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The Synthesis and Medicinal Chemical Study of Some Pyridazones

Winnifred M. Osner

THE
SYNTHESIS
OF SOME
PYRIDAZONES

OSNER

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CHEMICAL STUDY OF SOME PYRIDAZONES

By

Winnifred M. Osner

A Dissertation

Submitted in Partial Fulfillment of the

Requirements for the Degree of

Doctor of Philosophy in Chemistry

The University of New Mexico

1962

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

Stewart A. Northrop
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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

Committee

ACKNOWLEDGMENT AND DEDICATION

The author wishes to express sincere appreciation to Dr. R. N. Castle for his advice, encouragement, and patience during this investigation and to Dr. E. W. Rypka for his guidance and aid in interpretation of the biological screening.

The financial assistance provided by the National Institutes of Health, grant number CY 2653, is gratefully acknowledged.

To my mother for never-ending love and confidence and to my daughter, Jill, who has grown up so beautifully in spite of a student-mother, this work is dedicated.

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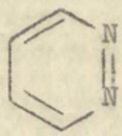
I. INTRODUCTION

An examination of the literature revealed that the majority of pyridazines prepared were substituted in the three and six positions. Therefore, it appeared appropriate to prepare four and five substituted pyridazines.

The facile reaction of hydrazine with 4,5-dichloro-3-pyridazone served as a starting point in this study because of the known physiological activity of many hydrazino derivatives. In this reaction a mono-hydrazino-mono-halopyridazone was obtained which was shown to be 4-halo-5-hydrazino-3-pyridazone by catalytic dehalogenation and subsequent cleavage of the hydrazino moiety with Raney nickel to the previously known 5-amino-3-pyridazone. From 4-chloro-5-hydrazino-3-pyridazone and 4-bromo-5-hydrazino-3-pyridazone a variety of carbonyl derivatives were prepared. In a few instances where dicarbonyl compounds were employed, cyclic products were obtained.

II. REVIEW OF THE LITERATURE

The pyridazine ring system has been far less thoroughly investigated than its structural isomers, pyrimidine and pyrazine, principally because of the limited methods of preparation. The name, pyridazine, (I) was suggested by Knorr[1] to describe the compound resulting from the reaction of ethyl α,α'-diacetosuccinate and phenylhydrazine to which he erroneously assigned the pyridazine structure and which was later shown to be a pyrrole derivative.[2]



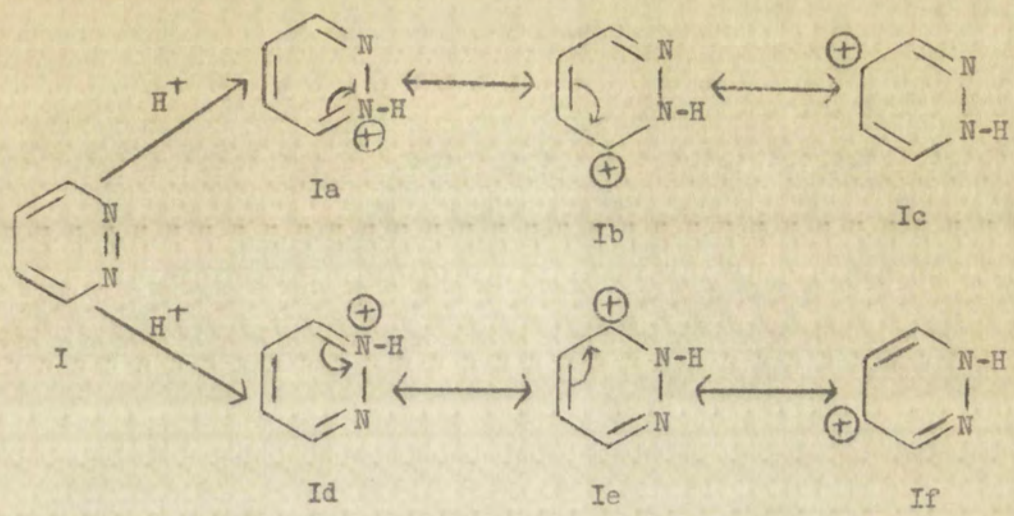
I

Pyridazine is a relatively stable heterocyclic compound, inert to electrophilic substitution. This fact was demonstrated by the experiments of Dixon and Wiggins[3] who attempted to nitrate pyridazine and several of its derivatives under various conditions. Dixon and Wiggins proposed that various resonance forms possessing a fractional positive charge on each of the four carbon atoms were responsible for the failure of these compounds to react with the NO_2^+ ion. On the basis of these

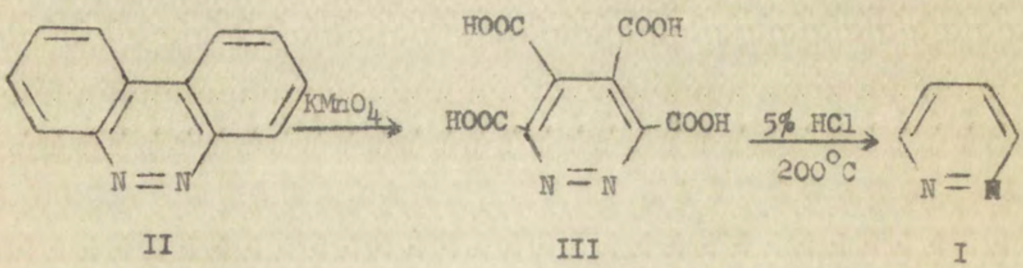
---

1. Knorr, Ber., 18, 304 (1885).
2. Knorr, Ann., 236, 294 (1886).
3. S. Dixon and L. F. Wiggins, J. Chem. Soc., 1950, 3236.

data they account for the inertness of pyridazine and pyridazine derivatives to electrophilic attack.



In as much as it is virtually impossible to substitute the pyridazine ring directly, derivatives are usually prepared from appropriately substituted starting materials or from the degradation of a polycyclic compound containing the pyridazine ring. The first pyridazine was in fact prepared from the oxidation of benzo[c]cinnoline (II) to 3,4,5,6-pyridazinetetracarboxylic acid (III) followed by decarboxylation.[4]



Until recently the known methods of preparation of pyridazines were of four basic types.[5]

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4. Tauber, Ber., 28, 451 (1895).

5. Elderfield: Heterocyclic Compounds, Vol. 6, p. 102.

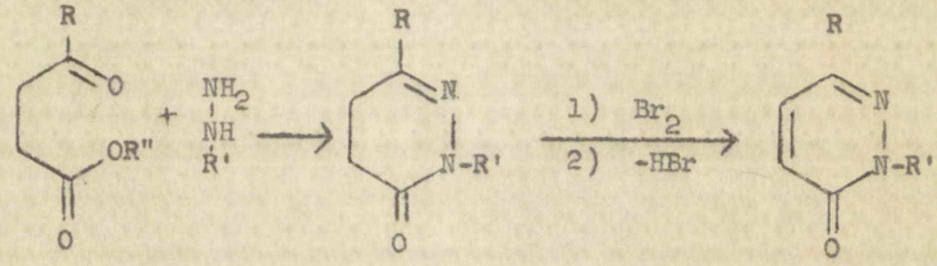
1. Oxidation and decarboxylation of a polycyclic compound as described above.

2. Oxidation of the 4,5-dihydropyridazone resulting from the action of hydrazine or substituted hydrazine on a γ-keto acid or γ-keto ester.

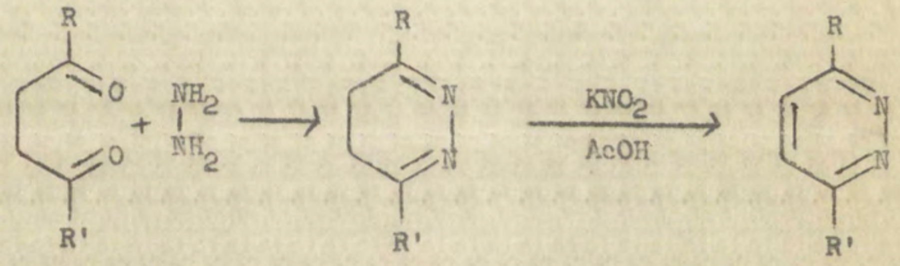
3. Oxidation of the dihydropyridazine formed from hydrazine and a 1,4-dicarbonyl compound.

4. The reaction of hydrazine with a 2,3-unsaturated 1,4-dicarbonyl compound.

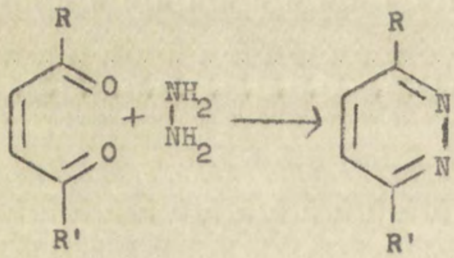
2.



3.



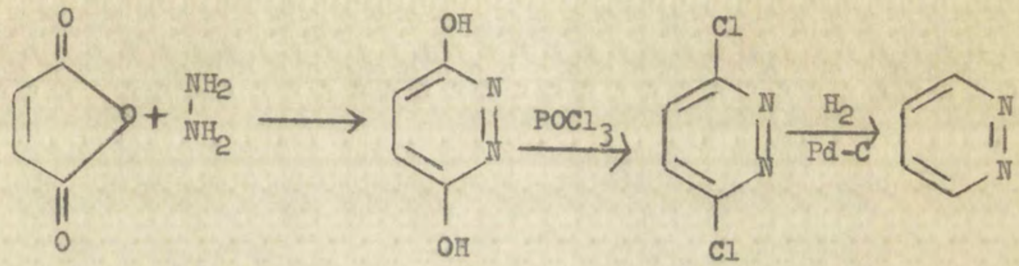
4.



These methods are in the main cumbersome and characterized by poor yields. They follow in general the procedure of Gabriel

and Colman[6,7] and are limited by the availability of the starting materials.

In 1951 Mizzoni and Spoerri[8] described an improved synthesis for pyridazine from maleic anhydride (IV) and hydrazine, first prepared by Curtius and Foersterling.[9] The three step preparation gave an overall yield of 60%.



IV V VI I

A novel new synthesis by Schmidt and Druey[10,11] developed in 1954 involves three simple starting materials, namely, an α-dicarbonyl compound, a carboxylic acid containing an active methylene group and a hydrazine with a minimum of three hydrogen atoms. This method yields a pyridazone which can be converted to a pyridazine. A much greater variety of substituents is

---

6. Gabriel and Colman, Ber., 42, 654 (1909).

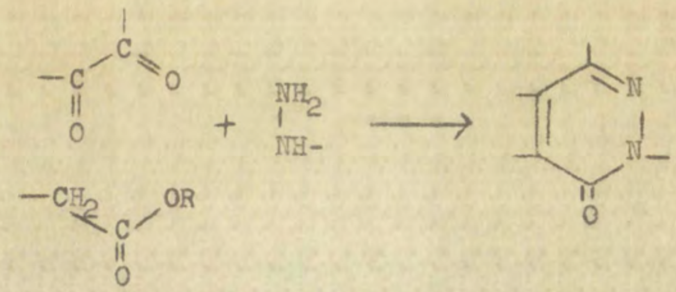
7. Gabriel and Colman, Ber., 32, 395 (1899).

8. R. H. Mizzoni and P. E. Spoerri, J. Am. Chem. Soc., 73, 1873 (1951).

9. T. Curtius and H. Foersterling, J. prak. Chem., 51, 391 (1895).

10. P. Schmidt and J. Druey, Helv. Chim. Acta., 37, 134 (1954).

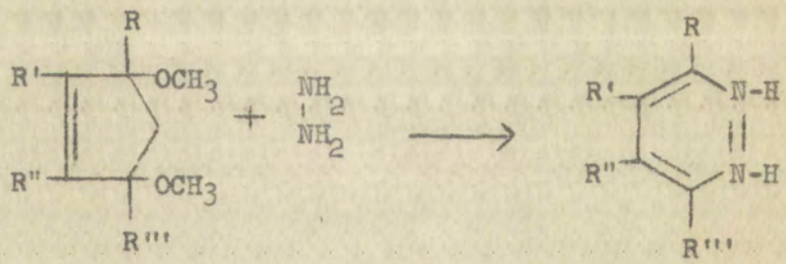
11. P. Schmidt and J. Druey, Helv. Chim. Acta., 37, 1467 (1954).



available using these starting materials. A complete review of the scope of the Schmidt reaction was published in 1958.[12]

Druey[13] and coworkers also reinvestigated the maleic hydrazide preparation of Curtius[9] and successfully prepared a vast number of substituted pyridazones. Utilizing chloromaleic anhydride[14] in a similar manner, the chloropyridazones were studied chemically and pharmacologically.

From the 2,5-dialkoxy-2,5-dihydrofurans (VII) first described by Clauson-Kaas,[15] Levisalles[16,17] prepared 3,4,5,6-tetrasubstituted pyridazines (VIII).



VII VIII

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12. P. Schmidt and J. Druey, Angew. Chem., 1, 5 (1958).

13. J. Druey, et. al., Helv. Chim. Acta., 37, 510 (1954).

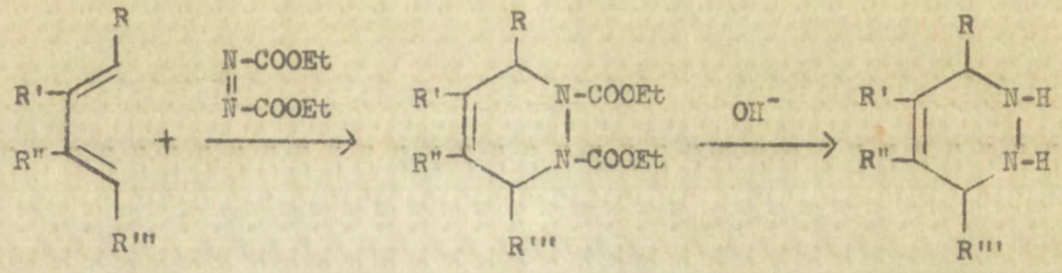
14. Kd. Meier and J. Druey, Helv. Chim. Acta., 37, 523 (1954).

15. N. Clauson-Kaas, Chem. Abstr., 42, 1930 (1948).

16. J. Levisalles, Bull. soc. chim. France, 997 (1957).

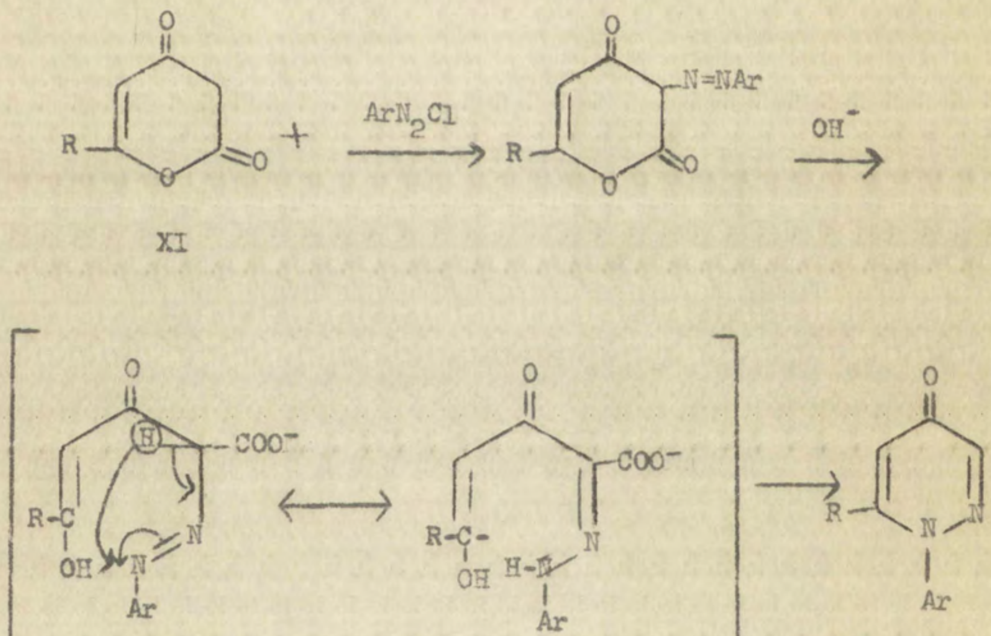
17. J. Levisalles, Bull. soc. chim. France, 1009 (1957).

Levisalles[18] also developed a method of preparation for tetrahydropyridazines (X) from substituted dienes (IX) and ethyl azodicarboxylate.



IX X

An entirely new and unusual synthesis by Morgan[19] yields 4-pyridazones (XII) through the coupling of a pyrandione (XI) and an aryldiazonium compound. Ring cleavage, recyclization and decarboxylation take place in basic solution.



XI XII

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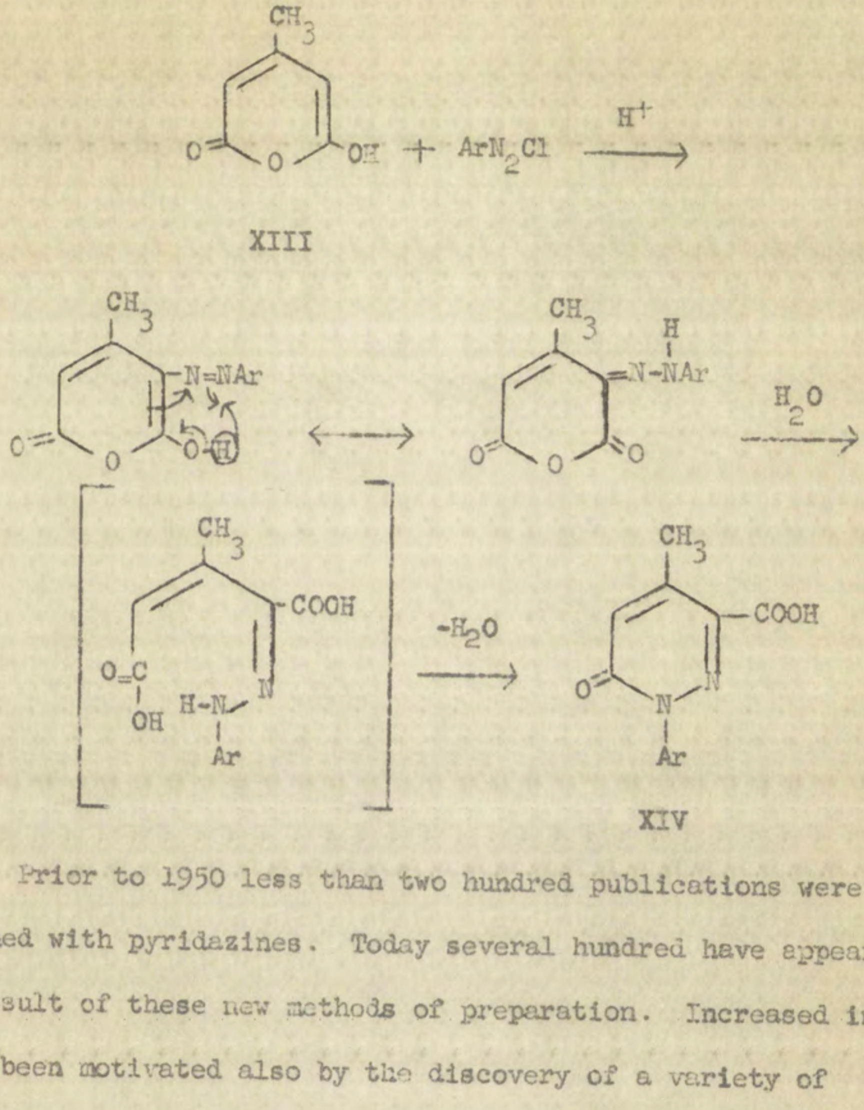
18. J. Levisalles and P. Baranger, Bull. soc. chim. France, 704 (1957).

19. J. F. Morgan, J. Am. Chem. Soc., 70, 2253 (1948).

Similarly, Wiley[20,21] allowed glutaconic anhydride (XIII) to couple with an aryldiazonium salt to produce 2-aryl-5-methyl-3-pyridazone-6-carboxylic acid (XIV).



Prior to 1950 less than two hundred publications were concerned with pyridazines. Today several hundred have appeared as a result of these new methods of preparation. Increased interest has been motivated also by the discovery of a variety of pharmacologically active compounds in this ring system.

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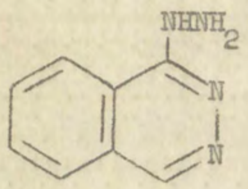
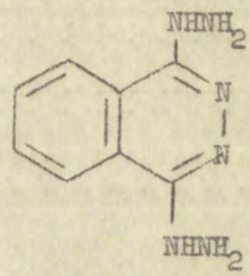
20. R. H. Wiley, J. Am. Chem. Soc., 77, 403 (1955).

21. R. H. Wiley and C. H. Jarboe, J. Am. Chem. Soc., 78, 624 (1956).

In 1951 Druey and Ringer[22] reported the preparation of 1-hydrazinophthalazine (XV). They found that this compound would lower blood pressure in laboratory animals. A year later this compound appeared in the United States as "Apresoline", and the 1,4-dihydrazinophthalazine (XVI) as "Nepresol". Both compounds had been shown to be effective hypotensive agents. These findings prompted Druey[23] and coworkers to prepare the analogous pyridazines.



XV



XVI

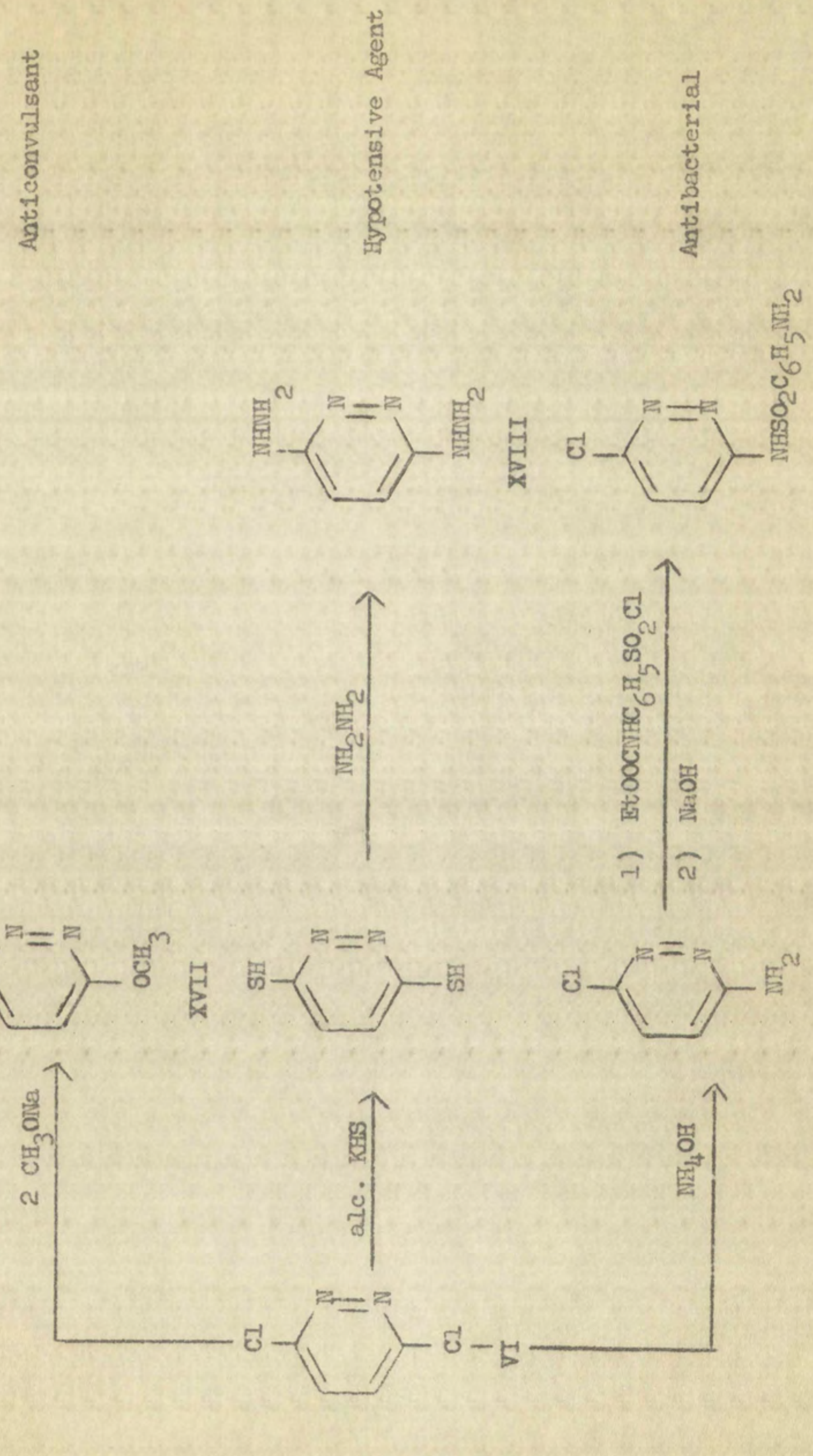
The monohydrazinopyridazine showed only slight activity but the 3,6-dihydrazinopyridazine (XVIII) demonstrated long-lasting blood pressure depressant action which exceeded that of Nepresol on a quantitative basis.

The following scheme illustrates the methods used by Druey, *et. al.*, to obtain three different pyridazines, each of which possessed a different pharmacological activity.

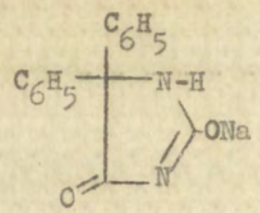
---

22. J. Druey and B. H. Ringer, *Helv. Chim. Acta.*, *34*, 195 (1951).

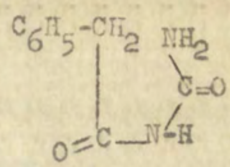
23. J. Druey, Kd. Meier, and K. Eichenberger, *Helv. Chim. Acta.*, *37*, 121 (1954).


