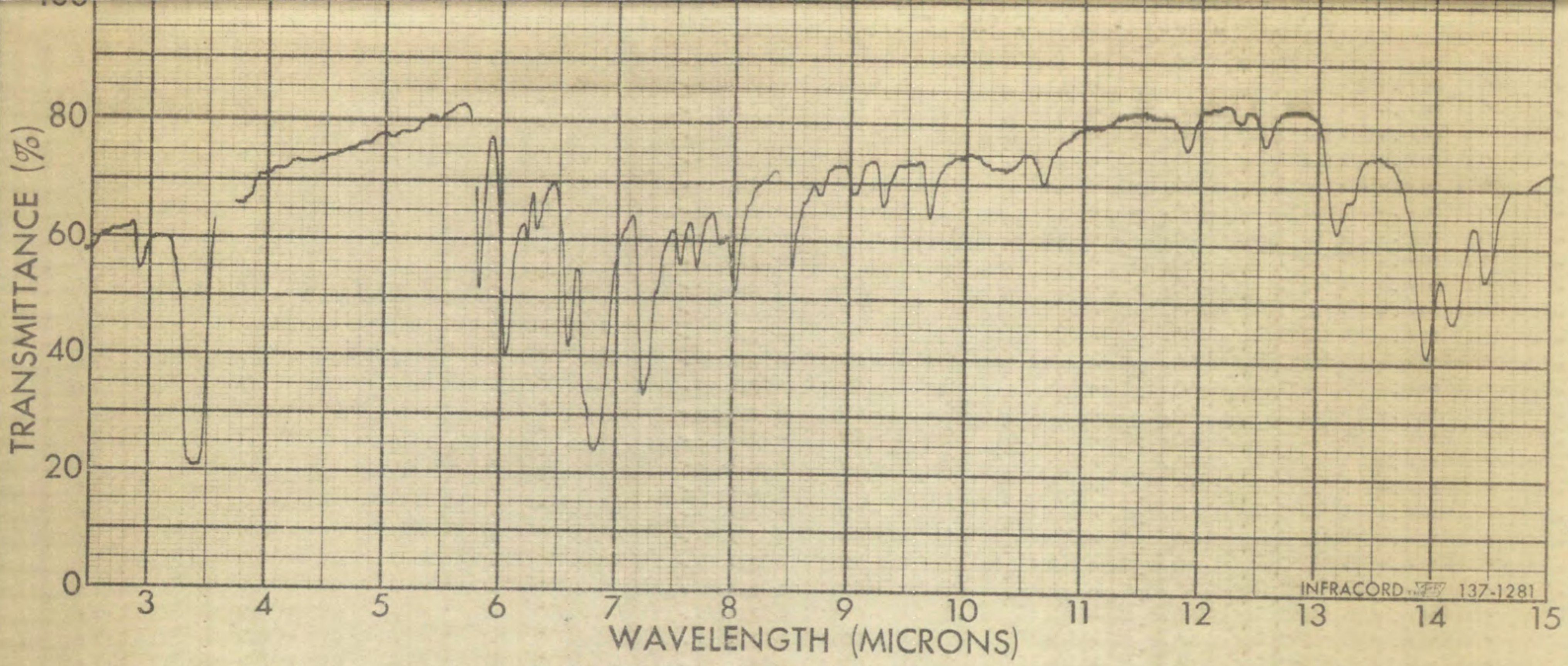
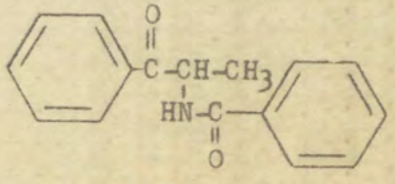


Plate XXVI: Infrared Spectrum of 2-Benzoylamido-1-phenyl-1-propanone



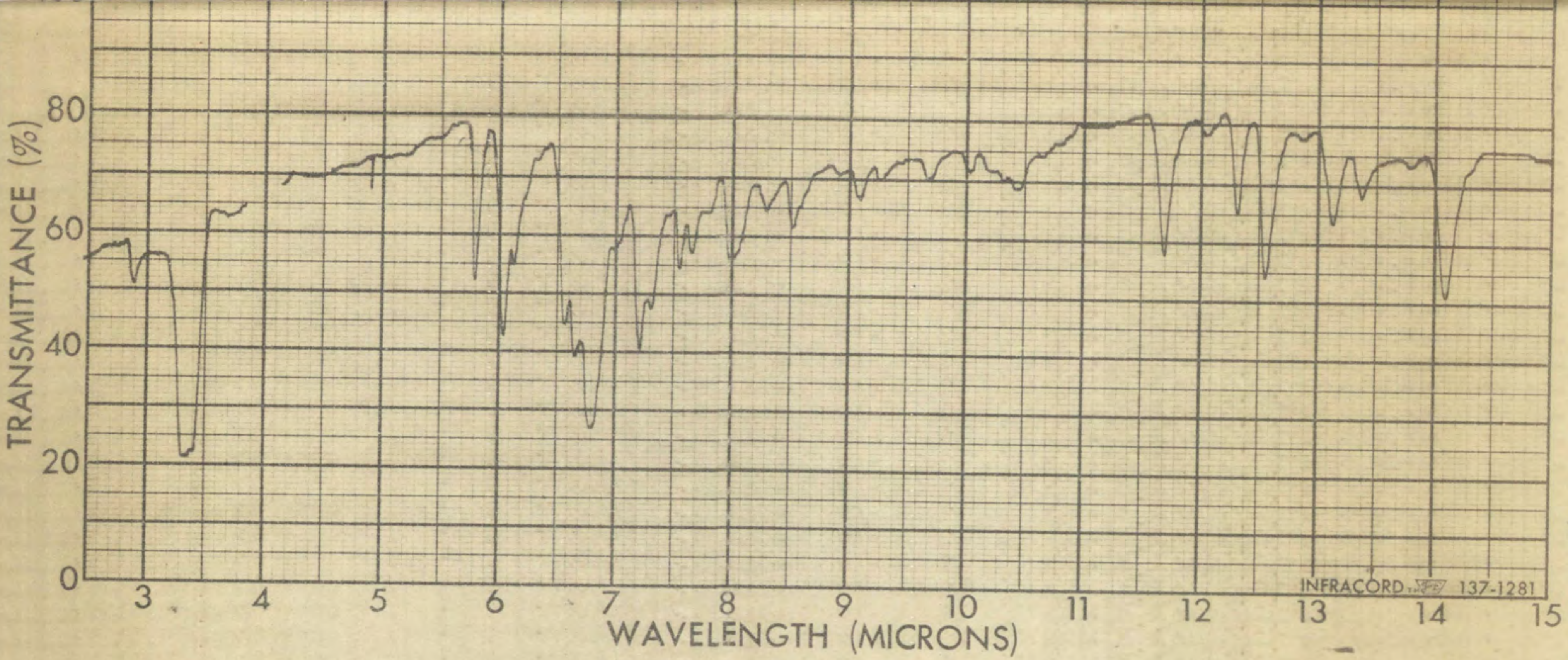
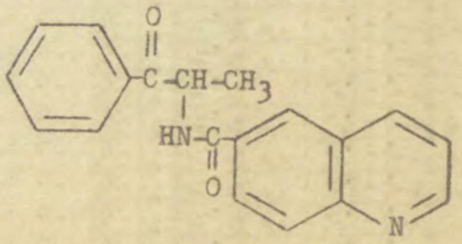


Plate XXVII: Infrared Spectrum of 1-Phenyl-2-(6-quinolinecarboxoylamido)-1-propanone



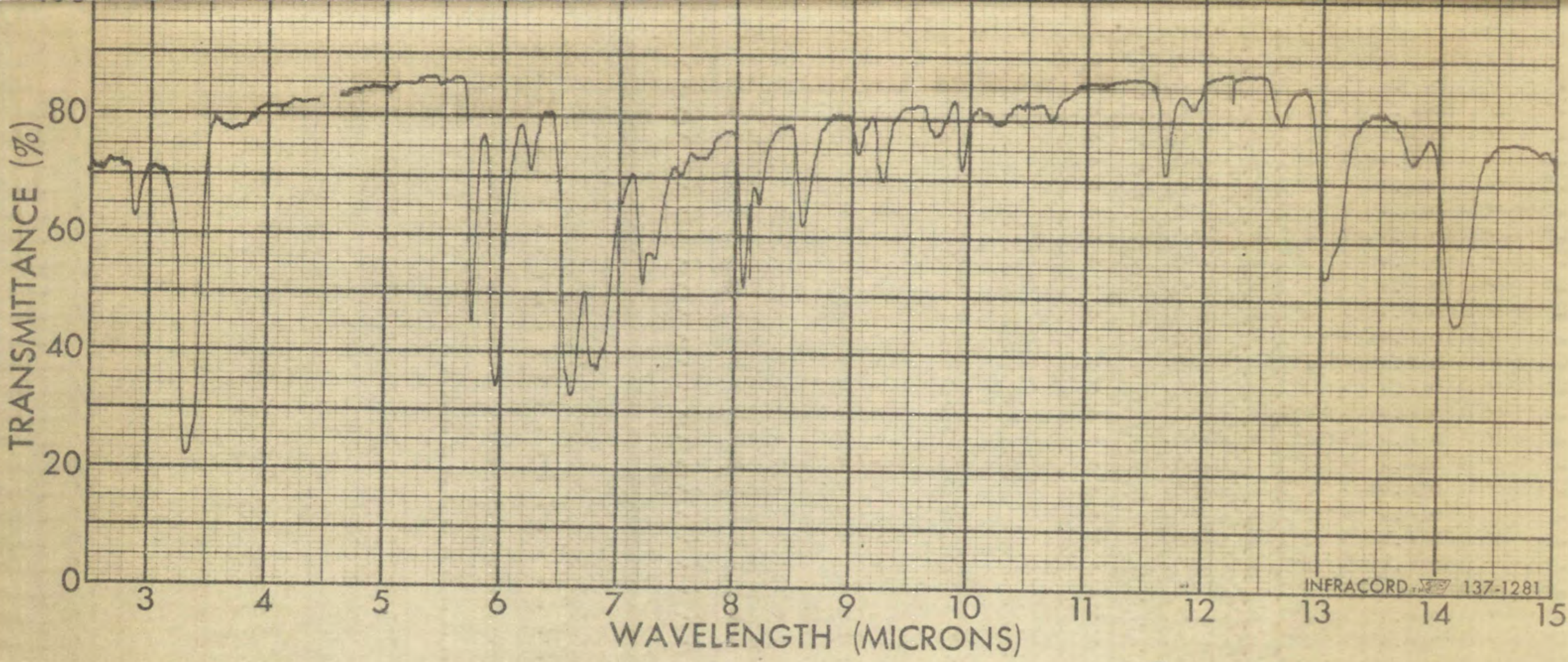
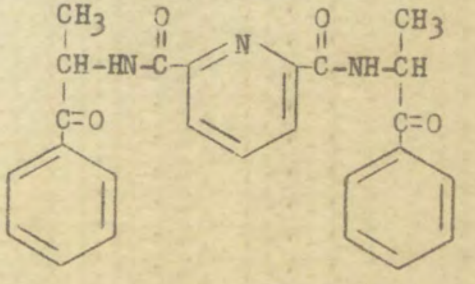


Plate XXVIII: Infrared Spectrum of N,N'-Bis(α-benzoylethyl) pyridine-2,6-dicarboxamide



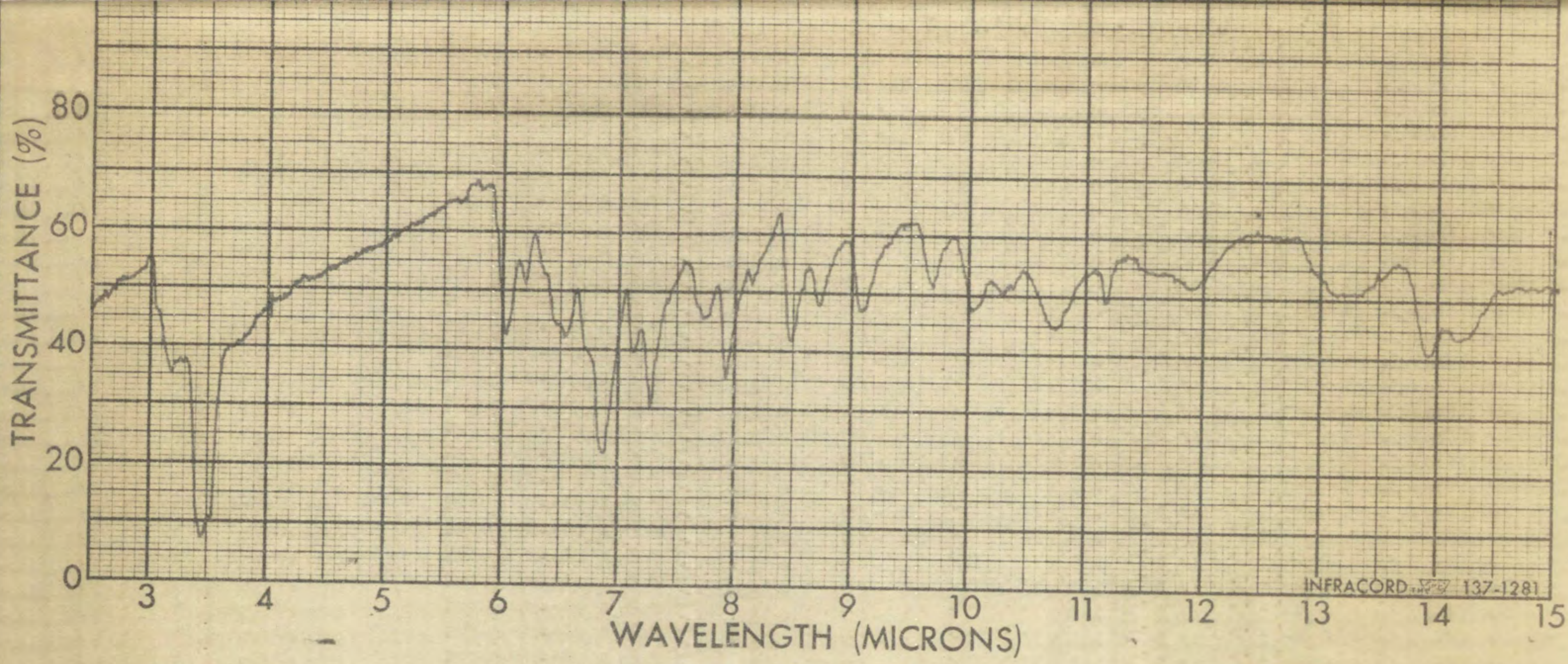
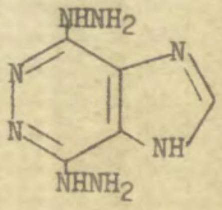


Plate XXIX: Infrared Spectrum of 4,7-Bishydrazino-imidazo[4,5-d]pyridazine



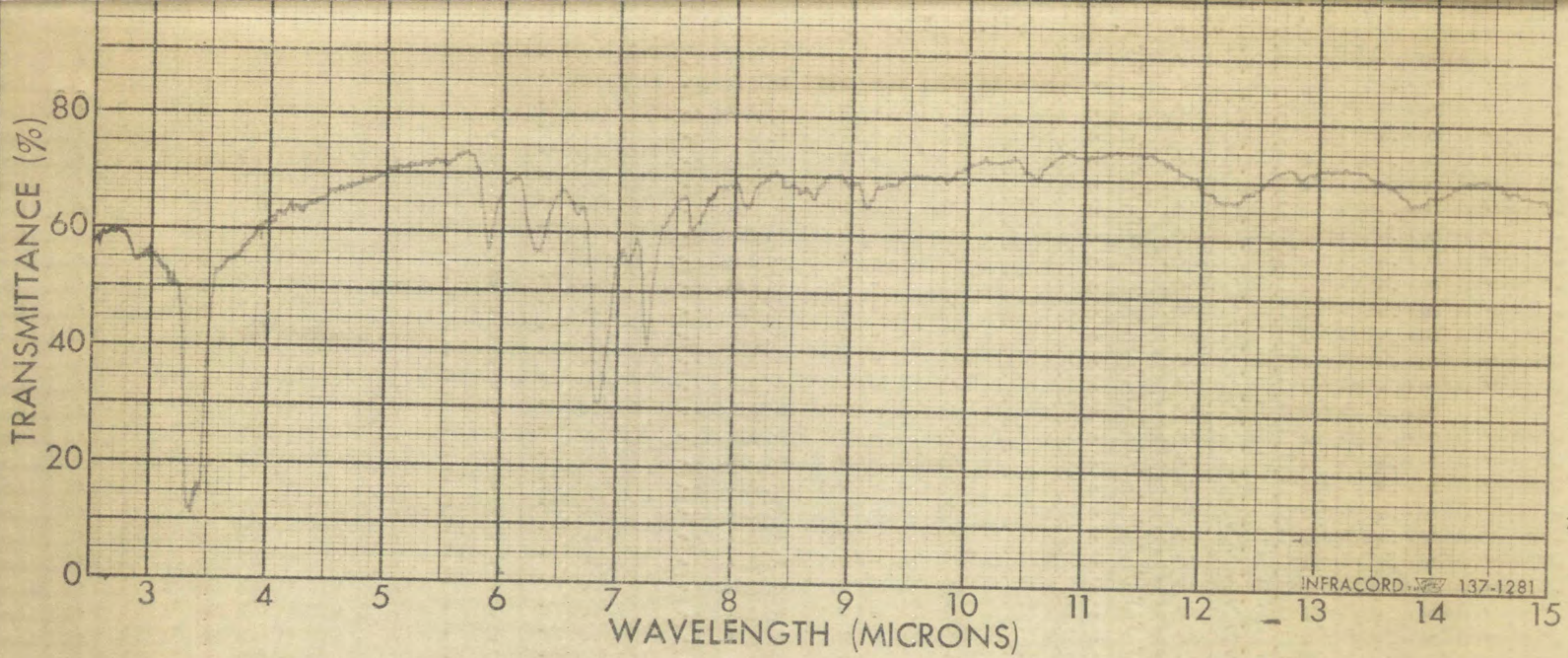
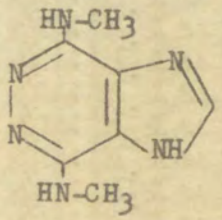


Plate XXX: Infrared Spectrum of 4,7-Bismethylamino-imidazo [4,5-d] pyridazine



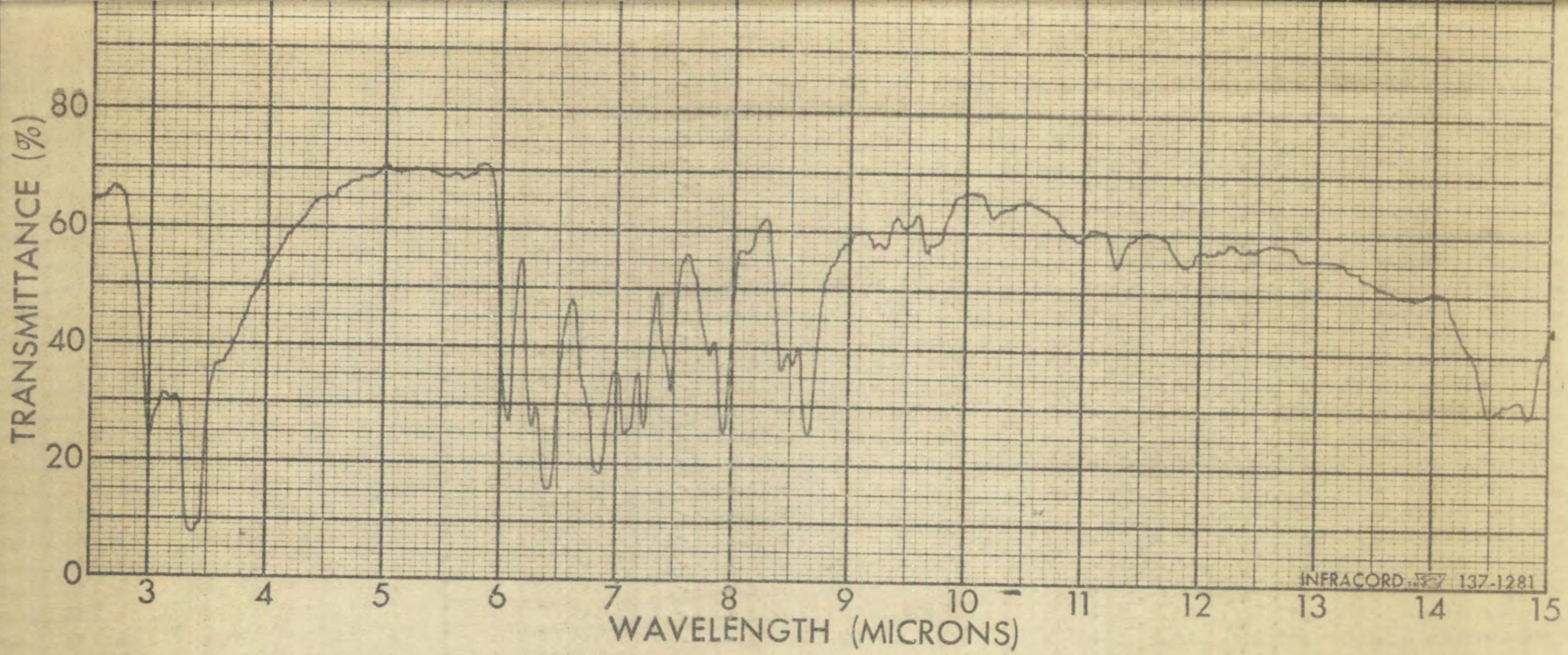
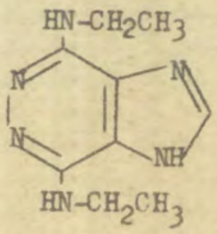


Plate XXXI: Infrared Spectrum of 4,7-Bisethylamino-imidazo[4,5-d]pyridazine



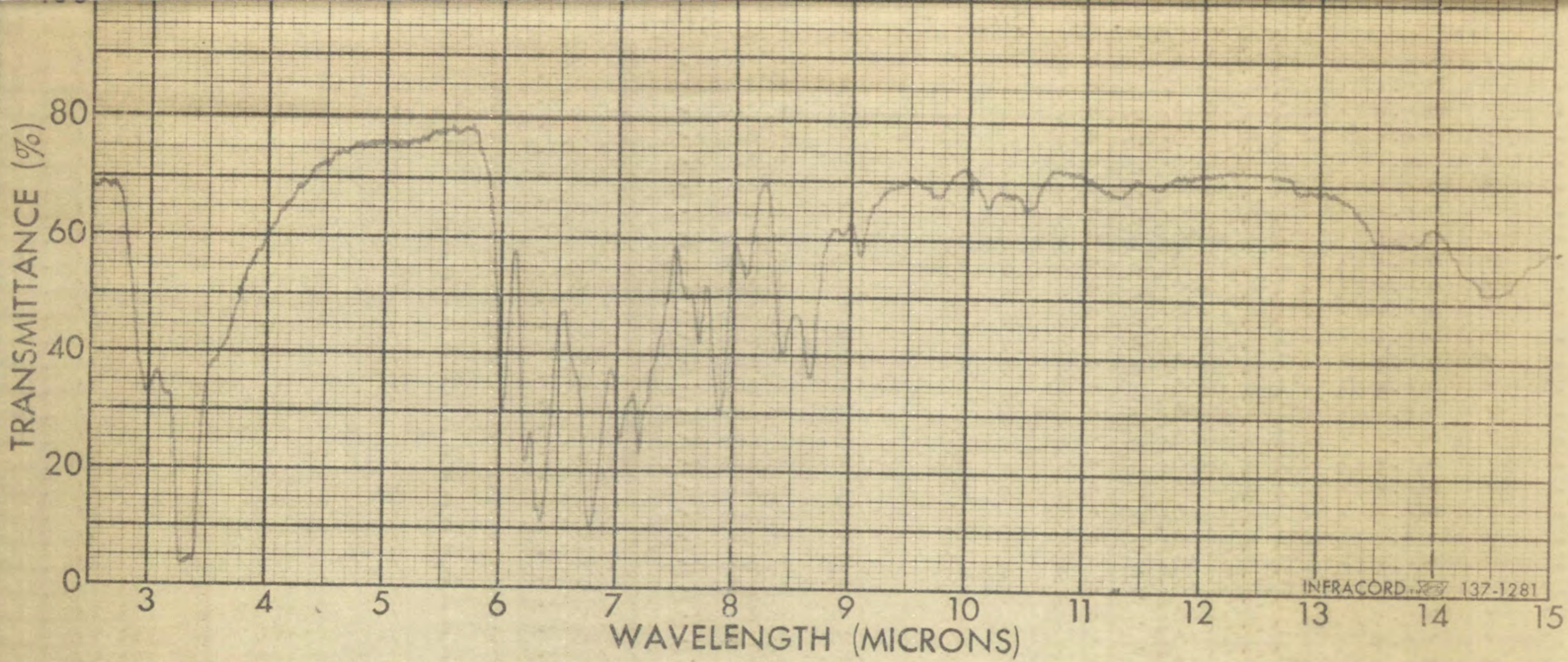
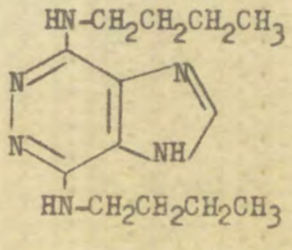