Cl
Cl
VI
2 CH3ONa
alc. KHS
NH4OH
OCH3
OCH3
XVII
Anticonvulsant
SH
SH
NH2NH2
NHNH2
NHNH2
XVIII
Hypotensive Agent
Cl
NH2
1) EtOOCNHC6H5SO2Cl
2) NaOH
Cl
NHSO2C6H5NH2
XIX
Antibacterial

The anticonvulsant activity of 3,6-dimethoxypyridazine (XVII) was observed by electroshock test on mice and is especially surprising in as much as the most commonly administered anticonvulsants currently have an amide structure, e.g.:



Diphenylhydantoin Sodium



Phenacemide

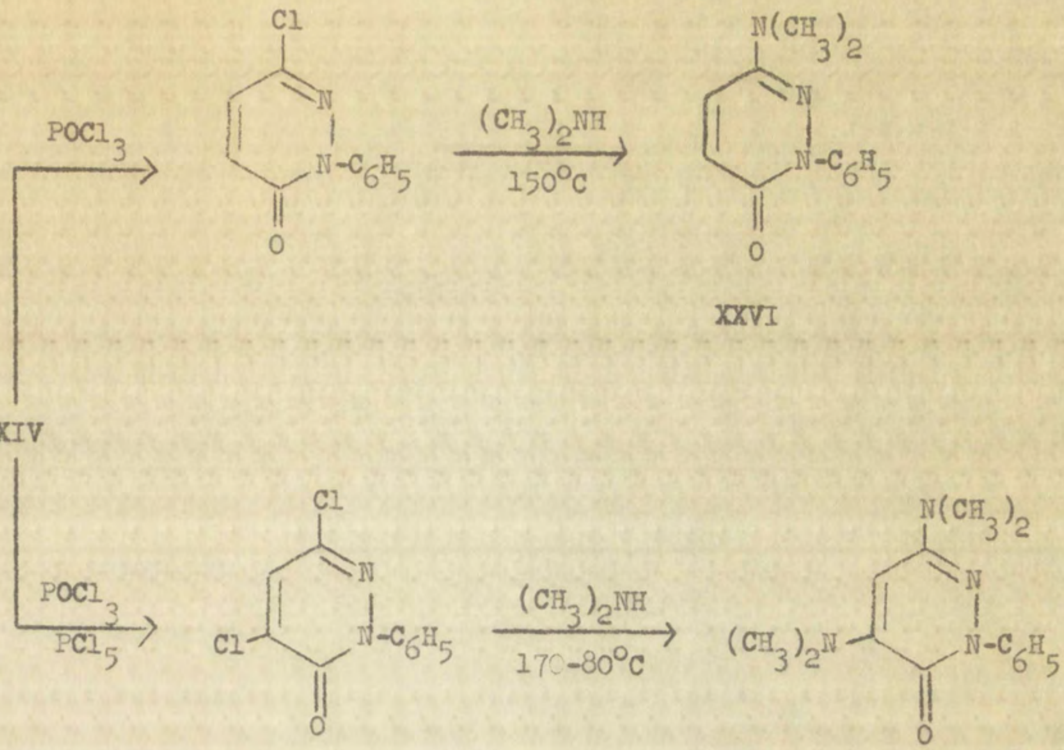
The antibacterial effect of 3-sulfanilamido-6-chloropyridazine (XIX) was demonstrated in vivo in mice.

Starting with levulinic acid and hydrazine, Overend and Wiggins[24] prepared, after several steps, 3-methyl-6-sulfanilamidopyridazine (XX) which showed antibacterial activity greater than sulfathiazole (XXI) on certain organisms. They also prepared the four and five derivatives, namely, 6-methyl-2-phenyl-4-sulfanilamido-3-pyridazone (XXII) and 2,6-dimethyl-5-sulfanilamido-3-pyridazone (XXIII)[25] both of which were found to have only slight antibacterial activity.

---

24. W. G. Overend and L. F. Wiggins, J. Chem. Soc., 1947, 549.

25. W. G. Overend and L. F. Wiggins, J. Chem. Soc., 1948, 2195.



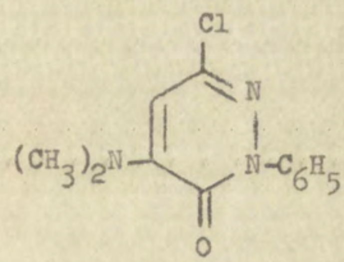
XXIV

XXVI

XXVII

XXVIII

Through a similar sequence of reactions using chloromaleic anhydride, Meier, Ringer, and Druey[14] prepared 6-chloro-4-dimethylamino-2-phenyl-3-pyridazone (XXIX), which also possessed good analgesic and antipyretic activity.



XXIX

Gregory and Wiggins[26] prepared a series of 6-methyl-2-phenyl-3-pyridazones substituted in the four position with different dialkylamino groups (XXX).

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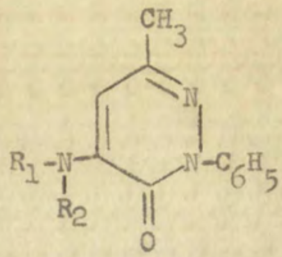
26. H. Gregory and L. F. Wiggins, _J_. _Chem_. _Soc_., _1949_, 2546.



XXX

They were able to show that the presence of such a basic group contributes markedly to the analgesic activity of the compound. When the four position was substituted with a hydroxy, chloro or ethoxy group, analgesic activity was destroyed entirely. When hydrogen occupied the four position, the activity was vastly reduced; but when a basic nitrogen atom in the form of an amino group was present, the activity increased from slight for amino ($R_1=R_2=H$) and dimethylamino ($R_1=R_2=CH_3$) to a maximum with diethylamino ($R_1=R_2=C_2H_5$). The diisopropylamino group ($R_1=R_2=$ $-CH(CH_3)_2$) resulted in reduced activity and when the nitrogen atom was incorporated in a ring such as morpholine or piperidine analgesic activity was lost.

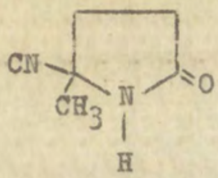
In view of the analgesic activity of the cyclic amide compound (XXXI) reported by Kneter and Richards,[27] Schmidt and Druey[28] prepared the cyclic hydrazide (XXXII) as a potential analgesic agent. Previously Schmidt and Druey[28] and Wiggins[26] had found analgesic activity in pyridazone derivatives which had an alkyl group on one nitrogen atom. It was for this reason that

---

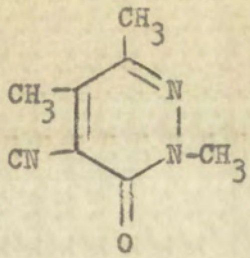
27. K. E. Kneter and R. K. Richards, J. Pharmacol. Exp. Therap., 106, 402 (1952).

28. P. Schmidt and J. Druey, Helv. Chim. Acta., 40, 1749 (1957).

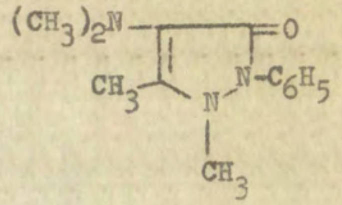
compound (XXXII) was N-methyl substituted. Compound (XXXII) was found to have two to three times the analgesic activity of commercial Pyramidone (XXXIII).



XXXI

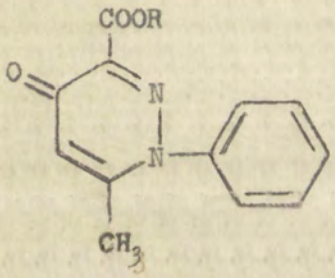


XXXII



XXXIII

The method of Morgan[19] was used by Staehelin, Eichenberger, and Druey[29] to synthesize 6-methyl-1-phenyl-4-pyridazone-3-carboxylic acid from which they prepared a series of previously unknown esters of the general formula (XXXIV).



R = $-CH_3$; $-C_2H_5$;
$-n-C_3H_7$;
$-C_2H_4-O-CH_3$;
$-C_2H_4-O-C_2H_5$

XXXIV

The esters were marked central nervous system stimulants. The activity was found to decrease as the number of carbon atoms in the alcohol moiety increased. The corresponding amide and hydrazide were not active.

Steck, Brundage and Fletcher[30] prepared a series of 3,6-bis quaternary pyridazines as potential neuromuscular blocking

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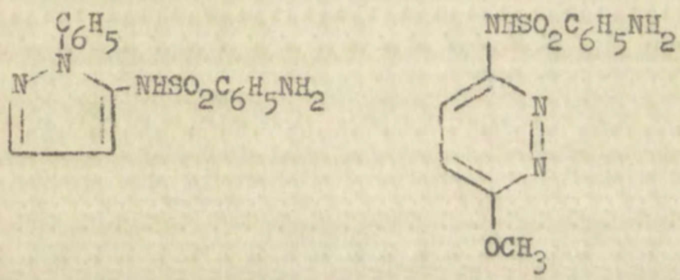
29. A. Staehelin, E. Eichenberger and J. Druey, Helv. Chim. Acta., 39, 171 (1956).

30. E. A. Steck, R. P. Brundage, and L. T. Fletcher, J. Am. Chem. Soc., 76, 4454 (1954).

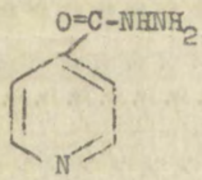
agents. Gesler and Hoppe[31] found that the most active compound of the series was 3,6-bisdiethylaminopropoxypyridazine bis-methiodide (XXXV).

XXXV

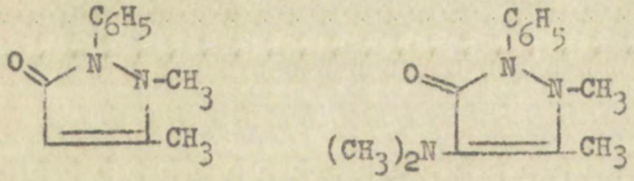
Jucker[32] recently reviewed all of the derivatives of hydrazine in the field of medicinal chemistry. A few of the more important pharmacologically active compounds of this catagory are shown below.



Bacteriostatic



Tuberculostatic



Analgesic and
Antipyretic

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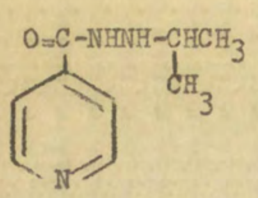
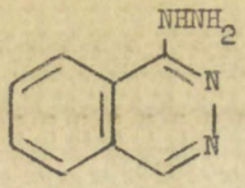
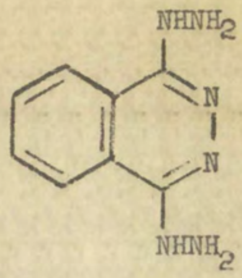
31. R. M. Gesler and J. O. Hoppe, J. Pharmacol. Exp. Therap., 118, 388 (1956).

32. E. Jucker, Angew. Chem., 10, 321 (1959).

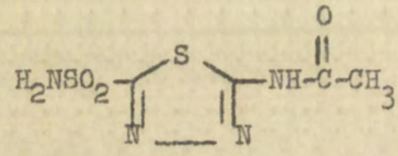


Monoamine oxidase Inhibitor



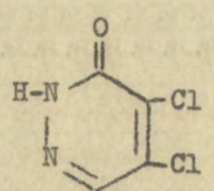


Hypotensive Agents

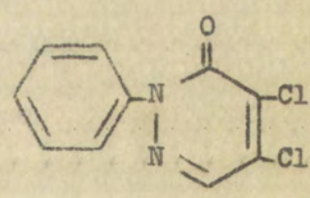


Diuretic

Mowry[33] prepared 4,5-dichloro-3-pyridazone (XXXVI) and 4,5-dichloro-2-phenyl-3-pyridazone (XLV) and both compounds were found to be effective fungicides and bactericides. 4,5-Dichloro-3-pyridazone (XXXVI) inhibited the growth of Mycobacterium tuberculosis at a concentration of two hundred parts per million.



XXXVI



XLV

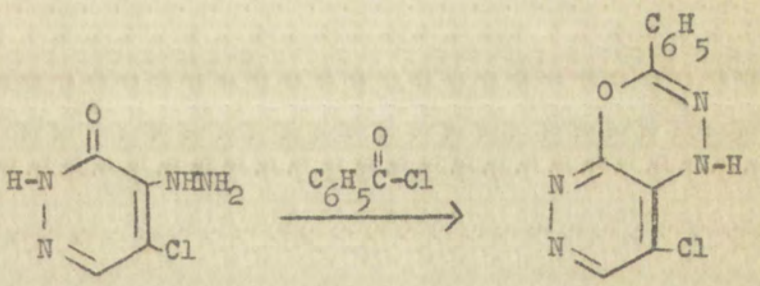
33. D. T. Mowry, Chem. Abstr., 47, 5065 (1953). U. S. Pat. 2,628,181.

III. DISCUSSION

A. Proof of Structure of 4-Chloro-5-hydrazino-3-pyridazone

The Method of Mowry[33] was used to prepare 4,5-dichloro-3-pyridazone (XXXVI) as starting material. When XXXVI was allowed to react with 95% hydrazine in methanol, the compound described by Castle and Aldous[34] was obtained. The product could be either 4-chloro-5-hydrazino-3-pyridazone (XXXVII) or 5-chloro-4-hydrazino-3-pyridazone (XXXVIII). The identity of XXXVII or XXXVIII was confirmed by elemental analysis.

If the product possessed structure XXXVIII, it should cyclize into 5-chloro-2-phenyl-4H-oxadiazino[6,5-c] pyridazine with benzoyl chloride following the procedure of Kuraishi.[35]



XXXVIII XXXVIIIa

In the hands of Castle and Aldous[34] no cyclization product was obtained and this was used as evidence that the product had structure XXXVII. This, however, did not constitute an unequivocal proof of structure. In order to establish

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34. R. N. Castle and D. A. Aldous, unpublished report.

35. T. Kuraishi, Chem. and Pharm. Bull., 6, 331 (1958).

unequivocally that the chlorohydrazinopyridazone had structure XXXVII, the following sequence of reactions was carried out.

When XXXVII was hydrogenated at room temperature in the presence of 5% Pd-C, a pale yellow material was isolated. That this compound was 5-hydrazino-3-pyridazone (XXXIX) was shown by reductive cleavage with Raney nickel to the known 5-amino-3-pyridazone (XL) using a method similar to that of Ueda and Tsuji.[36] A mixed melting point with a sample of XL which had been previously prepared by the method of Kuraishi[35] gave no depression.

5,6-Dichloro-3-pyridazone (XLI) had been prepared in this laboratory by the method of Kuraishi.[37] In order to further study the reactivity of the chlorine atom in the five position, Castle and Kaji[38] allowed XLI to react with 95% hydrazine in methanol and obtained a chlorohydrazinopyridazone. This compound was catalytically dehalogenated into 5-hydrazino-3-pyridazone (XXXIX). This constitutes unequivocal proof that the structure of Dr. Kaji's compound is 6-chloro-5-hydrazino-3-pyridazone (XLII).

These transformations are diagrammed below.

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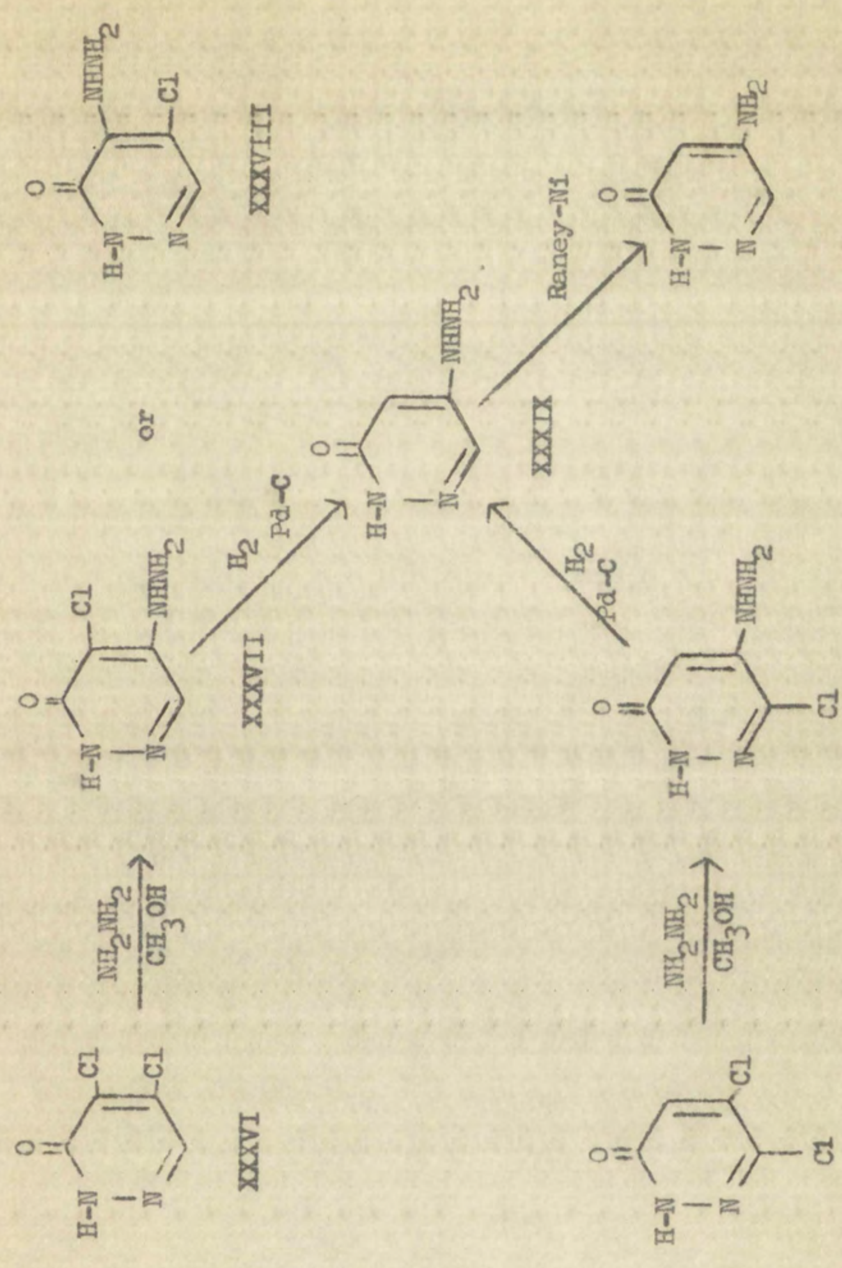
36. T. Ueda and T. Tsuji, Chem. and Pharm. Bull., 9, 71 (1961).

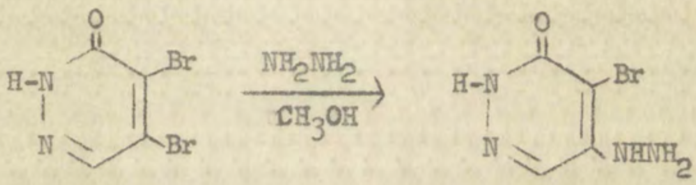
37. T. Kuraishi, Chem. and Pharm. Bull., 6, 646 (1958).

38. R. N. Castle and K. Kaji, unpublished report.


XXXVI
XXXVII
XXXVIII
or
XXXIX
XL
XLI
XLII
H₂ Pd-C
Raney-Ni
NH_2NH_2 / CH_3OH

B. Preparations and Reactions of Related Hydrazino Compounds

4,5-Dibromo-3-pyridazone (XLIII) was prepared in a manner analogous to Mowry's[36] method from mucobromic acid and semicarbazide hydrochloride. Treatment of XLIII with hydrazine gave a product (XLIV) which analyzed for a monohydrazino derivative and was shown to contain halogen. The structure of XLIV is assumed from analogy with the corresponding chloro compound (XXXVII).



XLIII XLIV

The 4,5-dichloro-2-phenyl-3-pyridazone (XLV) of Mowry[33] was prepared and likewise allowed to react with hydrazine to produce either 4-chloro-5-hydrazino-2-phenyl-3-pyridazone (XLVI) or 5-chloro-4-hydrazino-2-phenyl-3-pyridazone (XLVII). The structure (XLVI) is preferred based on analogy and the fact that Sonn[39] showed that 4,5-dibromo-2-phenyl-3-pyridazone (XLVIII) when treated with sodium ethoxide afforded 4-bromo-5-ethoxy-2-phenyl-3-pyridazone (XLIX) exclusively.

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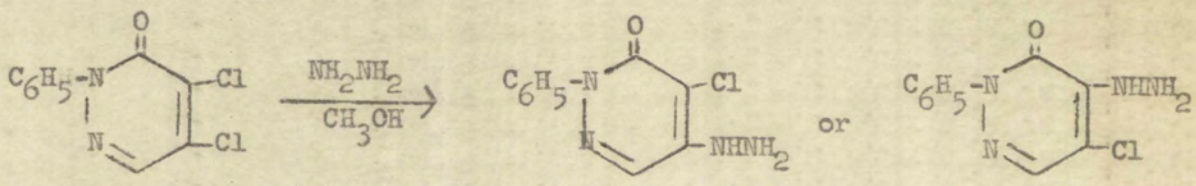
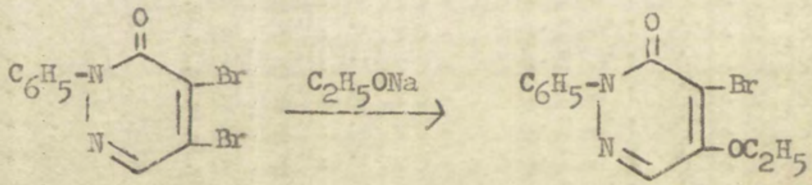
39. A. Sonn, Ann., 518, 290 (1935).



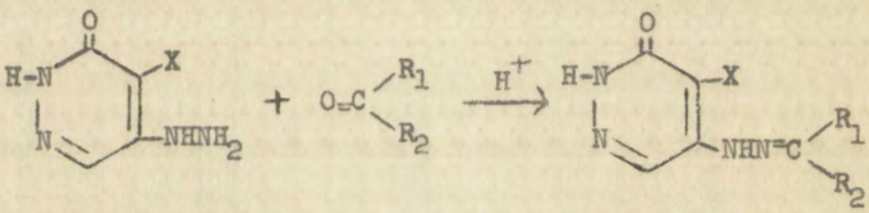
XLV XLVI XLVII



XLVIII XLIX

No further effort has been made to ellucidate the structure of compound (XLVI). Pertinent data on these compounds are listed in Table I.

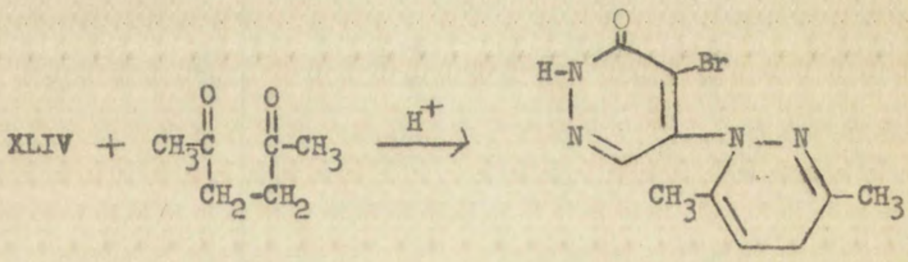
The carbonyl derivatives listed in Table II were nearly all prepared by the standard sulfuric acid method for phenylhydrazone formation. In a few instances the reactants were found to dissolve more readily and the products suffer less decomposition when hydrochloric acid was employed in place of sulfuric acid. The method used is indicated in Table I and Table II.



XXXVII, X=Cl R_1 = alkyl, aryl, H

XLIV, X=Br R_2 = aryl, heterocyclic

When XXXVII or XLIV was allowed to condense with a 1,3 or 1,4-dicarbonyl compound, a cyclized derivative was obtained. Thus, XLIV and 2,5-hexandione gave 4-bromo-5-[1-(3,6-dimethyl-1,4-dihydro)pyridazinyl]-3-pyridazone (L).



L

Likewise 4-chloro-5-[1-(3,5-diphenyl)pyrazolyl]-3-pyridazone (LI) was obtained from XXXVII and dibenzoylmethane. The cyclic derivatives are listed in Table III.

Table I Continued

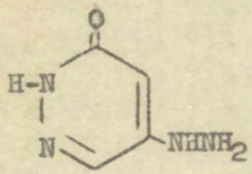
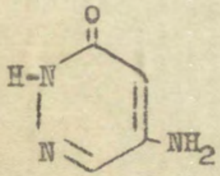
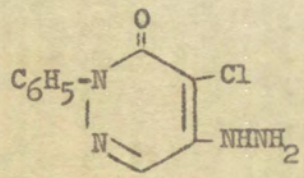
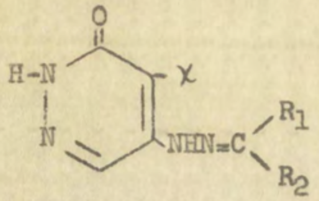
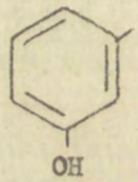
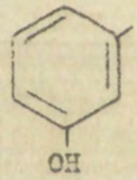
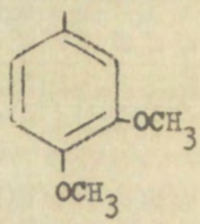
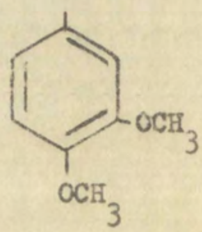
Compound	MP°C	Recrystallization Solvent	Formula	C Calc.	C Found	H Calc.	H Found
 XXXIX	d 259	95% Ethanol	$C_4H_6N_4O$	38.09	38.16	4.79	4.59
 XL	d 289	Water	$C_4H_5N_3O$	43.24	42.94	4.54	4.10
 XLVI	d 164	Methanol	$C_{10}H_9N_4OCl$	50.75	50.47	3.83	3.51

Table II

Derivatives of 4-Halo-5-hydrazino-3-pyridazone

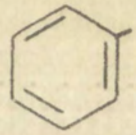
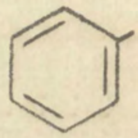
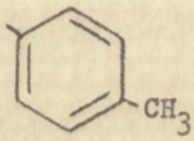
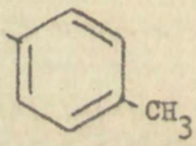
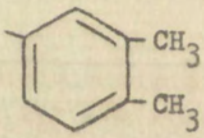
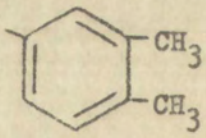
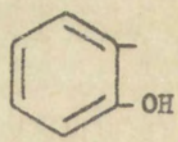
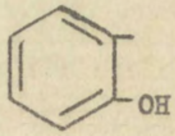
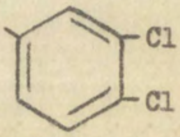


X	R_1	R_2	MP°C
Br	H	C_6H_5-	d 241
*Cl	H	C_6H_5-	d 304
Br	H		d 267
Cl	H		d 298-300
Br	H		d 248
Cl	H		d 276

* Prepared by Castle & Aldous, unpublished data.

Recrystallization Solvent	Formula	C Calc.	C Found	H Calc.	H Found	Method of Prep.
95% Ethanol	$C_{11}H_9N_4OBr$	45.07	44.93	3.09	3.01	A
95% Ethanol	$C_{11}H_9N_4OCl$	53.11	53.30	3.65	3.57	A
95% Ethanol	$C_{11}H_9N_4O_2Br$	42.74	42.49	2.93	2.86	A
95% Ethanol	$C_{11}H_9N_4O_2Cl$	49.91	49.73	3.42	3.21	A
95% Ethanol	$C_{13}H_{13}N_4O_3Br$	44.20	44.19	3.71	3.29	A
95% Ethanol	$C_{13}H_{13}N_4O_3Cl$	50.57	50.55	4.24	4.11	A

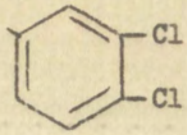
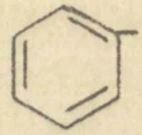
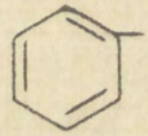
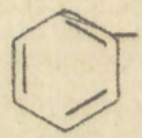
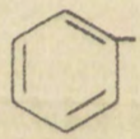
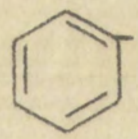
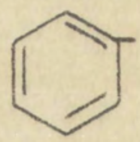
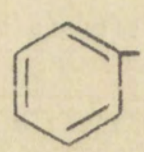
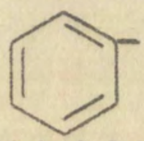
Table II Continued

X	R_1	R_2	MP°C
Br	CH_3		d 220
*Cl	CH_3		d 255
Br	CH_3		d 224
Cl	CH_3		d 280
Br	CH_3		d 220
Cl	CH_3		d 263
Br	CH_3		d 234
Cl	CH_3		d 289
Br	CH_3		d 240

* Prepared by Castle & Aldous, unpublished data.

Recrystallization Solvent	Formula	C Calc.	C Found	H Calc.	H Found	Method of Prep.
95% Ethanol	$C_{12}H_{11}N_4OBr$	46.92	46.96	3.61	3.40	A
95% Ethanol	$C_{12}H_{11}N_4OCl$	54.88	54.66	4.22	3.99	A
95% Ethanol	$C_{13}H_{13}N_4OBr$	48.61	48.70	4.08	3.92	A
Methanol	$C_{13}H_{13}N_4OCl$	56.42	56.29	4.73	4.64	A
95% Ethanol	$C_{14}H_{15}N_4OBr$	50.16	50.29	4.51	4.44	A
95% Ethanol	$C_{14}H_{15}N_4OCl$	57.83	57.81	5.20	4.78	A
95% Ethanol	$C_{12}H_{11}N_4OBr$	44.60	44.79	3.43	3.50	A
95% Ethanol	$C_{12}H_{11}N_4O_2Cl$	51.71	51.58	3.98	3.84	A
95% Ethanol	$C_{12}H_9N_4OBrCl_2$	38.32	38.72	2.41	2.41	A

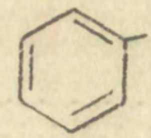
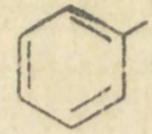
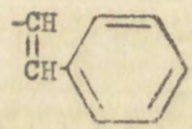
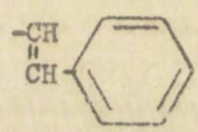
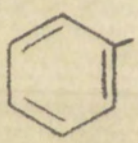
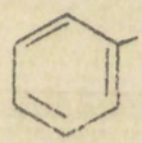
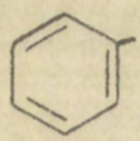
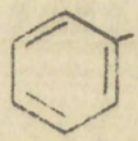
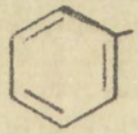
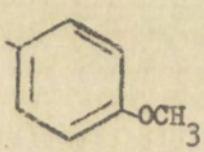
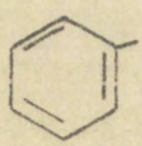
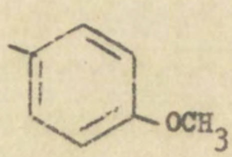
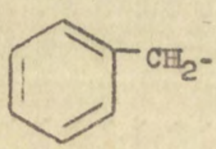
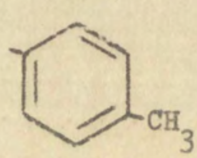
Table II Continued

X	R_1	R_2	MP$^{\circ}$C
Cl	CH_3		d 314
Br	$-CH_2CH_3$		182
*Cl	$-CH_2CH_3$		209-10
Br	$-CH_2CH_2CH_3$		175-6
*Cl	$-CH_2CH_2CH_3$		217-18
Br	$-\underset{\mid}{\overset{CH_3}{}}CHCH_3$		d 221
Cl	$-\underset{\mid}{\overset{CH_3}{}}CHCH_3$		250-1
Br	$-(CH_2)_4CH_3$		151
Cl	$-(CH_2)_4CH_3$		189-90

* Prepared by Castle & Aldous, unpublished data.

Recrystallization Solvent	Formula	C Calc.	C Found	H Calc.	H Found	Method of Prep.
Pyridine: Water	$C_{12}H_9N_4OCl_3$	43.46	43.78	2.74	2.68	A
95% Ethanol	$C_{13}H_{13}N_4OBr$	48.61	48.67	4.03	3.83	A
95% Ethanol	$C_{13}H_{13}N_4OCl$	56.43	56.38	4.74	4.49	A
95% Ethanol	$C_{14}H_{15}N_4OBr$	50.16	50.14	4.51	4.21	A
95% Ethanol	$C_{14}H_{15}N_4OCl$	57.84	57.57	5.20	4.90	A
Abs. Ethanol	$C_{14}H_{15}N_4OBr$	50.16	49.75	4.51	4.25	A
95% Ethanol	$C_{14}H_{15}N_4OCl$	57.83	57.56	5.20	4.95	A
95% Ethanol	$C_{16}H_{19}N_4OBr$	52.90	52.72	5.27	4.97	A
95% Ethanol	$C_{16}H_{19}N_4OCl$	60.27	60.15	6.01	5.68	A

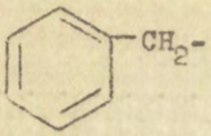
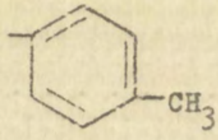
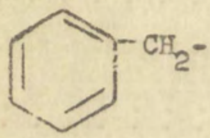
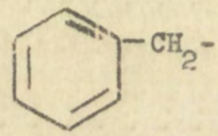
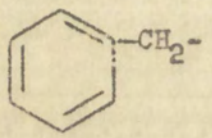
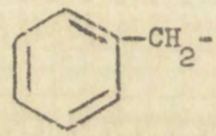
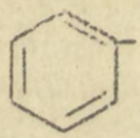
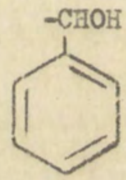
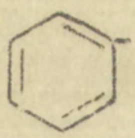
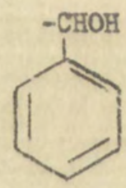
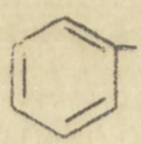
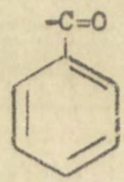
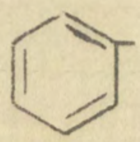
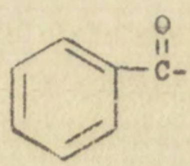
Table II Continued

X	R_1	R_2	MP°C
Br	$-CH=CHCOOH$		d 233
Cl	$-CH=CHCOOH$		d 255
Br	CH_3		d 207
Cl	CH_3		d 214
Br			d 299
Cl			d 304
Br			230-32
Cl			250-52
Br			d 236

Recrystallization Solvent	Formula	C Calc.	C Found	H Calc.	H Found	Method of Prep.
95% Ethanol	$C_{14}H_{11}N_4O_3Br$	46.30	46.36	3.05	2.78	A
95% Ethanol	$C_{14}H_{11}N_4O_3Cl$	52.76	52.62	3.47	3.44	A
95% Ethanol	$C_{14}H_{13}N_4OBr$	50.46	51.02	3.93	3.85	A
95% Ethanol	$C_{14}H_{13}N_4OCl$	58.34	58.96	4.54	4.47	A
95% Ethanol	$C_{17}H_{13}N_4OBr$	55.30	55.46	3.54	3.32	B
95% Ethanol	$C_{17}H_{13}N_4OCl$	62.87	62.87	4.03	4.02	B
Abs. Ethanol	$C_{18}H_{15}N_4O_2Br$	54.15	54.23	3.79	3.52	A
Ethanol: Water	$C_{18}H_{15}N_4O_2Cl$	61.11	61.11	4.27	4.29	A
95% Ethanol	$C_{19}H_{17}N_4OBr$	57.44	57.25	4.31	4.09	A

f. 123

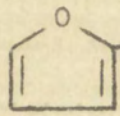
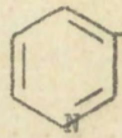
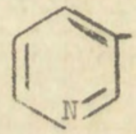
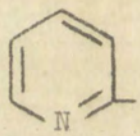
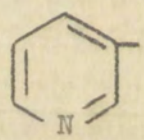
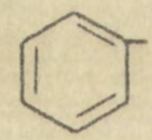
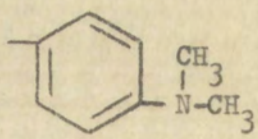
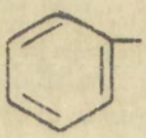
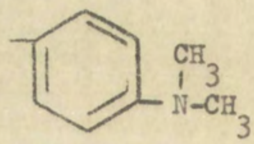
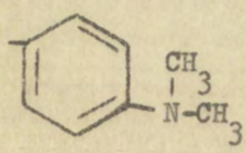
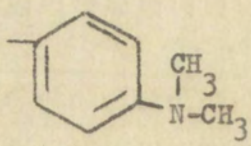
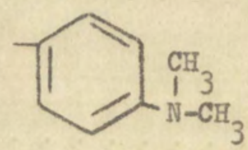
Table II Continued

X	R_1	R_2	MP°C
Cl			d 276
Br			d 192
Cl			205-7
Br			d 240
Cl			d 259
Br			224-5
Cl			d 220

Recrystallization Solvent	Formula	C Calc.	C Found	H Calc.	H Found	Method of Prep.
95% Ethanol	$C_{19}H_{17}N_4OCl$	64.68	64.41	4.86	4.73	A
95% Ethanol	$C_{19}H_{17}N_4OBr$	57.44	57.33	4.31	4.30	A
95% Ethanol	$C_{19}H_{17}N_4OCl$	64.68	64.53	4.86	4.41	A
95% Ethanol	$C_{18}H_{15}N_4O_2Br$	54.15	53.69	3.79	3.31	A
95% Ethanol	$C_{18}H_{15}N_4O_2Cl$	60.93	60.81	4.26	3.93	A
Ethanol: Water	$C_{18}H_{13}N_4O_2Br$	54.42	54.11	3.30	3.06	A
95% Ethanol	$C_{18}H_{13}N_4O_2Cl$	61.28	61.43	3.71	3.55	A

(over)

Table II Continued

X	R_1	R_2	MP°C
Cl	H		d 259
Br	CH_3		d 267
Cl	CH_3		d 280
Br	CH_3		d 251
Cl	H		d 287
Br			d 213
Cl			d 258
Cl			d 253
Cl	H		d 252

Recrystallization Solvent	Formula	C		H		Method of Prep.
		Calc.	Found	Calc.	Found	
95% Ethanol	$C_9H_7N_4O_2Cl$	45.30	45.05	2.96	2.78	A
95% Ethanol	$C_{11}H_{10}N_4OBr$	42.87	43.05	3.27	3.19	B
Pyridine: Water	$C_{11}H_{10}N_4OCl$	50.10	49.80	3.82	3.69	A
Abs. Ethanol	$C_{11}H_{10}N_4OBr$	42.87	42.81	3.27	3.18	B
95% Ethanol	$C_{10}H_8N_5OCl$	48.11	47.63	3.23	3.11	A
95% Ethanol	$C_{19}H_{18}N_5OBr$	55.35	55.34	4.40	4.66	A
95% Ethanol	$C_{19}H_{18}N_5OCl$	62.04	61.53	4.93	4.68	A
Pyridine: Water	$C_{21}H_{23}N_6OCl$	61.38	61.10	5.64	5.18	A
Pyridine: Water	$C_{13}H_{14}N_5OCl$	53.52	53.54	4.84	4.64	A

Table III

Cyclic Derivatives of 4-Halo-5-hydrazino-3-pyridazone

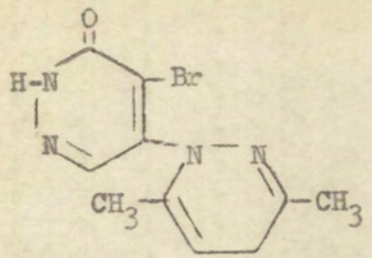
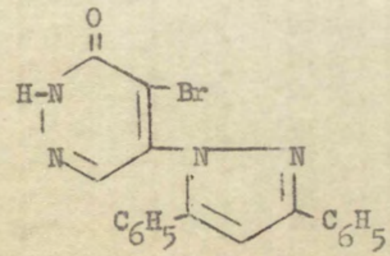
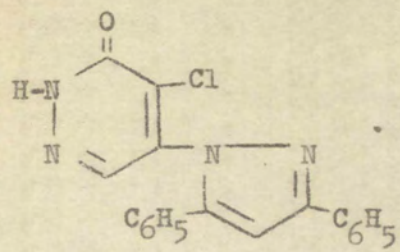
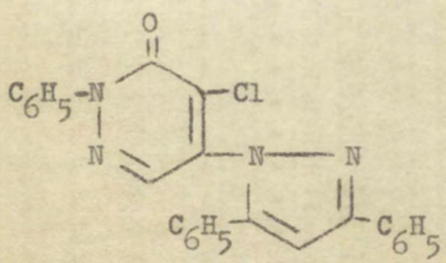
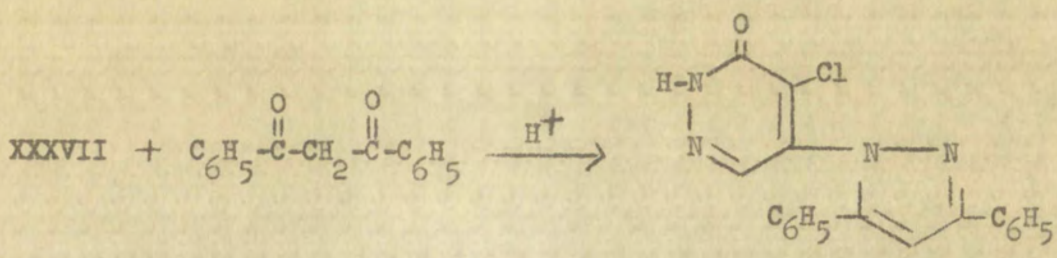
Compound	MP°C	Recrystallization Solvent	Formula	C Calc.	C Found	H Calc.	H Found	Method of Prep.
	d 264	95% Ethanol	$C_{10}H_{11}N_4OBr$	42.42	42.49	3.92	3.39	A
	211-13	95% Ethanol	$C_{19}H_{13}N_4OBr$	58.03	58.14	3.33	2.99	A

Table III Continued

Compound	MP°C	Recrystallization Solvent	Formula	C Calc.	C Found	H Calc.	H Found	Method of Prep.
	209	Ethanol: Water	$C_{19}H_{13}N_4OCl$	65.44	65.51	3.76	3.64	A
	176-8	95% Ethanol	$C_{25}H_{17}N_4OCl$	70.67	70.42	4.03	3.80	A



LI

β-Benzoylacrylic acid when allowed to react with XXXVII or XLIV failed to form a cyclic compound; however, β-benzoylacrylic acid 4-chloro-3-pyridazon-5-ylhydrazone and 4-bromo-3-pyridazon-5-ylhydrazone respectively were obtained. These structures are shown in Table II.

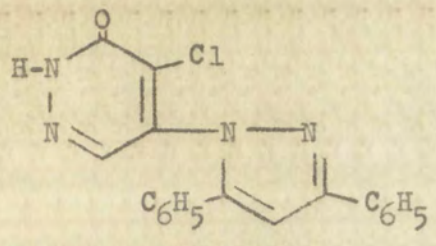
C. Infrared and Ultraviolet Absorption Data

Bellamy[40] points out that the wave lengths of the absorption peaks of the Amide I and Amide II bands are influenced by the nature of the R group adjacent to the carbonyl (C=O) carbon atom as well as by hydrogen bonding. Consistant with this information, it has been observed that the Amide I and Amide II absorption bands for this group of pyridazones vary in the regions 5.9-6.15 μ and 6.4-6.5 μ respectively. These absorption bands undoubtedly arise from the lactam structure of the pyridazones.

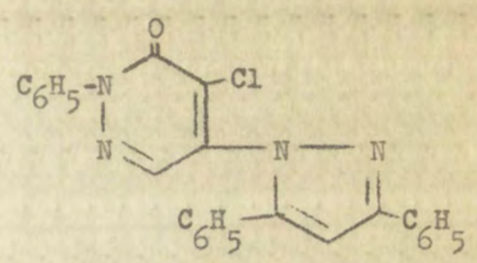
In the instance of 4-chloro-2-phenyl-5-[1-(3,5-diphenyl)-pyrazolyl]-3-pyridazone (LII) (Plate XII) a very strong, sharp Amide I band is observed at 5.96 μ which can only arise from the

40. L. J. Bellamy: <u>The Infrared Spectra of Complex Molecules</u>, p. 203.

lactam structure since this compound cannot exist as the fully aromatic pyridazine. However, the 3-pyridazones unsubstituted on position two, exhibit NH stretching in the 3.0-3.2 μ region, for example, 4-chloro-5-[1-(3,5-diphenyl)pyrazolyl]-3-pyridazone (LI) (Plate XI).



LI

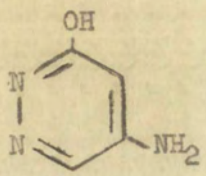


LII

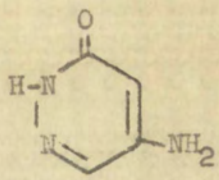
In the case of 4-halo-5-hydrazino-3-pyridazone (XXXVII) or (XLIV), the NH stretching band at 3.1 μ is more intense than in the case of LI as would be expected. Likewise the absorption in the 5.9-6.4 μ region exhibits a broad, diffuse band indicating the combined effects of the Amide I and II bands plus the absorption due to the NH and NH_2 groups.

When the NH_2 group of the hydrazino moiety is converted to the C=N double bond, the broad, diffuse 5.9-6.4 μ absorption band is resolved into two or three sharp absorption peaks (Plates XIII to (LVII).

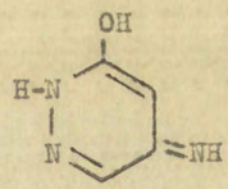
5-Amino-3-pyridazone (XL) (Plates VII and VIII) exhibits a broad, diffuse band from 2.8 μ to 3.3 μ which is indicative of both the OH and NH stretching vibrations. It is suggested that forms XLa and XLb could contribute to the structure of compound XL.



XLa



XL



XLb

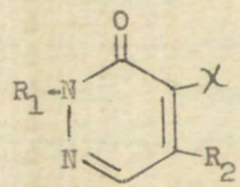
These spectra contribute confirmatory evidence for the structures assigned to the various pyridazones.

The ultraviolet absorption spectra of all the pyridazones were recorded in 95% ethanol. The absorption spectra of selected pyridazones were recorded in acidic or basic media also. These data are listed in Tables IV, V, VI, and VII.

The infrared absorption spectra were recorded as "Nujol" mulls using a Perkin-Elmer Infracord, Model 137. The ultraviolet absorption spectra were recorded using a Bausch and Lomb Spectronic 505 Spectrophotometer.

Table IV

Ultraviolet Absorption Data of Hydrazino and Amino-3-pyridazones



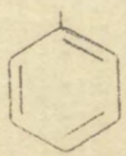
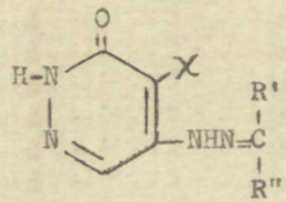
X	R_1	R_2	Neutral λ Max	Neutral $\epsilon \times 10^{-3}$	Neutral λ Min	Neutral $\epsilon \times 10^{-3}$	Base λ Max	Base $\epsilon \times 10^{-3}$	Base λ Min	Base $\epsilon \times 10^{-3}$
Br	H	$-NHNH_2$	224 303	22.15 6.0	255	28.2	224 300	9.25 5.0	256	2.0
Cl	H	$-NHNH_2$	226 302	26.5 6.3	252	2.5	224 290	18.5 6.25	251	3.25
Cl		$-NHNH_2$	207 236 298	17.7 23.6 11.25	216 263	17.0 37.5	226 295	7.03 4.95	258	3.30
H	H	$-NHNH_2$	224 279	26.6 5.3	250	3.0	228 292	7.55 3.78	255	2.25

Table V

Ultraviolet Absorption Data of 4-Halo-5-hydrazino-3-pyridazone Derivatives



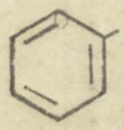
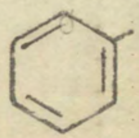
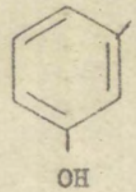
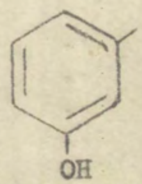
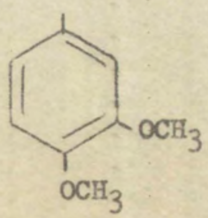
X	R'	R"	Neutral λ Max	Neutral $\epsilon \times 10^{-3}$	Neutral λ Min	Neutral $\epsilon \times 10^{-3}$	Base λ Max	Base $\epsilon \times 10^{-3}$	Base λ Min	Base $\epsilon \times 10^{-3}$
Br	H		205	19.2	213	16.0	232	18.0	272	6.95
			228	23.7	253	5.5	244 D.sh.	15.95	351	13.25
			292 D.sh.	15.5			328	16.12		
			333	34.0			387	23.0		
*Cl	H		205	16.5	213	14.6				
			229	24.3	254	5.0				
			283	13.25						
			332	35.5						

Table V Continued

X	R'	R"	Neutral λ Max	Neutral $\epsilon \times 10^{-3}$	Neutral λ Min	Neutral $\epsilon \times 10^{-3}$	Base λ Max	Base $\epsilon \times 10^{-3}$	Base λ Min	Base $\epsilon \times 10^{-3}$
Br	H		207 228 286 D.sh. 336	25.5 24.5 14.5 34.0	217 258	21.5 6.75				
Cl	H		205 229 288 D.sh. 335	24.2 23.5 13.5 33.0	215 256	20.0 6.0	230 325 382	23.24 18.62 17.05	280 361	8.86 15.6
Br	H		207 230 288 sh. 343	23.4 22.5 14.5 36.25	220 255	20.9 8.15				

85

Table V Continued

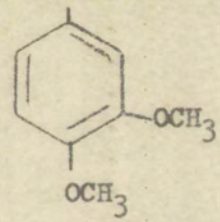
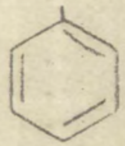
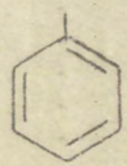
X	R'	R"	Neutral λ Max	Neutral $\epsilon \times 10^{-3}$	Neutral λMin	Neutral $\epsilon \times 10^{-3}$	Base λ Max	Base $\epsilon \times 10^{-3}$	Base λMin	Base $\epsilon \times 10^{-3}$
Cl	H		209	21.5	220	19.25	230	19.25	278	8.5
			231	21.5	255	6.25	339	20.75	363	17.37
			286 sh.	11.75			387	21.55		
			343	38.0						
Br	$-CH_3$		207	17.66	212	15.0	231	19.1	262	9.62
			226	21.0	249	6.3	315	22.4	354	7.65
			285	15.6	293	15.43	378	9.2		
			329	24.6						
*Cl	$-CH_3$		206	15.3	210	15.15				
			227	22.15	249	6.3				
			284	14.6						
			326	25.0						