Plate XXXII: Infrared Spectrum of 4,7-Bis-n-butylamino-imidazo[4,5-d]pyridazine



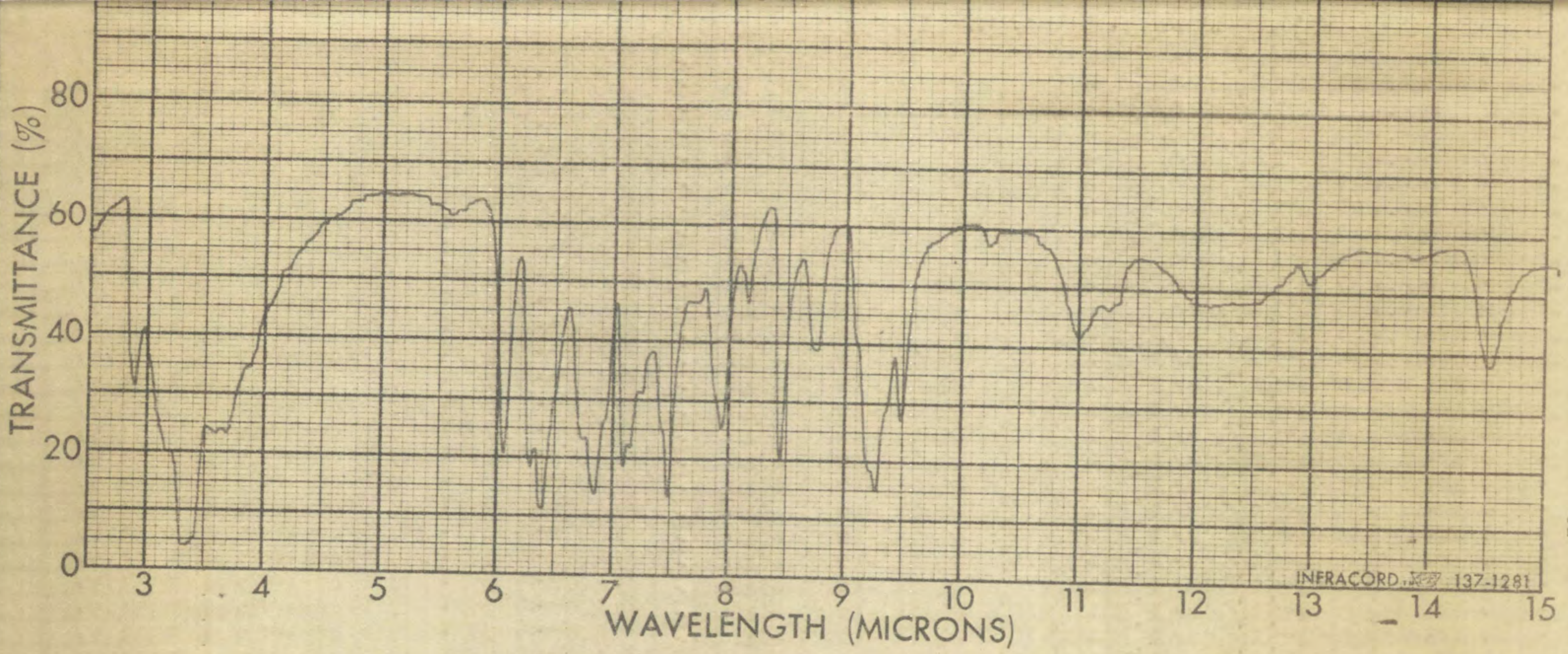
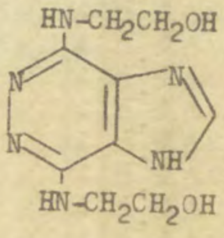


Plate XXXIII: Infrared Spectrum of 4,7-Bis-β-hydroxyethylaminoimidazo[4,5-d]pyridazine



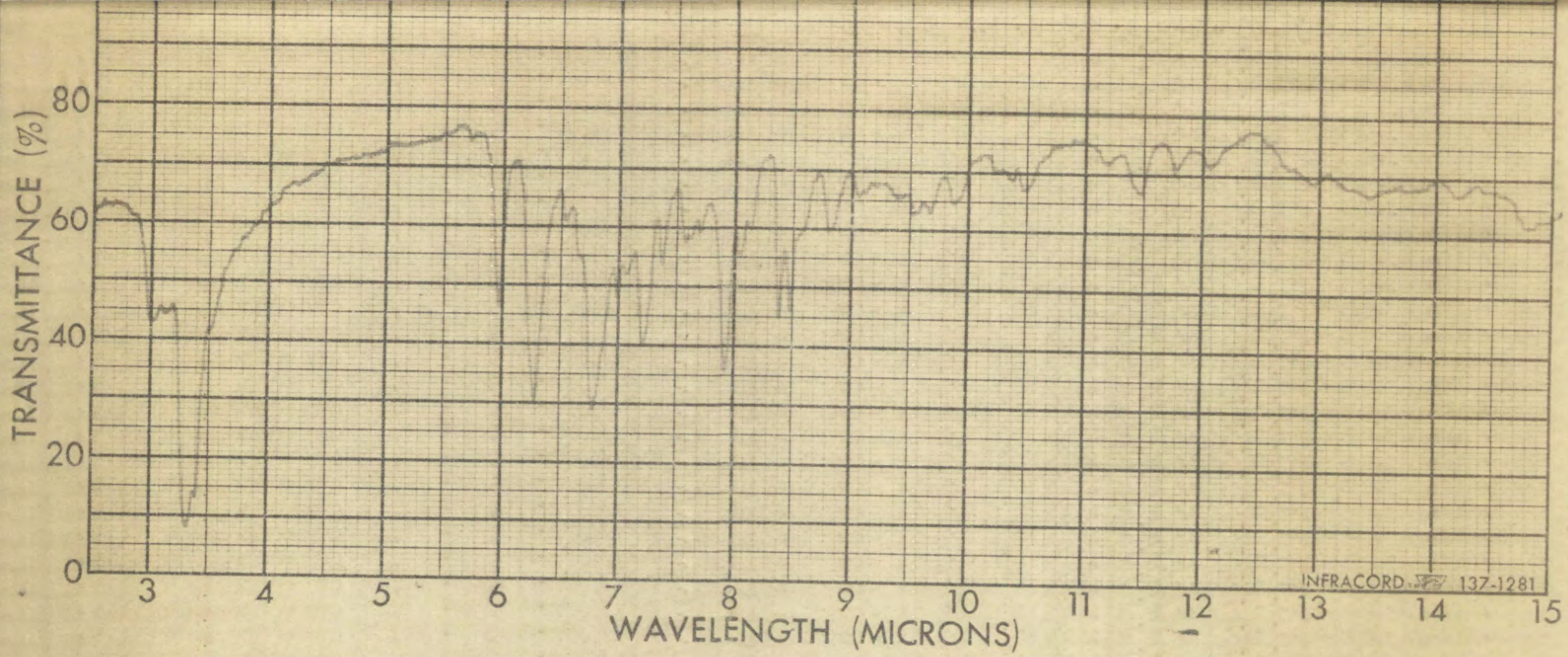
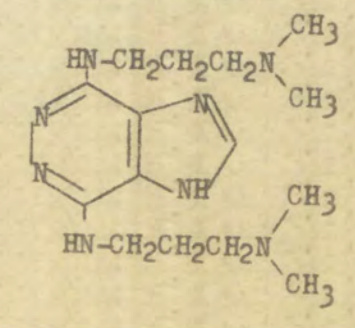


Plate XXXIV: Infrared Spectrum of 4,7-Bisdimethylaminopropylaminoimidazo [4,5-d] pyridazine



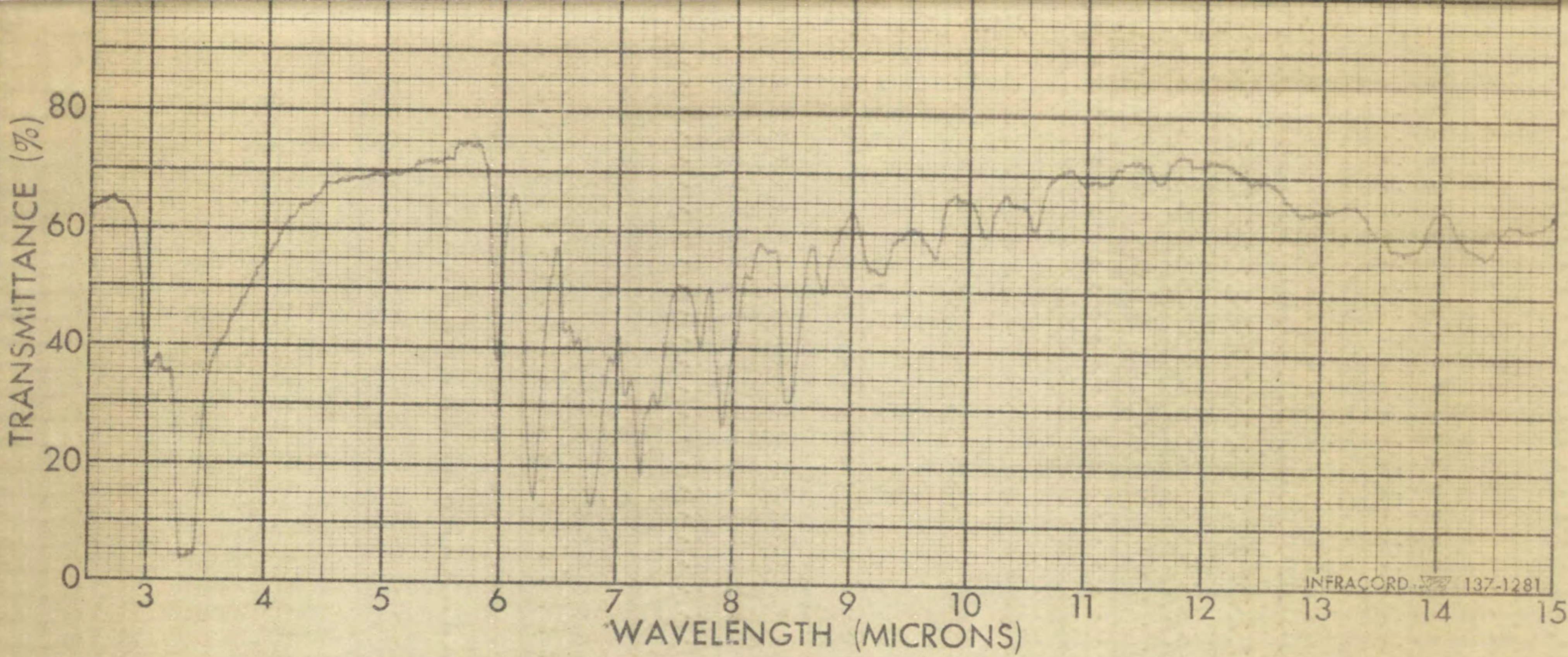
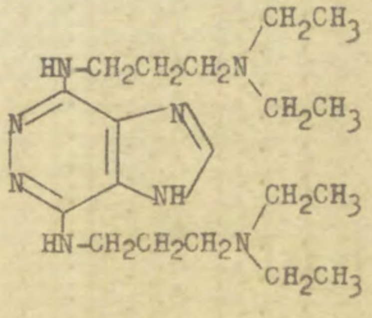


Plate XXXV: Infrared Spectrum of 4,7-Bisdiethylaminopropylaminoimidazo [4,5-d] pyridazine



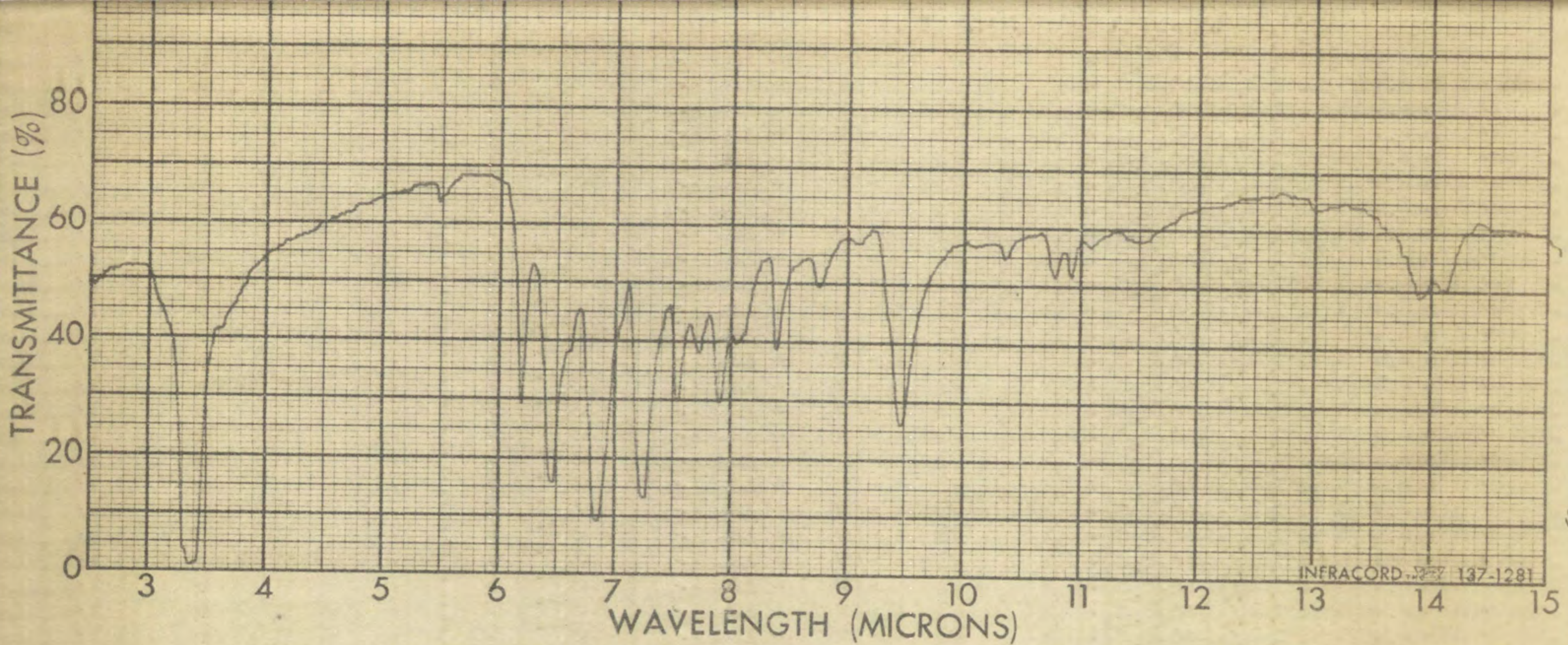
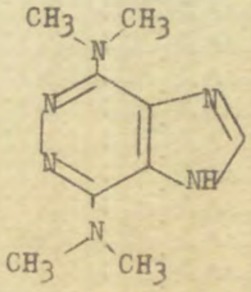


Plate XXXVI: Infrared Spectrum of 4,7-Bisdimethylamino-imidazo [4,5-d] pyridazine



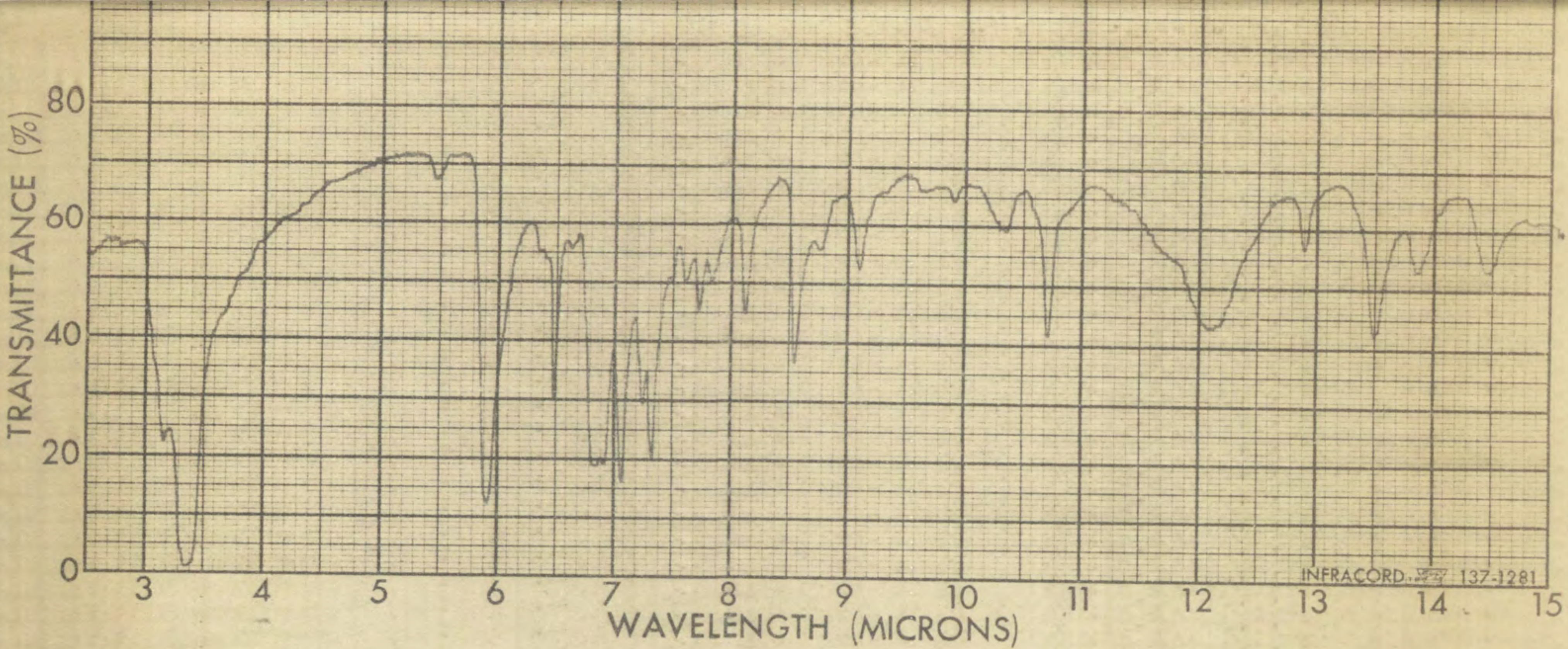
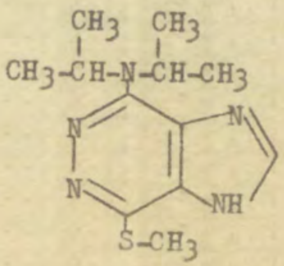


Plate XXXVII: Infrared Spectrum of 4(7)-Diisopropylamino-7(4)-methylthioimidazo[4,5-d]pyridazine



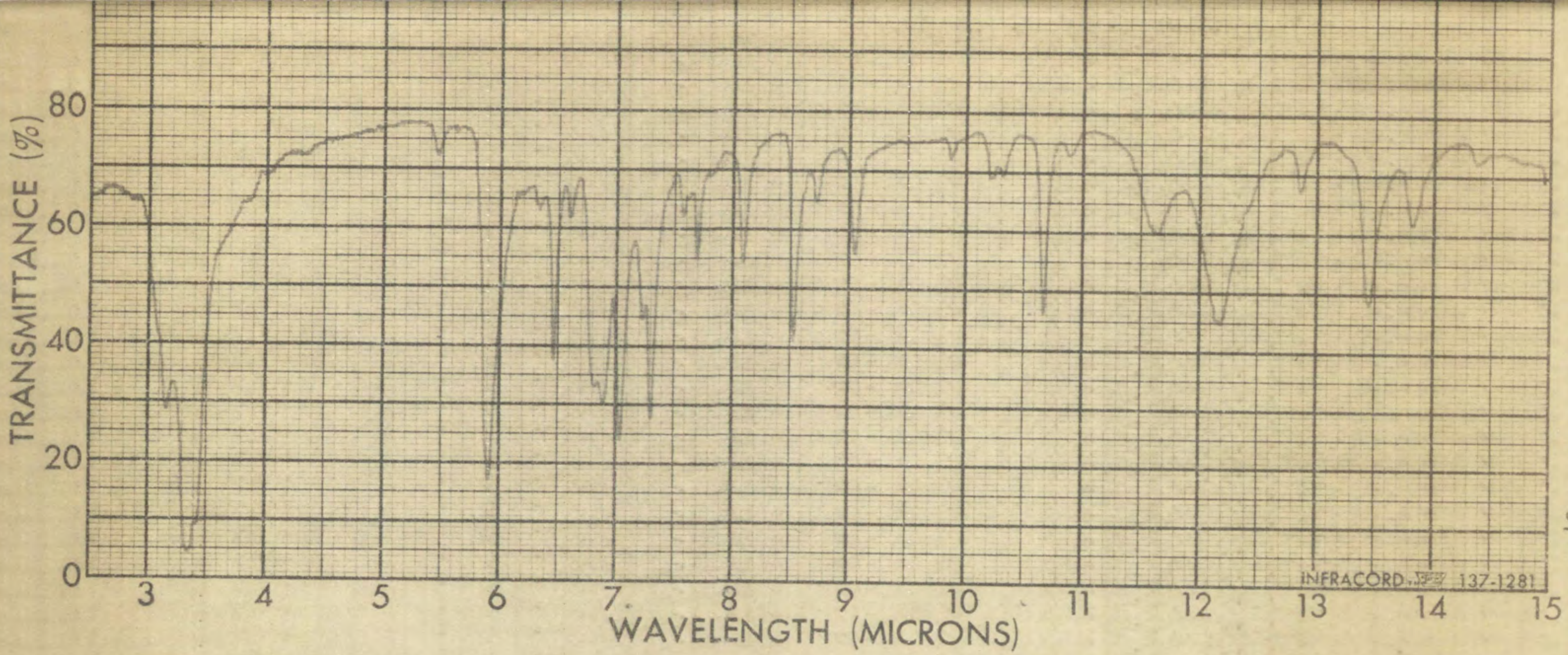
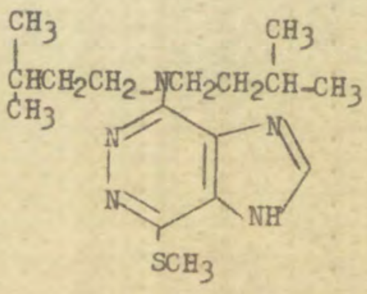


Plate XXXVIII: Infrared Spectrum of 4(7)-Di-(3-methylbutyl)-amino 7(4)-methylthioimidazo [4,5-d] pyridazine



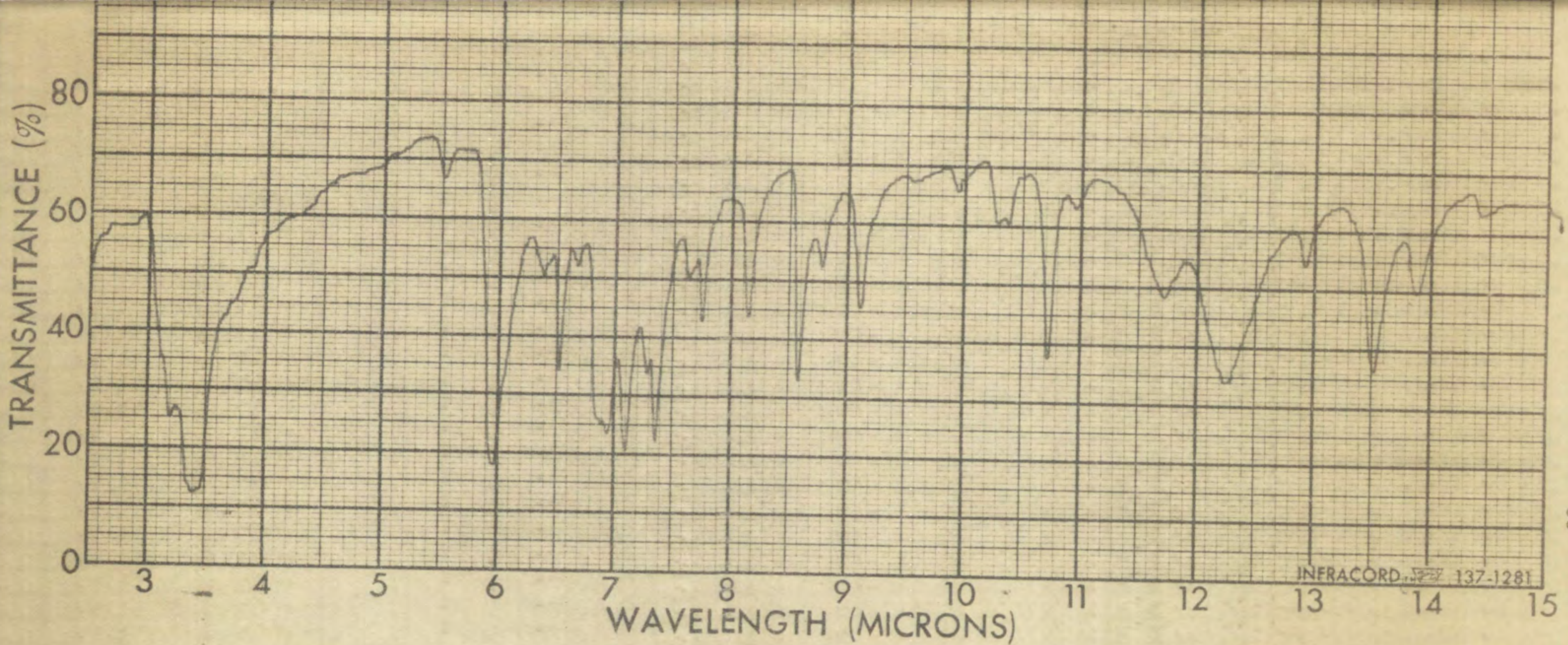
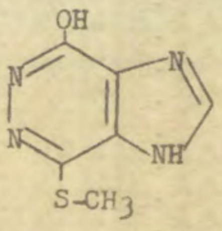


Plate XXXIX: Infrared Spectrum of 4(7)-Hydroxy-7(4)-methylthioimidazo [4,5-d] pyridazine