Table V Continued

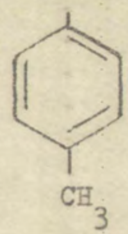
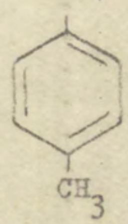
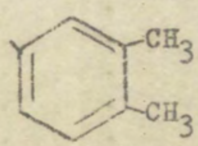
X	R'	R"	Neutral λ Max	Neutral $\epsilon \times 10^{-3}$	Neutral λ Min	Neutral $\epsilon \times 10^{-3}$	Base λ Max	Base $\epsilon \times 10^{-3}$	Base λ Min	Base $\epsilon \times 10^{-3}$
Br	CH_3		203	20.5	213	16.0	230	19.55	262	9.55
			227	22.5	249	7.0	319	22.55	358	6.75
			286 sh.	17.0			379	7.45		
			331	27.0						
Cl	CH_3		203	23.0	213	18.5				
			227	24.5	248	7.5				
			289 sh.	17.0						
			329	27.5						
Br	CH_3		205	24.0	215	18.0				
			228	22.5	250	6.5				
			290 sh.	16.5						
			331	27.0						

Table V Continued

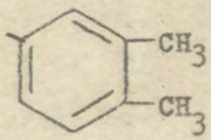
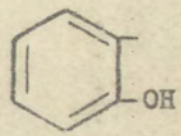
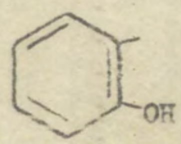
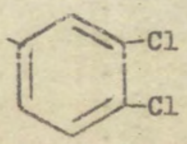
			Neutral				Base			
X	R'	R"	λ Max	∈ x 10^{-3}	λ Min	∈ x 10^{-3}	λ Max	∈ x 10^{-3}	λ Min	∈ x 10^{-3}
Cl	CH_3		204	24.5	214	18.0	229	21.85	263	9.75
			229	23.0	249	7.25	316	21.62	358	6.25
			284 sh.	16.0			375	6.65		
			329	27.5						
Br	CH_3		207	22.0	216	19.25	227	22.35	283	11.45
			229	22.6	252	7.75	264 sh.	12.35		
			285	14.5	298	13.25	310	12.3		
			340	21.5						
Cl	CH_3		206	27.0	217	22.0				
			230	26.5	251	8.5				
			286	15.0	297	14.0				
			339	22.5						
Br	CH_3		206	30.0	219	19.5	222	15.62	278	6.7
			232	22.0	257	7.5	240	15.45	356	5.0
			290 D.sh.	15.0			320	10.12		
			331	31.0			390	7.35		

Table V Continued

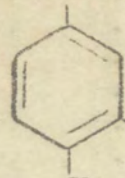
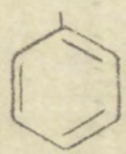
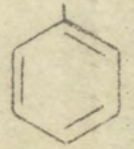
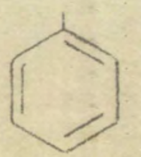
			Neutral				Base			
X	R'	R"	λ Max	∈ x 10^{-3}	λ Min	∈ x 10^{-3}	λ Max	∈ x 10^{-3}	λ Min	∈ x 10^{-3}
Cl	CH_3		205 232 280 D.sh. 330	30.3 23.15 13.0 29.6	219 258	18.5 7.75				
Br	$-CH_2CH_3$		203 226 288 sh. 328	17.5 21.0 15.75 24.75	211 248	14.5 6.1	230 316 379	17.15 22.15 4.8	261 361	6.56 4.5
*Cl	$-CH_2CH_3$		206 226 279 326	16.6 23.0 14.75 26.0	211 249	15.75 6.5				
Br	$-CH_2CH_2CH_3$		205 227 287 sh. 328	17.0 21.2 15.9 24.8	212 249	14.9 6.4	232 316 378 sh.	16.25 21.37 3.32	261	6.8

Table V Continued

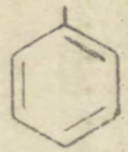
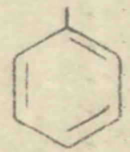
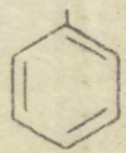
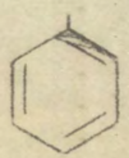
X	R'	R"	Neutral λ Max	Neutral $\epsilon \times 10^{-3}$	Neutral λ Min	Neutral $\epsilon \times 10^{-3}$	Base λ Max	Base $\epsilon \times 10^{-3}$	Base λ Min	Base $\epsilon \times 10^{-3}$
*Cl	$-CH_2CH_2CH_3$		204	17.0	212	15.6				
			227	22.75	250	6.4				
			281	14.6						
			327	25.5						
Br	$-CH(CH_3)-CH_3$		206	17.6	216	15.9				
			228	17.1	236	16.8				
			240	17.0	244	16.9				
			256	19.4	282	11.0				
			312	12.9						
Cl	$-CH(CH_3)-CH_3$		205	17.5	215	16.1	232	21.75	269	14.2
			229 sh.	16.9	245	17.6	255 sh.	15.3		
			240	18.0	279	11.4	290	16.25		
			255	19.4						
			310	13.1						
Br	$-(CH_2)_4CH_3$		204	18.9	212	15.6				
			226	21.6	247	6.5				
			287 sh.	15.8						
			328	24.4						

Table V Continued

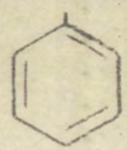
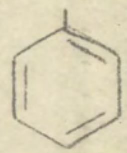
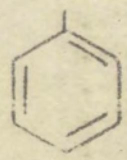
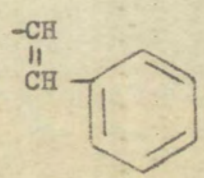
X	R'	R"	Neutral λ Max	Neutral $\epsilon \times 10^{-3}$	Neutral λ Min	Neutral $\epsilon \times 10^{-3}$	Base λ Max	Base $\epsilon \times 10^{-3}$	Base λ Min	Base $\epsilon \times 10^{-3}$
Cl	$-(CH_2)_4CH_3$		204 227 284 sh. 327	16.5 21.6 15.0 24.7	211 249	14.1 6.1	231 315 378 sh.	18.3 22.5 3.3	260	6.7
Br	-CH=CH-COOH		204 221 232 sh. 289 D.sh. 337	22.5 16.66 16.10 14.75 37.5	215 261	16.5 8.25				
Cl	-CH=CH-COOH		206 230 293 sh. 336	20.5 18.25 14.3 37.25	215 261	17.75 8.6	229 333 419	19.0 26.25 13.5	279 373	9.25 6.2
Br	$-CH_3$		206 238 299 D.sh. 345	20.15 16.65 19.4 44.3	222 258	13.9 7.15	239 338 409	15.2 18.95 12.17	276 375	10.95 8.75

Table V Continued

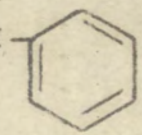
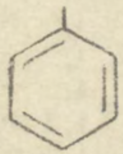
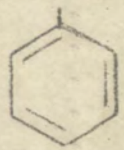
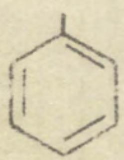
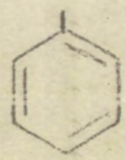
χ	R'	R"	Neutral λ Max	Neutral $\epsilon \times 10^{-3}$	Neutral λ Min	Neutral $\epsilon \times 10^{-3}$	Base λ Max	Base $\epsilon \times 10^{-3}$	Base λ Min	Base $\epsilon \times 10^{-3}$
Cl	$-CH_3$	-CH=CH– 	206 238 297 D.sh. 345	18.5 16.5 17.8 44.9	222 257	12.3 6.5				
Br			205 228 292 D.sh. 334	28.5 25.4 14.2 29.7	215 260	19.0 7.20				
Cl			205 229 285 D.sh. 332	29.75 26.75 13.25 30.3	215 260	19.65 7.25	227 326 392 sh.	24.9 23.8 2.3	273	9.9

Table V Continued

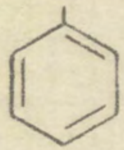
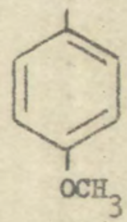
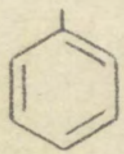
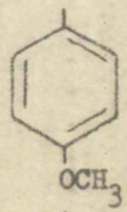
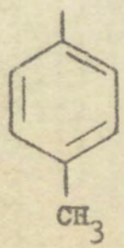
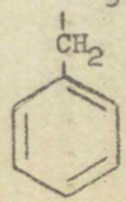
			Neutral				Base			
χ	R'	R"	λ Max	∈ x 10^{-3}	λ Min	∈ x 10^{-3}	λ Max	∈ x 10^{-3}	λ Min	∈ x 10^{-3}
Br			205 231 295 sh. 341	34.65 24.25 14.75 32.75	219 271	22.25 11.0				
Cl			206 231 296 sh. 340	34.65 25.0 14.65 33.25	219 270	22.25 11.15	229 254 sh. 330	28.5 16.0 26.8	273	12.6
Br			203 228 288 sh. 331	32.8 25.2 16.4 28.0	217 250	21.75 8.5				

Table V Continued

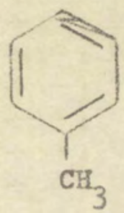
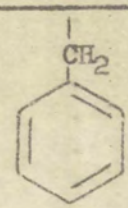
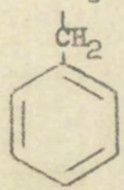
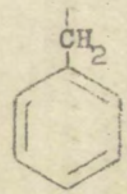
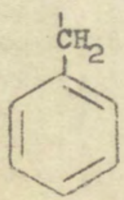
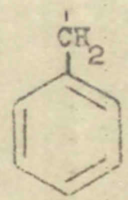
			Neutral				Base			
χ	R'	R"	λ Max	$\epsilon \times 10^{-3}$	λ Min	$\epsilon \times 10^{-3}$	λ Max	$\epsilon \times 10^{-3}$	λ Min	$\epsilon \times 10^{-3}$
Cl			204 229 286 sh. 329	33.3 25.6 15.5 27.5	219 250	22.75 8.25				
Br			209 256 310	27.7 24.2 12.8	235 275	12.0 9.3				
Cl			208 254 309	29.25 25.5 13.75	235 278	13.3 10.5	224 258 288	19.9 15.65 13.95	245 272	14.37 12.75

Table V Continued

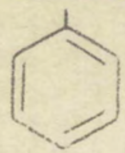
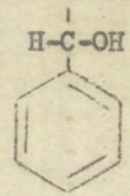
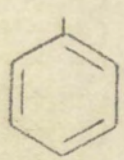
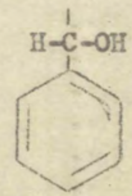
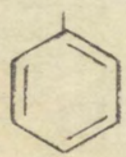
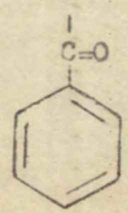
			Neutral				Base			
χ	R'	R"	λ Max	$\epsilon \times 10^{-3}$	λ Min	$\epsilon \times 10^{-3}$	λ Max	$\epsilon \times 10^{-3}$	λ Min	$\epsilon \times 10^{-3}$
Br			205 228 285 sh. 333	26.65 24.5 13.25 27.75	216 251	20.5 7.25				
Cl			205 229 284 sh. 331	26.75 25.0 12.85 28.25	217 250	20.65 6.75	227 328	24.55 20.5	263	8.2
Br			206 222 266 334	28.5 23.8 15.65 23.0	216 244 294	23.65 13.25 13.75				

Table V Continued

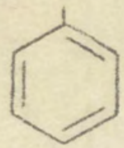
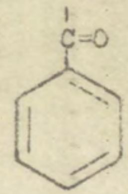
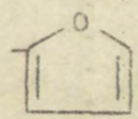
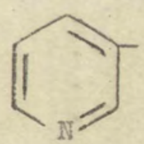
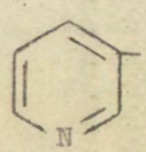
			Neutral				Base			
X	R'	R"	λ Max	$\epsilon \times 10^{-3}$	λ Min	$\epsilon \times 10^{-3}$	λ Max	$\epsilon \times 10^{-3}$	λ Min	$\epsilon \times 10^{-3}$
Cl			205 225 266 330	29.25 24.0 17.9 21.25	218 242 292	23.25 12.75 14.75	224 252 429	16.9 14.5 33.0	240 339	14.0 5.4
Cl	H		207 225 288 D.sh. 339	17.0 13.75 11.75 32.3	220 250	13.6 4.25	236 340 D.sh. 388	14.0 15.8 29.15	221 277	0.50 7.0
Br	$-CH_3$		206 226 285 sh. 328	13.5 16.5 13.5 26.4	209 252	13.0 7.0	230 318 386	15.0 15.25 13.25	273 351	8.6 8.6
Cl	$-CH_3$		206 sh. 228 284 sh. 327	13.65 19.15 13.25 27.4	253	7.75				

Table V Continued

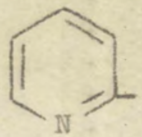
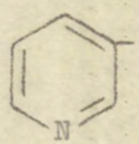
X	R'	R"	Neutral λ Max	Neutral $\epsilon \times 10^{-3}$	Neutral λ Min	Neutral $\epsilon \times 10^{-3}$	Base λ Max	Base $\epsilon \times 10^{-3}$	Base λ Min	Base $\epsilon \times 10^{-3}$
Br	$-CH_3$		206	21.25	215	18.7	228	14.82	262	8.5
			228	22.4	252	7.75	332	15.87		
			285	14.0	297	12.9	392 D.sh.	8.45		
			341	20.8						
Cl	H		203	14.25	211	12.5	234	16.3	278	6.9
			229	17.0	256	6.4	333	12.3	349	11.55
			277 D.sh.	11.15			397	24.87		
			333	35.7						
Br	$-CH_2CH_2-$	$-CH_2CH_2-$	219	14.6	232	10.6	233	16.45	242	15.7
			255	24.4	278	7.7	255	17.37	272	11.07
			312	11.6			288	12.07		
*Cl	$-CH_2CH_2-$	$-CH_2CH_2-$	218	14.75	232	10.1				
			254	24.9	278	7.6				
			313	11.3						

Table VI

Ultraviolet Absorption Data of 4-Halo-5-hydrazino-3-pyridazone Derivatives

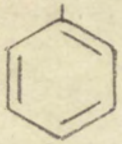
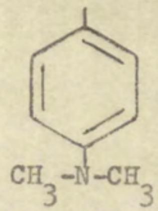
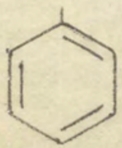
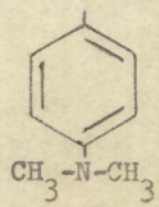
			Neutral				Acid			
X	R'	R"	λ Max	$\epsilon \times 10^{-3}$	λ Min	$\epsilon \times 10^{-3}$	λ Max	$\epsilon \times 10^{-3}$	λ Min	$\epsilon \times 10^{-3}$
Br			207 240 D.sh. 277 D.sh. 373	34.65 17.0 13.25 35.0	298	9.75				
Cl			206 243 D.sh. 275 D.sh. 372	36.0 17.25 13.8 35.5	297	10.0	207 253	33.9 19.25	229	10.9

Table VI Continued

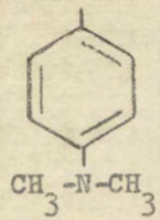
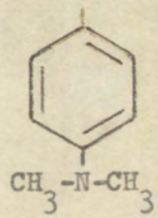
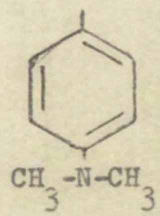
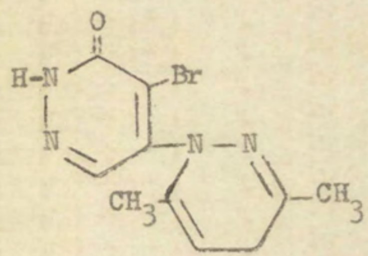
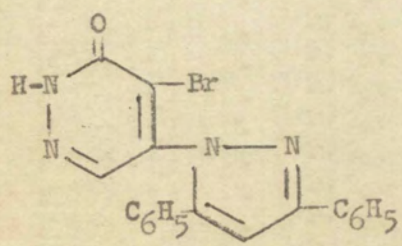
X	R'	R"	Neutral λ Max	$\epsilon \times 10^{-3}$	λ Min	$\epsilon \times 10^{-3}$	Acid λ Max	$\epsilon \times 10^{-3}$	λ Min	$\epsilon \times 10^{-3}$
Cl			208 264 320 D.sh. 374	42.75 24.5 23.65 34.25	243 288	22.5 16.6	206 221 245 D.sh. 337	32.25 28.7 19.0 17.0	214 299	26.85 9.2
Cl	H		206 222 314 D.sh. 368	19.5 18.5 14.5 41.5	213 283	18.0 7.0	205 229 283 sh. 334	19.45 18.55 8.55 24.0	213 260	14.62 5.5

Table VII

Ultraviolet Absorption Data of Cyclic Derivatives of 4-Halo-5-hydrazino-3-pyridazone

Compound	Neutral				Base			
	λ Max	$\epsilon \times 10^{-3}$	λ Min	$\epsilon \times 10^{-3}$	λ Max	$\epsilon \times 10^{-3}$	λ Min	$\epsilon \times 10^{-3}$
	221 287	39.15 8.0	252	4.3	225 274	24.12 6.57	254	5.07
	206 248 299	43.0 34.3 11.65	222 280	23.1 10.25				

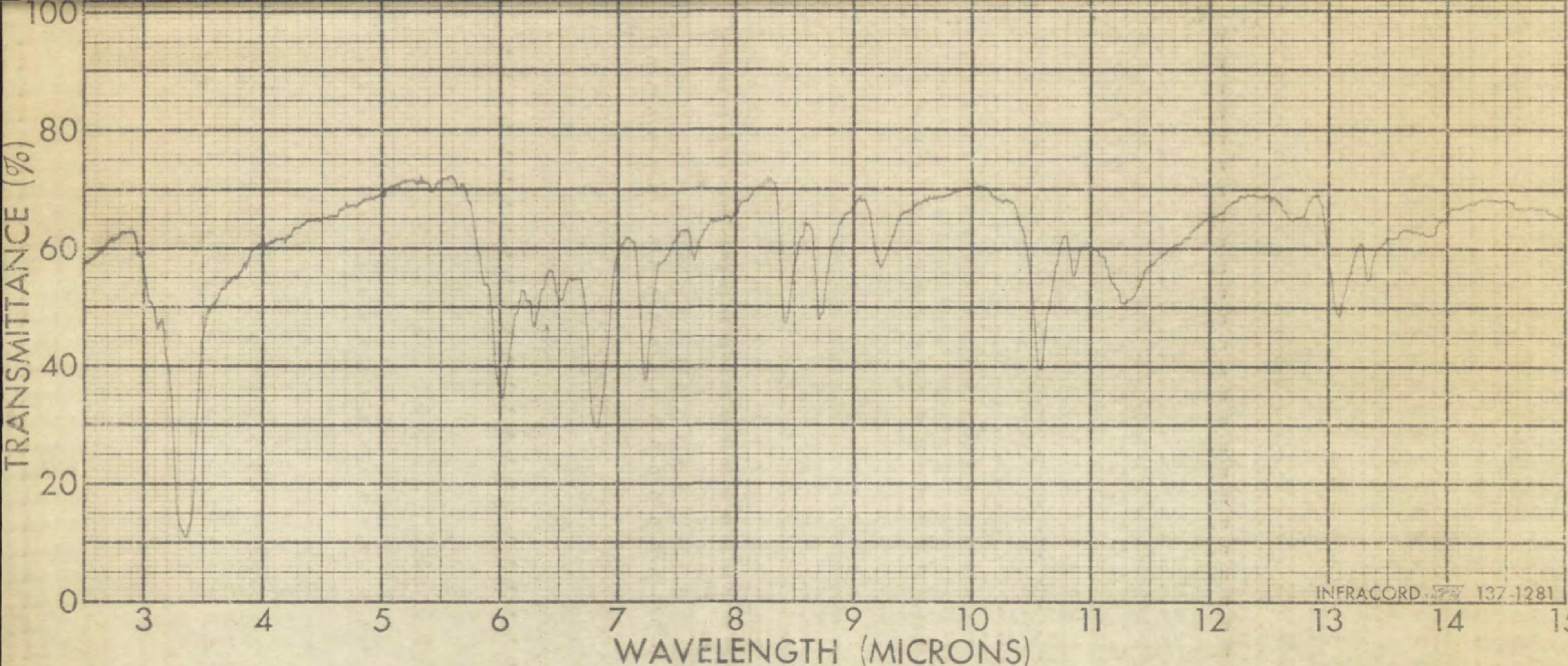
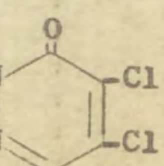


Plate I: Infrared Spectrum of 4,5-Dichloro-3-pyridazone



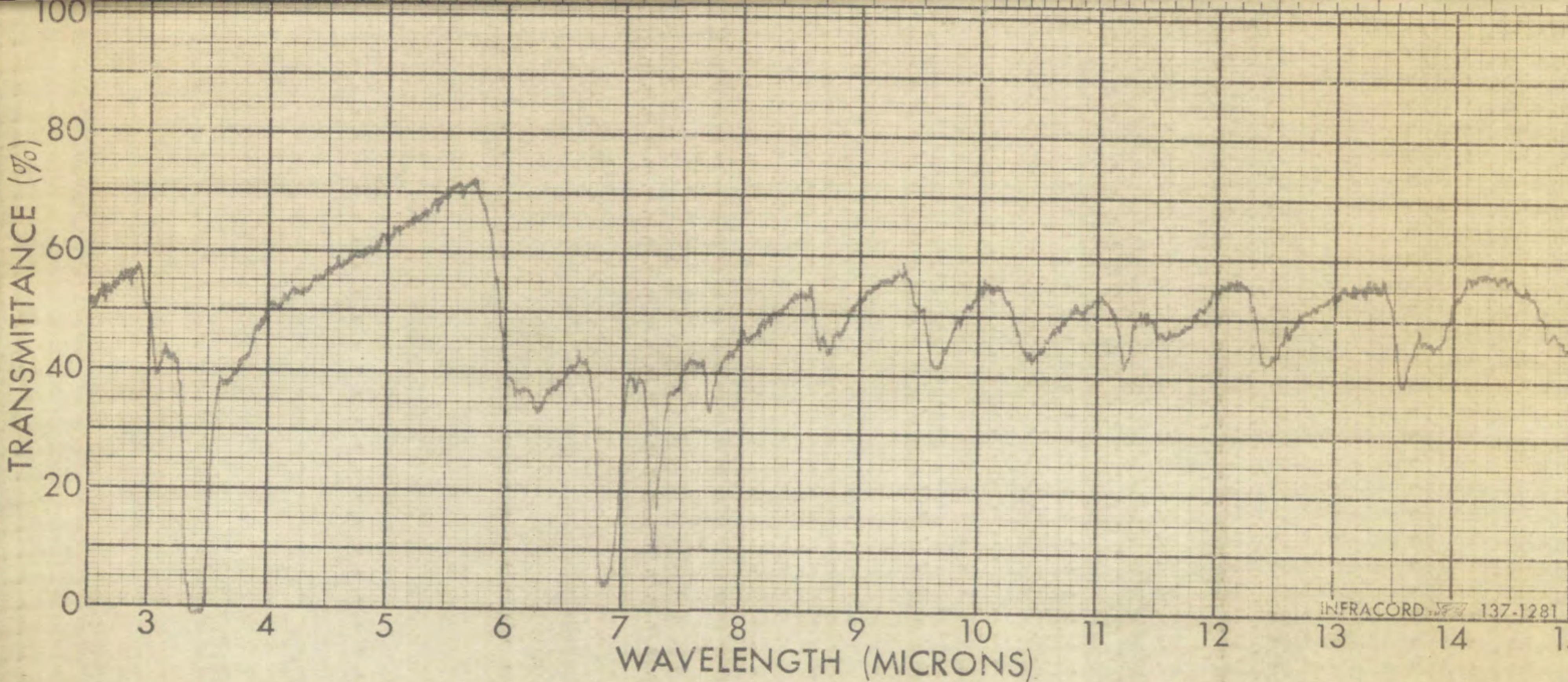
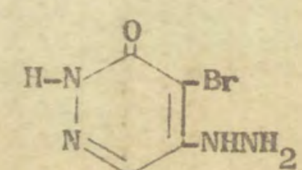


Plate II: Infrared Spectrum of 4-Bromo-5-hydrazino-3-pyridazone



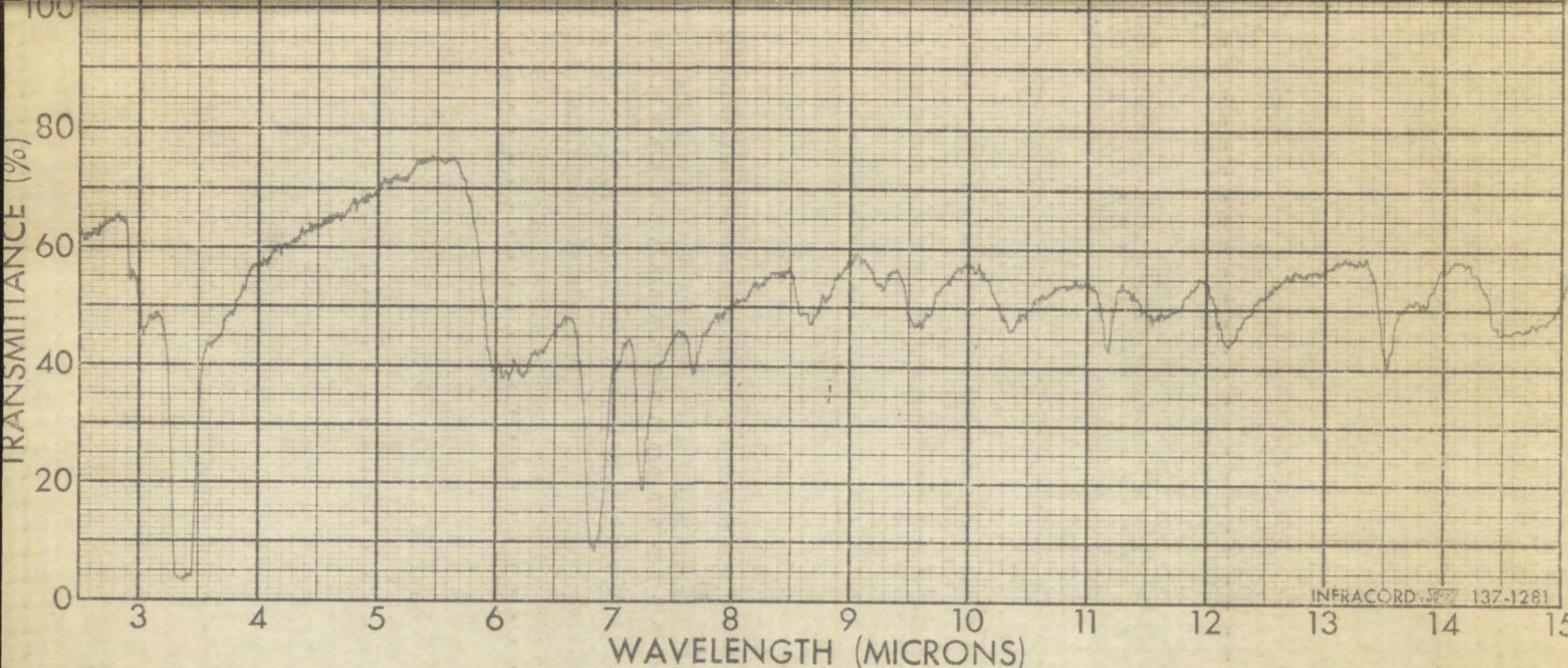
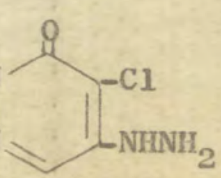


Plate III: Infrared Spectrum of 4-Chloro-5-hydrazino-3-pyridazone



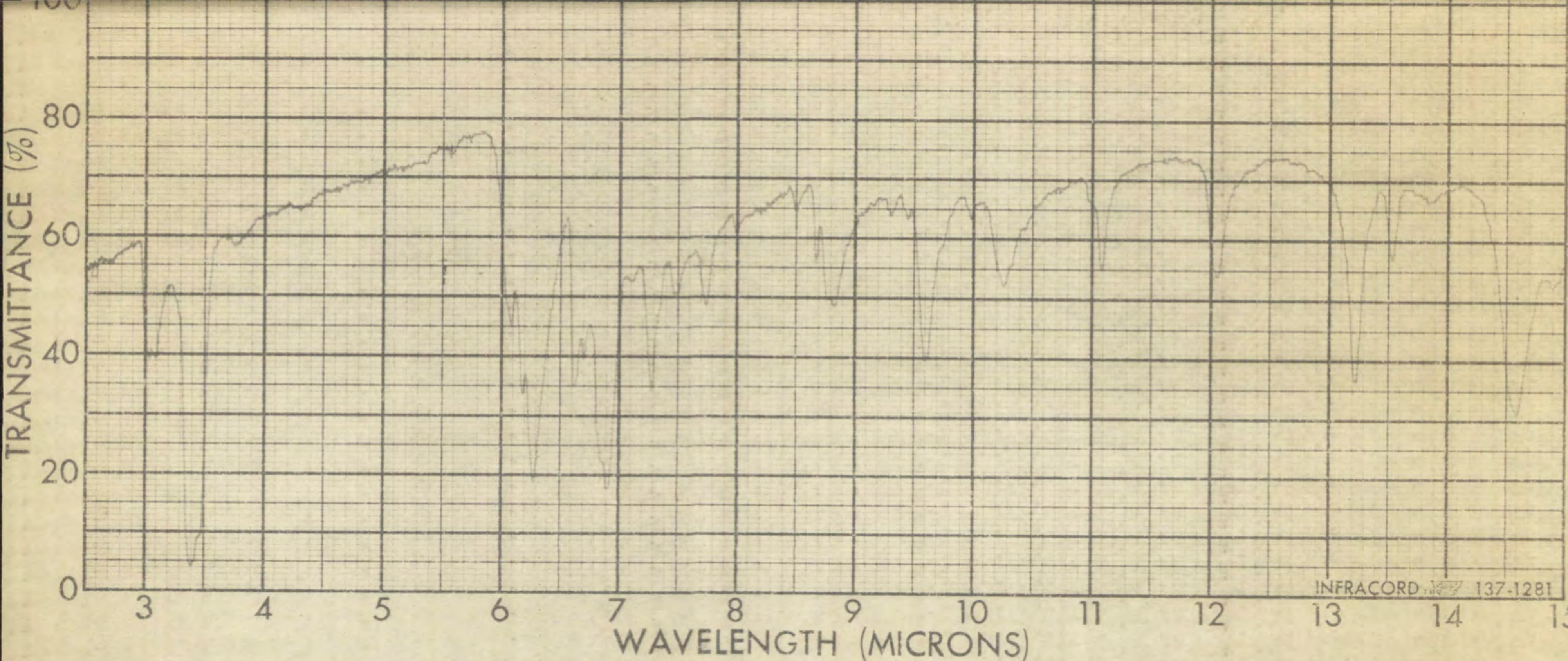
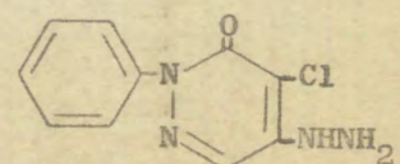
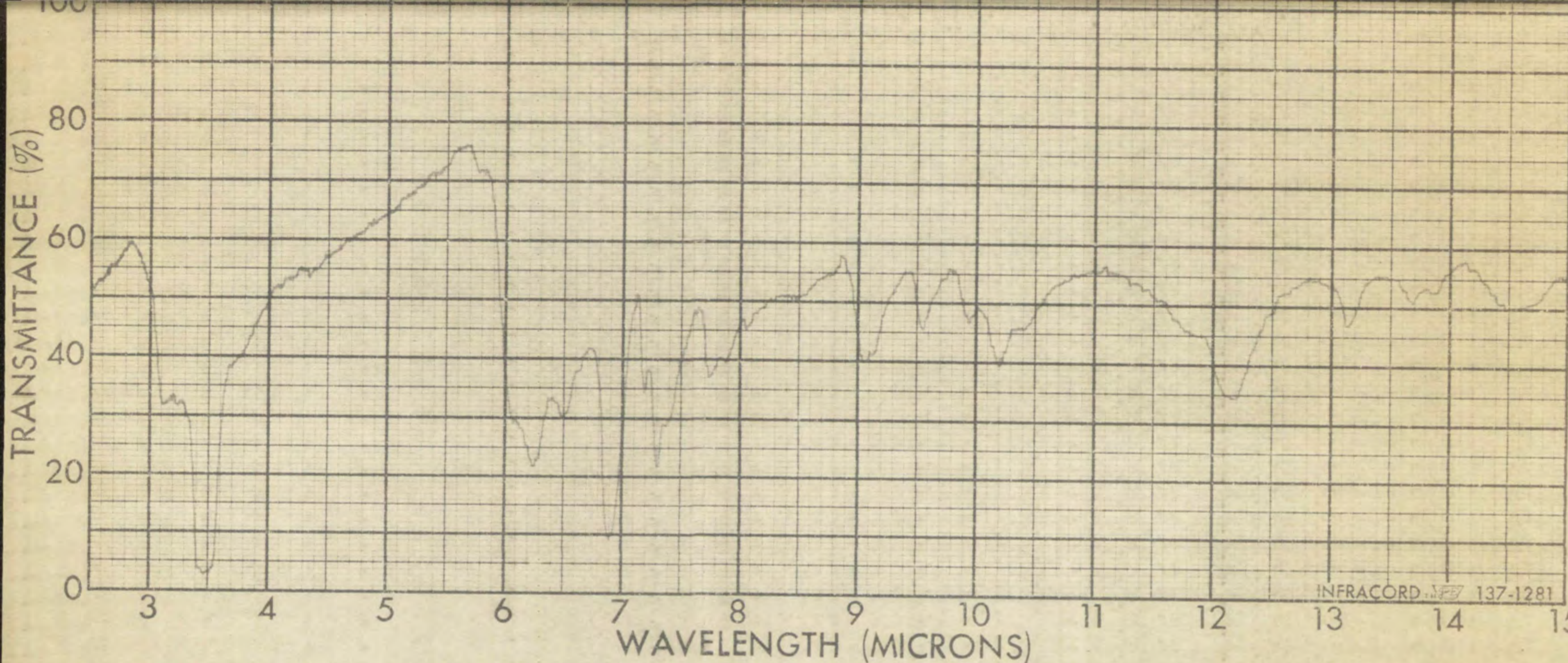


Plate IV: Infrared Spectrum of 4-Chloro-5-hydrazino-2-phenyl-3-pyridazone





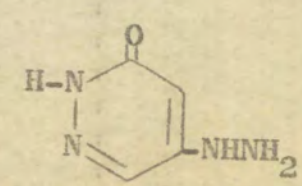


Plate V: Infrared Spectrum of 5-Hydrazino-3-pyridazone

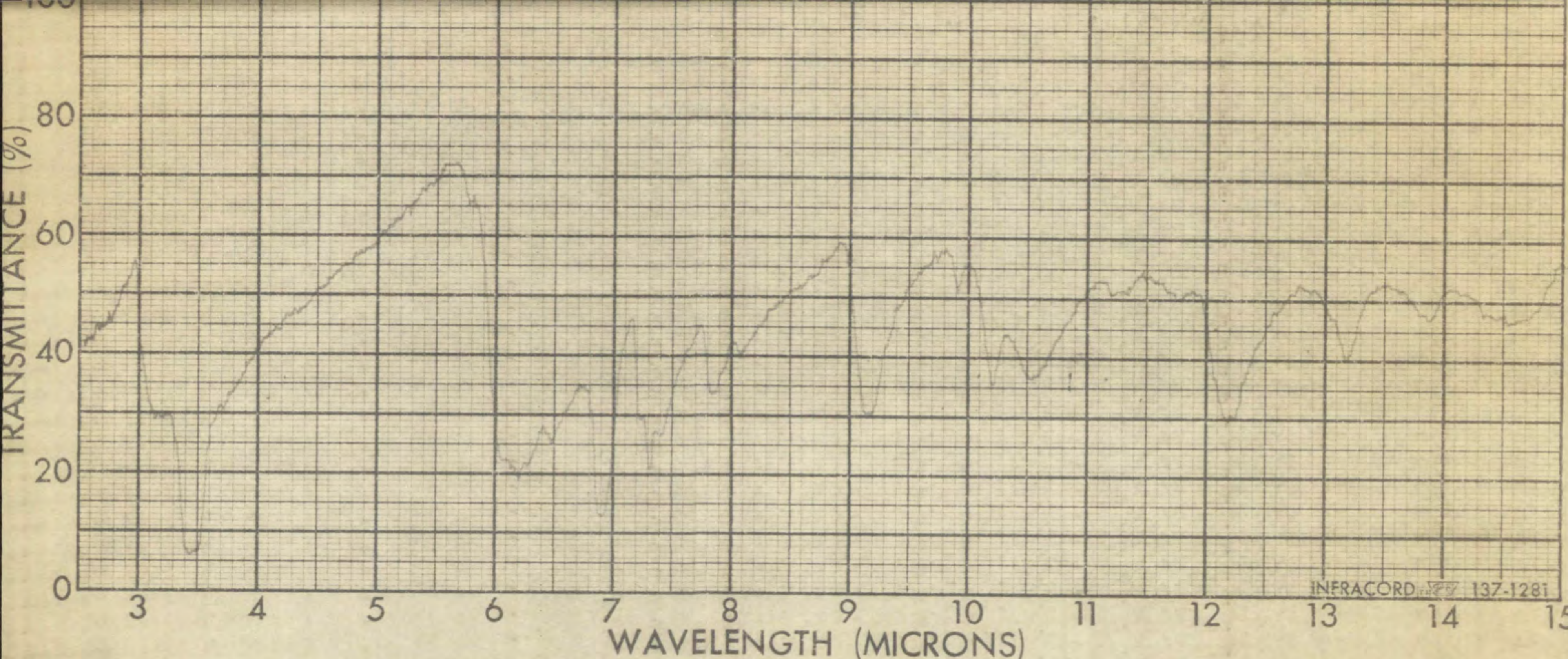
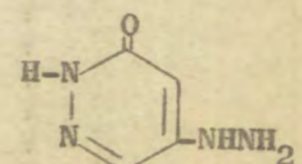


Plate VI: Infrared Spectrum of 5-Hydrazino-3-pyridazone
(From 5,6-Dichloro-3-pyridazone)



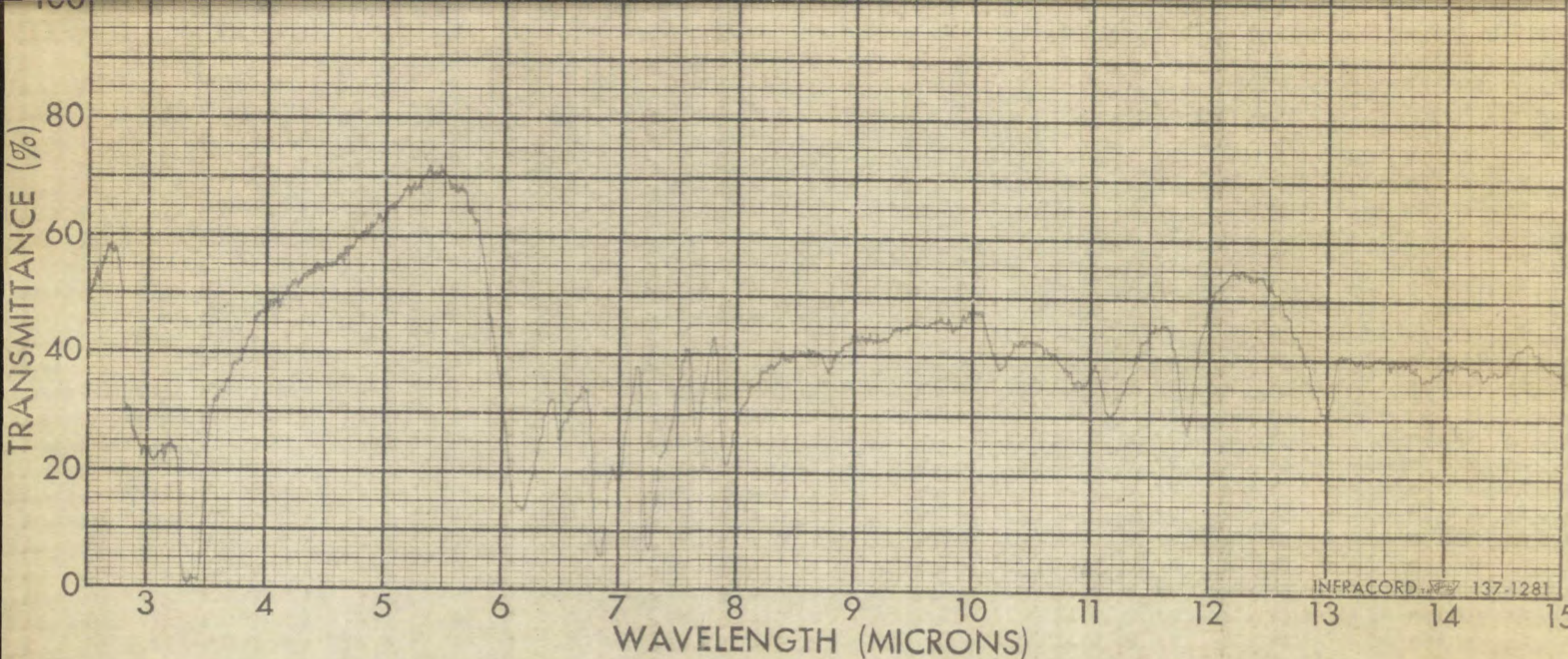
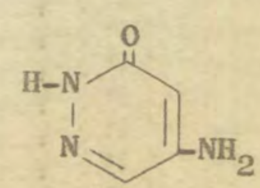


Plate VII: Infrared Spectrum of 5-Amino-3-pyridazone



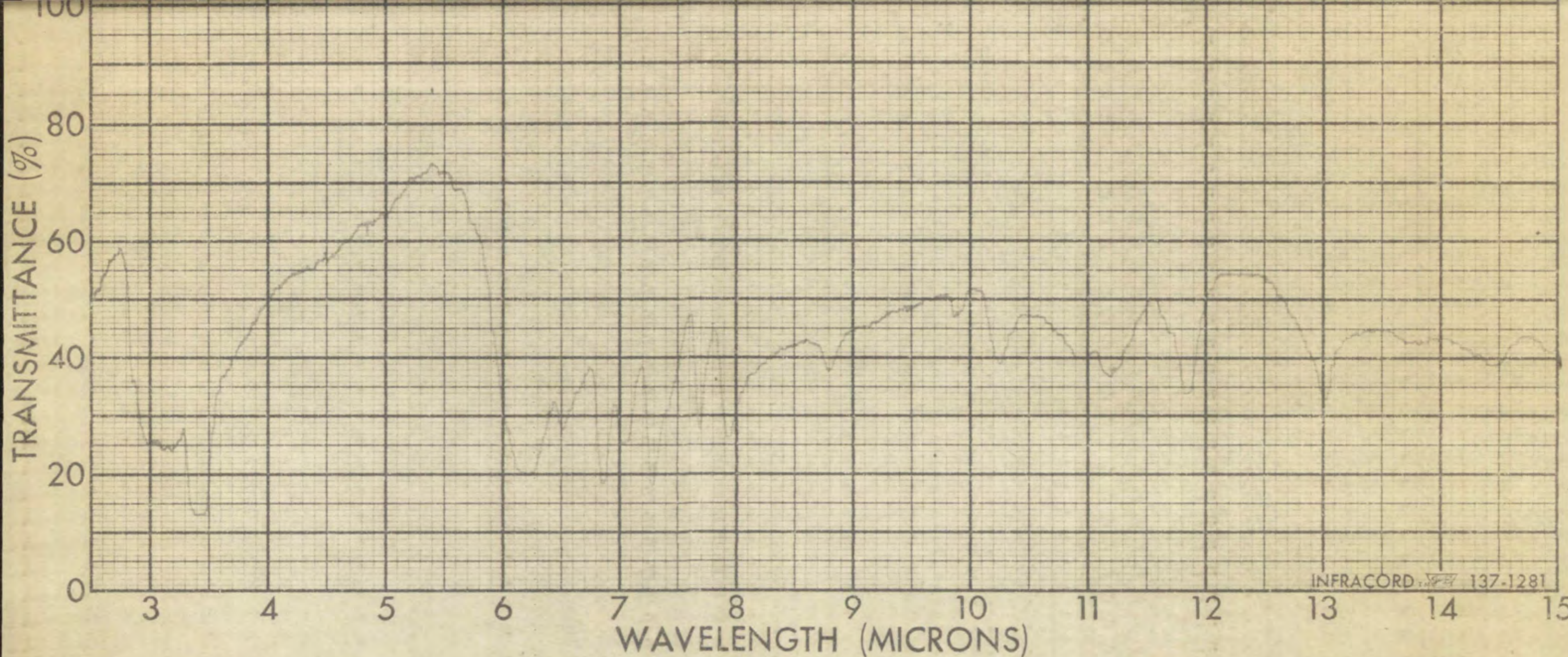
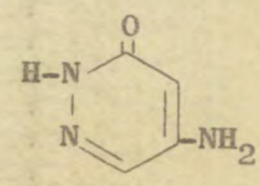


Plate VIII: Infrared Spectrum of 5-Amino-3-pyridazone
(Authentic Sample)



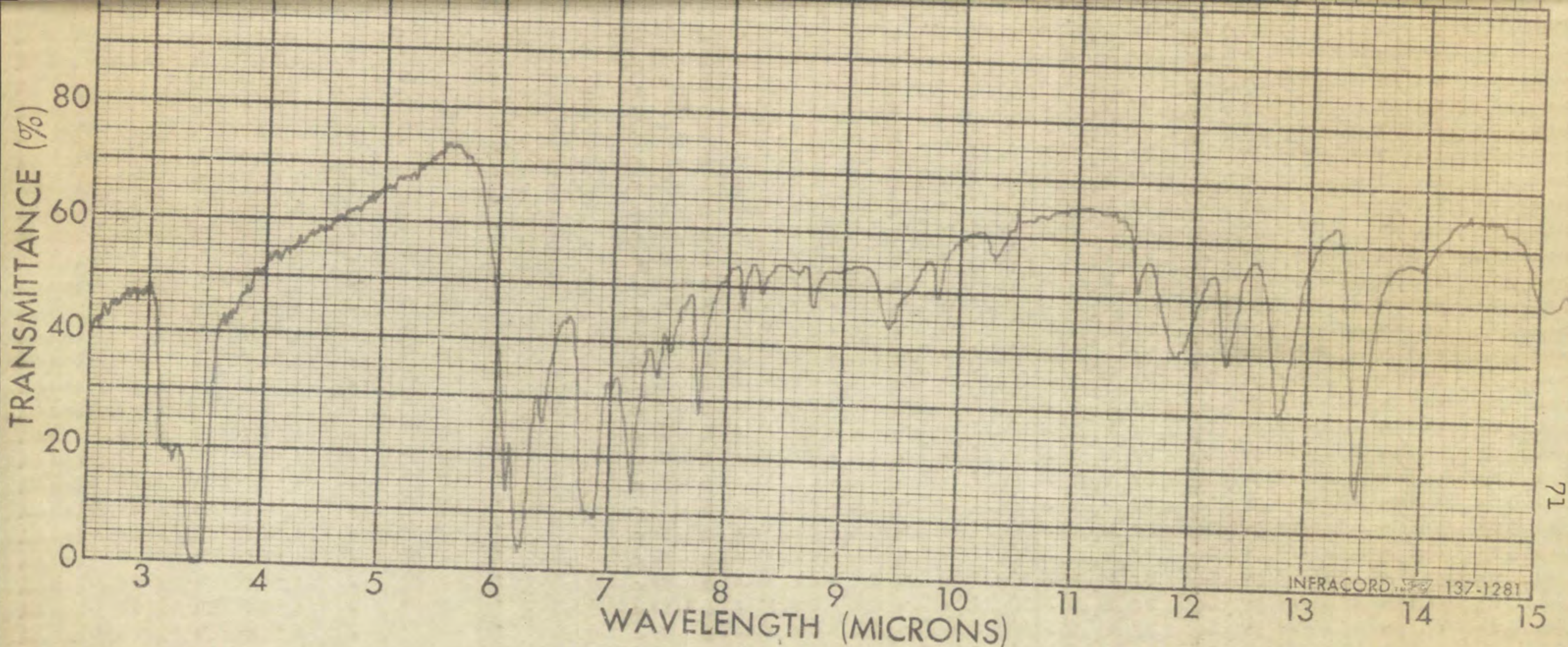
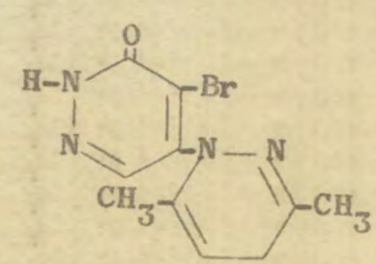
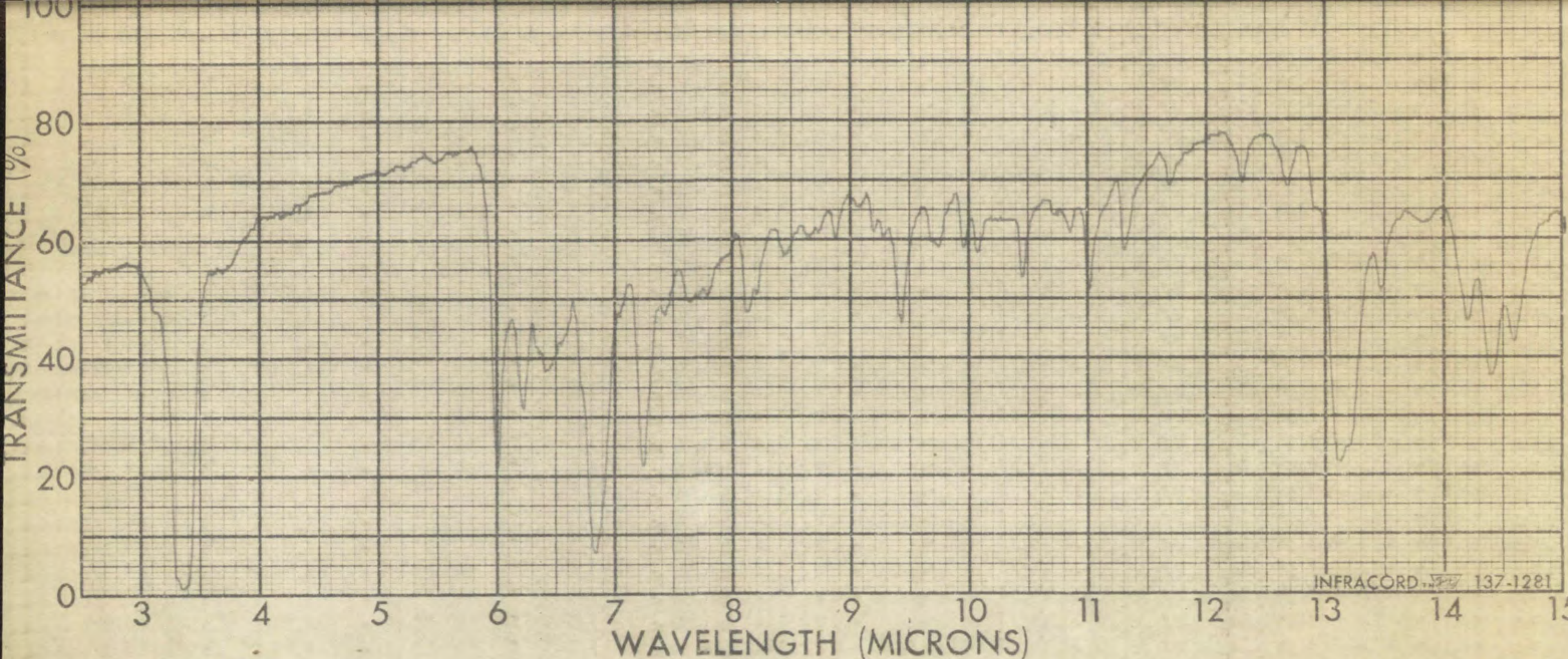