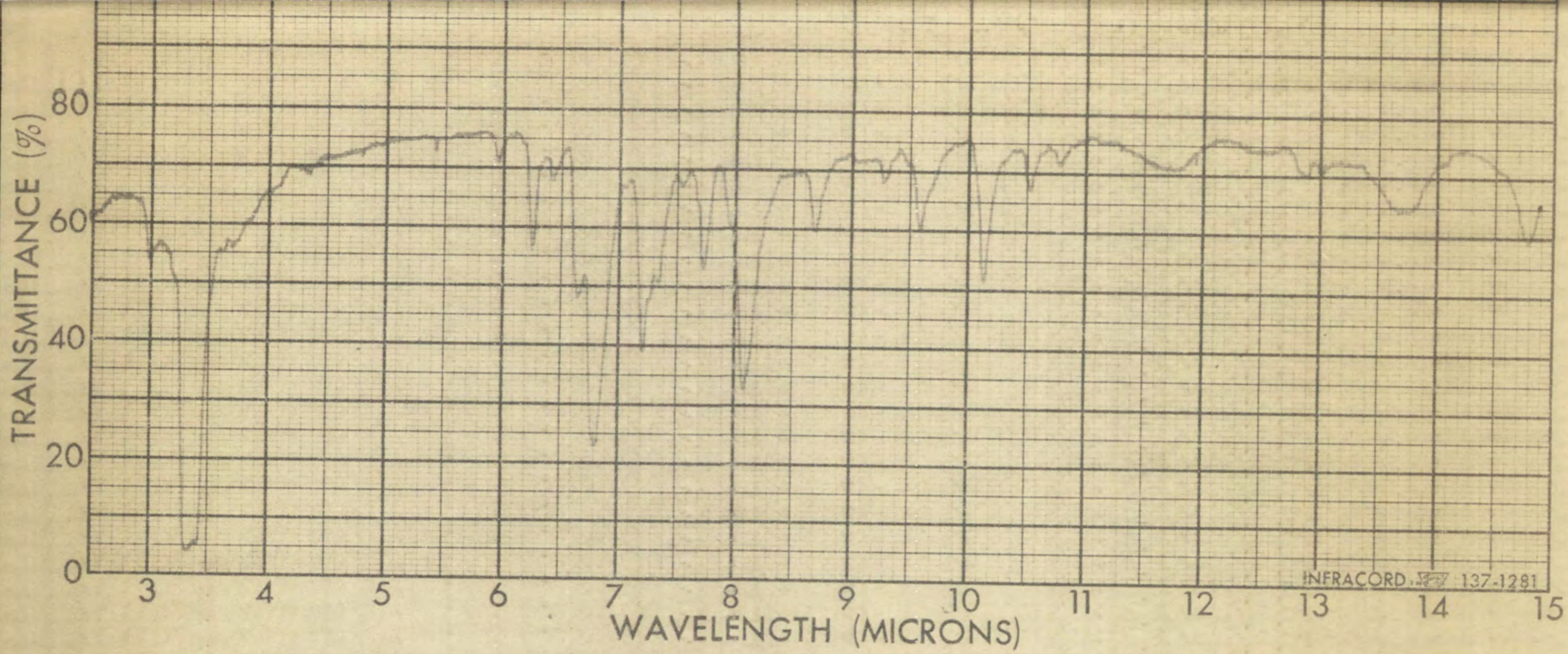
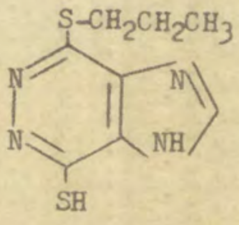
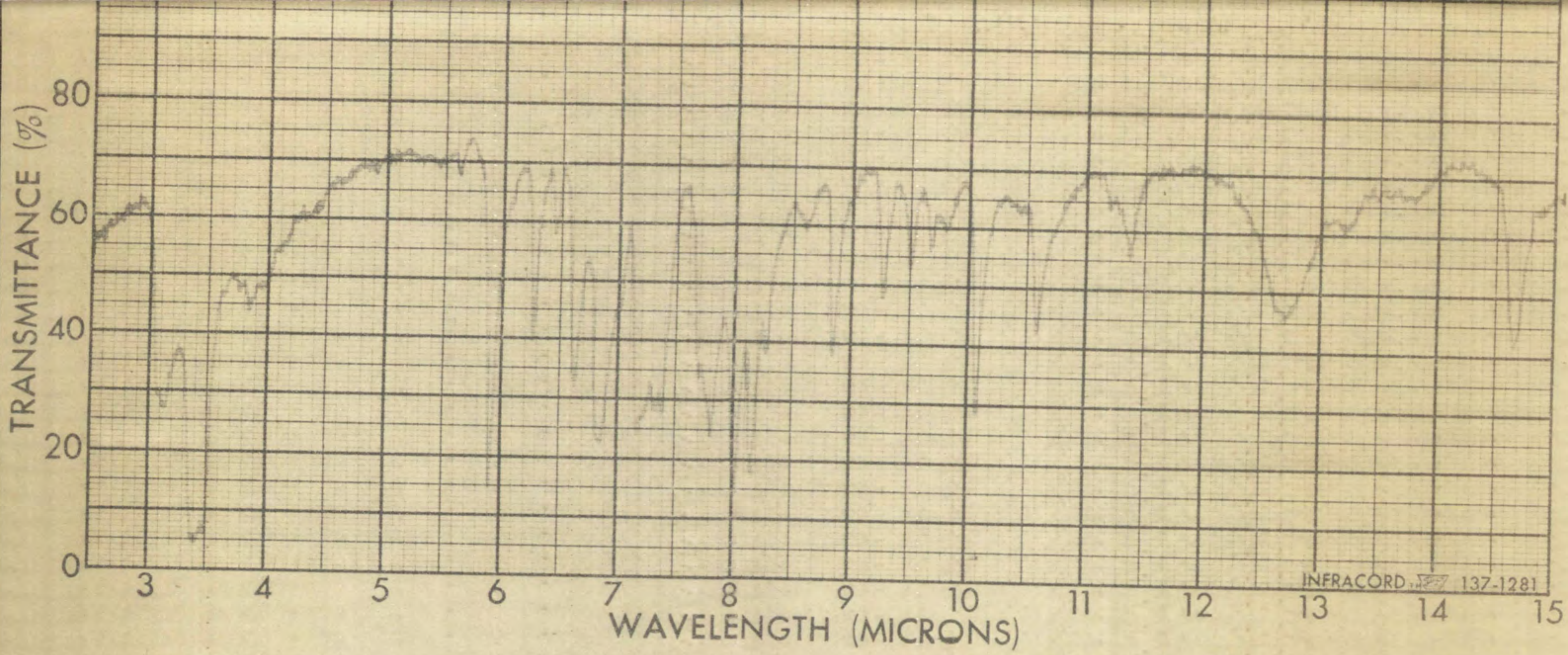


Plate XL: Infrared Spectrum of 4(7)-n-Propylthio-imidazo [4,5-d] pyridazine-7(4)-thiol





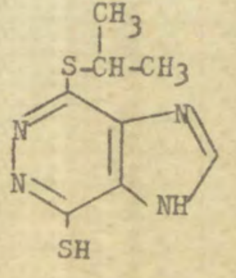


Plate XLI: Infrared Spectrum of 4(7)-Isopropylthio-imidazo[4,5-d]pyridazine-7(4)-thiol

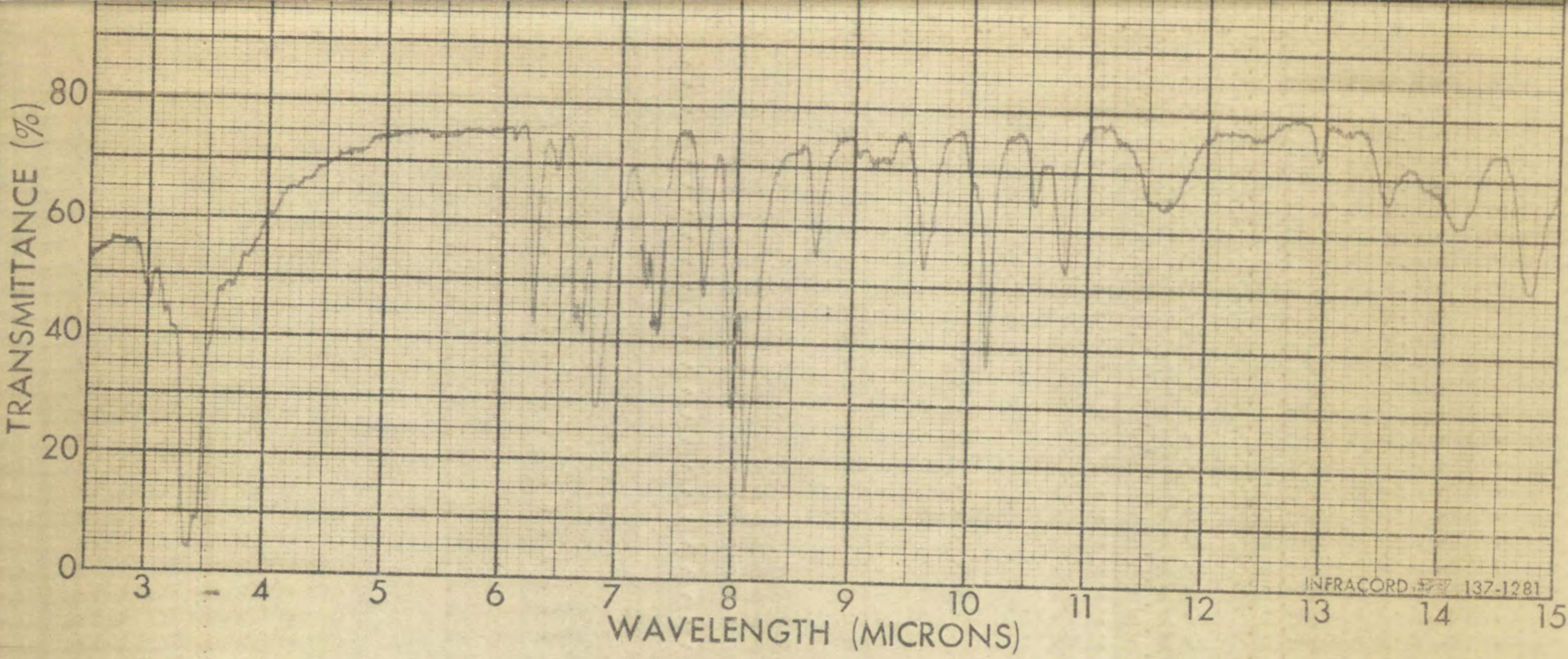
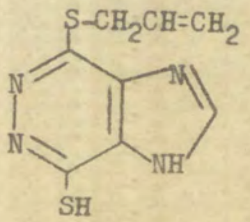


Plate XLII: Infrared Spectrum of 4(7)-Allylthioimidazo-[4,5-d] pyridazine-7(4)-thiol



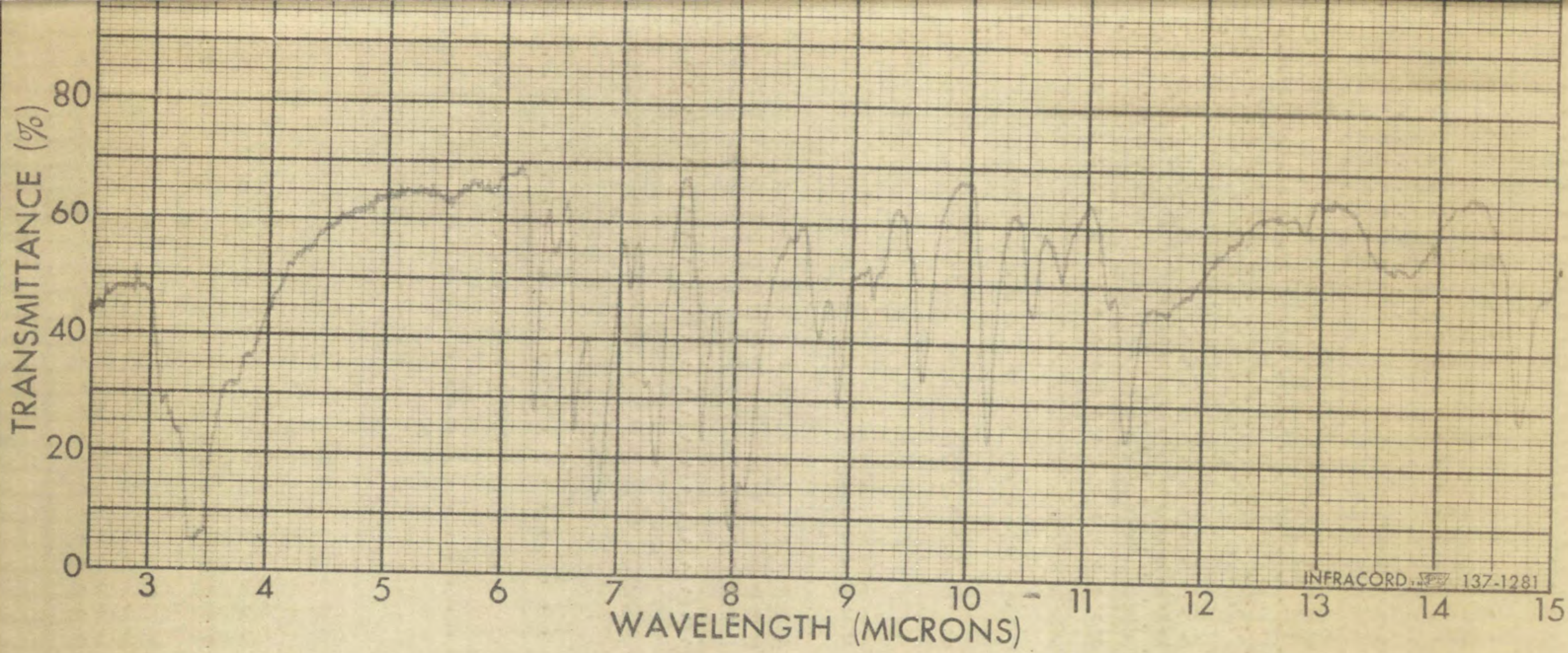
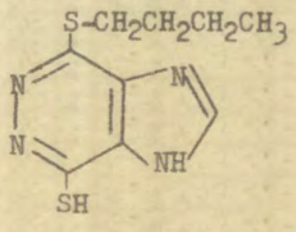


Plate XLIII: Infrared Spectrum of 4(7)-n-Butylthio-imidazo [4,5-d] pyridazine-7(4)-thiol



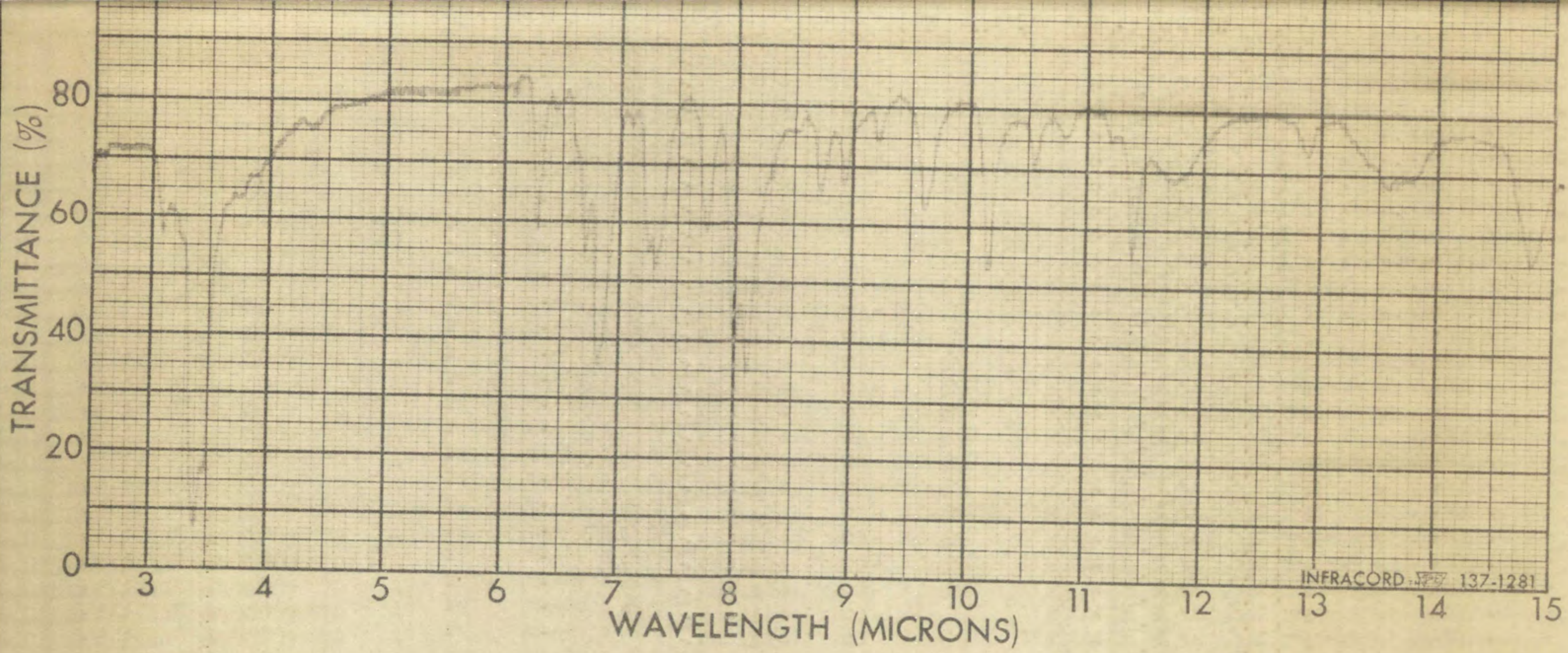
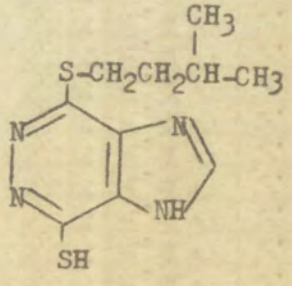


Plate XLIV: Infrared Spectrum of 4(7)-(3-methylbutylthio)-imidazo [4,5-d] pyridazine-7(4)-thiol



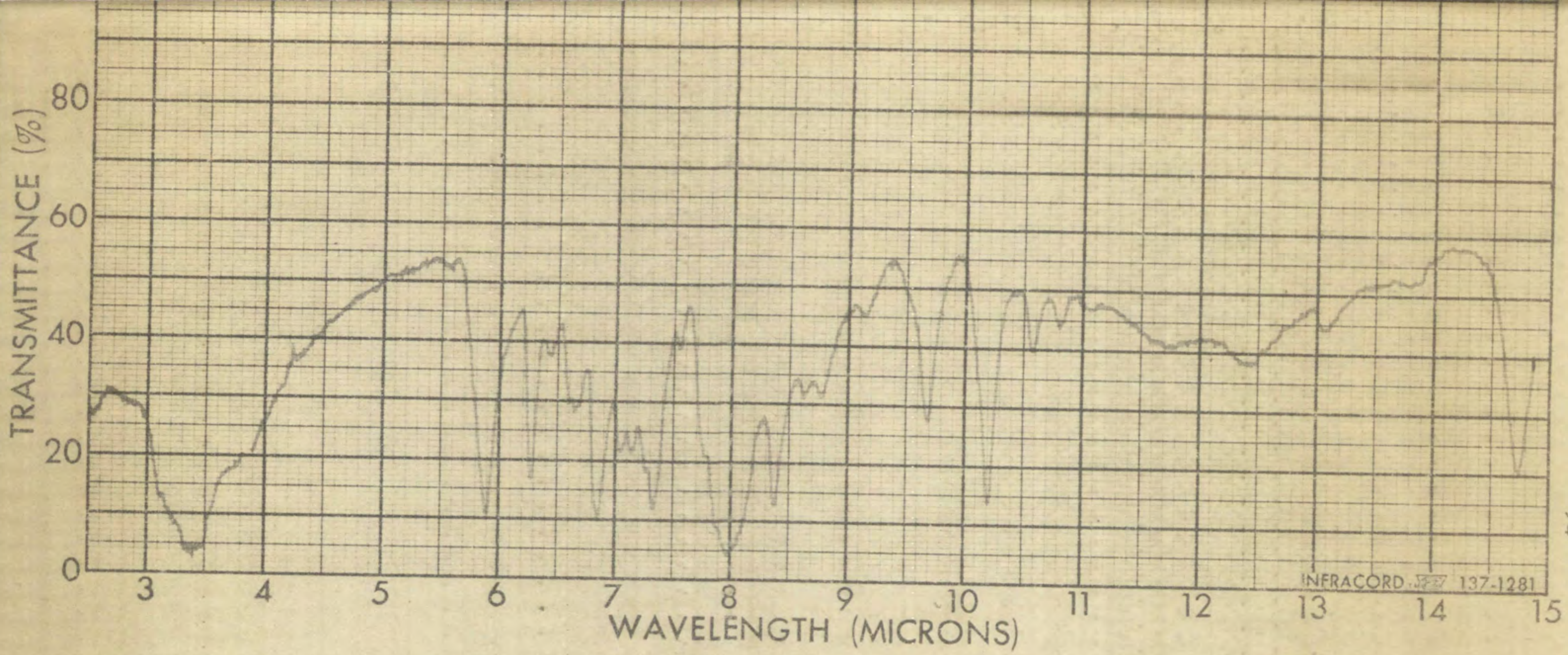
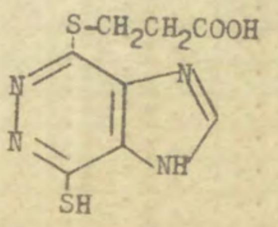


Plate XLV: Infrared Spectrum of 4(7)-β-Carboxyethylthioimidazo [4,5-d] pyridazine-7(4)-thiol



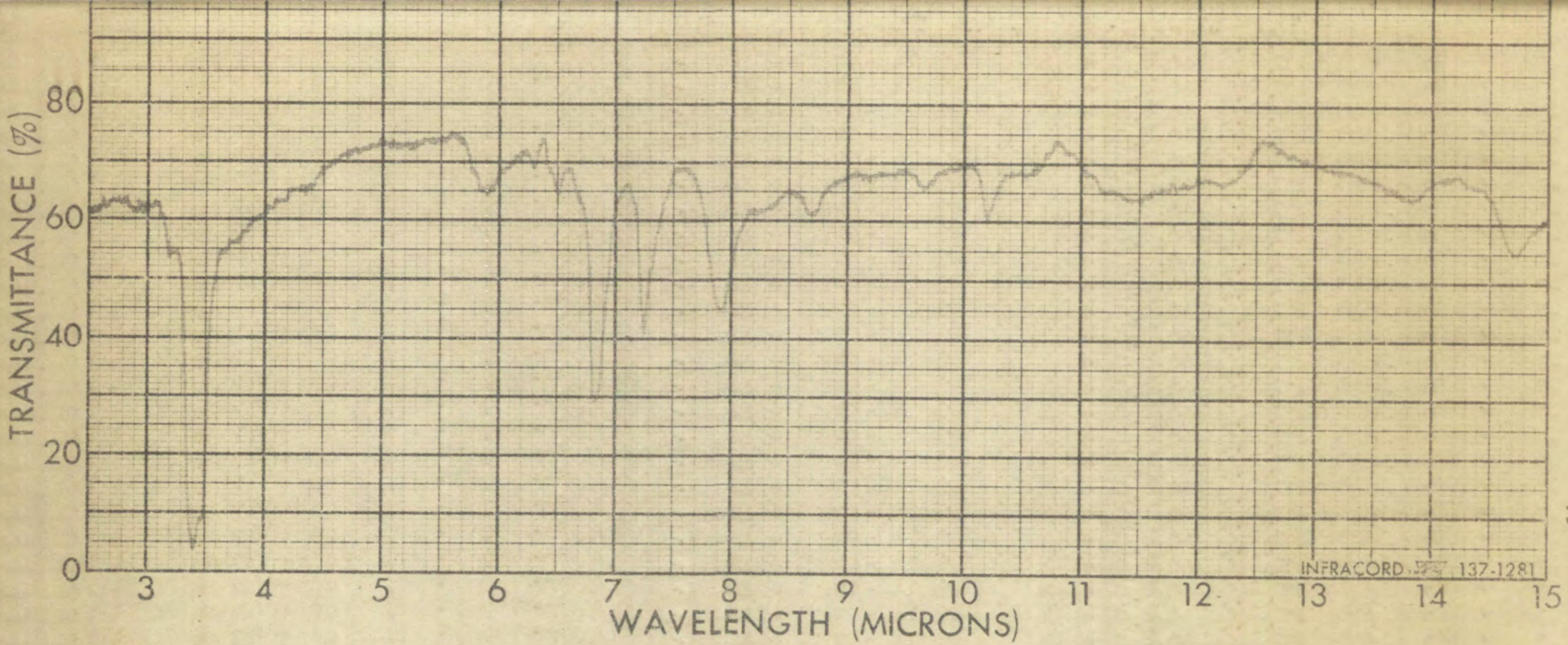
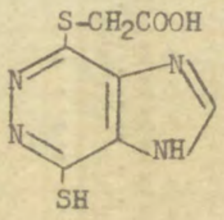


Plate XLVI: Infrared Spectrum of 4(7)-Carboxymethylthioimidazo [4,5-d] pyridazine-7(4)-thiol



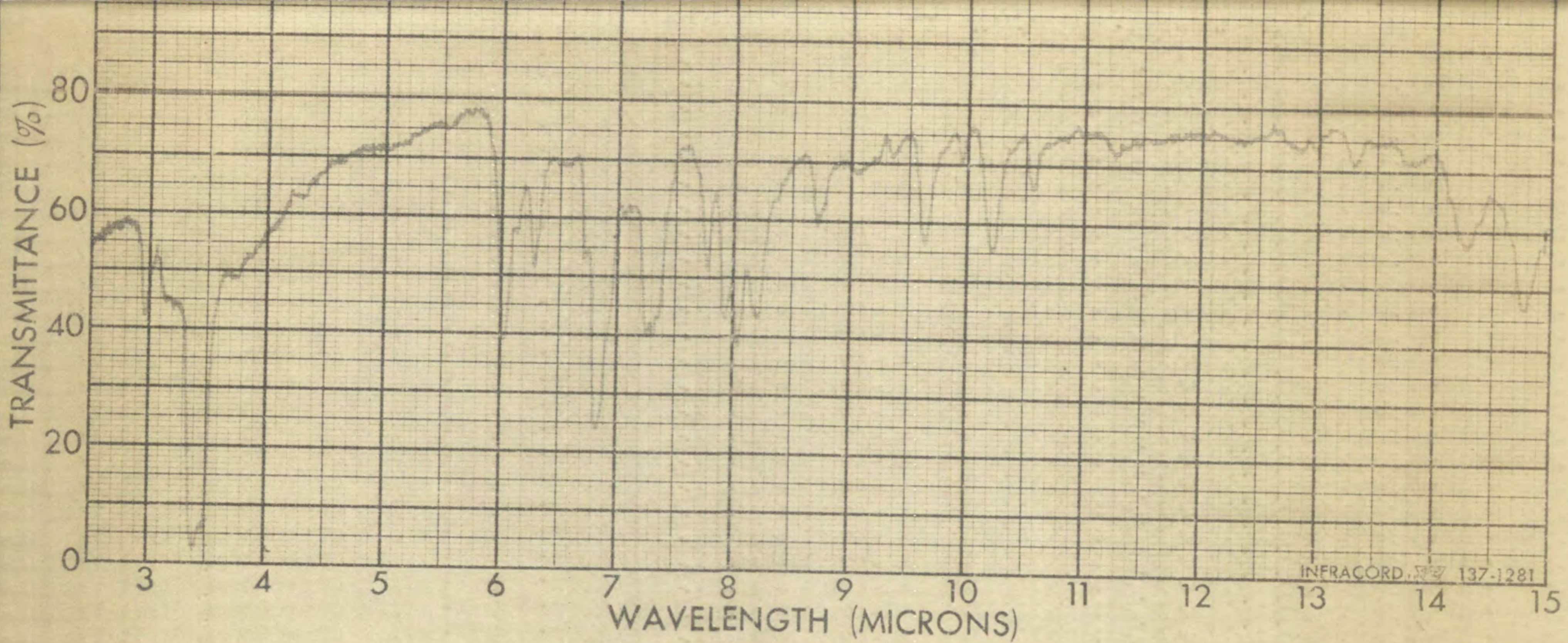
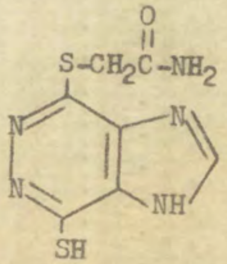