Plate IX: Infrared Spectrum of 4-Bromo-5- [1-(3,6-dimethyl-1,4-dihydro)pyridazinyl] -3-pyridazone





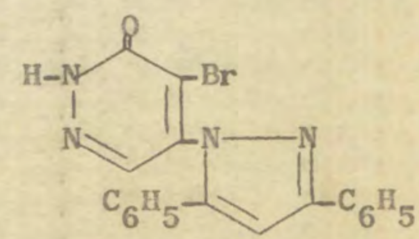
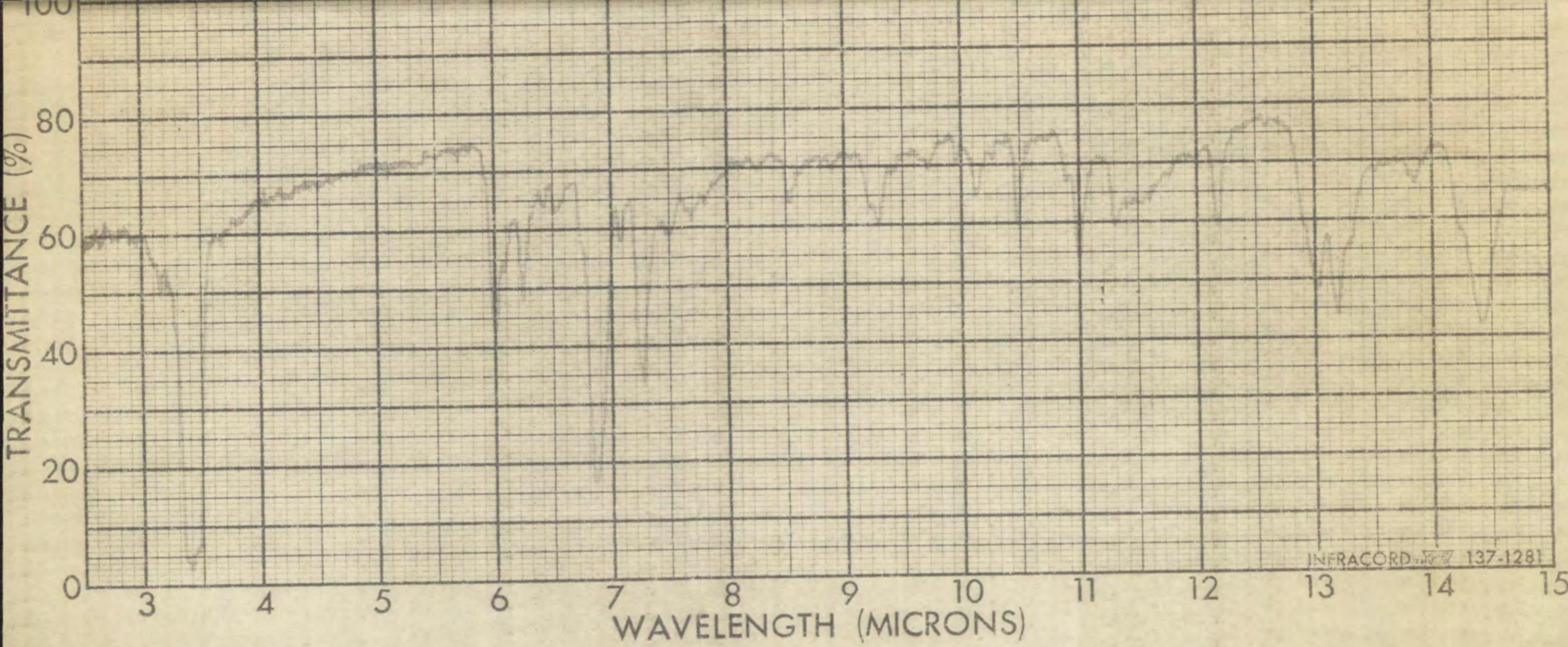


Plate X: Infrared Spectrum of 4-Bromo-5-[1-(3,5-diphenyl)-pyrazolyl]-3-pyridazone



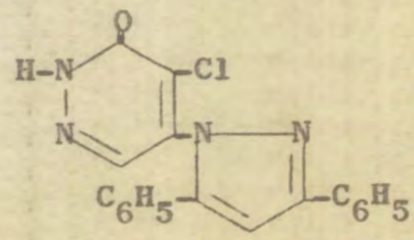


Plate XI: Infrared Spectrum of 4-Chloro-5-[1-(3,5-diphenyl)-pyrazolyl]-3-pyridazone

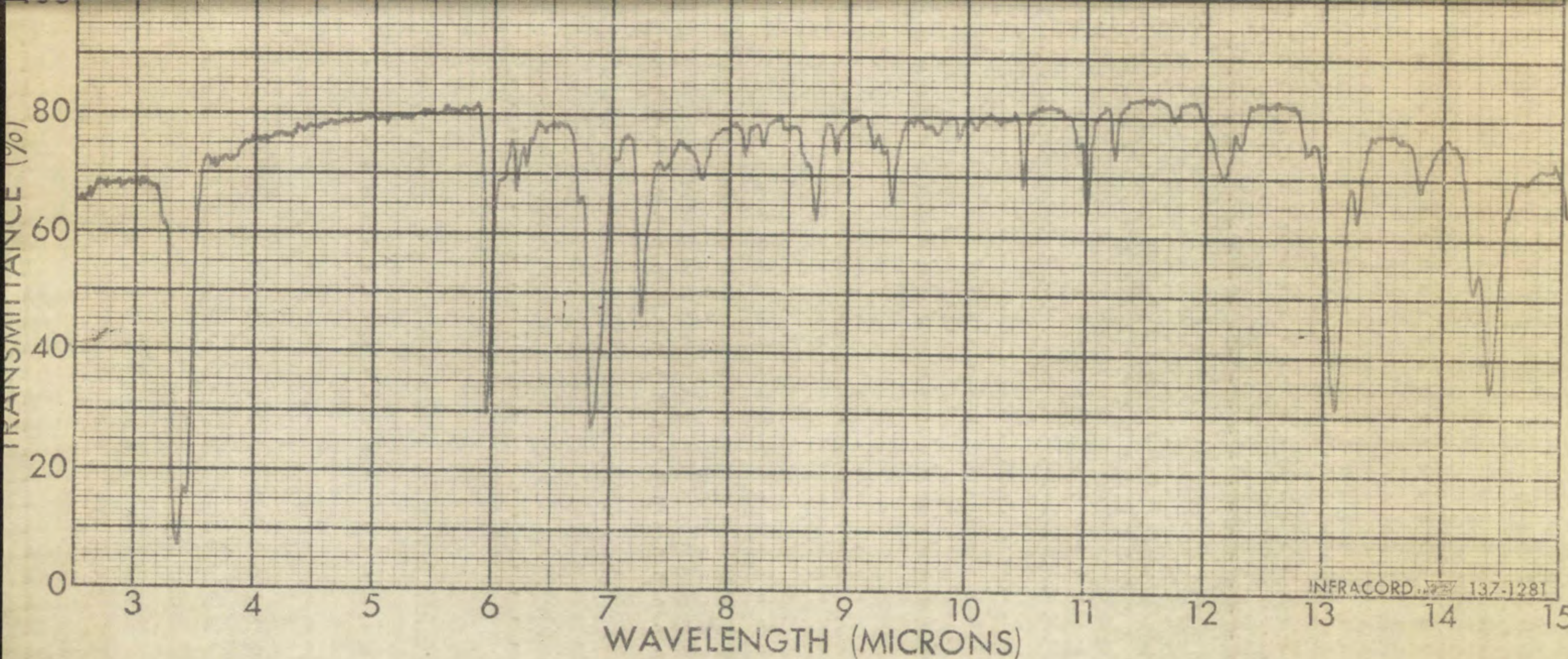
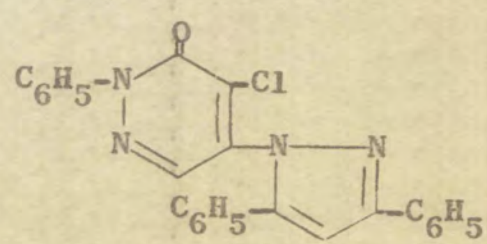


Plate XII: Infrared Spectrum of 4-Chloro-2-phenyl-5-[1-(3,5-diphenyl)pyrazolyl]-3-pyridazone



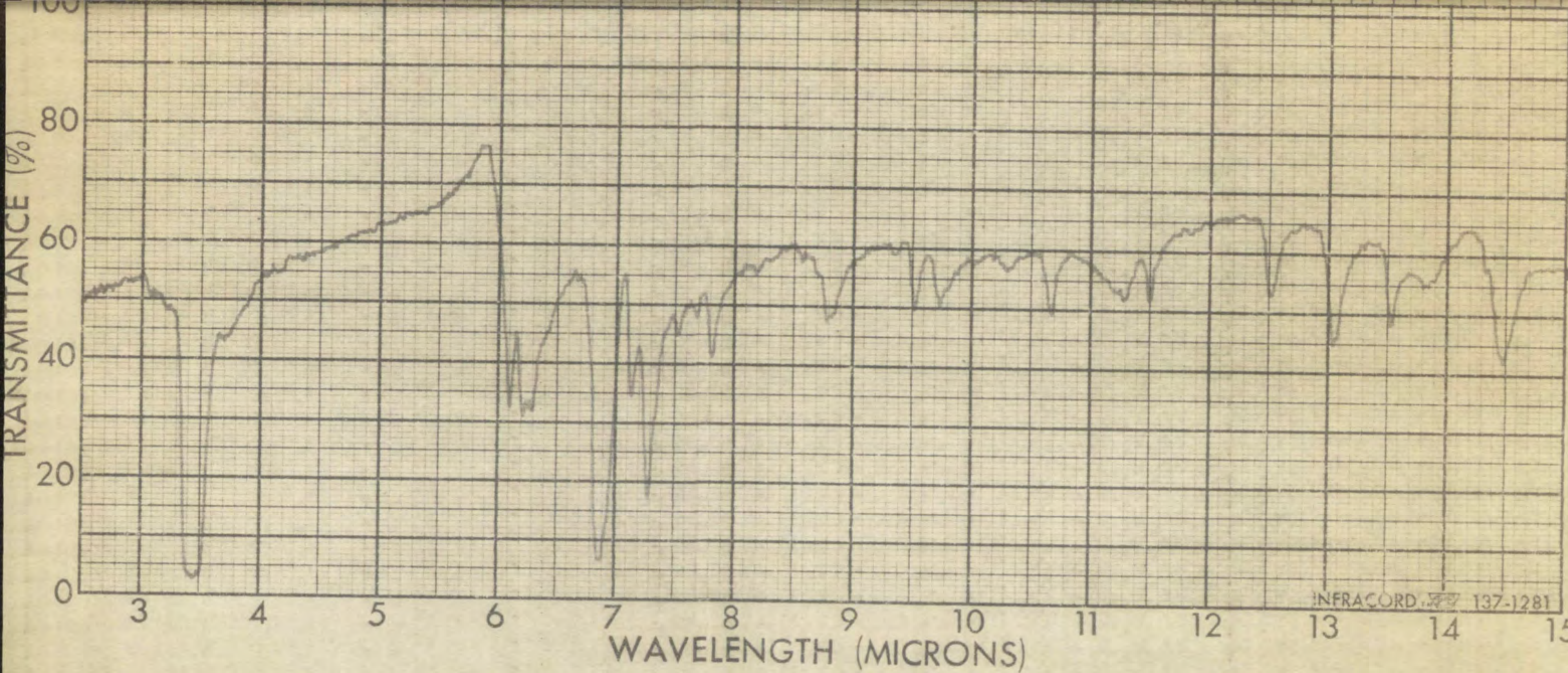
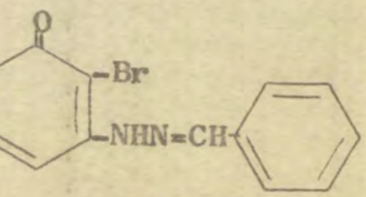


Plate XIII: Infrared Spectrum of Benzaldehyde 4-bromo-3-pyridazon-5-ylhydrazone



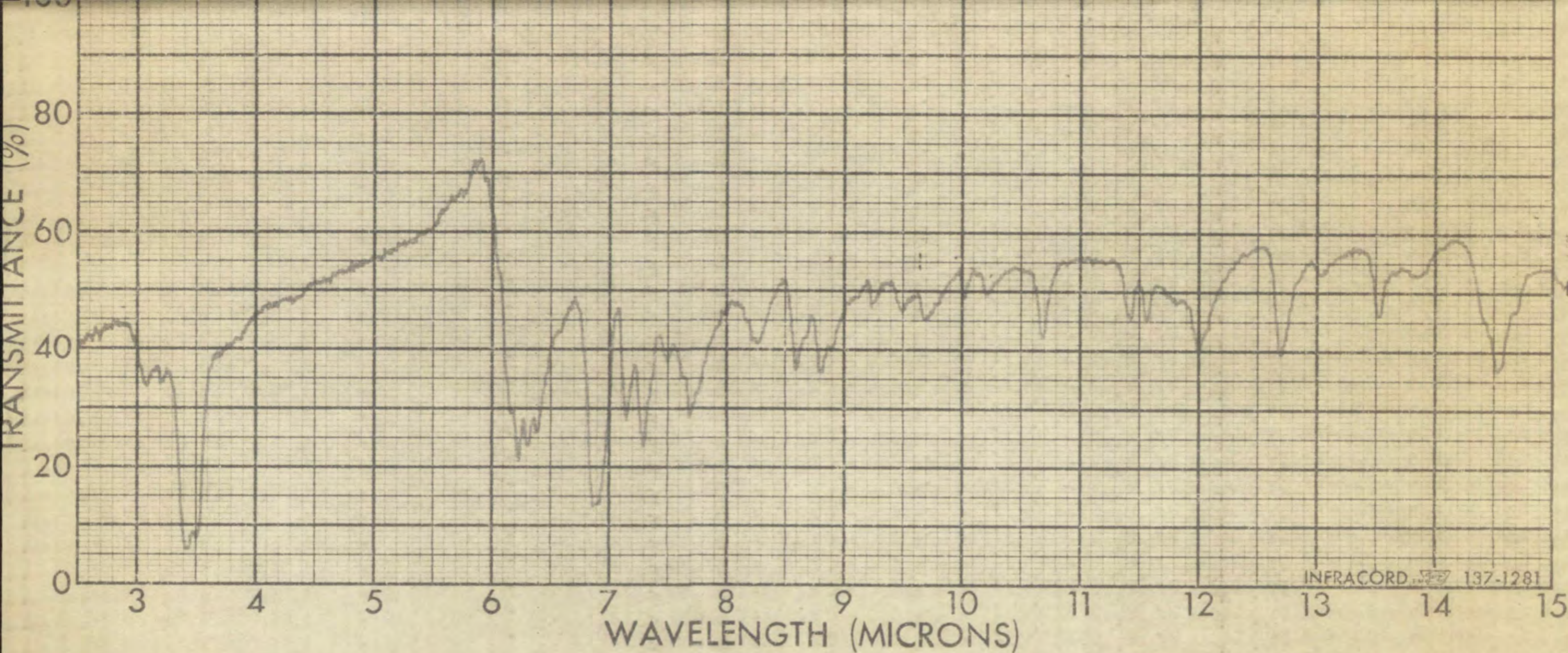
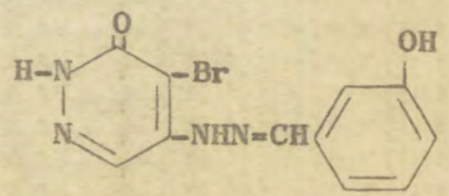


Plate XIV: Infrared Spectrum of m-Hydroxybenzaldehyde 4-bromo-3-pyridazon-5-ylhydrazone



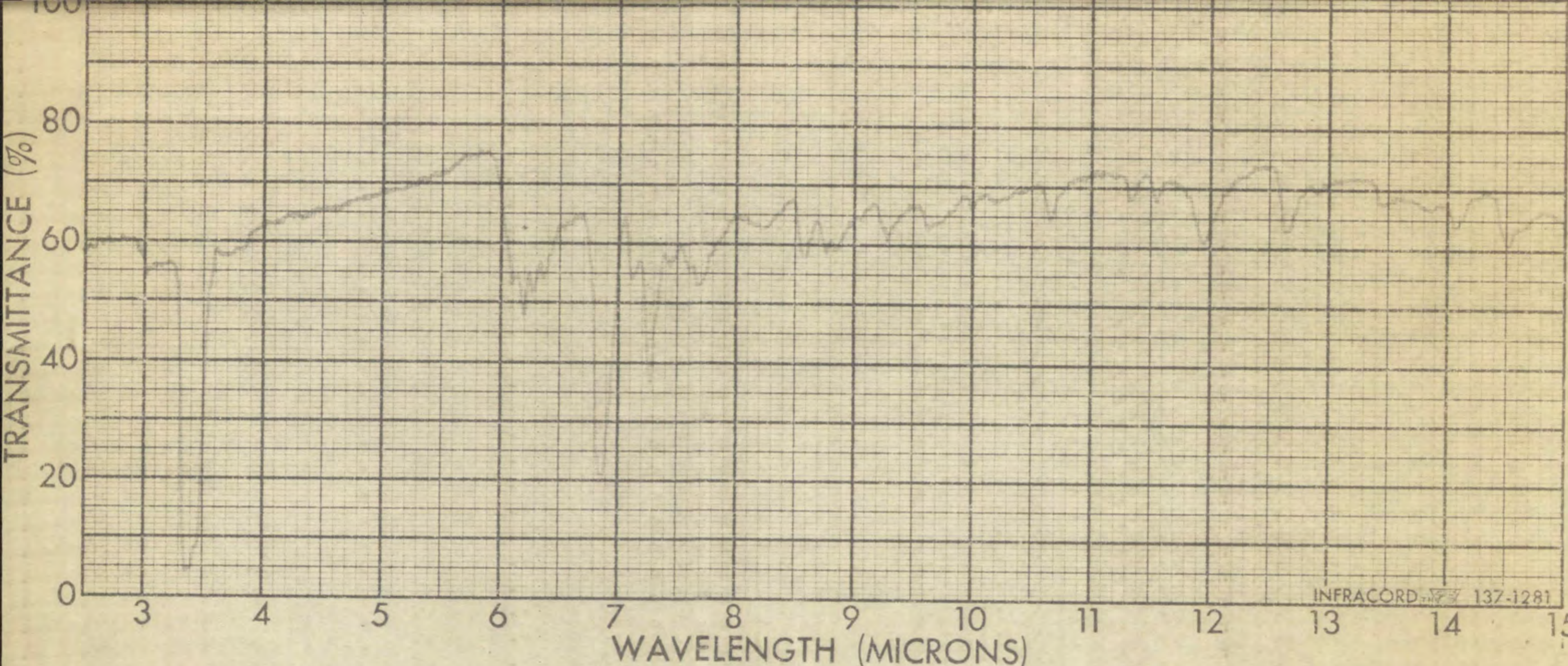
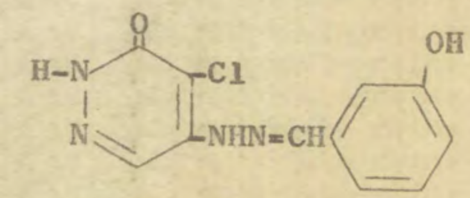


Plate XV: Infrared Spectrum of m-Hydroxybenzaldehyde 4-chloro-3-pyridazon-5-ylhydrazone



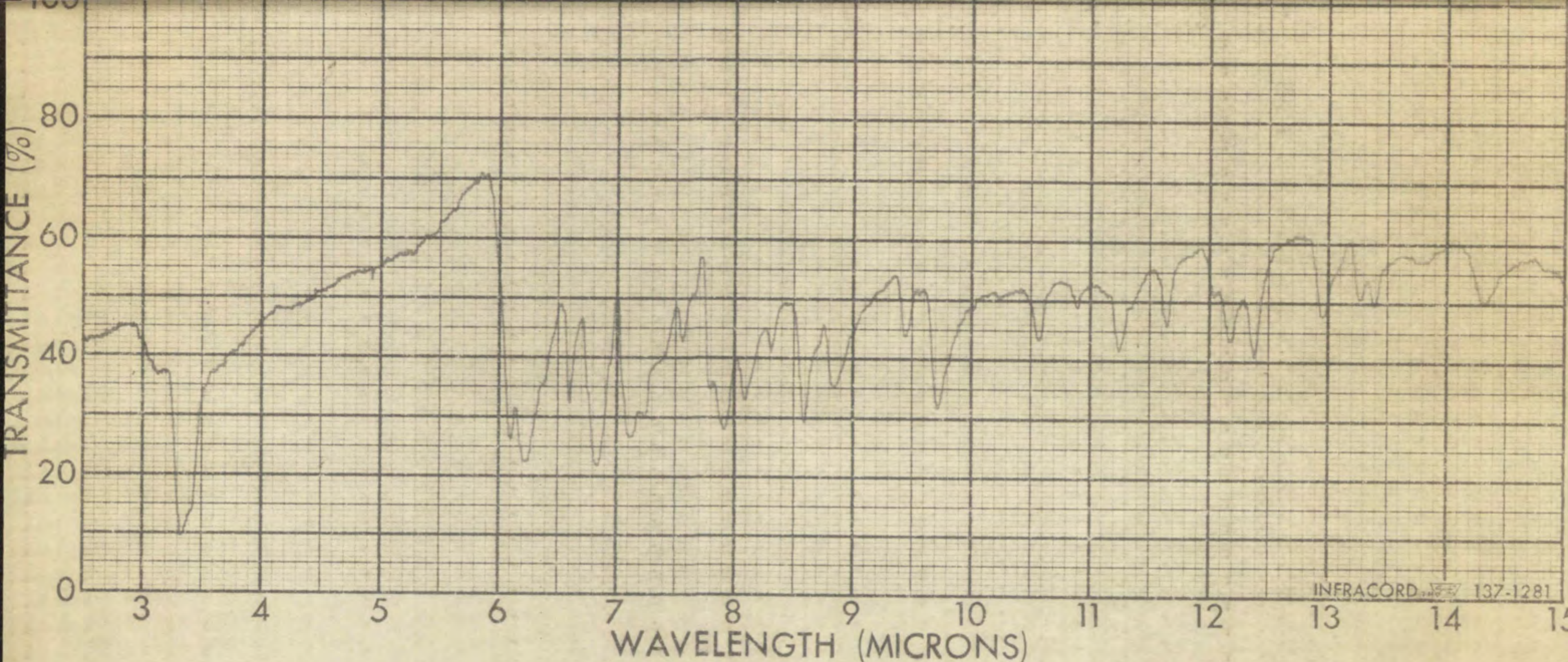
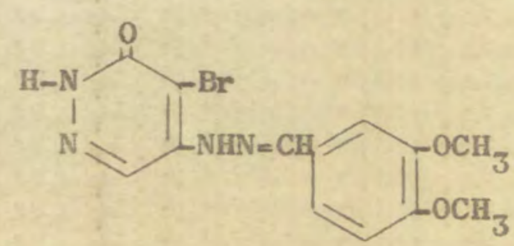


Plate XVI: Infrared Spectrum of 3,4-Dimethoxybenzaldehyde 4-bromo-3-pyridazon-5-ylhydrazone