Plate XLVII: Infrared Spectrum of 4(7)-Carboxamidomethylthioimidazo [4,5-d] pyridazine-7(4)-thiol



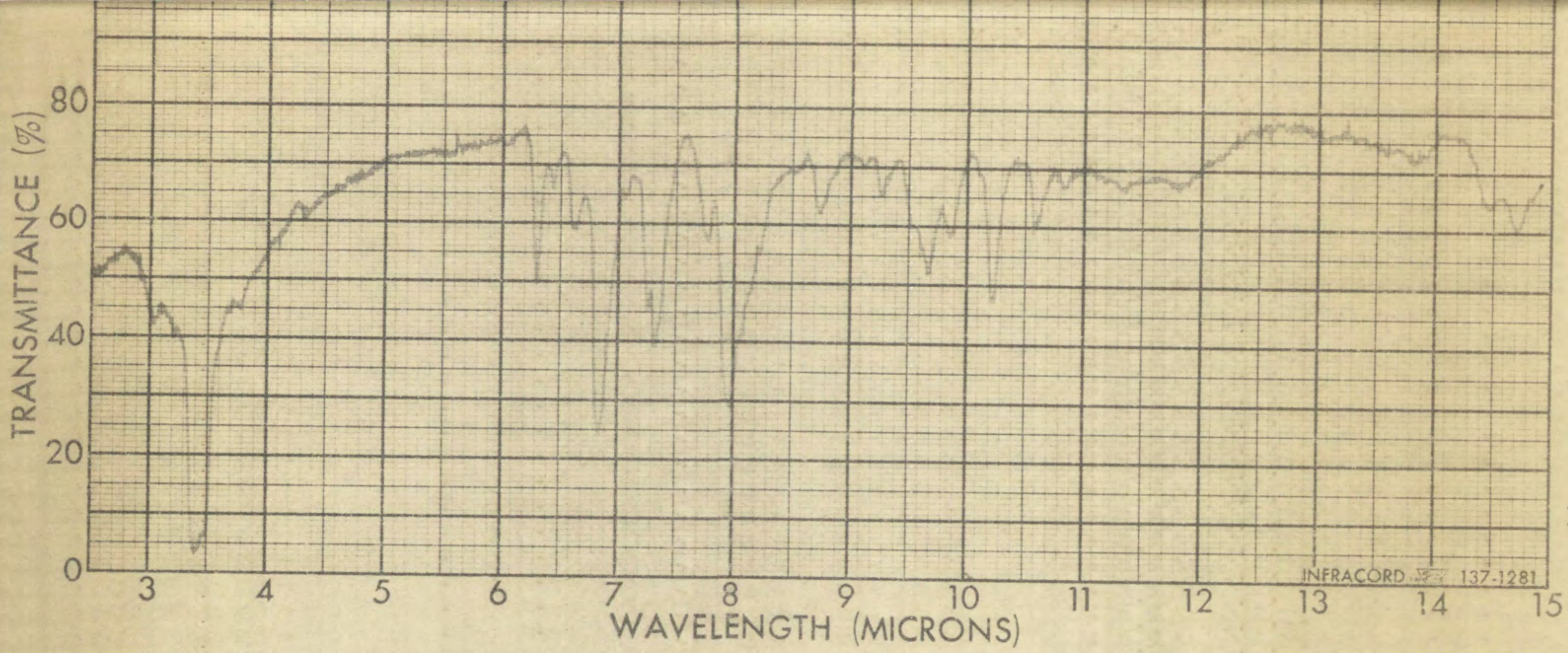
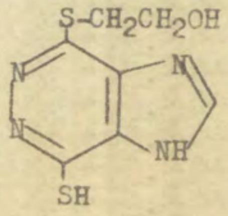


Plate XLVIII: Infrared Spectrum of 4(7)-β Hydroxyethylthio-imidazo [4,5-d] pyridazine-7(4)-thiol



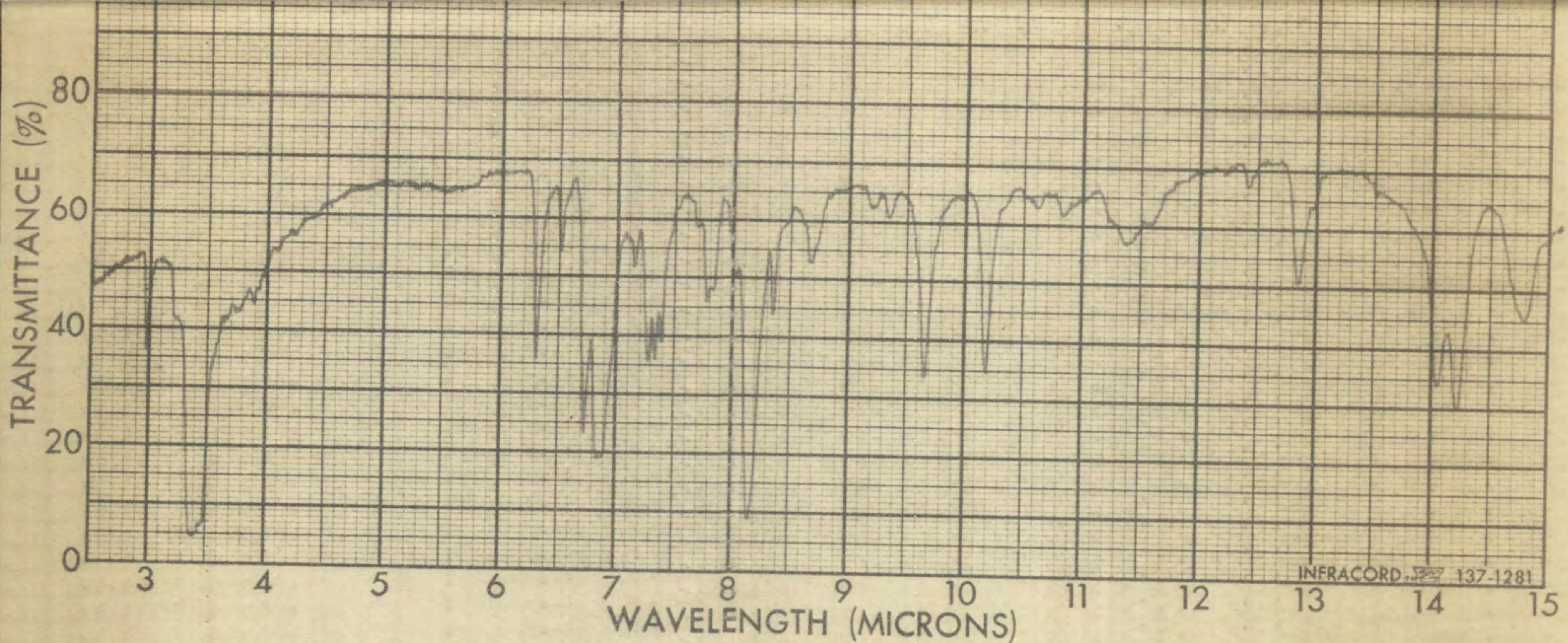
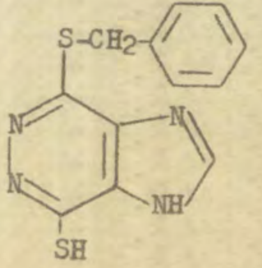


Plate XLIX: Infrared Spectrum of 4(7)-Benzylthioimidazo-[4,5-d]pyridazine-7(4)-thiol



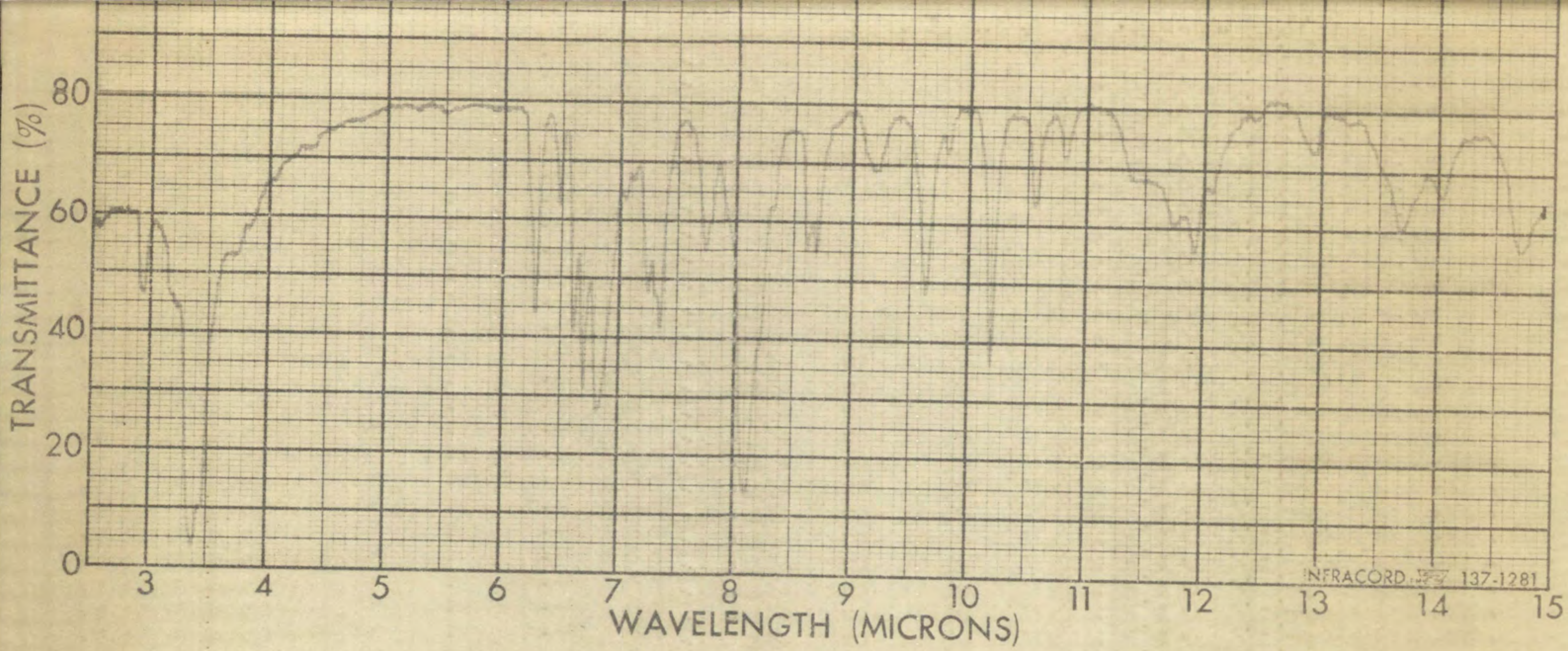
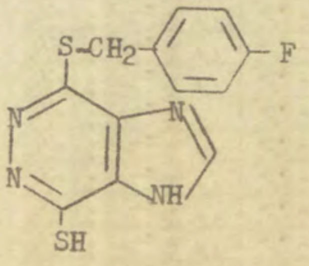


Plate L: Infrared Spectrum of 4(7)-p-Fluorobenzylthioimidazo [4,5-d] pyridazine-7(4)-thiol



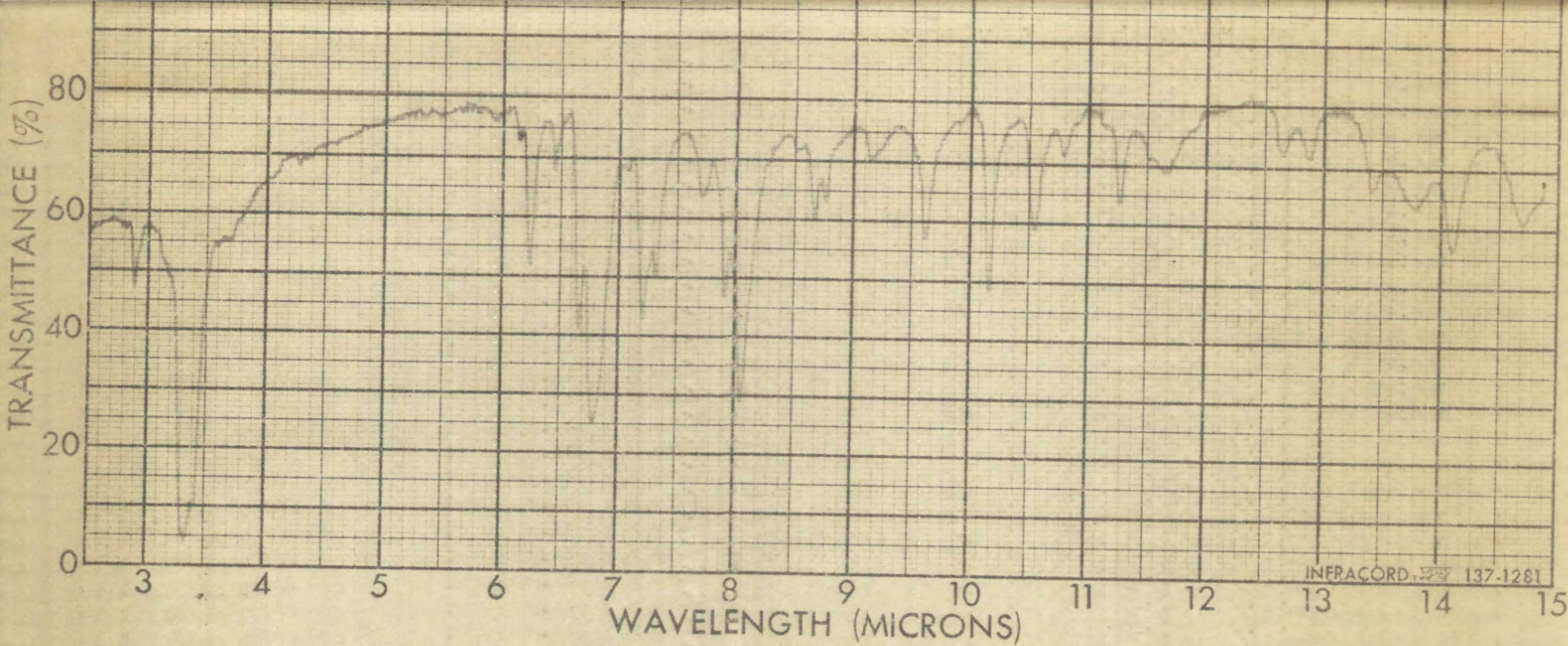
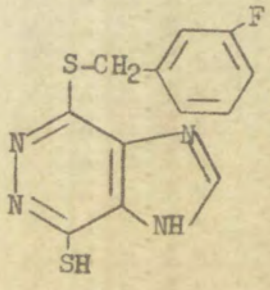


Plate LI: Infrared Spectrum of 4(7)-m-Fluorobenzylthioimidazo [4,5-d] pyridazine-7(4)-thiol



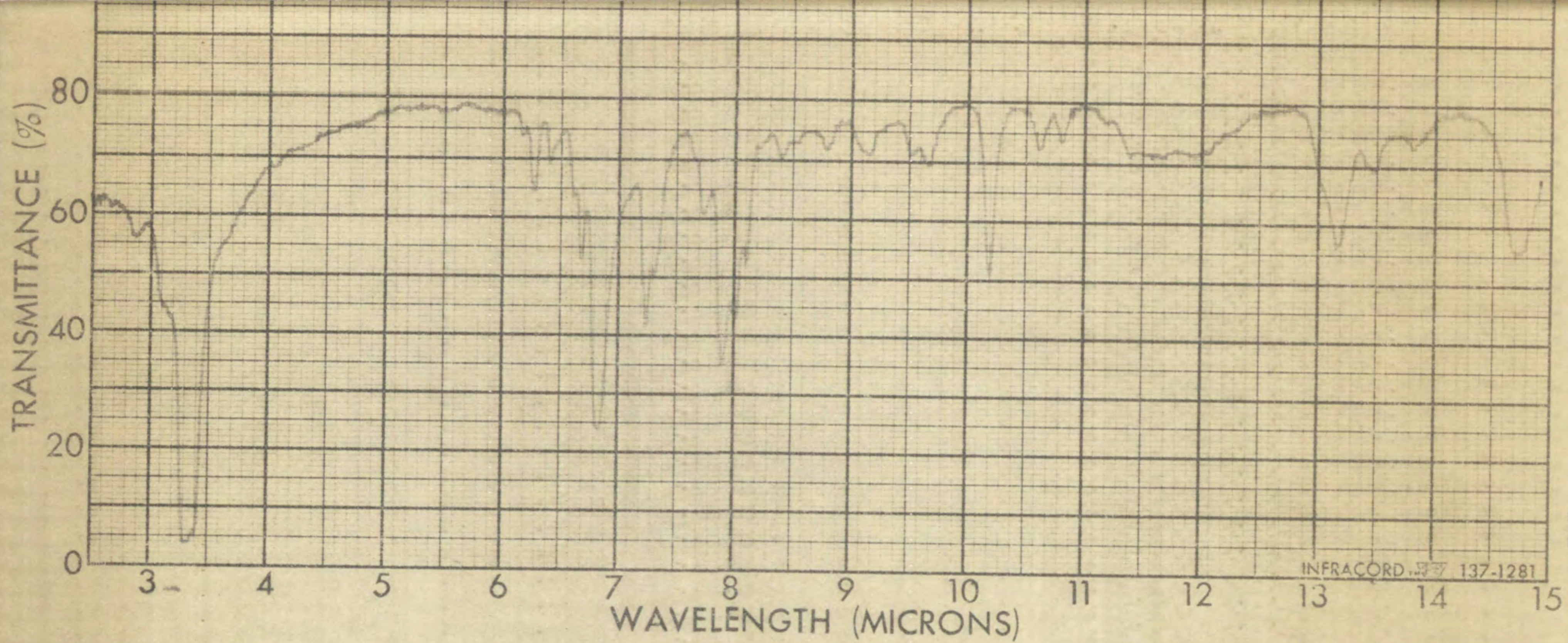
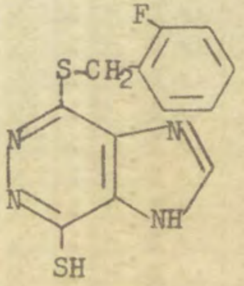


Plate LII: Infrared Spectrum of 4(7)-o-Fluorobenzylthioimidazo [4,5-d] pyridazine-7(4)-thiol



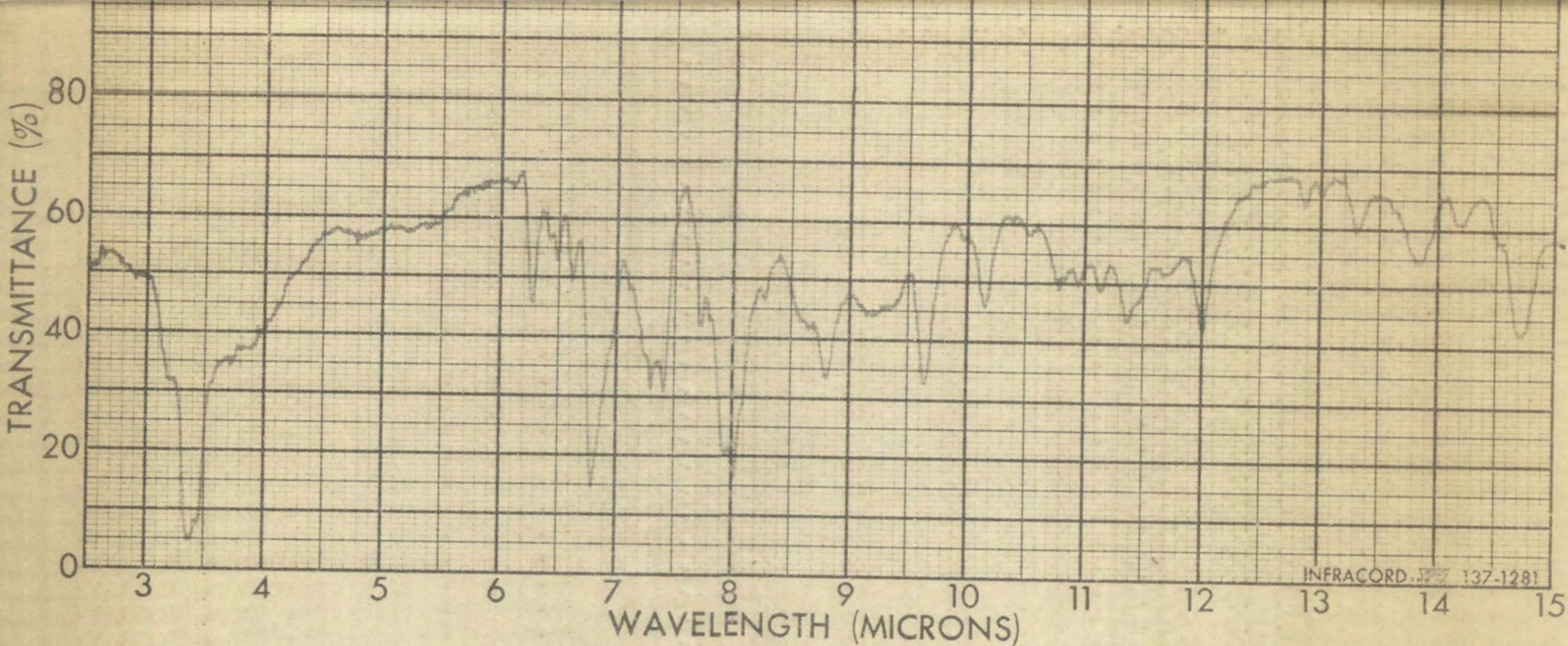
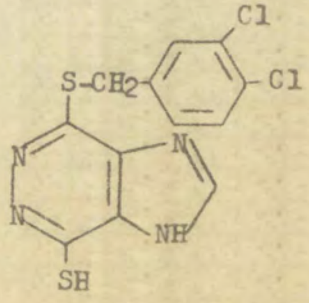


Plate LIII: Infrared Spectrum of 4(7)-3,4-Dichlorobenzylthioimidazo [4,5-d] pyridazine-7(4)-thiol



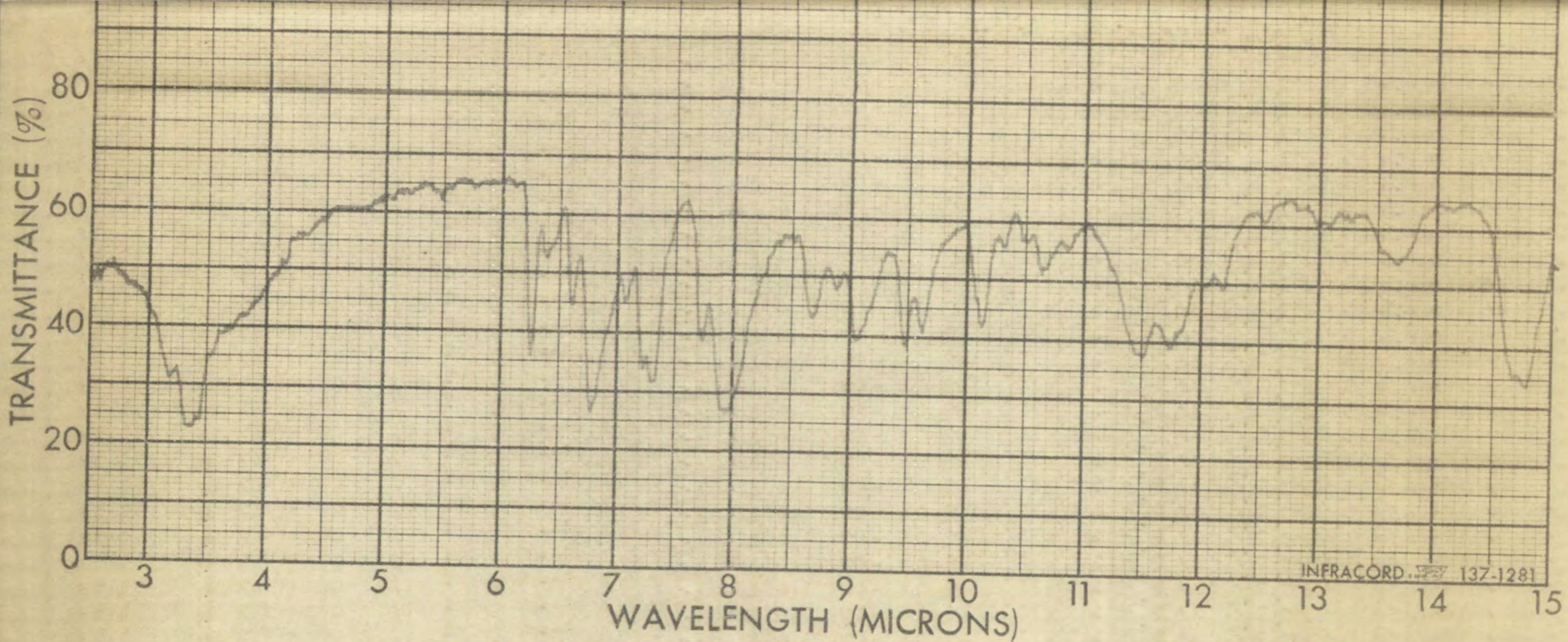
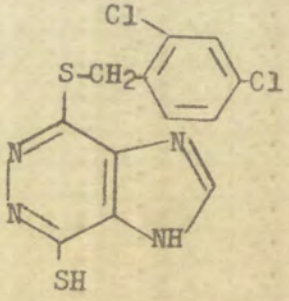


Plate LIV: Infrared Spectrum of 4(7)-2,4-Dichlorobenzylthioimidazo [4,5-d] pyridazine-7(4)-thiol



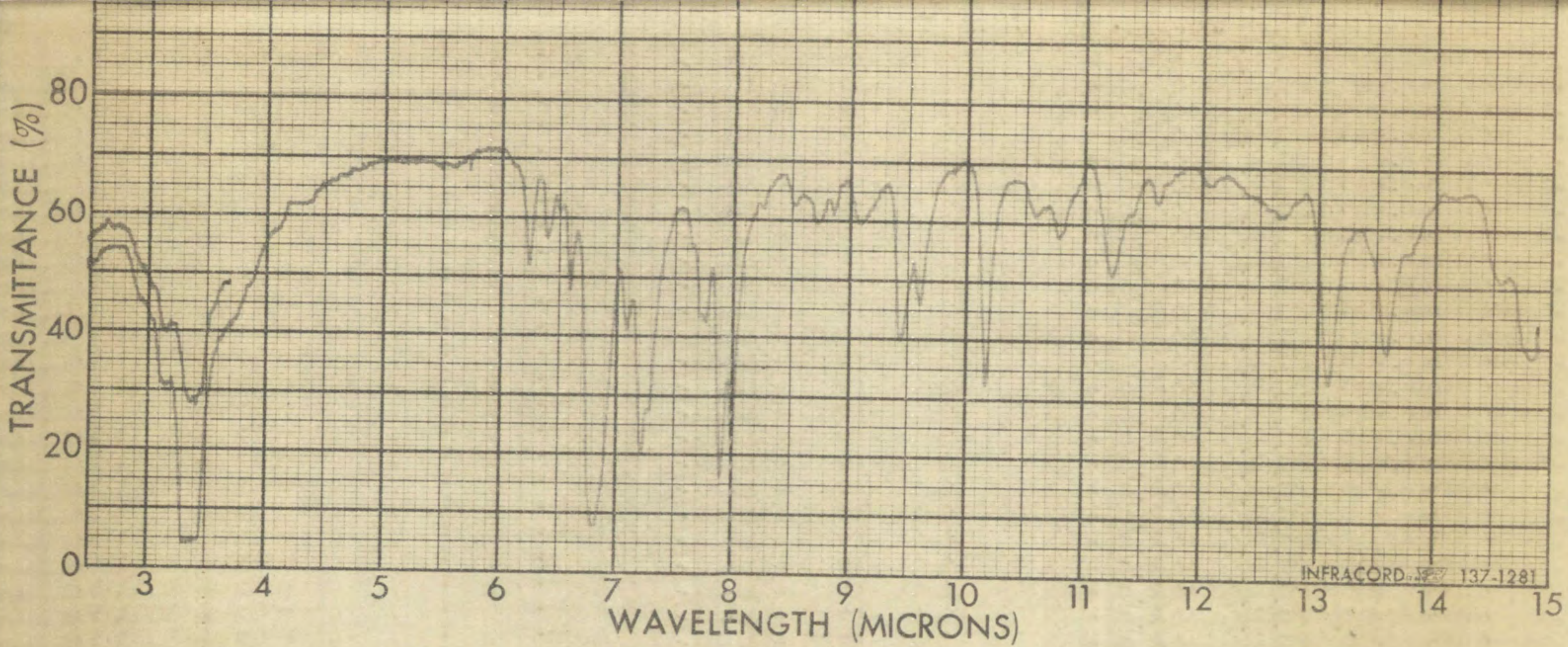
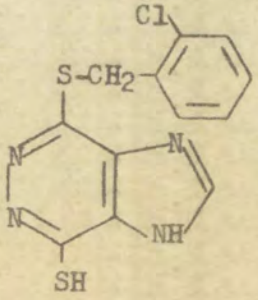


Plate LV: Infrared Spectrum of 4(7)-o-Chlorobenzylthioimidazo [4,5-d] pyridazine-7(4)-thiol



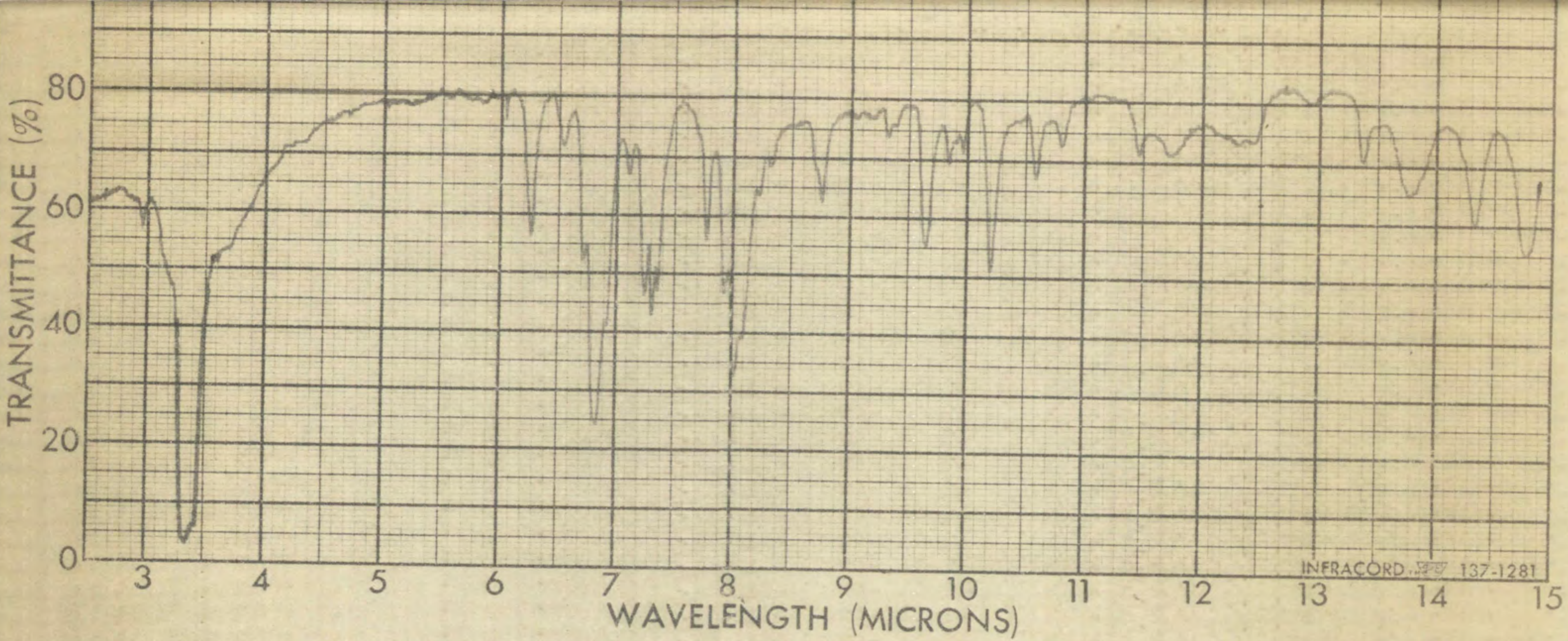
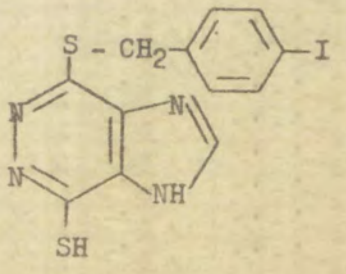


Plate LVI: 4(7)-p-Iodobenzylthioimidazo[4,5-d]pyridazine-7(4)-thiol



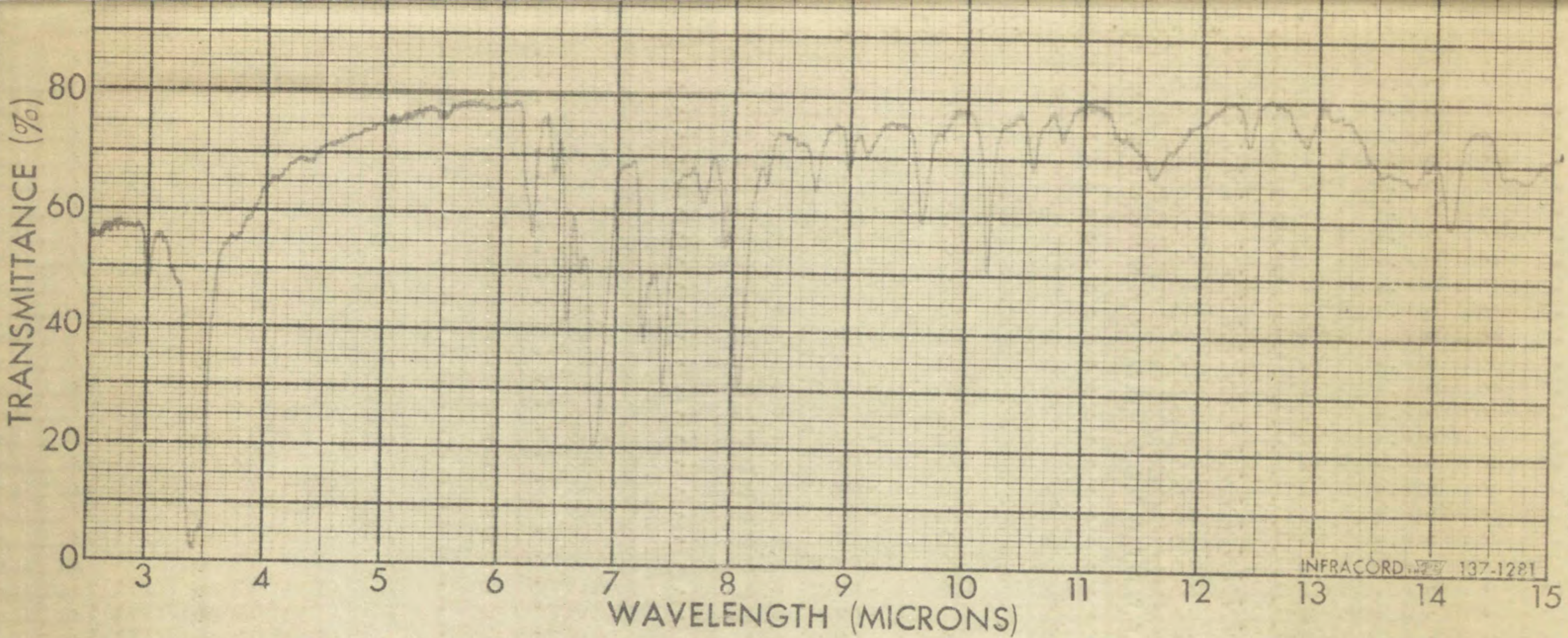
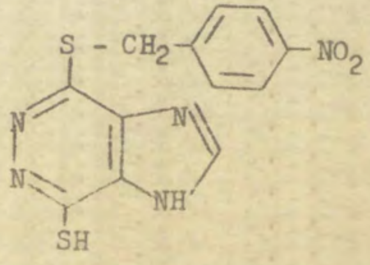


Plate LVII: 4(7)-p-Nitrobenzylthioimidazo[4,5-d] pyridazine-7(4)-thiol



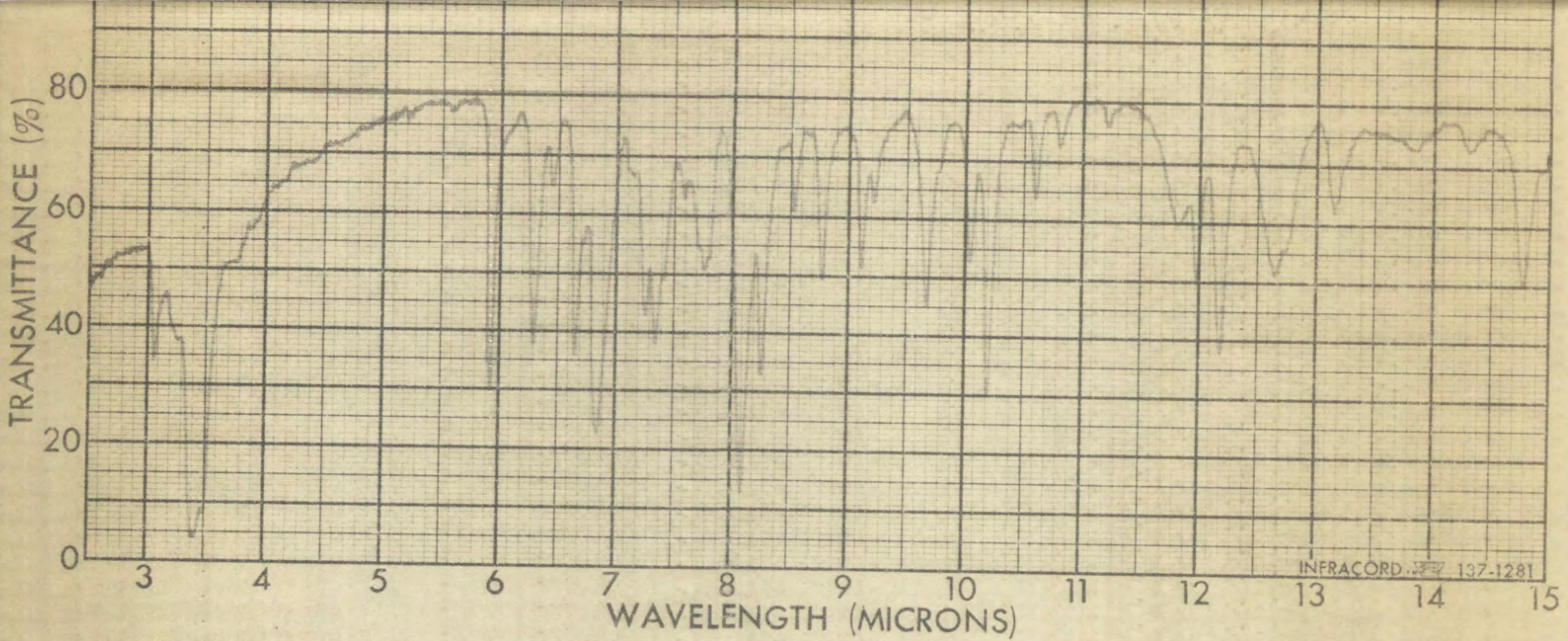
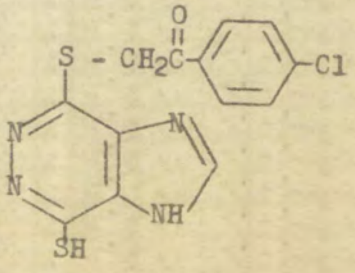


Plate LVIII: 4(7)-p-Chlorophenacylthioimidazo[4,5-d]-
pyridazine-7(4)-thiol



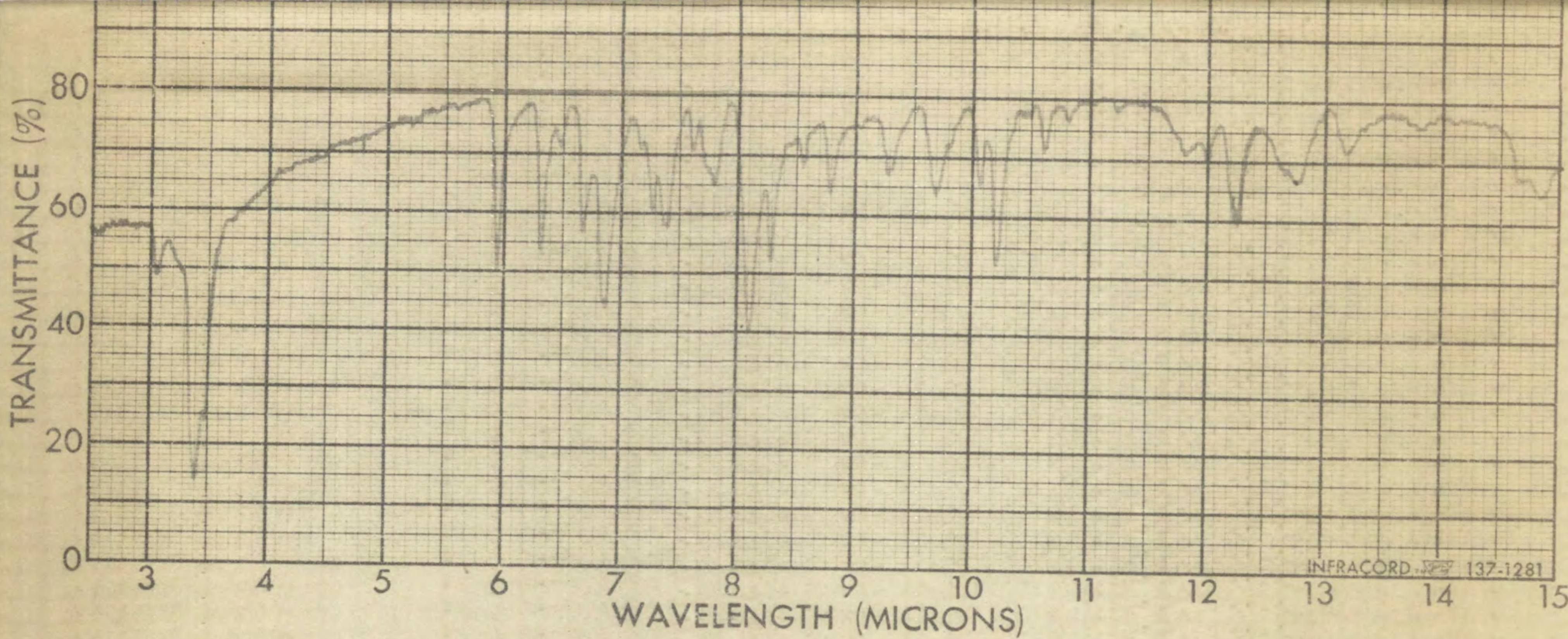
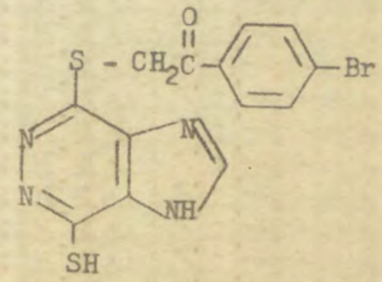


Plate LIX: 4(7)-p-Bromophenacylthioimidazo[4,5-d]-pyridazine-7(4)-thiol



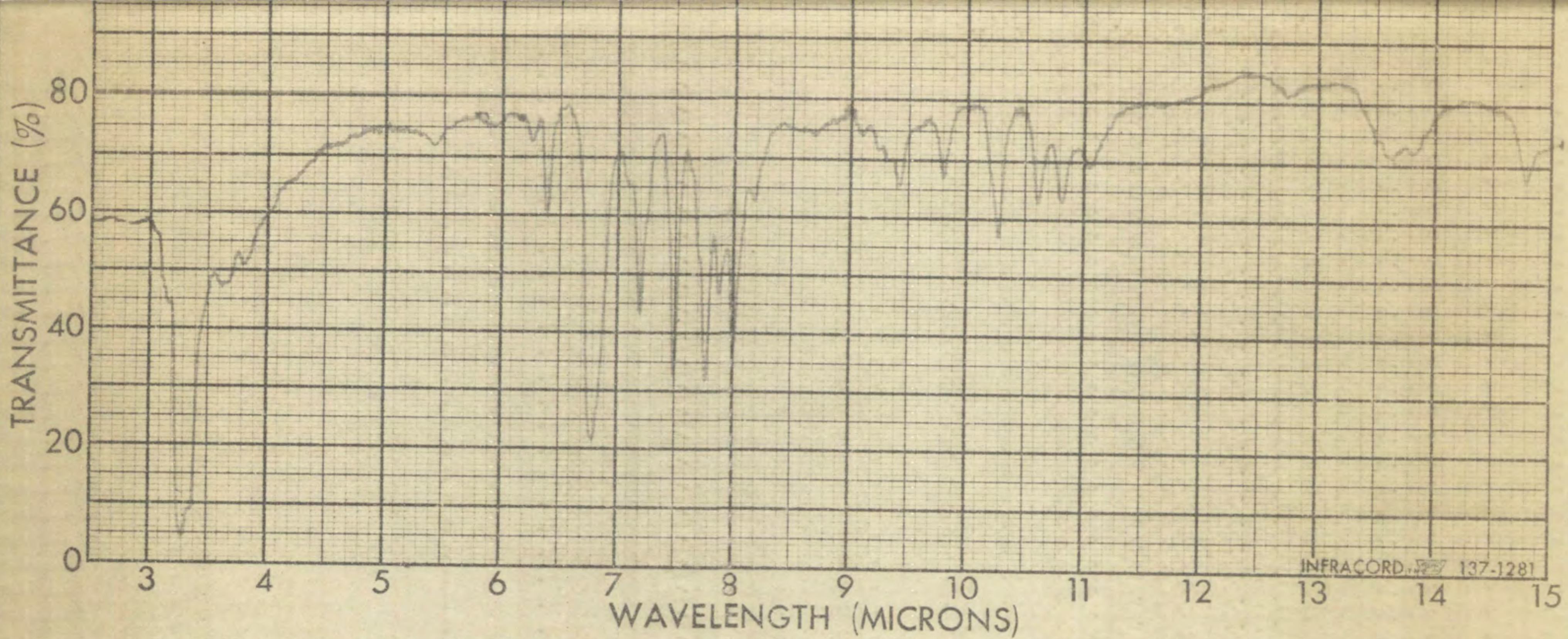
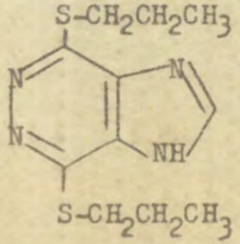


Plate LX: 4,7-Bis-n-propylthioimidazo[4,5-d]-pyridazine



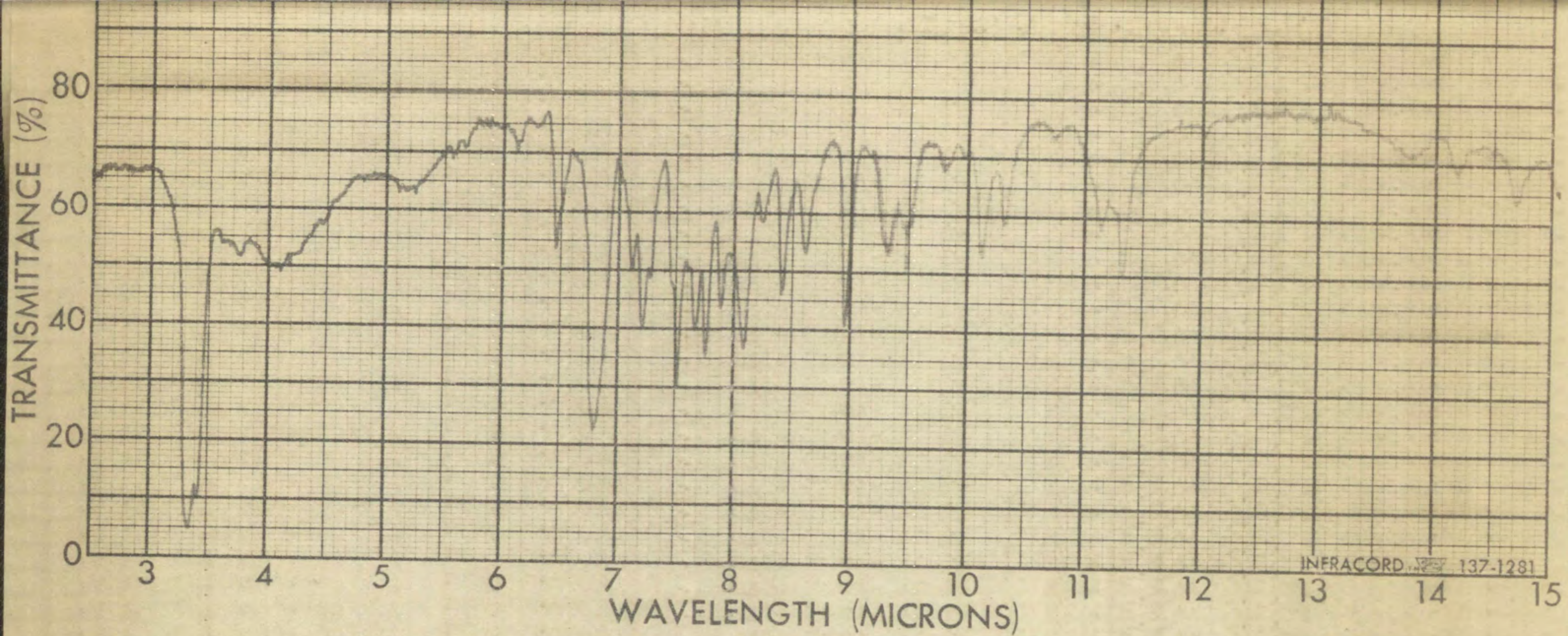
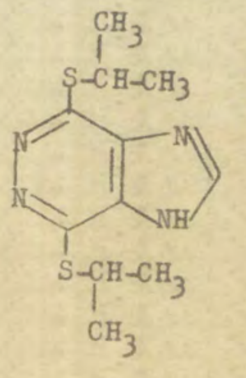


Plate LXI: 4,7-Bisisopropylthioimidazo[4,5-d] pyridazine



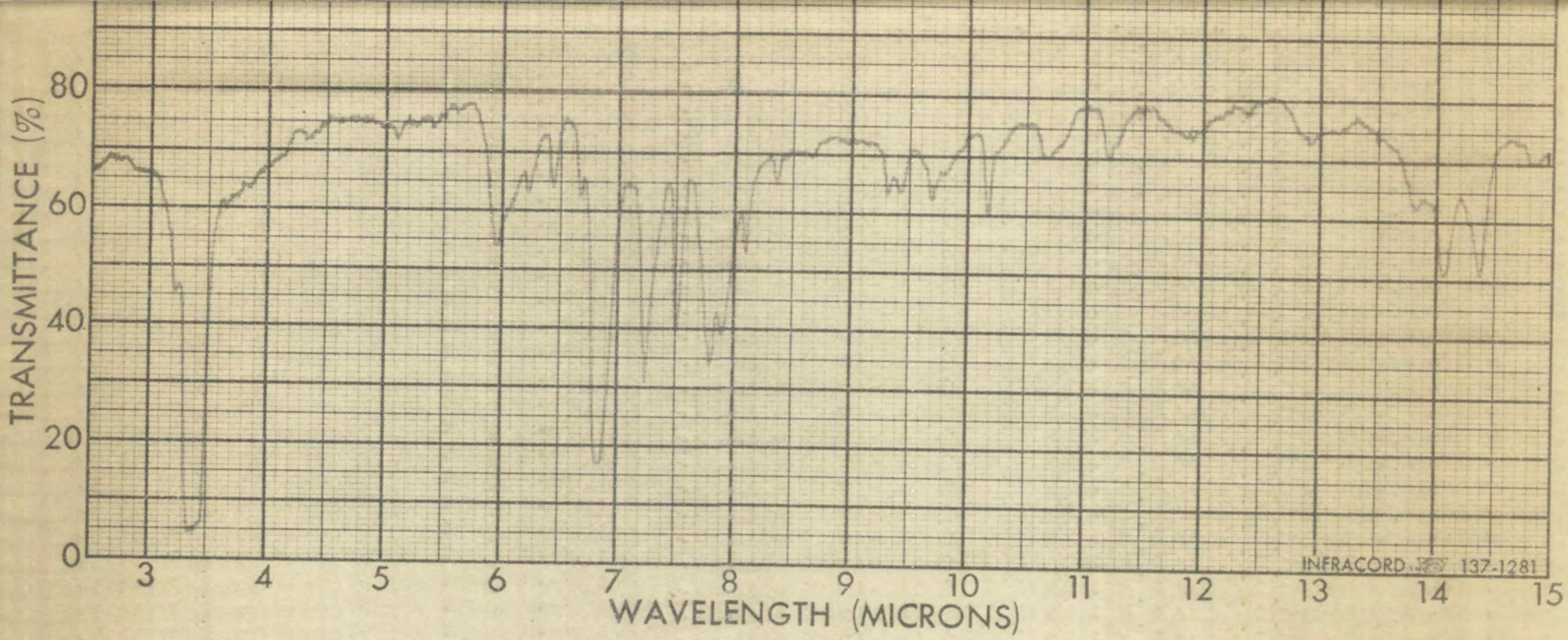
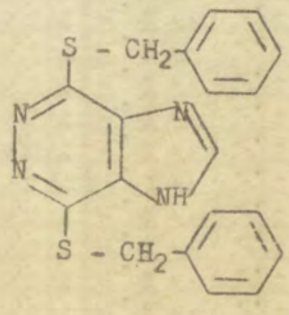