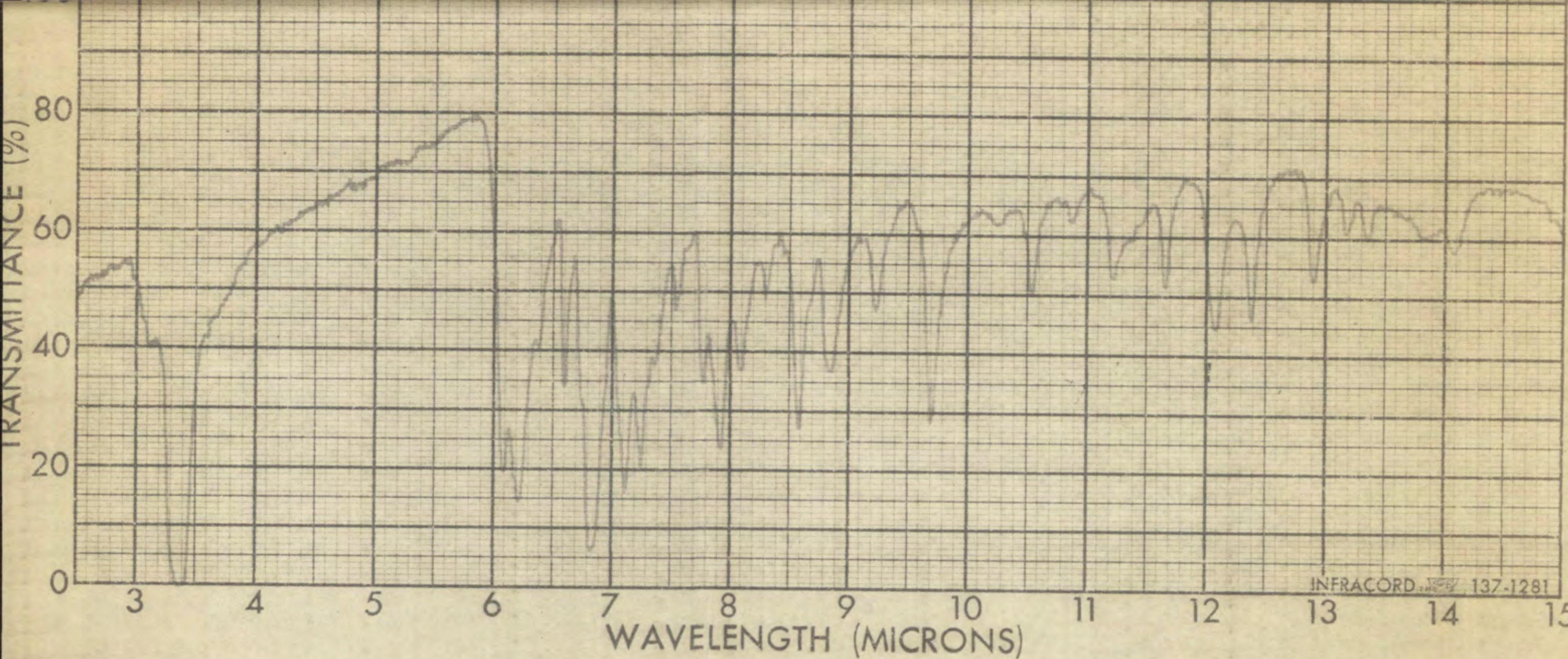
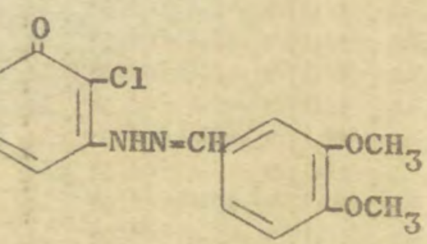


Plate XVII: Infrared Spectrum of 3,4-Dimethoxybenzaldehyde 4-chloro-3-pyridazon-5-ylhydrazone



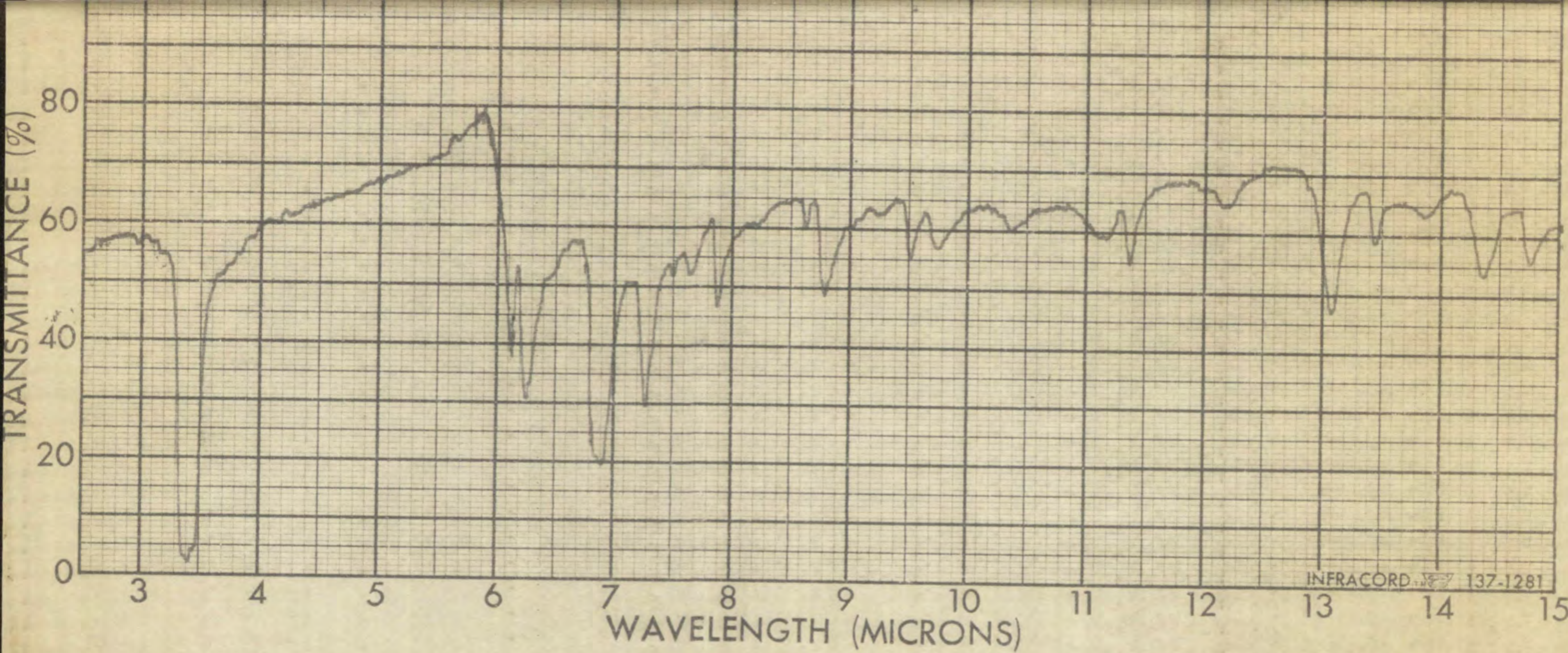
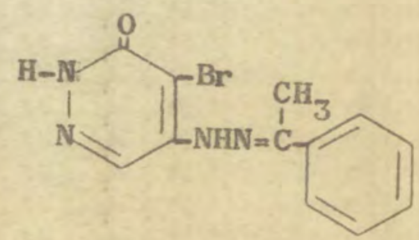
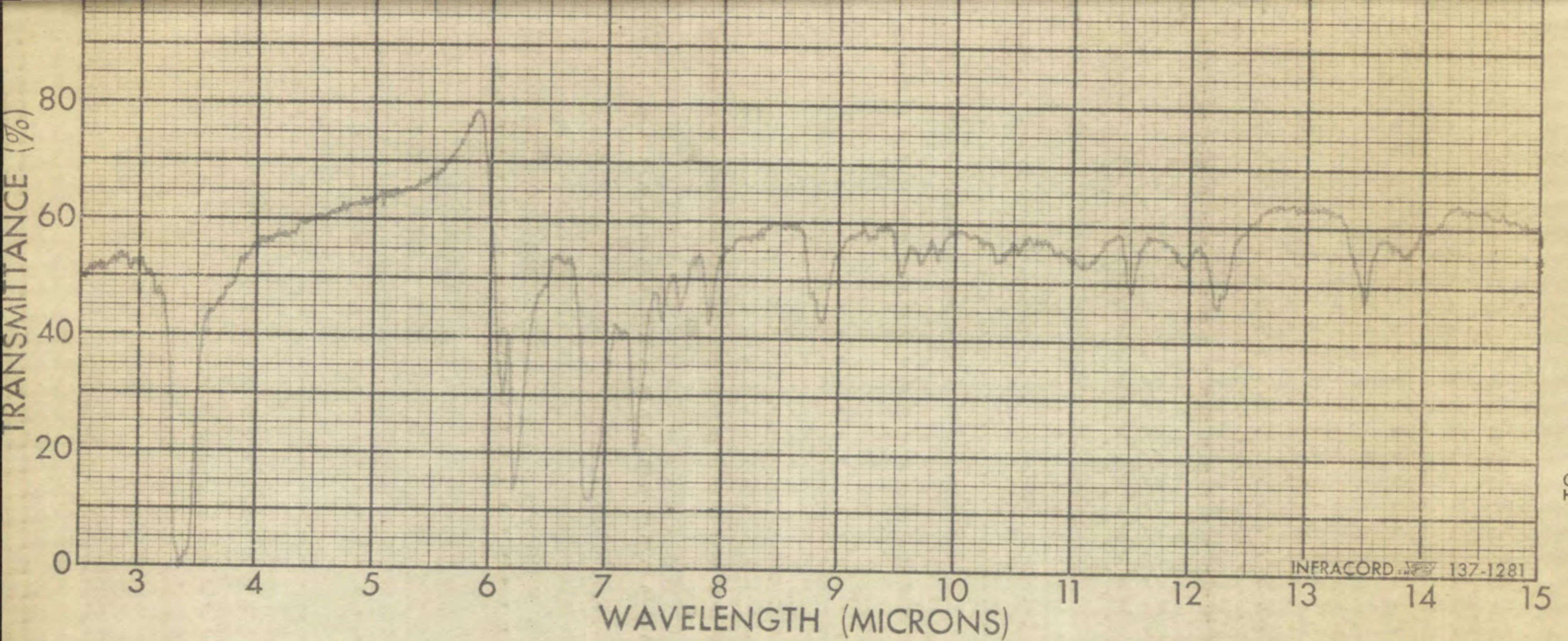


Plate XVIII: Infrared Spectrum of Acetophenone 4-bromo-3-pyridazon-5-ylhydrazone





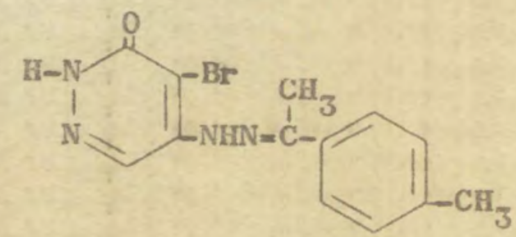


Plate XIX: Infrared Spectrum of p-Methylacetophenone 4-bromo-3-pyridazon-5-ylhydrazone

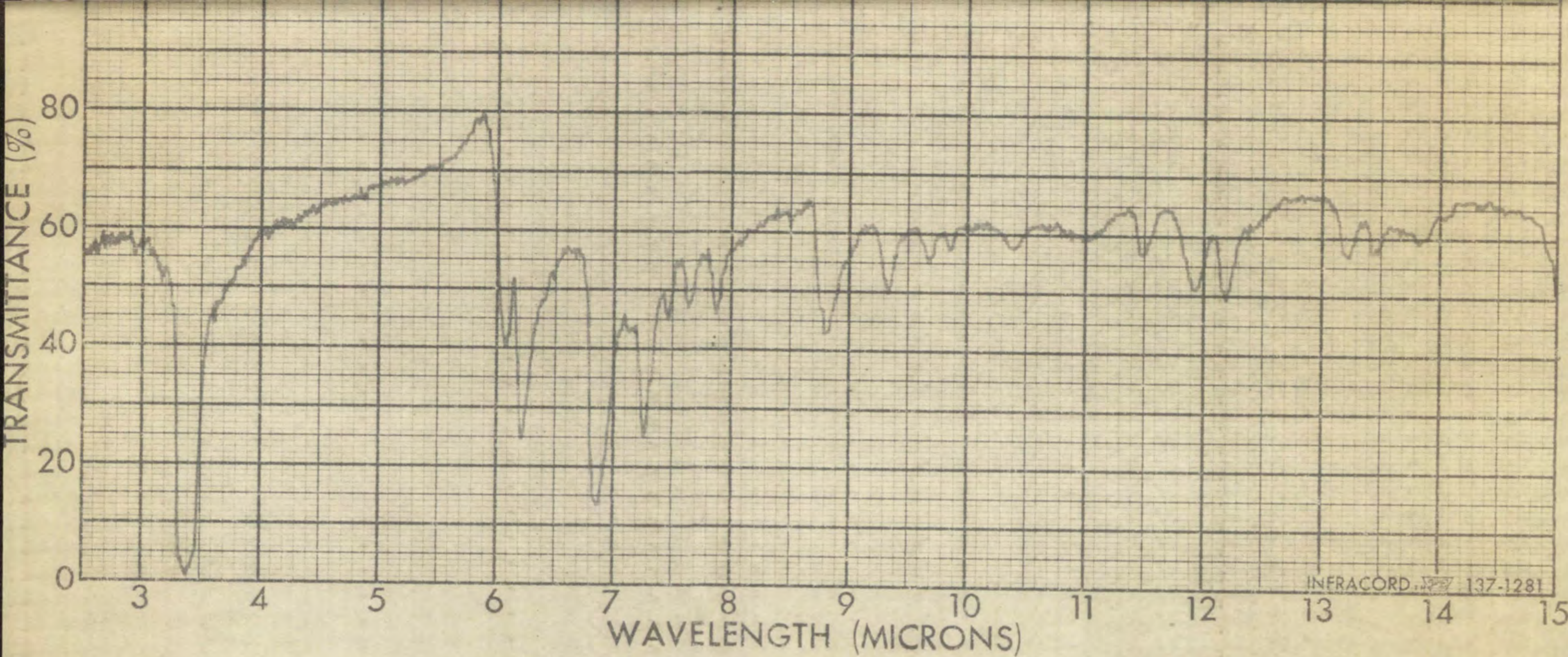
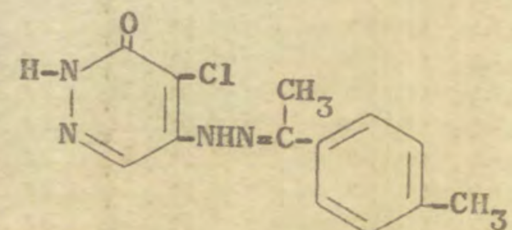


Plate XX: Infrared Spectrum of p-Methylacetophenone 4-chloro-3-pyridazon-5-ylhydrazone



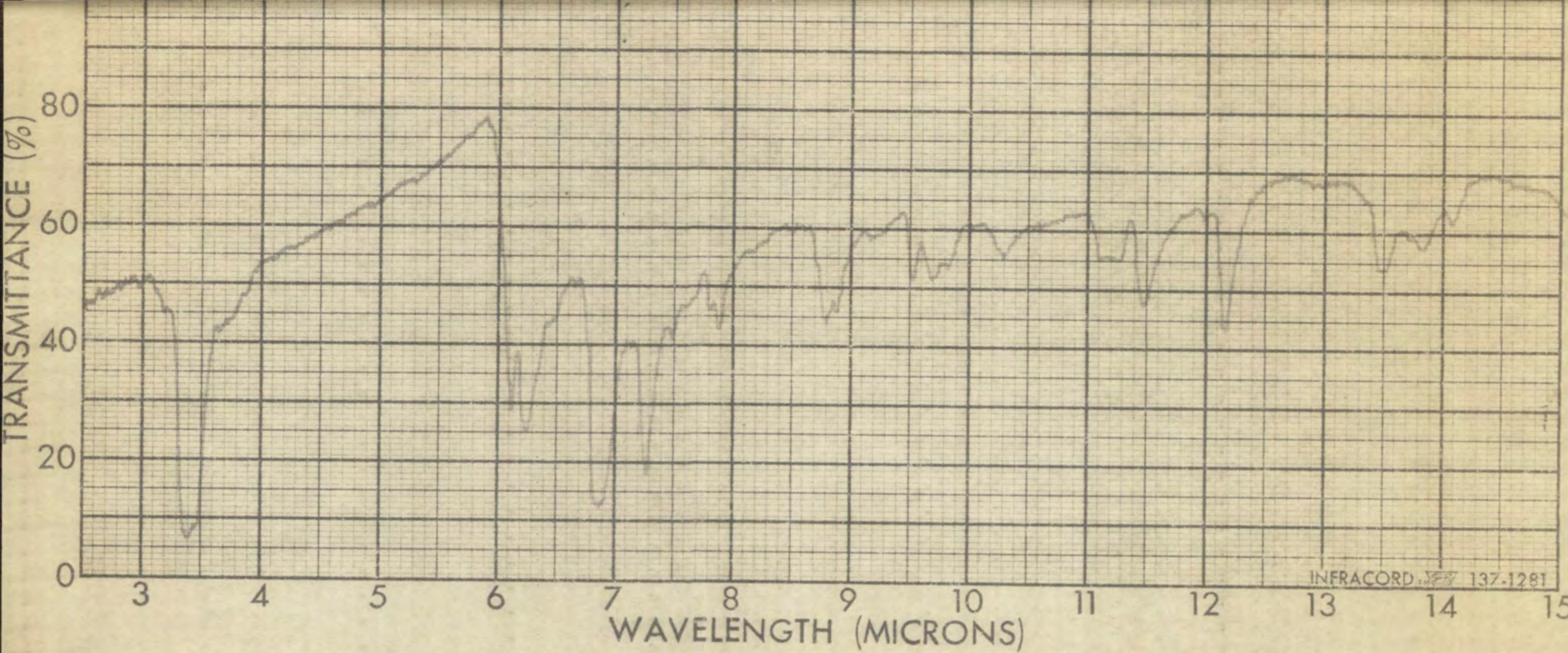
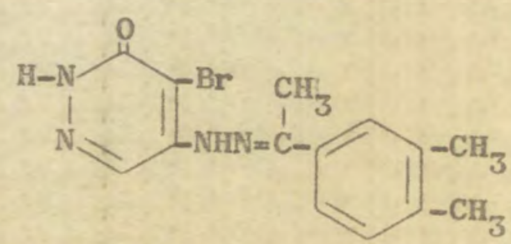
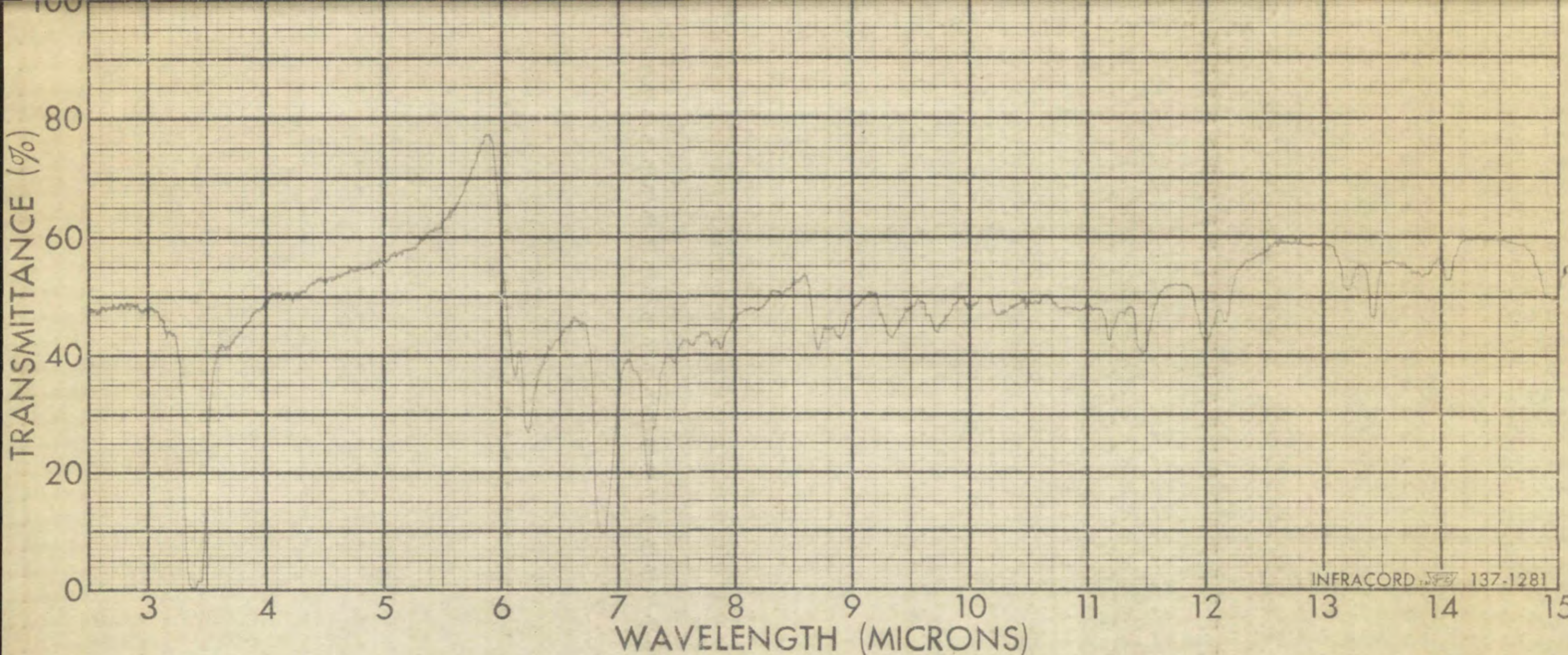


Plate XXI: Infrared Spectrum of 3,4-Dimethylacetophenone 4-bromo-3-pyridazon-5-ylhydrazone





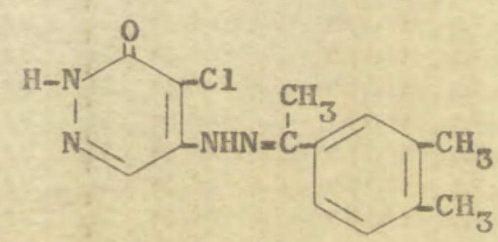


Plate XXII: Infrared Spectrum of 3,4-Dimethylacetophenone 4-chloro-3-pyridazon-5-ylhydrazone

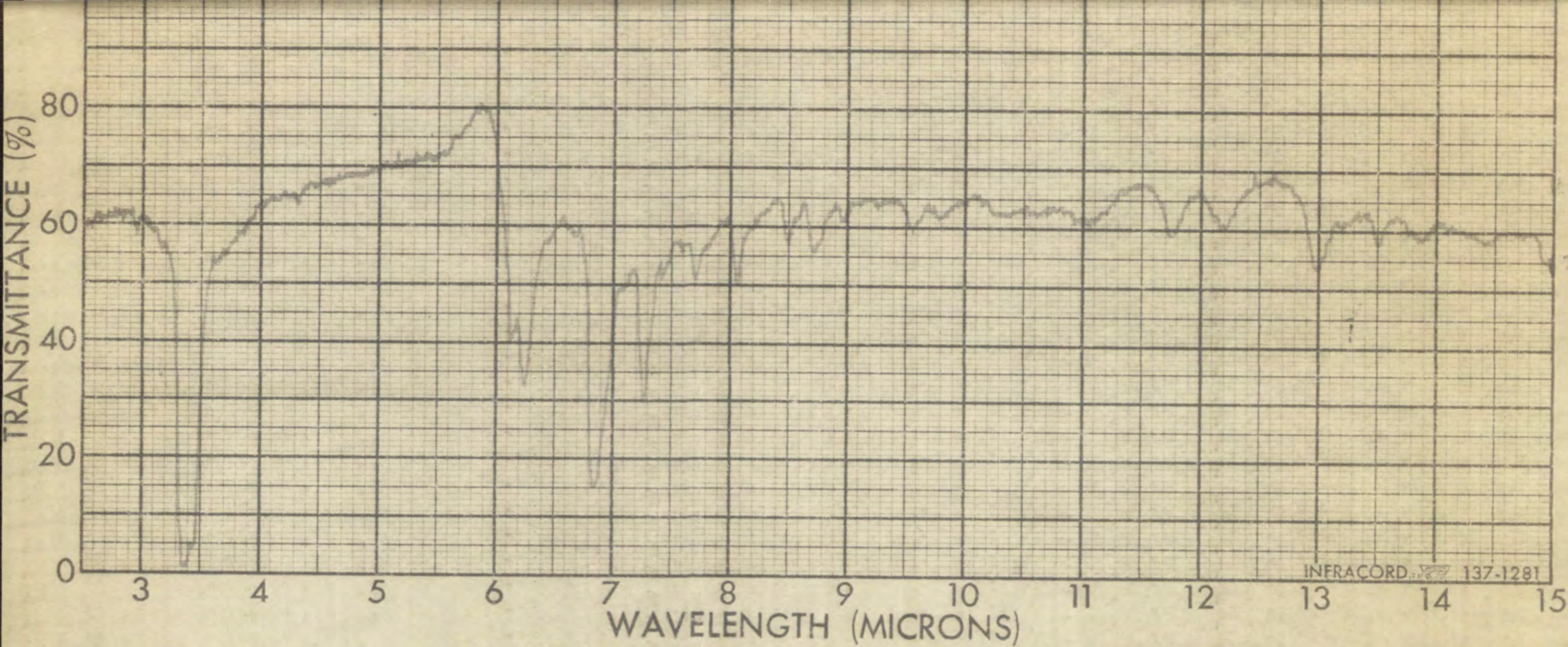
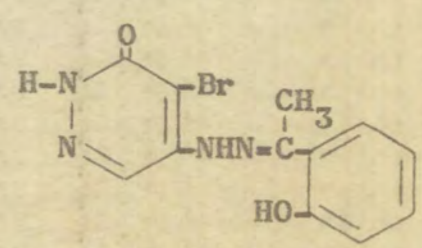
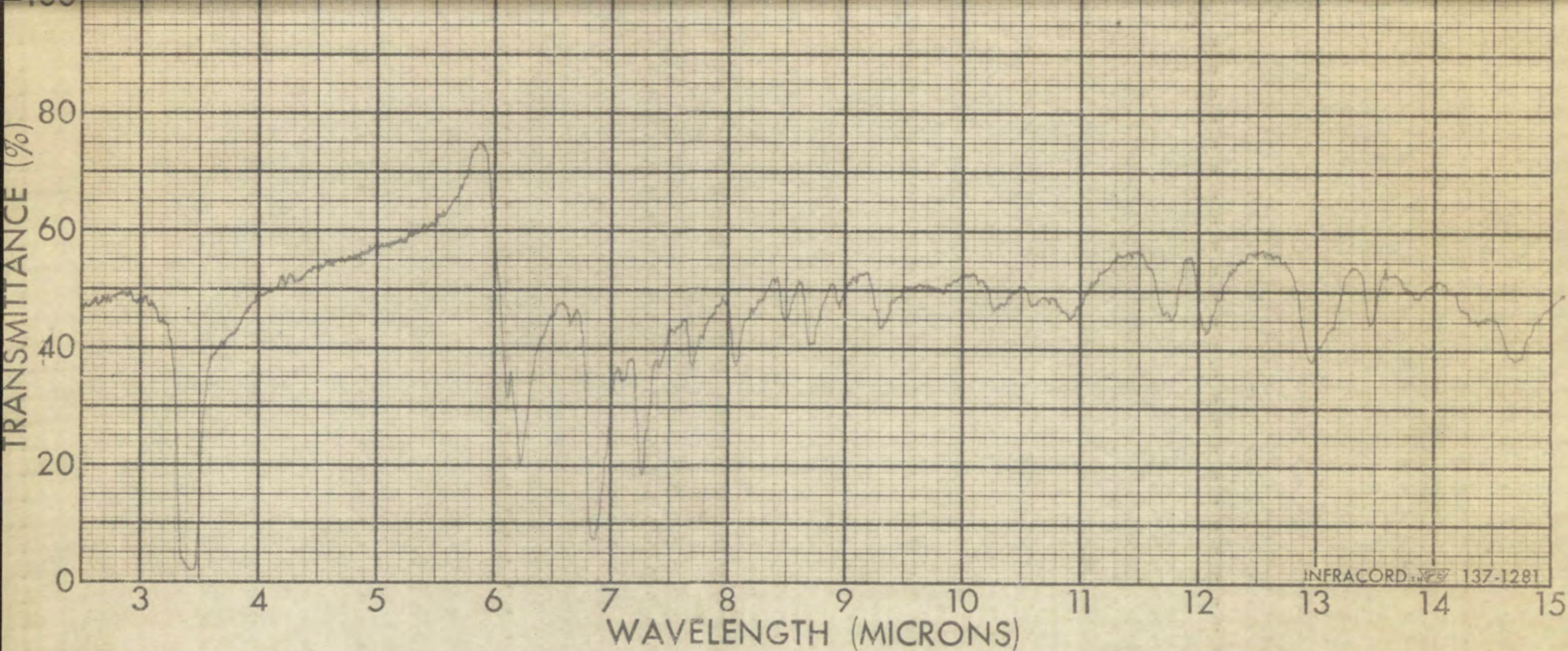