Plate LXII: 4,7-Bisbenzylthioimidazo[4,5-d]pyridazine



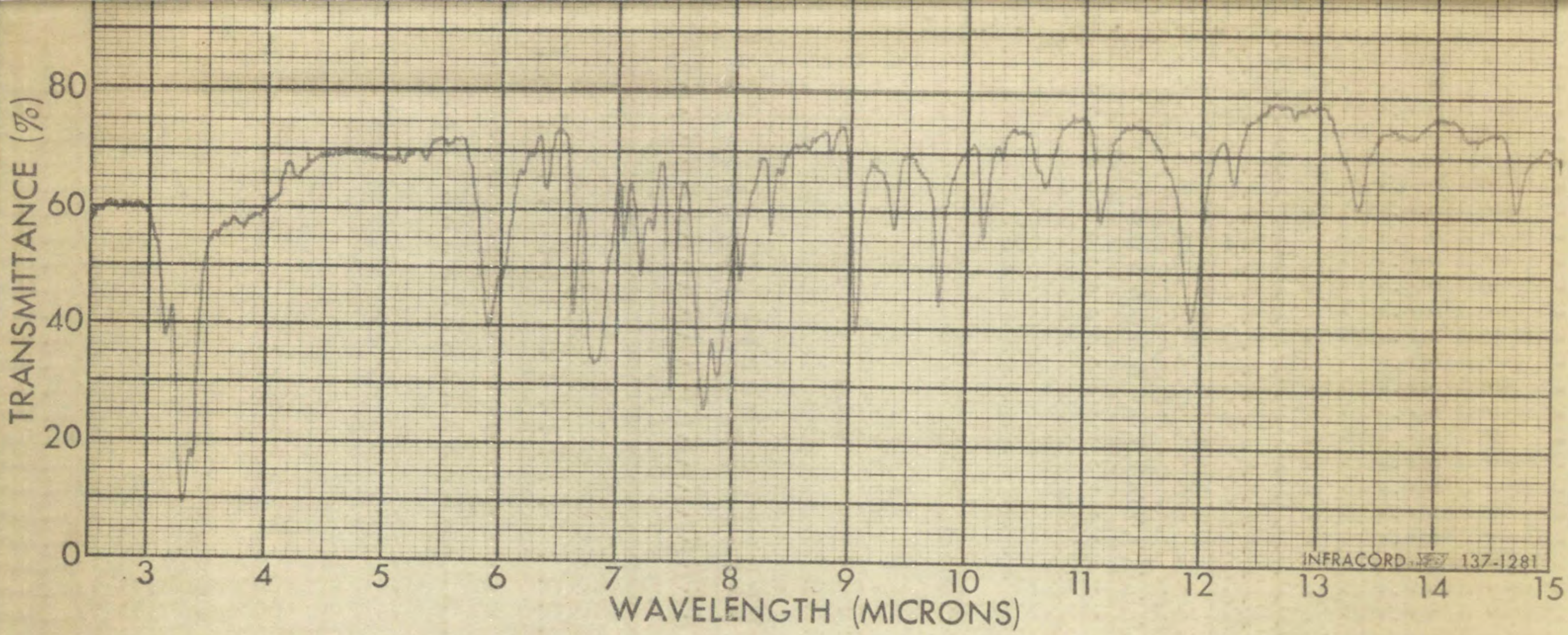
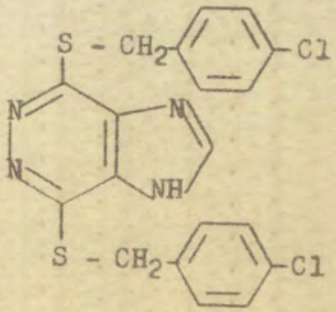


Plate LXIII: 4,7-Bis-p-chlorobenzylthioimidazo[4,5-d]-pyridazine



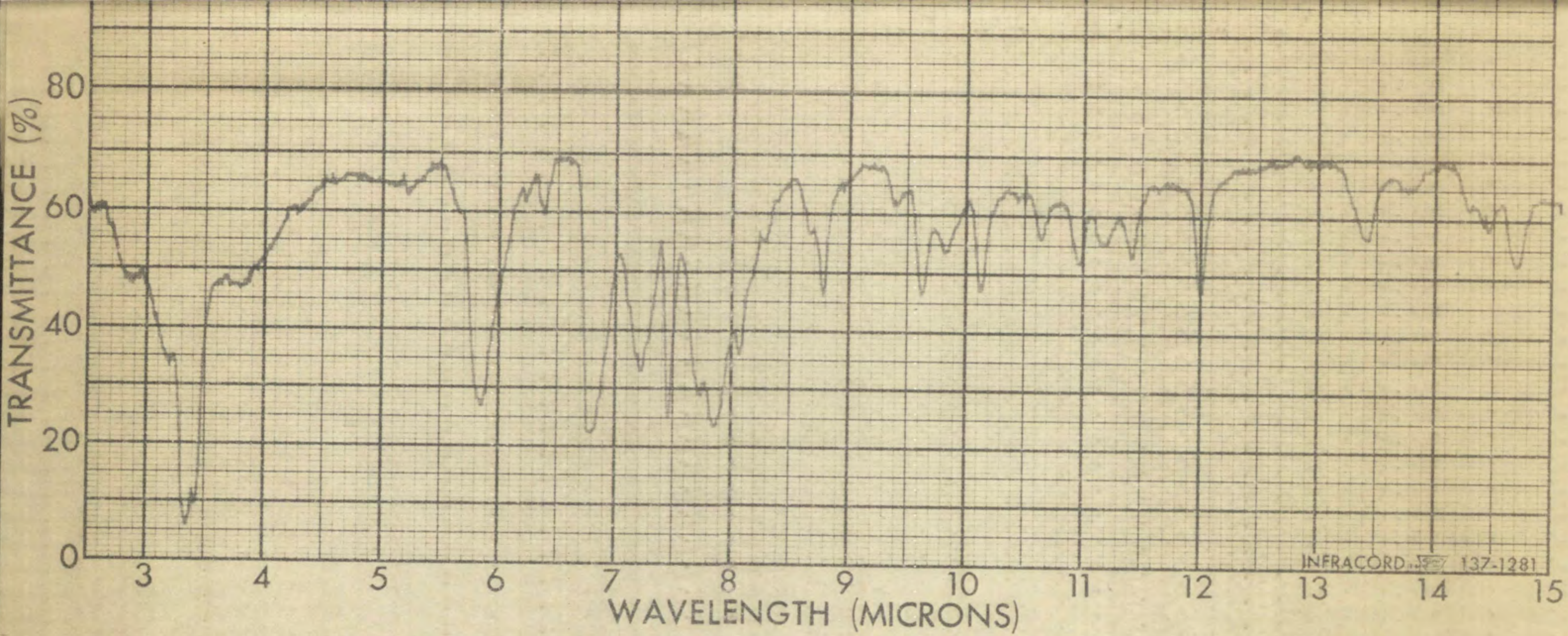
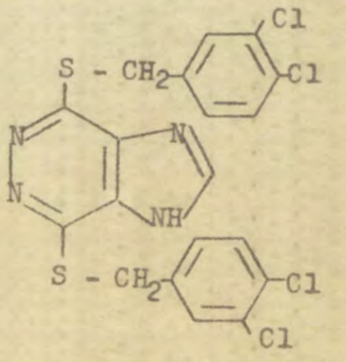


Plate LXIV: 4,7-Bis-(3,4-dichlorobenzylthio)imidazo-[4,5-d] pyridazine



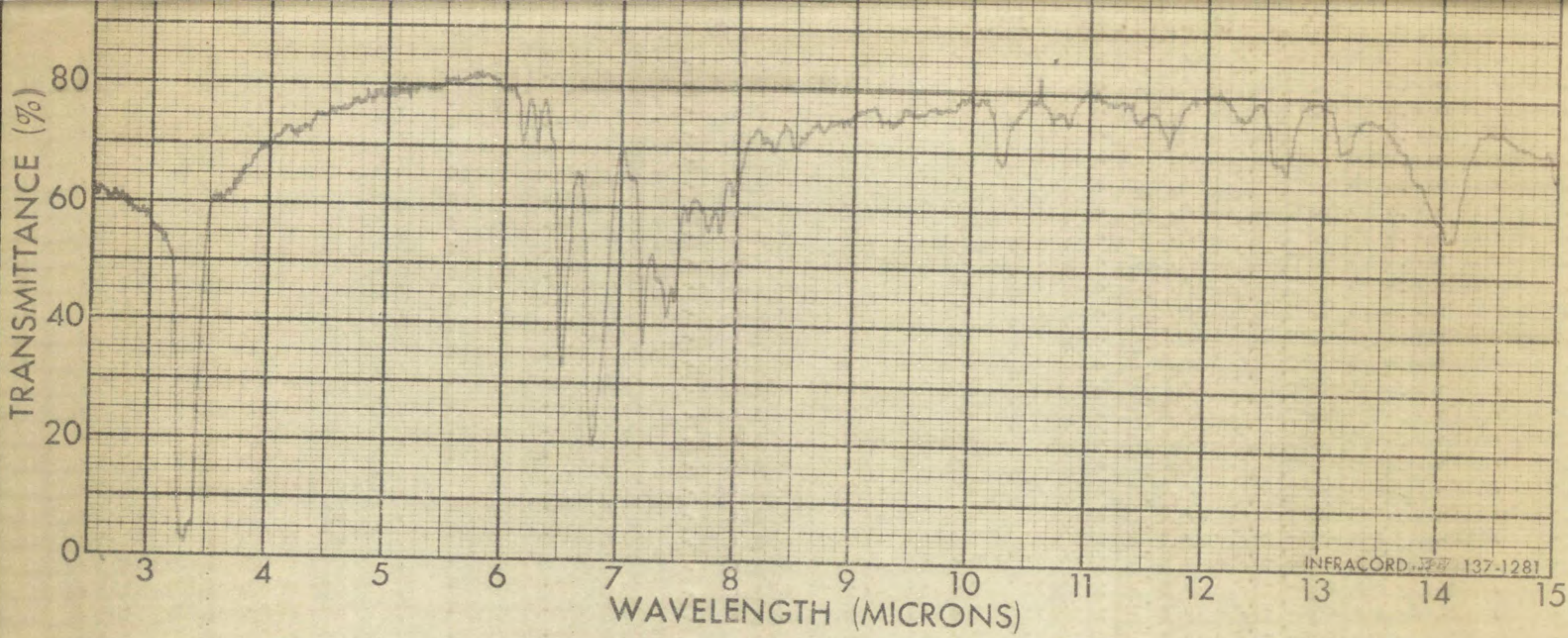
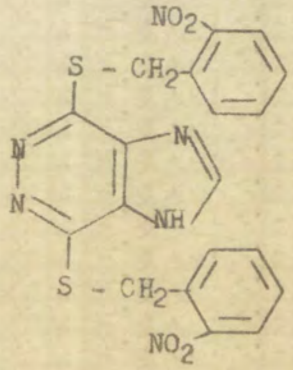


Plate LXV: 4,7-*Bis*-o-nitrobenzylthioimidazo-[4,5-*d*] pyridazine



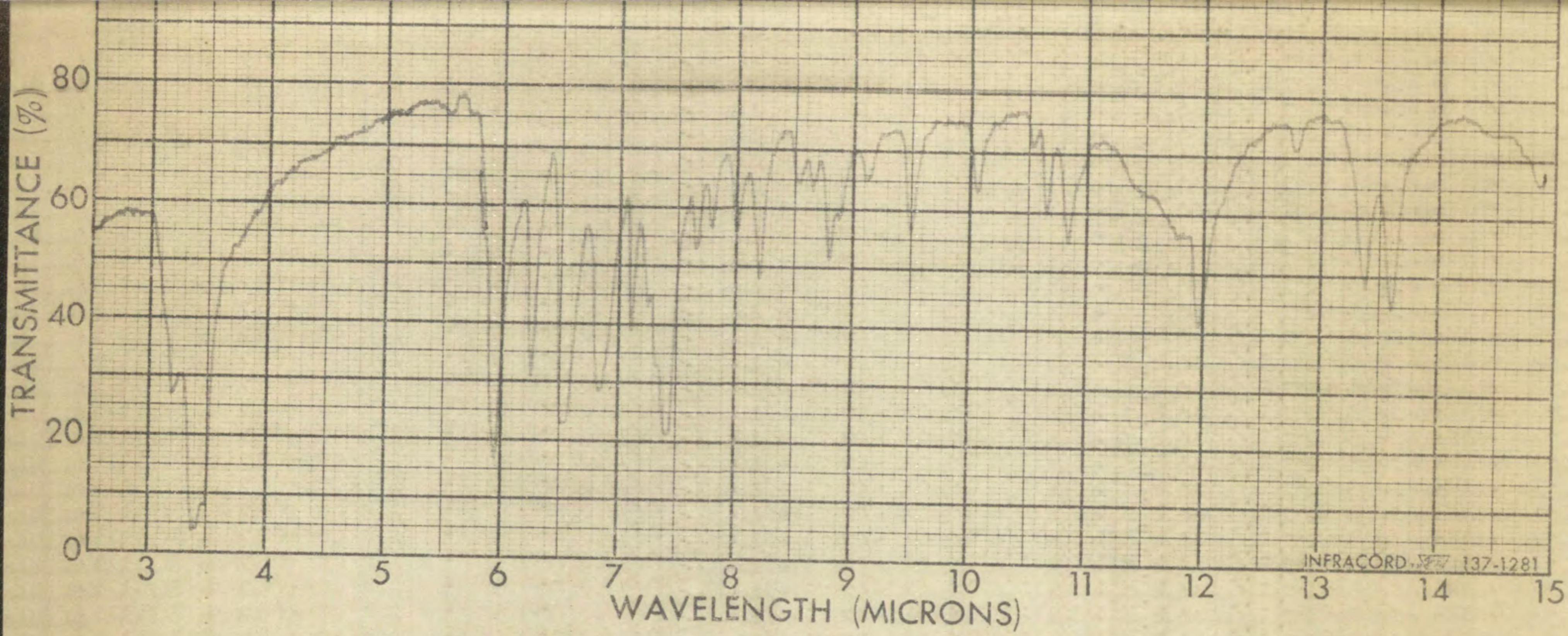
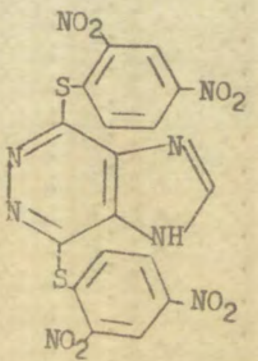


Plate LXVI: 4,7-Bis-(2,4-dinitrophenylthio)imidazo-[4,5-d]pyridazine



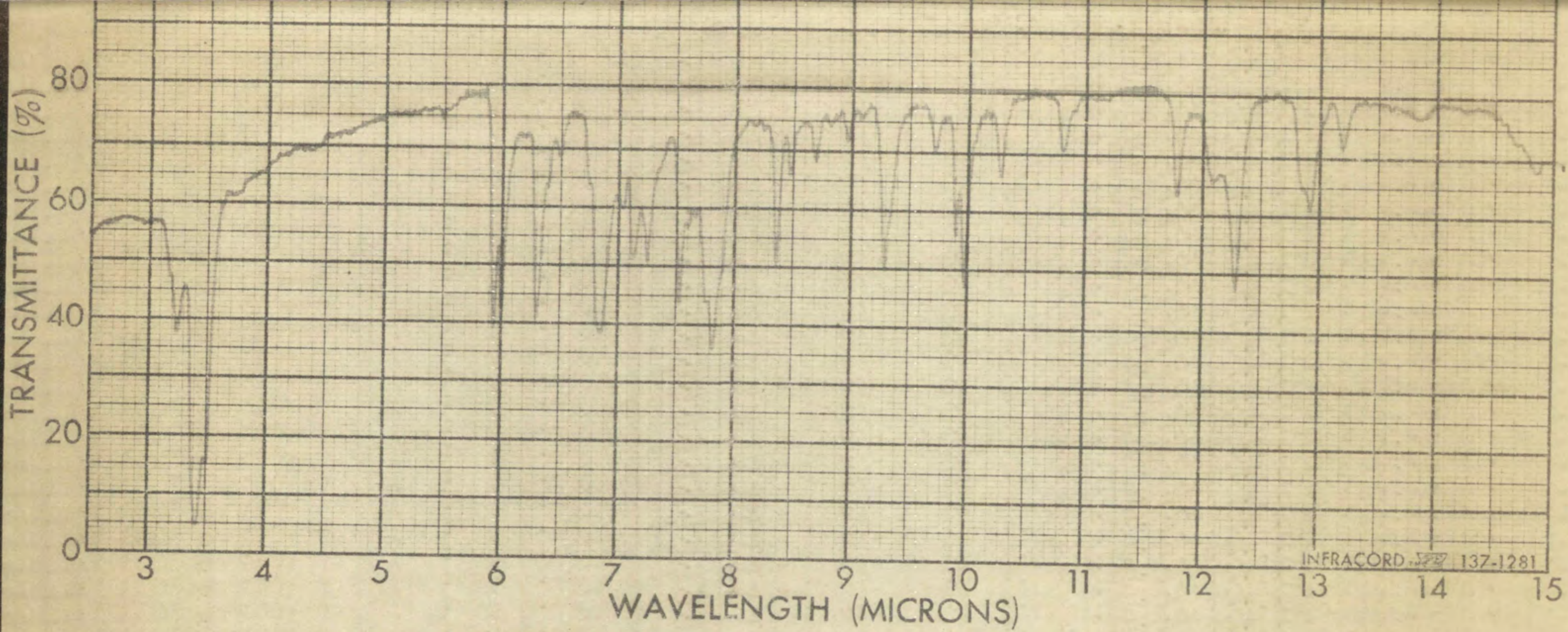
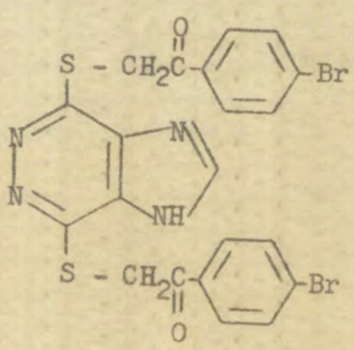


Plate LXVII: 4,7-Bis-p-bromophenacylthioimidazo-
[4,5-d] pyridazine



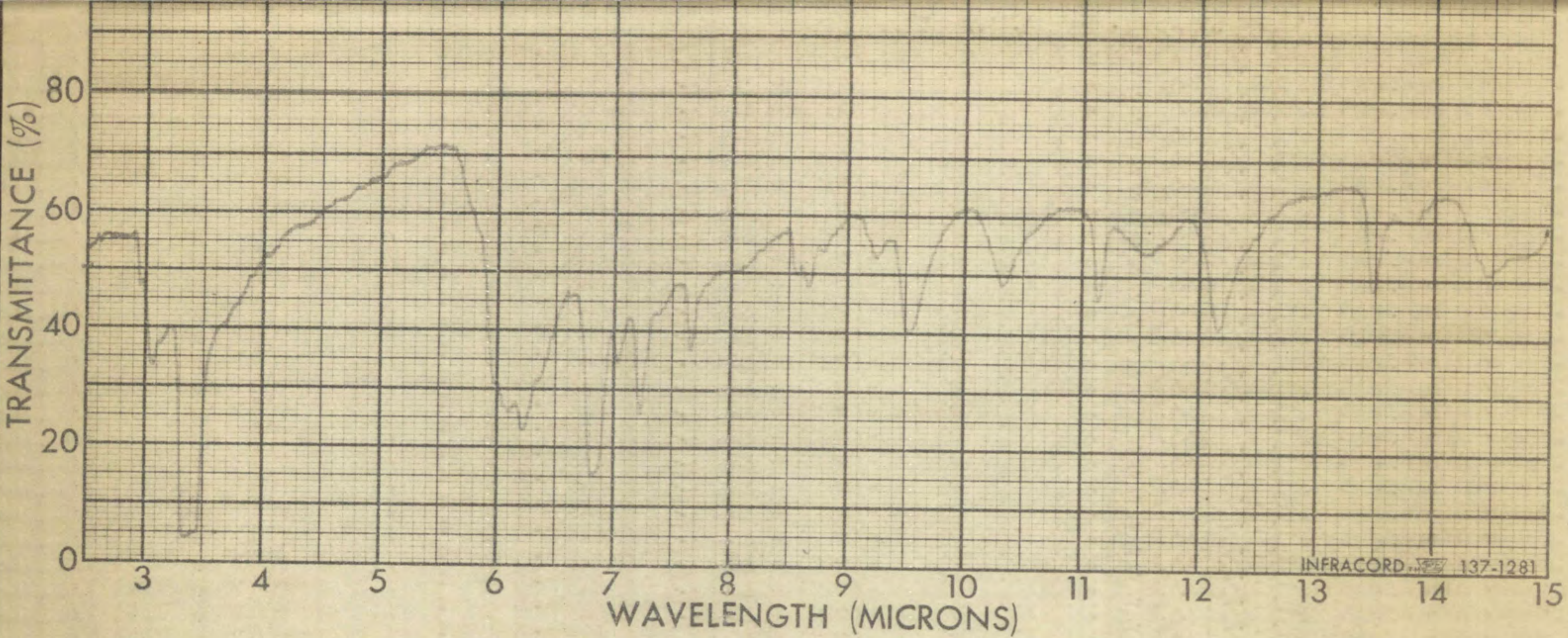
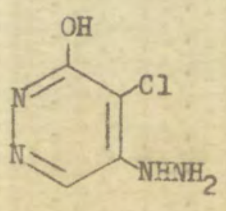


Plate LXVIII: 4(5)-Chloro-5(4)-hydrazino-3-pyridazone



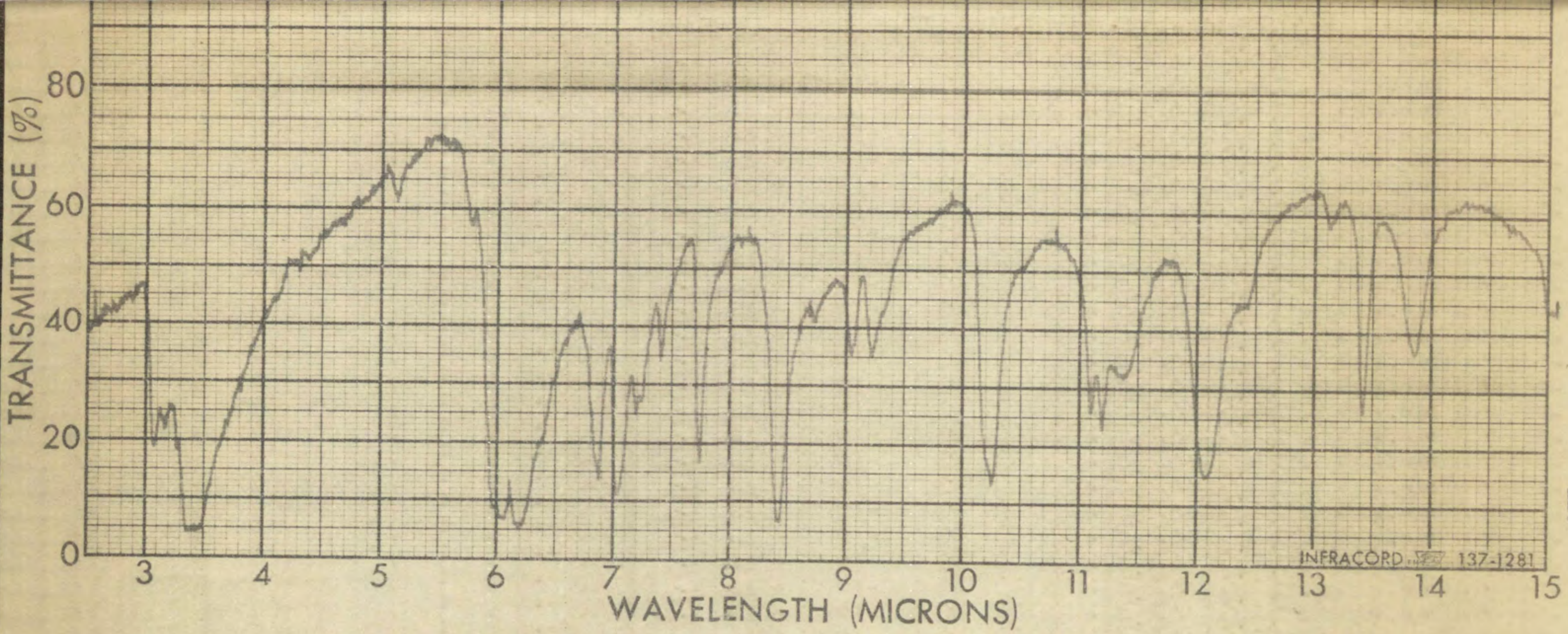
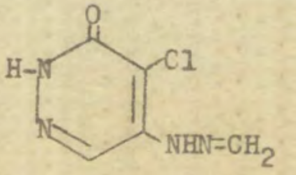


Plate LXIX: 4(5)-Chloro-5(4)-methylenehydrazino-3-pyridazone



IV. EXPERIMENTAL

The elemental analyses were determined by the following institutions: Weiler and Strauss, Oxford, England, Department of Chemistry, New Mexico Highlands University, Tanabe Seiyaku Co., Ltd., Tokyo, Japan, and this laboratory. All melting points were determined by a stirred melting point bath or a copper block and are uncorrected.

Synthesis and Reactions of the Substituted Imidazo[4,5-d]-pyridazines.

Imidazole-4,5-dicarboxylic Acid Bishydrazide (II). A mixture of 50 g. (0.32 mole) of imidazole-4,5-dicarboxylic acid and 1.5 l. of anhydrous methanol was saturated with dry hydrogen chloride gas. A slow stream of hydrogen chloride gas was passed through the mixture until nearly all the acid had dissolved. (9 hours). The methanolic hydrogen chloride was removed on the steam bath at reduced pressure. One liter of methanol was added to dissolve the residue and the solution was filtered to remove any unreacted acid. Fifty ml. of hydrazine (1.58 mole) was added to the filtrate and it was refluxed 0.5 hours on a steam bath. A light tan solid was obtained, m.p. >360°C.

This compound has previously been reported by Gardner, Smith, Wenis and Lee[66] and Castle and Seese[1].

4,7-Dithioimidazo[4,5-d]pyridazine (IV). To 1 l. of dry

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[66] T. S. Gardner, F. A. Smith, E. Wenis, and J. Lee, J. Org. Chem., 21, 530 (1956)

redistilled pyridine was added 20 g. (0.131 mole) of 4,7-dihydroxyimidazo[4,5-d]pyridazine and 175 g. of phosphorous pentasulfide. The mixture was protected from moisture by means of a drying tube and refluxed overnight (ca. 15-16 hours). About three fourths of the pyridine was recovered from the hot mixture at reduced pressure on a steam bath. Three hundred and fifty ml. of water was cautiously added to the cooled flask with constant agitation. After the copious evolution of hydrogen sulfide had subsided the contents of the flask were heated on a steam bath for 2.5 hours. The mixture was filtered with suction while hot. The filtrate was cooled and acidified to pH 1 with concentrated hydrochloric acid. A yellowish-brown solid precipitated which was filtered, washed with water, and dried in air, yield, 23 g. (95%).

This compound has previously been prepared by Castle and Seese[1] by a somewhat different procedure.

4,7-Bismethylthioimidazo[4,5-d]pyridazine (V). Ten grams of 4,7-dithioimidazo[4,5-d]pyridazine was dissolved in 100 ml. of 1.25 N. potassium hydroxide solution. To this rapidly stirred solution was added 19.4 g. (8.5 ml.) of methyl iodide. Stirring was continued for 0.5 hours whereupon the mixture was filtered (gravity) to remove a small amount of dark gummy material. The filtrate was acidified to pH 6 with glacial acetic acid and a large amount of a tan solid was removed by filtration and the residue was washed with water. The solid was dried in air and recrystallized from 95% ethanol to yield a light tan solid m.p. 243-245°C. Castle and Seese[1] reported

a white solid m.p. 243-245°C.

4,7-Bismethylaminoimidazo[4,5-d]pyridazine. In a 500 ml. stainless steel autoclave was placed 2.12 g. (0.01 mole) of 4,7-bismethylthioimidazo[4,5-d]pyridazine and 200 ml. of absolute ethanol containing 11.6 g. (0.37 mole) of methylamine. The autoclave was rocked and heated for 24 hours at 170-175°C. The solution was removed from the autoclave and filtered. The filtrate was reduced to dryness under reduced pressure on a steam bath. The tan solid was recrystallized from an ethanol-benzene mixture to yield a cream colored solid which decomposed at 314-315°C. The compound was found to be a hydrate. Castle and Seese[1] reported the 4,7-diamino derivative to also be hydrated.

Anal. Calcd for $C_7H_{10}N_6 \cdot \frac{1}{4} H_2O$: C, 46.03; H, 5.79; N, 46.02. Found: C, 46.39; H, 5.69; N, 45.86.

4,7-Bishydrazinoimidazo[4,5-d]pyridazine. To 4.24 g. (0.02 mole) of 4,7-bismethylthioimidazo[4,5-d]pyridazine was added 29 ml. (29.32 g.) of hydrazine. This solution was refluxed for 1.5 hours. The excess hydrazine was removed under reduced pressure on the steam bath and the resulting solid washed repeatedly with ethanol. (2.65 g. 74%). A sulfur test was negative.

Anal. Calcd for $C_5H_8N_8$: C, 33.34; H, 4.48; N, 62.26. Found: C, 33.03; H, 4.40; N, 61.32.

4(7)-Diisopropylamino-7(4)-methylthioimidazo[4,5-d]pyridazine. In a 500 ml. stainless steel autoclave was placed 4.24 g. (0.02 mole) of 4,7-bismethylthioimidazo[4,5-d]pyridazine and 60 g. (0.59 mole)

of diisopropylamine in a volume of absolute ethanol sufficient to make the total volume equal to 200 ml. The autoclave was rocked and heated for 13 hours at 195°C. The solution was filtered and evaporated to dryness under reduced pressure on a steam bath. The tan solid was recrystallized from a benzene-ethanol mixture to yield a cream colored powder, m.p. 305-307°C. A qualitative test for sulfur was positive.

Anal. Calcd for $C_{12}H_{19}N_5S$: C, 54.30; H, 7.21. Found: C, 54.12; H, 7.40.

4(7)-Di-(3-methylbutyl)amino-7(4)-methylthioimidazo[4,5-d]-pyridazine. Twenty grams of di-(3-methylbutyl)amine in a sufficient quantity of absolute ethanol to make 200 ml. of solution was placed 4.24 g. (0.02 mole) of 4,7-bismethylthioimidazo[4,5-d]pyridazine in a stainless steel autoclave. The autoclave was rocked and heated for 9 hours at 195°C. The solution was filtered and the filtrate evaporated to dryness under reduced pressure. A qualitative test for sulfur was positive. The solid was recrystallized from a benzene-ethanol mixture whereupon a light tan solid separated, m.p. 319-321°C.

Anal. Calcd. for $C_{16}H_{27}N_5S$: C, 59.75; H, 8.47. Found: C, 60.04: H, 8.42.

4(7)-Hydroxy-7(4)-methylthioimidazo[4,5-d]pyridazine. Sixty grams (0.59 mole) of di-n-propylamine in a sufficient quantity of absolute ethanol to make 200 ml. of solution and 4.24 g. (0.02 mole) of 4,7-bismethylthioimidazo[4,5-d]pyridazine were placed in a stainless steel autoclave. The autoclave was rocked and heated for 8 hours at 195°C. The solution was filtered and the filtrate evaporated to

dryness under reduced pressure. The resulting tan solid was recrystallized twice from ethanol (norite) to yield a light tan solid m.p. 322-323°C.

Anal. Calcd. for $C_6H_6N_4SO$: C, 39.55; H, 3.32. Found: C, 39.86; H, 3.62.

This compound was also obtained from similar procedures using diethylamine and di-n-butylamine.

4,7-Diethylaminoimidazo[4,5-d]pyridazine. In 200 ml. of absolute ethanol was dissolved 22.3 g. (0.5 mole) of ethylamine. This solution along with 4.24 g. (0.02 mole) of 4,7-bismethylthioimidazo[4,5-d]pyridazine was placed in a stainless steel autoclave. The autoclave was rocked and heated for 8 hours at 195°C. The solution was filtered and the filtrate reduced to dryness under reduced pressure. A tan solid 4.2 g. (100%) was recrystallized from an ethanol-benzene mixture to yield a white solid m.p. 247-249°C. A qualitative test for sulfur was negative.

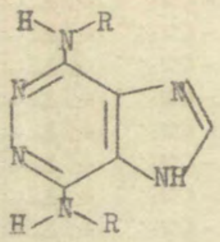
Anal. Calcd. for $C_9H_{14}N_6 \cdot \frac{1}{2} H_2O$: C, 50.21; H, 7.03. Found: C, 50.27; H, 6.97.

This general procedure was used for all the 4,7-disubstitutedamino compounds in Table XVII.

4(7)-Methylsulfonyl-7(4)-methoxyimidazo[4,5-d]pyridazine (VI). One gram (0.0047 mole) of 4,7-bismethylthioimidazo[4,5-d]pyridazine was nearly dissolved in 260 ml. of absolute methanol. Nitrogen was bubbled through the mixture for 10 minutes then dry chlorine gas for 30 minutes. The mixture immediately became a clear pale yellow

Table XVII

4,7-Disubstitutedaminoimidazo [4,5-d] pyridazine



Amine Used	Molar Excess of Amine	R	m.p. °C	Recrystallization Solvent	C		H	
					Calcd.	Found	Calcd.	Found
Ethanolamine	25	β-hydroxy-ethyl	251-253	Water	45.36	45.70	5.92	6.50
Dimethylamino-propylamine	20	Dimethylamino-propyl	174-176	Benzene	56.23	56.35	8.81	8.93
Diethylamino-propylamine	19	Diethylamino-propyl	140-142	Benzene-Cyclohexane	60.60	60.34	9.64	9.23
n-Butylamine	20	n-Butyl	110	Dioxane-Ligroin	59.51	59.74	8.45	8.52
Dimethylamine	26	Dimethyl	209-211	Benzene-Ethanol	52.41	52.23	6.84	7.00

solution and during the course of the addition of chlorine the temperature rose to 58°C. The solvent was removed under reduced pressure leaving a white solid. This was recrystallized twice from absolute ethanol to yield a white solid, m.p. 312-313°C.

Anal. Calcd. for $C_7H_8N_4SO_3$: C, 36.84; H, 3.54; N, 24.55: S, 14.05. Found: C, 37.18; H, 3.79; N, 24.36; S, 13.99.

4(7)-Hydroxyimidazo-7(4)-methylsulfonyl [4,5-d] pyridazine (VII). In 150 ml. of 50% aqueous methanol was suspended 1 gram of 4-methylthioimidazo [4,5-d] pyridazine. Chlorine gas was passed through the mixture for 15 minutes during which time the starting material dissolved. Then the reaction mixture became hazy. The solvent was partially removed under reduced pressure and a light grey solid was removed by filtration. The nature of this substance is unknown. The filtrate deposited fine yellow crystals after standing ten days at room temperature. These were further purified by recrystallization from water, m.p. 342-343°C.

Anal. Calcd. for $C_6H_6N_4SO_3$: C, 33.64; H, 2.82; N, 26.16. Found: C, 33.63; H, 3.11; N, 26.10.

This compound was also prepared in similar manner from 4,7-bismethylthioimidazo [4,5-d] pyridazine.

This compound was also obtained from 4,7-bismethylthioimidazo-[4,5-d] pyridazine by the action of dry chlorine gas in anhydrous methanol.

4,7-Bismethylsulfonyl-1-methylimidazo [4,5-d] pyridazine (VIII). One gram (0.0047 mole) of 4,7-bismethylthioimidazo [4,5-d] pyridazine

was suspended in 150 ml. of 50% aqueous methanol. Chlorine gas was bubbled through the mixture for 20 minutes. It appeared that the starting material went into solution while at the same time a grey-white solid began to precipitate from the reaction mixture. The solid was filtered and washed with aqueous methanol m.p. 233-234°C. A portion was recrystallized from 95% ethanol yielding a white fluffy solid decomposing at 236°C. A positive sulfur test and a negative halogen test were observed.

Anal. Calcd. for $C_8H_{10}N_4S_2O_4$: C, 33.11; H, 3.47; N, 19.31; S, 22.10. Found: C, 33.07; H, 3.32; N, 19.29; S, 21.82.

4(7)-Benzylthioimidazo[4,5-d]pyridazine-7(4)-thiol. In 125 ml. of 1.25 N. potassium hydroxide was dissolved 11.04 g. (0.06 mole) of 4,7-dithioimidazo[4,5-d]pyridazine. Seven and six-tenths grams (6.8 ml., 0.06 mole) of benzyl chloride was added to the rapidly stirred mixture and stirring continued for 0.75 hours. The solution was filtered and acidified to pH 6 with glacial acetic acid. The product was filtered and dried in air. Thirteen and five-tenths grams of a tan solid was obtained (82%). The solid was recrystallized from absolute ethanol (norite) and a pinkish-tan solid, m.p. 283-285°C, was obtained.

Anal. Calcd. for $C_{12}H_{10}N_4S_2$: C, 52.52; H, 3.67. Found: C, 53.00; H, 4.21.

4(7)-n-Propylthioimidazo[4,5-d]pyridazine-7(4)-thiol. To 9.21 g. (0.05 mole) of 4,7-dithioimidazo[4,5-d]pyridazine dissolved in 80 ml. of 1.25 N. potassium hydroxide was added 8.5 g. (0.05 mole) of n-propyl

iodide. Five ml. of ethanol was added to the rapidly stirred mixture. The mixture was stirred for 1.5 hours, boiled with norite, and filtered. The filtrate was acidified to pH 6 with glacial acetic acid and a tan solid and some gummy material precipitated. The product was purified by precipitation with acetic acid from a 5% solution of sodium hydroxide (norite). Dark red crystals m.p. 257-258°C were obtained by recrystallization from absolute ethanol.

Anal. Calcd. for $C_8H_{10}N_4S_2$: C, 42.46; H, 4.45; N, 24.76. Found: C, 42.84; H, 4.14; N, 24.92.

4(7)-Isopropylthioimidazo[4,5-d]pyridazine-7(4)-thiol. This compound was prepared in a similar manner to 4(7)-n-propylthioimidazo[4,5-d]pyridazine-7(4)-thiol. Because two layers were noted in the reaction mixture after 0.75 hours of stirring, the mixture was stirred and refluxed for an additional hour. Upon acidification of the filtered reaction mixture a large amount of tar was obtained. Glacial acetic acid was found suitable as a recrystallization solvent. After an additional recrystallization from glacial acetic acid pale orange crystals were obtained, m.p. 254-255.5°C.

Anal. Calcd. for $C_8H_{10}N_4S_2$: C, 42.46; H, 4.45; N, 24.76; S, 28.41. Found: C, 42.65; H, 4.85; N, 24.95; S, 28.69.

4(7)-n-Butylthioimidazo[4,5-d]pyridazine-7(4)-thiol. This compound was prepared in a similar manner to 4(7)-n-propylthioimidazo[4,5-d]pyridazine-7(4)-thiol. A tan solid was obtained (58%). Recrystallization from a benzene-dioxane mixture yielded small yellow spheres, m.p. 244-246°C.

Anal. Calcd. for $C_9H_{12}N_4S_2$: C, 44.98; H, 5.03; N, 23.31; S, 26.69. Found: C, 45.28; H, 5.18; N, 23.40; S, 26.72.

4(7)-(3-Methylbutyl)thioimidazo [4,5-d] pyridazine-7(4)-thiol. This compound was prepared in a similar manner to 4(7)-n-propylthioimidazo [4,5-d] pyridazine-7(4)-thiol. The mixture was stirred and refluxed for 1.5 hours. After acidification of the filtrate a brown solid was obtained. (44%). The solid was recrystallized from a dioxane-benzene mixture to yield a buff colored solid, m.p. 239-241°C.

Anal. Calcd. for $C_{10}H_{14}N_4S_2$: C, 47.21; H, 5.55; N, 22.03. Found: C, 47.18; H, 5.66; N, 22.30.

4(7)-Allylthioimidazo [4,5-d] pyridazine-7(4)-thiol. The general model for the preparation of this compound was obtained from Daves, Noell, Robins, Koppel, and Beaman.[57] In 150 ml. of 28% ammonium hydroxide was dissolved 9.21 g. (0.05 mole) of 4,7-dithioimidazo-[4,5-d] pyridazine. To this rapidly stirred solution was added 6.1 g. (0.05 mole) of allyl bromide dissolved in 25 ml. of dioxane over a 15 minute period. The reaction mixture was warmed to 35-40°C, then allowed to cool to room temperature with continuous stirring for 2.5 hours. After filtration and acidification to pH 6 with glacial acetic acid a brick red precipitate was obtained. This was filtered and dried in air. There was obtained 7.27 g. (65%). The product was recrystallized twice from absolute ethanol to give a cream colored solid, m.p. 244.5-245°C.

Anal. Calcd. for $C_8H_8N_4S_2$: C, 42.85; H, 3.60; N, 24.98. Found: C, 42.86; H, 3.19; N. 25.15.

4(7)-β-Hydroxyethylthioimidazo[4,5-d]pyridazine-7(4)-thiol. This compound was prepared in a similar manner to 4(7)-allylthioimidazo[4,5-d]pyridazine-7(4)-thiol. The halide used was 2-bromoethanol. A dark red solid was obtained (55%). This was recrystallized from aqueous-ethanol with the aid of norite to give a cream colored solid, m.p. >360°C.

Anal. Calcd. for $C_7H_8N_4S_2O$: C, 36.83; H, 3.53. Found: C, 36.82; H, 3.36.

4(7)-β-Carboxyethylthioimidazo[4,5-d]pyridazine-7(4)-thiol. In 185 ml. of 1 N potassium hydroxide was dissolved 9.21 g. (0.05 mole) of 4,7-dithioimidazo[4,5-d]pyridazine. Five and five-tenths grams (0.05 mole) of β-chloropropionic acid was added and the mixture stirred and refluxed for 3.5 hours. The solution was acidified to pH 2 with concentrated hydrochloric acid whereupon a dark brown solid precipitated. The mixture was cooled and the solid removed by filtration. The precipitate was added to a saturated solution of sodium bicarbonate and stirred for 2 hours. The mixture was filtered and the filtrate acidified to pH 3 with concentrated hydrochloric acid. A yellow solid was filtered, washed with water, and dried in an oven at 100°C for 2 hours, 9.04 g. (71%). The solid was recrystallized from water to give a fine yellow solid decomposing at 256°C.

Anal. Calcd. for $C_8H_8N_4S_2O_2$: C, 37.49; H, 3.15; N, 21.86. Found: C, 36.92; H, 3.11; N, 22.01.

4(7)-Carboxymethylthioimidazo[4,5-d]pyridazine-7(4)-thiol. This compound was prepared in a similar manner to 4(7)-β-carboxyethylthioimidazo[4,5-d]pyridazine-7(4)-thiol. Seven and ninety-five one hundredths grams (66%) of a yellow solid was obtained. This was recrystallized from water using norite to give a yellow solid decomposing at 248°C.

Anal. Calcd. for $C_7H_6N_4S_2O_2$: C, 34.70; H, 2.50. Found: C, 34.58; H, 2.53.

4(7)-Carboxamidomethylthioimidazo[4,5-d]pyridazine-7(4)-thiol. This compound was prepared in a similar manner to 4(7)-allylthioimidazo[4,5-d]pyridazine-7(4)-thiol. About 40 ml. of dioxane was required to keep the 2-chloroacetamide in solution. The reaction mixture was stirred for 4.5 hours. A deep red solid was obtained, 9.19 g. (76%). The compound was recrystallized from pyridine using norite to yield a cream colored solid, m.p. >360°C.

Anal. Calcd. for $C_7H_7N_5S_2O$: C, 34.85; H, 2.93. Found: C, 34.86; H, 3.35.

4(7)-o-Chlorobenzylthioimidazo[4,5-d]pyridazine-7(4)-thiol. This compound was prepared in a manner similar to 4(7)-n-propylthioimidazo[4,5-d]pyridazine-7(4)-thiol. o-Chlorobenzyl chloride was the reagent. The reaction was stirred for 0.75 hours. A brown solid was obtained which was first purified by dissolving in 5% sodium hydroxide, boiling with norite, filtering, and precipitating with acid. Nine grams of dry tan solid was obtained, (58%). This was recrystallized from an ethanol-benzene mixture to give a light tan solid, m.p. 244.5-246°C.

Anal. Calcd. for $C_{12}H_9N_4S_2Cl$: C, 46.68; H, 2.94; N, 18.14. Found: C, 46.43; H, 3.56; N, 17.55.

4(7)-(3,4-Dichlorobenzylthio)imidazo[4,5-d]pyridazine-7(4)-thiol. To 40 ml. of 2.5 N potassium hydroxide solution was dissolved 9.21 g. (0.05 mole) of 4,7-dithioimidazo[4,5-d]pyridazine. To this rapidly stirred solution was added 14.35 g. (0.05 mole) of 3,4-dichlorobenzyl iodide dissolved in 40 ml. of ethanol. The solution was stirred for 2 hours whereupon it was filtered and acidified to pH 6 with glacial acetic acid. A light brown solid separated which was filtered, washed with water, and dried in air, 13.95 g., (81%). The product was recrystallized from dioxane to yield a tan solid, m.p. 301-303°C.

Anal. Calcd. for $C_{12}H_8N_4S_2Cl_2$: C, 41.98; H, 2.35. Found: C, 41.70; H, 2.55.

4(7)-2,4-Dichlorobenzylthioimidazo[4,5-d]pyridazine-7(4)-thiol. This compound was prepared in a similar manner to 4(7)-3,4-dichlorobenzylthioimidazo[4,5-d]pyridazine-7(4)-thiol. The solution was stirred for one hour. A brown solid was obtained, (75%). The product was recrystallized from dioxane to give a fine tan solid, m.p. 269-271°C.

Anal. Calcd. for $C_{12}H_8N_4S_2Cl_2$: C, 41.98; H, 2.35. Found: C, 41.82; H, 2.50.

4(7)-o-Fluorobenzylthioimidazo[4,5-d]pyridazine-7(4)-thiol. This compound was prepared in a manner similar to 4(7)-allylthioimidazo[4,5-d]pyridazine-7(4)-thiol. The halide used was o-fluorobenzyl bromide. Total stirring time was 4.5 hours. A brown solid

(36%) was obtained along with a considerable amount of tar. After repeated recrystallization from 95% ethanol using norite a pale yellow crystalline solid was obtained, m.p. 239-241°C.

Anal. Calcd. for $C_{12}H_9N_4S_2F$: C, 49.30; H, 3.10; N, 19.16. Found: C, 49.32: H, 3.30; N, 18.93.

4(7)-m-Fluorobenzylthioimidazo[4,5-d]pyridazine-7(4)-thiol. This compound was prepared in a similar manner to 4(7)-allylthioimidazo[4,5-d]pyridazine-7(4)-thiol. Total stirring time was 4.5 hours. An orange solid was obtained, (43%) along with some tar. The compound was recrystallized from 95% ethanol (norite) to give yellow platelets, m.p. 270-272°C.

Anal. Calcd. for $C_{12}H_9N_4S_2F$: C, 49.30; H, 3.10; N, 19.16. Found: C, 49.32; H, 3.30; N, 18.94.

4(7)-p-Fluorobenzylthioimidazo[4,5-d]pyridazine-7(4)-thiol. This compound was prepared in a similar manner to 4(7)-allylthioimidazo[4,5-d]pyridazine-7(4)-thiol. Total stirring time was 3.5 hours. A tan solid was obtained (51%). Recrystallization was effected with 95% ethanol and norite to yield fine pale yellow crystals, m.p. 276-277°C.

Anal. Calcd. for $C_{12}H_9N_4S_2F$: C, 49.30; H, 3.10; N, 19.16. Found: C, 49.41; H, 3.46; N, 18.95.

4(7)-p-Iodobenzylthioimidazo[4,5-d]pyridazine-7(4)-thiol . p-Iodobenzyl iodide (14.85 g., 0.05 mole) was dissolved in 30 ml. of dioxane and this solution added to a rapidly stirred solution of 9.21 g. (0.05 mole) of 4,7-dithioimidazo[4,5-d]pyridazine in 150 ml.

of concentrated ammonium hydroxide solution. Stirring was continued for 4.5 hours at which time a large amount of yellow solid was removed by filtration, 12.57 g. The identity of this compound has not yet been determined. The filtrate was acidified to pH 6 with glacial acetic acid whereupon another yellow solid was obtained, 3.63 g.(18%). This solid was recrystallized from an aqueous-pyridine mixture (norite) to yield a buff colored solid, m.p. 288-289°C.

Anal. Calcd. for $C_{12}H_9N_4S_2I$: C, 36.00; H, 2.27. Found: C, 36.39; H, 2.27.

4(7)-p-Nitrobenzylthioimidazo[4,5-d]pyridazine-7(4)-thiol. This compound was prepared in a similar manner to 4(7)-p-iodobenzylthioimidazo[4,5-d]pyridazine-7(4)-thiol. A solid was removed by filtration from the reaction mixture. The solid has not been identified. The filtrate, however, was acidified to pH 6 with glacial acetic acid and a brown solid recovered (44%). This was recrystallized from an aqueous-pyridine mixture (norite) to yield long very fluffy cream needles, m.p. 298-299°C.

Anal. Calcd. for $C_{12}H_9N_5S_2O_2$: C, 45.11; H, 2.84. Found: C, 45.06; H, 2.85.

4(7)-p-Bromophenacylthioimidazo[4,5-d]pyridazine-7(4)-thiol. The filtrate after the removal of 4,7-bis-p-bromophenacylthioimidazo-[4,5-d]pyridazine (described p.138) was acidified to pH 6 with glacial acetic acid whereupon a brown solid was obtained, 3.96 g.(20%). This was recrystallized from an aqueous-pyridine mixture (norite) to yield fine yellow crystals, m.p. 261-262°C.

Anal. Calcd. for $C_{13}H_9N_4S_2OBr$: C, 40.96; H, 2.38. Found: C, 41.15; H, 2.44.

4(7)-p-Chlorophenacylthioimidazo[4,5-d]pyridazine-7(4)-thiol. This compound was prepared in a similar manner to 4(7)-p-Iodobenzylthioimidazo[4,5-d]pyridazine-7(4)-thiol. A brick red solid was obtained from the reaction mixture the identity of which has not been determined. The filtrate upon acidification to pH 6 with glacial acetic acid produced a light brown solid (22%). The solid was recrystallized from aqueous-pyridine (norite) to yield a tan solid, m.p. 263-264°C.

Anal. Calcd. for $C_{13}H_9N_4S_2OCl$: C, 46.36; H, 2.70. Found: C, 46.54; H, 2.40.

4,7-Bis-n-propylthioimidazo[4,5-d]pyridazine. Into 150 ml. of 1.25 N potassium hydroxide solution was dissolved 9.21 g. (0.05 mole) of 4,7-dithioimidazo[4,5-d]pyridazine. Seventeen grams (0.1 mole) of n-propyl iodide was added to the rapidly stirred solution. The mixture was refluxed for 0.5 hours; norite and talc were added and the mixture filtered (gravity). The filtrate was acidified to pH 6 with glacial acetic acid and the product was precipitated as a tar. Recrystallization from benzene-cyclohexane (norite) gave large tan crystals, m.p. 126-128°C.

Anal. Calcd. for $C_{11}H_{16}N_4S_2$: C, 49.21; H, 6.01. Found: C, 48.70; H, 5.79.

4,7-Bisisopropylthioimidazo[4,5-d]pyridazine. In 150 ml. of 1.25 N potassium hydroxide solution was dissolved 9.21 g. (0.05 mole)

of 4,7-dithioimidazo[4,5-d]pyridazine. To the rapidly stirred solution was added 17 g. (0.1 mole) of isopropyl iodide. The mixture was refluxed for 0.75 hours, boiled with norite, and filtered. The filtrate was cooled, acidified to pH 6 with glacial acetic acid whereupon a tan gum was obtained. The product was recrystallized from morpholine to yield tan crystals, 3.7 g. (28%). Upon recrystallization from benzene a white fluffy solid was obtained, m.p. 127-129°C.

Anal. Calcd. for $C_{11}H_{16}N_4S_2$: C, 49.21; H, 6.01. Found: C, 49.71; H, 6.30.

4,7-Bisbenzylthioimidazo[4,5-d]pyridazine. 4,7-Dithioimidazo-[4,5-d]pyridazine, 9.21 g. (0.05 mole) was dissolved in 175 ml. of 1.25 N potassium hydroxide solution. Twelve and sixty-six one hundredths grams (0.1 mole) of benzyl chloride was added to the rapidly stirred solution and stirring continued for 1 hour. The mixture was boiled with norite and filtered. The filtrate was cooled and acidified to pH 6 with glacial acetic acid, whereupon a tan solid separated. The product was recrystallized from an aqueous-acetic acid mixture (norite) to give light tan needles, m.p. 125°C.

Anal. Calcd. for $C_{19}H_{16}N_4S_2$: C, 62.61; H, 4.42; N, 15.37; S, 17.60. Found: C, 62.16; H, 4.54; N, 15.64; S, 17.80.

4,7-Bis-p-chlorobenzylthioimidazo[4,5-d]pyridazine. 4,7-Dithioimidazo[4,5-d]pyridazine, 9.21 g. (0.05 mole) was dissolved in 40 ml. of 2.5 N potassium hydroxide solution. Twelve and sixty-two one hundredths grams (0.05 mole) of p-chlorobenzyl iodide was dissolved in 45 ml. of 95% ethanol with the aid of heat. This mixture was

added to the basic solution and stirring continued for 1.5 hours. The solution was filtered (gravity) and acidified to pH 6 with glacial acetic acid. A large amount of tar was obtained which solidified after standing one day, 12.12 g. (72%). The solid was recrystallized from glacial acetic acid (norite) to give fine tan needles, m.p. 147-149°C.

Anal. Calcd. for $C_{19}H_{14}N_4S_2Cl_2$: C, 52.65; H, 3.26. Found: C, 52.34; H, 3.16.

4,7-Bis(3,4-dichlorobenzylthio)imidazo[4,5-d]pyridazine. To 60 ml. of 2.5 N potassium hydroxide solution was dissolved 9.21 g. (0.05 mole) of 4,7-dithioimidazo[4,5-d]pyridazine. To this rapidly stirred solution was added 28.7 g. (0.1 mole) of 3,4-dichlorobenzyl iodide in 60 ml. of 95% ethanol. The mixture was stirred 4.5 hours. A solid separated which was removed by filtration. The filtrate was acidified to pH 6 with glacial acetic acid whereupon a large amount of yellow solid was obtained, (15.17 g., 60%). The product was recrystallized from an aqueous-acetic acid mixture to yield a cream colored solid, m.p. 186-187.5°C.

Anal. Calcd. for $C_{19}H_{12}N_4S_2Cl_4$: C, 45.42; H, 2.41; N, 11.15. Found: C, 45.46; H, 2.72; N, 10.91.

4,7-Bis-o-nitrobenzylthioimidazo[4,5-d]pyridazine. 4,7-Dithioimidazo[4,5-d]pyridazine , 9.21 g. (0.05 mole) was dissolved in 150 ml. of concentrated ammonium hydroxide solution. A solution of 8.58 g. (0.05 mole) of o-nitrobenzyl bromide in 25 ml. of dioxane was added to the rapidly stirred alkaline solution over a 15 minute

period. The temperature was kept at 35-40°C. during the addition and stirring was continued for 4.5 hours. Two and five-tenths grams of a solid (22%) was removed by filtration and washed with water. The solid was recrystallized repeatedly from methanol (norite) to give pale yellow needles, m.p. 97-98°C.

Anal. Calcd. for $C_{19}H_{14}N_6S_2O_4$: C, 50.20; H, 3.11. Found: C, 50.34; H, 3.22.

The filtrate from which the above solid was removed was acidified to pH 6 with glacial acetic acid whereupon 9.49 g. of a solid was recovered. This product has not been identified.

4,7-Bis-(2,4-dinitrophenylthio)imidazo[4,5-d]pyridazine. 4,7-Dithioimidazo[4,5-d]pyridazine, 9.21 g., (0.05 mole) was dissolved in 150 ml. of concentrated ammonium hydroxide solution. To this solution was added 10.13 g. (0.05 mole) of 2,4-dinitrochlorobenzene dissolved in 25 ml. of dioxane. The addition was completed in 25 minutes during which time the temperature was maintained at 35-40°C. The reaction mixture was stirred for an additional hour whereupon a large amount of yellow solid was observed. This was removed by filtration, washed with water, and dried in air, 9.99 g. (77%). The yellow solid was recrystallized repeatedly from glacial acetic acid (norite) to give yellow crystals, m.p. 323-324°C.

Anal. Calcd. for $C_{17}H_8N_8O_8S_2$: C, 39.54; H, 1.56. Found: C, 39.24; H, 1.66.

The filtrate from which the above solid was removed was acidified to pH 6 with glacial acetic acid whereupon 4.21 g. of a brown solid was

obtained. This product has not been identified.

4,7-Bis-p-bromophenacylthioimidazo[4,5-d]pyridazine. In 150 ml. of concentrated ammonium hydroxide solution was dissolved 9.21 g. (0.05 mole) of 4,7-dithioimidazo[4,5-d]pyridazine. Thirteen and nine-tenths grams (0.05 mole) of p-bromophenacyl bromide was dissolved in 35 ml. of dioxane and this solution added to the rapidly stirred basic mixture over a 25 minute period. The mixture was stirred for 3 hours whereupon a light brown solid was removed by filtration, 12.8 g. (88%). The solid was recrystallized from dioxane and then aqueous-pyridine to yield pale yellow crystals m.p. 216-217°C.

Anal. Calcd. for $C_{21}H_{14}N_4S_2O_2Br_2$: C, 43.62; H, 2.44. Found: C, 43.36; H, 2.37.

Bis-4(7)-hydroxyimidazo[4,5-d]pyridazine-7(4)-thiol diaquotrinickel(II). In 250 ml. of absolute ethanol was placed 5.52 g. (0.03 mole) of 4,7-dithioimidazo[4,5-d]pyridazine, ten sodium hydroxide pellets, and approximately 12 g. of Raney Nickel. This mixture was refluxed for 5.5 hours. The Raney Nickel was removed by filtration and washed with 5% sodium hydroxide solution. A green solid was observed forming in the suction flask. This was removed by filtration, washed with water, and dried in air. The compound turned brown about 180°C with a loss of water but failed to melt at 360°C.

Anal. Calcd. for $C_{10}H_6N_8S_2O_4Ni_3$: C, 22.14; H, 1.12; N, 20.65; S, 11.82; Ni, 32.45. Found: C, 22.42; H, 1.42; N, 20.57; S, 12.48; Ni, 31.32.

4(5)-Chloro-5(4)-hydrazino-3-pyridazone. Sixteen and five-tenths obtained. This product did not melt below 300°.

[illegible]

[illegible] over a 25 minute period. The mixture was [illegible]

[illegible]

The solid was recrystallized [illegible]

[illegible]

Anal. Calcd. for [illegible] Found:

[illegible]

[illegible]

[illegible]

grams (0.1 mole) of 4,5-dichloro-3-pyridazone was dissolved in boiling methanol (about 300 ml.). To this solution was added 9.62 g. (0.3 mole) of 95%+ hydrazine. After six minutes a yellow precipitate began to appear in the reaction flask. The mixture was refluxed for 1.5 hours, cooled, and the solid removed, 16.2 g. (100%). The solid was recrystallized from hot water (norite) to yield long pale yellow needles which darkened to an orange color upon standing, m.p. 195°C with decomposition.

Anal. Calcd. for $C_4H_5N_4OCl$: C, 29.91; H, 3.14. Found: C, 30.27; H, 3.22.

4(5)-Chloro-5(4)-methylenehydrazino-3-hydroxypyridazine. One and six-tenths grams (0.01 mole) of 4(5)-chloro-5(4)-hydrazino-3-pyridazone was added to 21.5 ml. of formalin. The mixture was swirled occasionally for two hours and a pale yellow solid was observed forming in the reaction mixture. This solid was removed by filtration and dried in air. Upon recrystallization from ethanol two products were obtained. One, a cream colored powder was not identified. The product recrystallized as light yellow needles, m.p. 207°C. with decomposition.

Anal. Calcd. for $C_5H_5N_4ClO$: C, 34.81; H, 2.92; N, 32.47. Found: C, 35.02; H, 3.10; N, 32.68.

Synthesis of Diaryloxazoles.

2-Bromo-1-phenyl-1-propanone. To 160.8 g. of propiophenone (1.2 moles) was added 150 ml. of anhydrous ether and the solution was stirred in an ice bath. To this cold solution was added 1.5 g. of anhydrous aluminum chloride. Over a 45-minute period, 192 g. (1.2 moles)

of bromine was added. Additional ether (150 ml.) was added and the contents poured into water. The ether layer was washed with water until bromide ion was removed, the ether solution dried over anhydrous magnesium sulfate, filtered, and the ether removed under reduced pressure. There was obtained 228 g. (89%) of yellow oil boiling at 135-144°C. (19mm.).

The esters in Table XVIII were prepared by the model procedure illustrated below.

2-Benzoyloxy-1-phenyl-1-propanone. Sodium benzoate, 14.4 g. (0.1 mole), 2-bromo-1-phenyl-1-propanone, 21 g. (0.1 mole), absolute ethanol, 125 ml., and 3 drops of concentrated sulfuric acid were stirred and refluxed for 8 hours. The mixture was poured into 300 ml. of water with stirring and extracted with benzene. The benzene layer was washed with 200 ml. of 1% sodium hydroxide solution and twice with 200 ml. of water. The benzene layer was dried over anhydrous magnesium sulfate, filtered, and the benzene removed under reduced pressure. A white powder (14.9 g.) was obtained. A second crop amounted to 2.6 g. (69% yield). The product was recrystallized from ethyl acetate, m.p. 109-110°C. Temnikova[67] reported 109°C.

4,5-Diphenyl-2-methyloxazole. This compound was prepared according to the procedure of Davidson, Weiss, and Jelling.[58]

4,5-Diphenyl-2-styryloxazole. 4,5-Diphenyl-2-methyloxazole (4.7 g., 0.02 mole), benzaldehyde (15.7 g., 0.148 mole) and zinc

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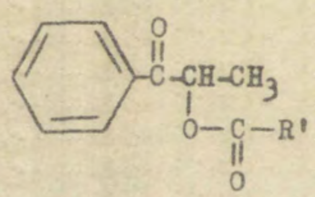
[67] T. I. Temnikova and E. M. Kropacheva, *Doklady Acad. Nauk. S.S.S.R.*, 78, 291 (1951). (*Chem. Abstr.*, 46, 2010^{b}, 1952).

Table XVII

Esters of α-hydroxypropiophenone



R'	M.P.°	Yield, %	Recrystallization Solvent	Formula	C		H		N	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
Phenyl	109-110	69	Ethyl acetate	$C_{16}H_{14}O_3$	76.20	75.70	5.60	5.67		
α-Naphthyl	104.5-105.5	83	Ethyl acetate	$C_{20}H_{16}O_3$	78.90	79.10	5.30	5.56		
β-Naphthyl	105-107	67	Ethyl acetate	$C_{20}H_{16}O_3$	78.94	79.29	5.30	5.44		
2-Quinolyl	121-122	55	Ethyl acetate	$C_{20}H_{15}NO_3$	74.74	74.80	4.95	5.04	4.62	4.95
6-Quinolyl	120-121	62	95% Ethanol	$C_{19}H_{15}NO_3$	74.70	74.30	4.95	5.09	4.62	4.53
4-Pyridyl	112-113	23	95% Ethanol	$C_{15}H_{13}NO_3$	70.60	70.65	5.13	5.36	5.49	5.58
3-Pyridyl	84.5-85.5	trace	50% Ethanol	$C_{15}H_{13}NO_3$	70.60	70.28	5.13	5.30	5.49	5.37
2-Pyridyl	93-94	39	95% Ethanol	$C_{15}H_{13}NO_3$	70.60	70.39	5.13	5.33	5.49	5.75
2,6-Dipyridyl	187-189	5	Ethyl acetate	$C_{25}H_{21}NO_6$	69.60	69.70	4.91	4.90	3.25	3.24

chloride (1.4 g., 0.01 mole) were refluxed for 3 hours under an atmosphere of nitrogen. The solution was cooled, benzene added and the mixture washed three times with water. The benzene layer was dried over anhydrous magnesium sulfate, filtered, and the benzene removed under reduced pressure. The unreacted benzaldehyde was removed by distillation (74°C at 17.5 mm.). The unchanged oxazole was recovered by distillation (165-175°C. at 1 mm.). The residue in the distilling flask was dissolved in 95% ethanol and upon crystallization, 1.9 g. of a yellow-orange powder was obtained (29%). The product was recrystallized from 95% ethanol, m.p. 119-119.5°C. (previously reported 118.5°C.). This compound was previously prepared by direct cyclization by Dornow and Eichholz.[59]

Anal. Calcd. for $C_{23}H_{17}ON$: C, 85.43; H, 5.30; N, 4.33. Found: C, 86.05; H, 5.78; N, 4.16.

This general procedure was used for all the styryloxazoles shown in Table XVIII.

2-Bromomethyl-4,5-diphenyloxazole. 4,5-Diphenyl-2-methyloxazole (11.8 g., 0.05 mole), N-bromosuccinimide (9 g., 0.05 mole), benzoyl peroxide, 2 g., and 40 ml. of dry carbon tetrachloride were refluxed for 6 hours. The mixture was cooled and the succinimide removed by filtration. The carbon tetrachloride was removed under reduced pressure leaving a viscous orange-red liquid, which was purified by distillation, b.p. 170°C. at 0.025 mm., micromelting point 104-106°C.

Anal. Calcd. for $C_{16}H_{12}BrNO$: C, 61.16; H, 3.85. Found: C, 61.35; H, 4.13.

[illegible] (1.4 g., 0.01 mole) [illegible]

atmosphere of nitrogen. The solution was [illegible]

the mixture [illegible] three times with water. The organic layer

[illegible]

[illegible]. The [illegible]

[illegible] 170° at 12.5 mm. [illegible]

[illegible] 175° C. at 1 mm. [illegible]

[illegible]

[illegible], 3.9 g. of a yellow-orange [illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

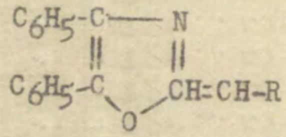
[illegible]

[illegible]

[illegible]

Table XVIII

Styryloxazoles



R	M.P.°	Yield %	Recrystallization Solvent	Formula	C		H		N	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
Phenyl	119-119.5	29	95% Ethanol	$C_{23}H_{17}NO$[59]					4.33	4.16
p -Anisyl	269-271	Trace	95% Ethanol	$C_{24}H_{19}NO_2$	81.55	81.31	5.42	5.13		
o -Hydroxyphenyl	216-217	62	95% Ethanol	$C_{23}H_{17}NO_2$	81.37	81.49	5.05	5.44	4.13	3.95
3,4-Methylenedioxyphenyl	142.5-143	Trace	95% Ethanol	$C_{24}H_{17}NO_3$	78.43	77.93	4.67	4.84		

4,5-Diphenyl-2-hydroxymethyloxazole. 2-Bromomethyl-4,5-diphenyloxazole (15.7 g., 0.05 mole) was dissolved in 100 ml. of 95% ethanol. Silver nitrate, 10 g., was dissolved in 12 ml. of water and this solution was added to the swirled alcoholic solution. The mixture was refluxed on a steam bath for 1 hour, the silver bromide filtered and the ethanol removed on the steam bath. The yellow oil which remained was dissolved in ether and washed several times with water to remove the silver ion. The ether layer was dried over anhydrous magnesium sulfate, filtered, and the ether removed under reduced pressure. It distilled at 151-156°C. at less than 0.1 mm. to yield a viscous yellow liquid.

Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22. Found: C, 76.12; H, 5.53.

Ethyl α-bromobenzoylacetate. This was prepared in a manner similar to α-bromopropiophenone starting with ethyl benzoylacetate. An 88% yield of a yellow oil boiling at 113-133°C. at 0.1 mm. was obtained.[68]

Ethyl-α-benzoyloxybenzoylacetate. This compound was prepared in a manner similar to 2-benzoyloxy-1-phenyl-1-propanone. The cream colored solid was recrystallized from 95% ethanol (75% yield), m.p. 61-62°C.

Anal. Calcd. for $C_{18}H_{16}O_5$: C, 69.24; H, 5.17. Found: C, 69.65; H, 5.45.

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[68] B. W. Howk and S. M. McElvain, J. Am. Chem. Soc., 54, 282 (1932)

Ethyl 2,4-diphenylimidazole-5-carboxylate. This compound was prepared according to the procedure of Davison, Weiss, and Jelling.[58] A cream colored solid (24 g.) was obtained. It was recrystallized from 95% ethanol, m.p. 166-167.5°C.

Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.99; H, 5.52; N, 9.59. Found: C, 73.85; H, 5.67; N, 9.71.

2,4-Diphenyloxazole-5-carboxylic acid. Ethyl 2,4-diphenylimidazole-5-carboxylate (5.86 g., 0.02 mole), potassium hydroxide (1.6 g.), and 50 ml. of water were refluxed. The reflux condenser was equipped with a side arm for the removal of the condensate. The condensate was removed until a negative test was obtained for the presence of ethanol using ceric nitrate reagent. This required 1.75 hours. The solution was filtered and acidified with 5% hydrochloric acid. A white solid, 5.3 g., m.p. 222-223°C, was obtained (quantitative).

Anal. Calcd. for $C_{16}H_{11}NO_3$: C, 72.44; H, 4.18; N, 5.28. Found: C, 72.64; H, 4.41; N, 5.00.

N,N-Dimethylaminopropyl-2,4-diphenyloxazole-5-carboxamide. Potassium 2,4-diphenyloxazole-5-carboxylate (9.1 g., 0.03 mole) was passed through a 100 mesh sieve and dried overnight at 120°C. This was added to 60 ml. of dry benzene in a three neck flask fitted with condenser, mercury seal stirrer, dropping funnel, and drying tube. Over a period of 20 minutes, a solution of 3.8 g. (0.03 mole) of oxalyl chloride in 15 ml. of dry benzene was added to the reaction mixture cooled in an ice bath. This cooled reaction mixture was stirred an additional 30 minutes, the ice bath removed, and the reaction

mixture stirred an additional 3 hours. Dimethylaminopropylamine (3.2 g., 0.031 mole) was mixed with 15 ml. of dry benzene and added over a period of 20 minutes. The mixture was stirred for an additional 15 minutes, and then heated to boiling. The mixture was cooled and a 5% solution of hydrochloric acid was added. The dense yellow precipitate was filtered and the product dissolved in 5% hydrochloric acid solution. The acidic solution was filtered and upon neutralization with ammonium hydroxide, a white precipitate was obtained. The product was recrystallized from ethyl acetate whereupon long white needles separated, m.p. 161.5-163°C.

Anal. Calcd. for $C_{21}H_{23}O_2N_3$: N, 12.02. Found: N, 11.65.

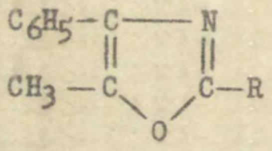
2,4-Diphenyl-5-methyloxazole. To 12.6 g. (0.05 mole) of 2-benzoyloxy-1-phenyl-1-propanone was added 19.3 g. (0.25 mole) of ammonium acetate in 50 ml. of glacial acetic acid. After the mixture had been refluxed for 1 hour, it was poured into ice and water and extracted with ether. The ether was washed with water and the ether layer dried over anhydrous magnesium sulfate. After filtration of the drying agent and evaporation of the ether the crude product was collected. Upon purification by repeated recrystallization from cyclohexane a buff-colored solid (m.p. 108-109.5°) was separated. The 2,4-diphenyl-5-methyloxazole separated upon concentration of the mother liquors, m.p. 74-75°C.

Anal. Calcd. for $C_{16}H_{13}NO$: C, 81.70; H, 5.57; N, 5.95. Found: C, 81.80; H, 5.54; N, 5.58.

The other oxazoles listed in Table XIX were prepared in a similar manner.

Table XIX

Oxazoles



R	M.P.°	Yield %	Recrystallization Solvent	Formula	C		H		N	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
α-Naphthyl	77.5-78.5	53	95% Ethanol	$C_{20}H_{15}NO$	84.20	84.46	5.30	5.54	4.91	5.23
β-Naphthyl	98.5-100	77	95% Ethanol	$C_{20}H_{15}NO$	84.20	84.65	5.30	5.83	4.91	5.20
2-Quinolyl	163-163.5	18	95% Ethanol	$C_{19}H_{14}NO_2$	79.66	79.58	4.93	5.09	9.79	10.33
6-Quinolyl	150-151	49	95% Ethanol	$C_{19}H_{14}NO_2$	79.66	79.64	4.93	5.29	9.79	10.42

The product, m.p. 108-109.5°C., described on page 146 as separating first during the purification proved to be 2-benzoylamido-1-phenyl-1-propanone.

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.86; H, 5.97; N, 5.53. Found: C, 75.60; H, 6.07; N, 5.82.

This compound was characterized by the infrared absorption spectra detailed in the discussion and by the preparation of a semicarbazone.

2-Benzoylamido-1-phenyl-1-propanone semicarbazone. The semicarbazone was prepared by the method of Shriner, Fuson, and Curtin,[69] m.p. 202-203°C.

Anal. Calcd. for $C_{17}H_{18}N_4O_2$: C, 65.77; H, 5.58. Found: C, 65.22; H, 5.63.

1-Phenyl-2-(6-quinolinecarboxoylamido)-1-propanone. This compound was isolated in a manner similar to 2-benzoylamido-1-phenyl-1-propanone during the preparation of 5-methyl-4-phenyl-2-(6-quinolyl)oxazole. This compound was purified by crystallization from ethanol, m.p. 195-197°C.

Anal. Calcd. for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.21. Found: C, 74.80; H, 5.70; N, 8.78.

This compound was characterized by the infrared spectra detailed in the discussion and by the preparation of a semicarbazone.

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69. R. L. Shriner, R. C. Fuson, and D. Y. Curtin, The Systematic Identification of Organic Compounds, 4th Ed., J. Wiley & Sons, Inc., New York, 1956.

The ureas, m.p. 204-205°, [illegible]

separating these, hence the purification procedure [illegible]

[illegible]-1-propanone.

Anal. Calcd. for [illegible]

[illegible]

This compound was characterized by the infrared absorption

bands described in the discussion and by the preparation of a [illegible]

derivative.

[illegible] semicarbazone. The

derivative was prepared by the method of Shriner, Fuson, and Curtin[40],

m.p. [illegible]

Anal. Calcd. for [illegible]

[illegible]

[illegible]. This

compound was isolated as a [illegible]

[illegible] compound during the preparation of [illegible]

[illegible]. This compound was purified by [illegible]

[illegible]

Anal. Calcd. for [illegible]

Found: [illegible]

This compound was characterized by the infrared spectra described

in the discussion and by the preparation of a semicarbazone.

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[40] R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley & Sons, Inc., New York, 1956.

1-Phenyl-2-(6-quinolinecarboxoylamido)-1-propanone semicarbazone. This derivative was prepared in the usual manner, m.p. 209-211°C.

Anal. Calcd. for $C_{20}H_{19}N_5O_2$: C, 66.46; H, 5.30. Found: C, 66.72; H, 5.15.

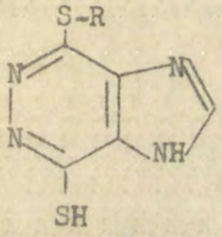
N,N'-Bis(α-benzoylethyl)pyridine-2,6-dicarboxamide. This compound was isolated in a manner similar to 2-benzoylamido-1-phenyl-1-propanone during the attempted preparation of 2,6-bis[2-(5-methyl-4-phenyl)oxazolyl] pyridine, m.p. 211-213°C.

Anal. Calcd. for $C_{25}H_{23}N_3O_4$: C, 69.90; H, 5.40; N, 9.78. Found: C, 70.36; H, 5.69; N, 9.86.

This compound was characterized by the infrared spectra detailed in the discussion.

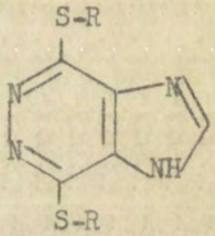
SUMMARY

A total of seventy four new compounds have been prepared. These include forty three imidazo[4,5-*d*]pyridazines, two pyridazines, twelve oxazoles, ten β-keto esters, three β-keto amides, one ketone, and one imidazole. The imidazo[4,5-*d*]pyridazines may be classified into twenty monothio derivatives represented by formula (A), eight dithio derivatives represented by formula (B), ten 4 and (or) 7 amino compounds, and five miscellaneous compounds.



A

R
alkyl,
substituted benzyl,
substituted phenacyl



B

Improved syntheses of 4,7-dihydroxy-, 4,7-dithio-, and 4,7-bismethylthioimidazo[4,5-*d*]pyridazine were devised. An additional attempt was made to prepare imidazo[4,5-*d*]pyridazine which resulted in the formation of a green nickel complex. Both infrared and ultraviolet absorption spectra have been determined for all the compounds and these have been used as an adjunct in the proof of structure of the various compounds.