Plate XXIII: Infrared Spectrum of o-Hydroxyacetophenone 4-bromo-3-pyridazon-5-ylhydrazone





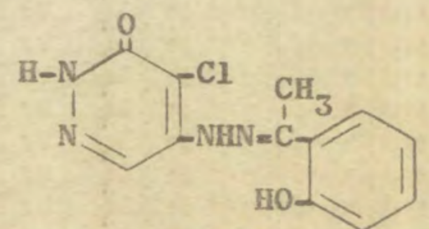


Plate XXIV: Infrared Spectrum of o-Hydroxyacetophenone 4-chloro-3-pyridazon-5-ylhydrazone

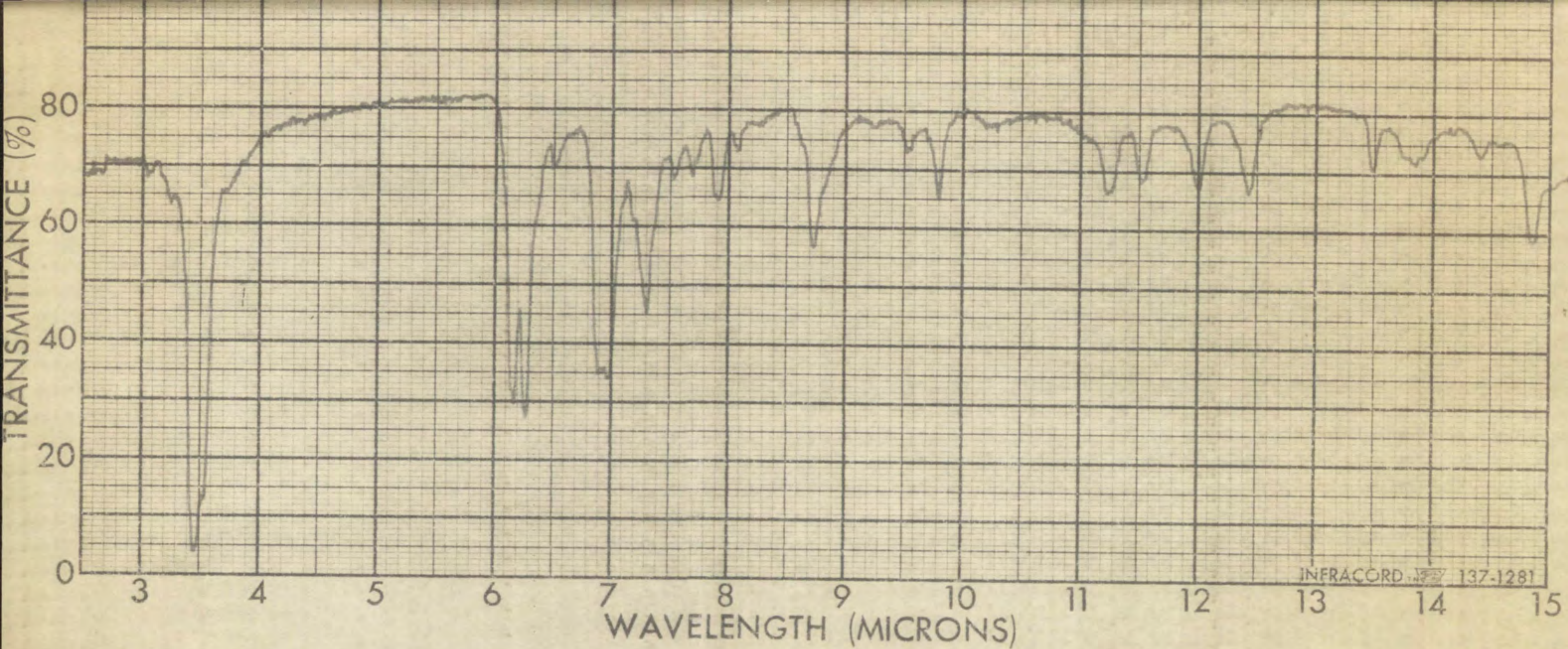
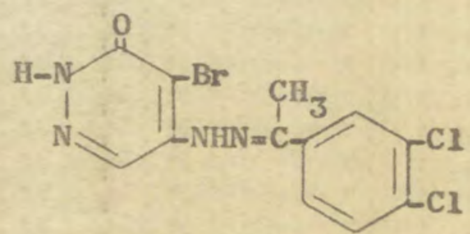


Plate XXV: Infrared Spectrum of 3,4-Dichloroaceto-phenone 4-bromo-3-pyridazon-5-ylhydrazone



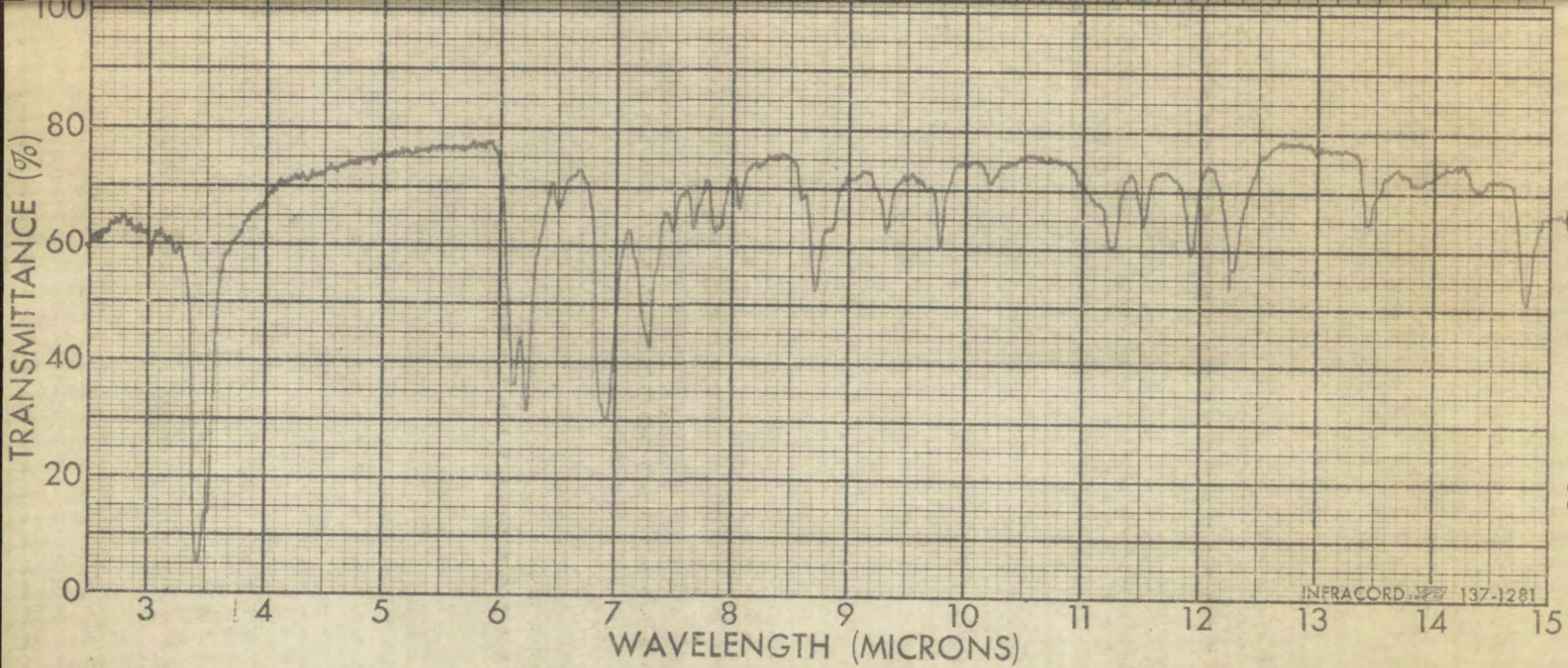
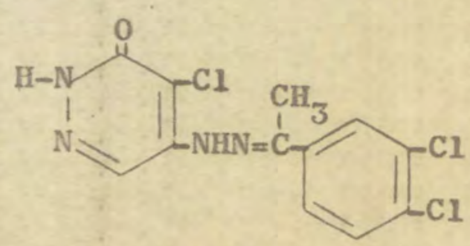


Plate XXVI: Infrared Spectrum of 3,4-Dichloroaceto-phenone 4-chloro-3-pyridazon-5-ylhydrazone



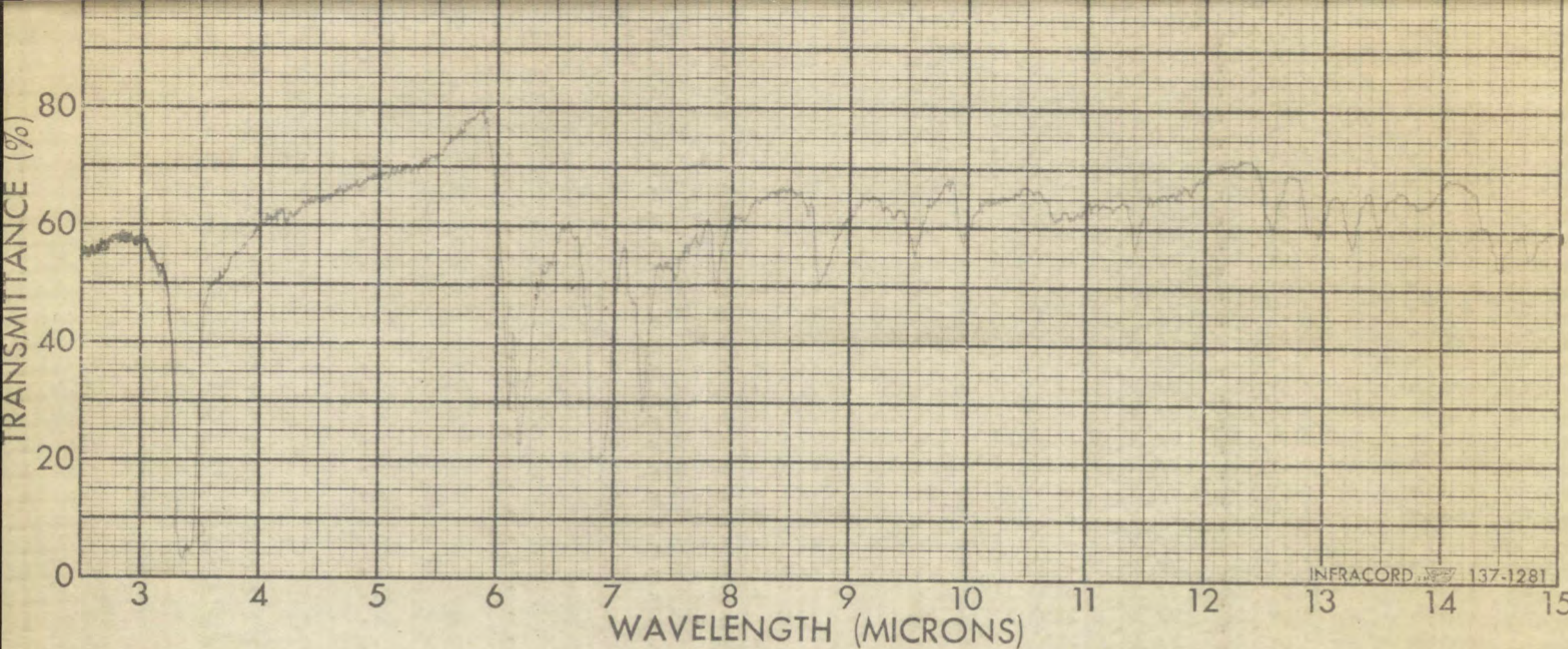
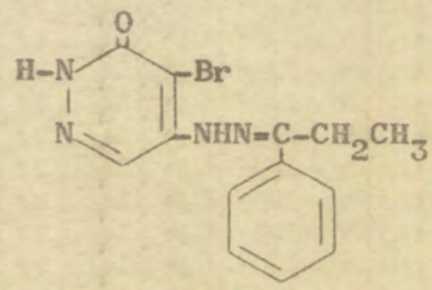


Plate XXVII: Infrared Spectrum of Propiophenone 4-bromo-3-pyridazon-5-ylhydrazone



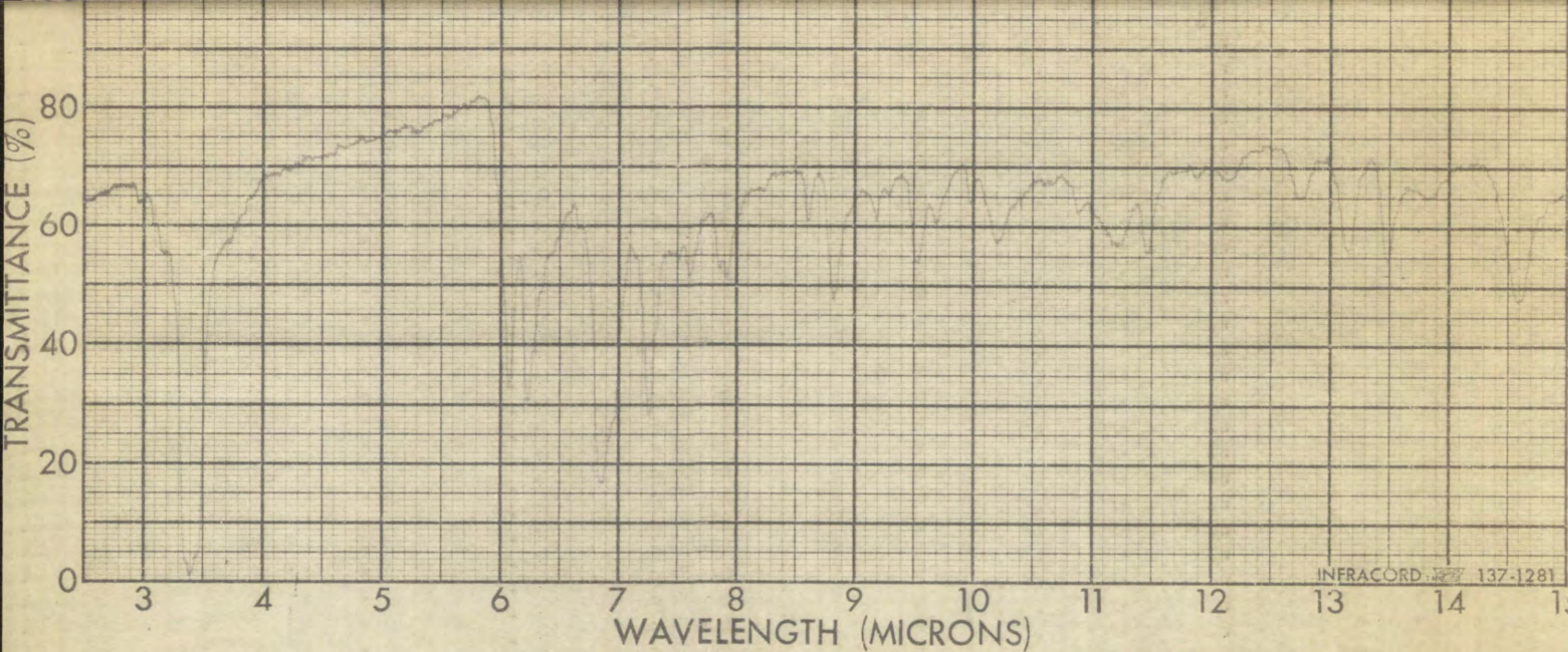
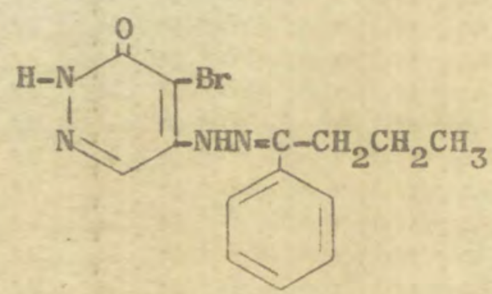
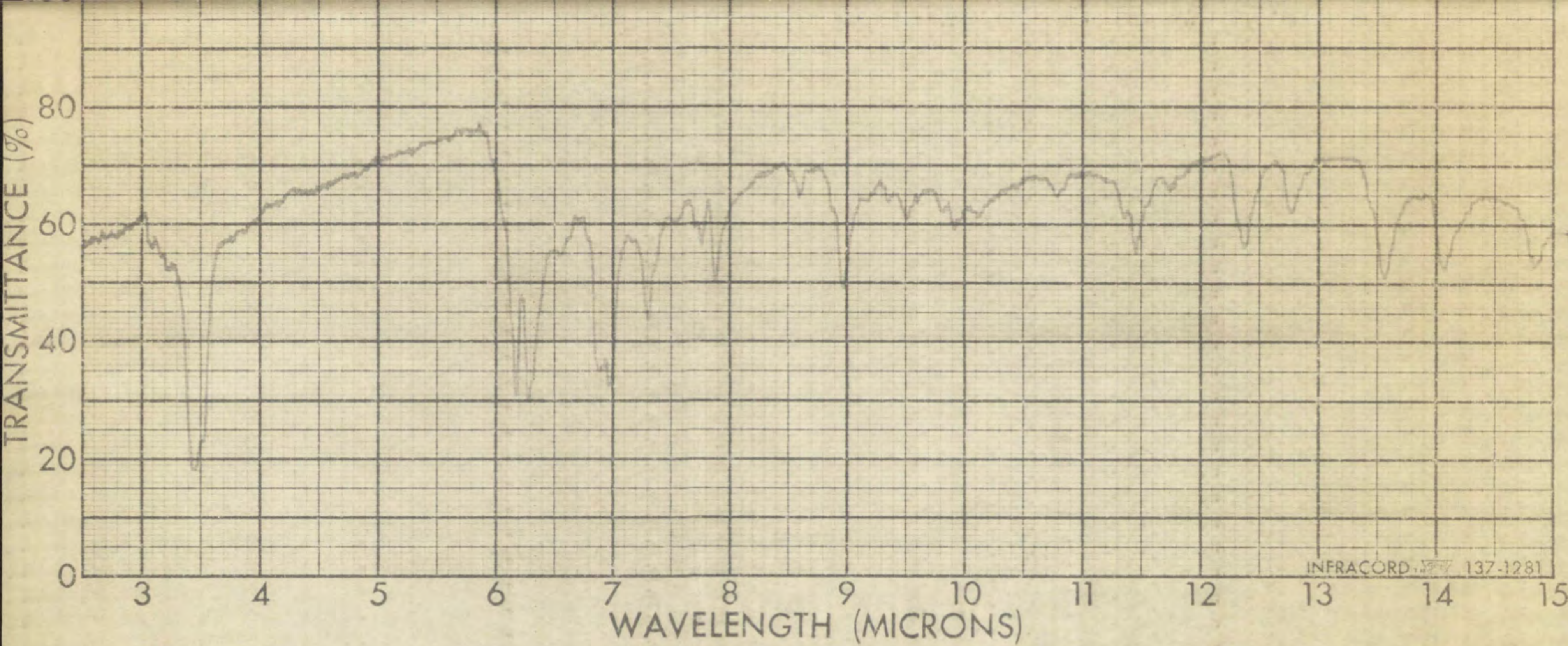


Plate XXVIII: Infrared Spectrum of Butyrophenone 4-bromo-3-pyridazon-5-ylhydrazone





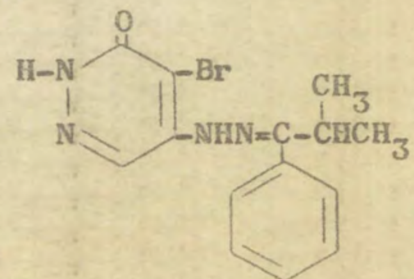


Plate XXIX: Infrared Spectrum of Isobutyrophenone 4-bromo-3-pyridazon-5-ylhydrazone

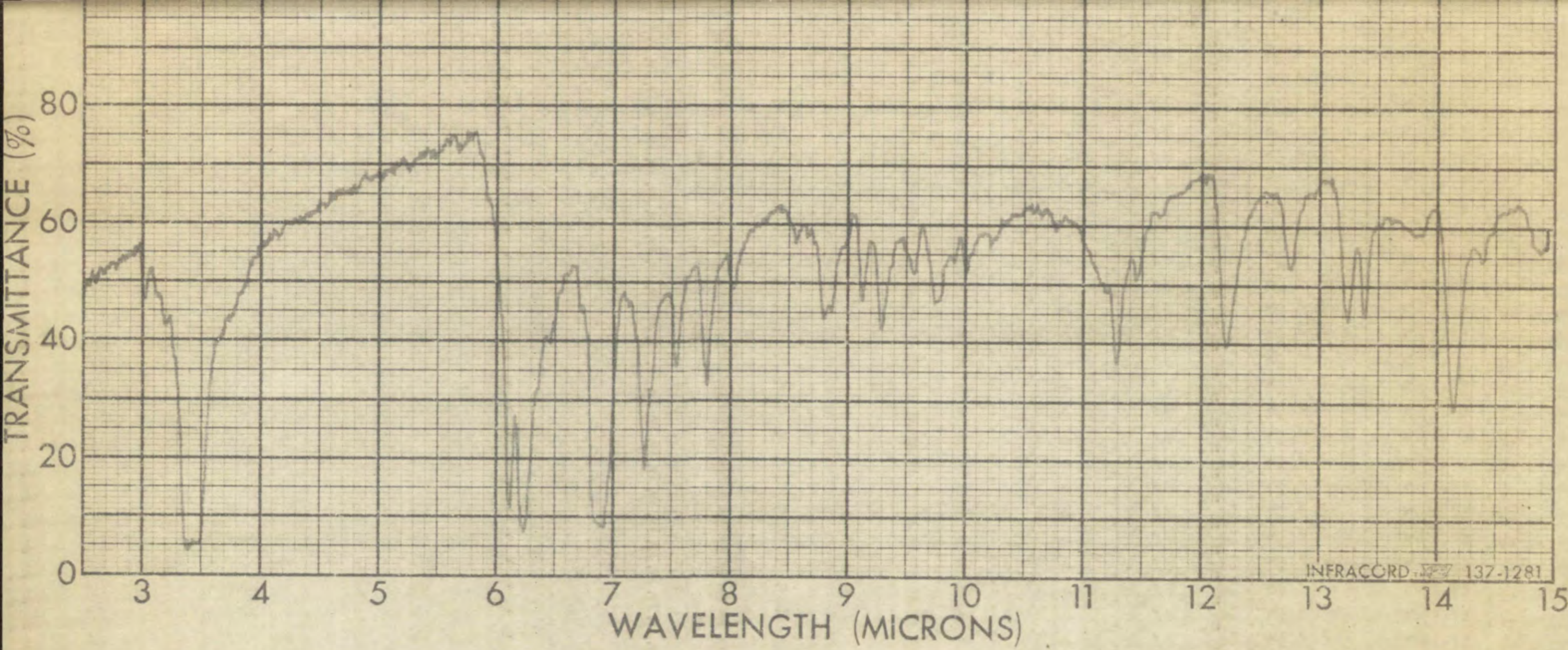
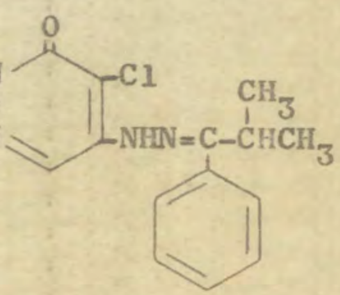


Plate XXX: Infrared Spectrum of Isobutyrophenone 4-chloro-3-pyridazon-5-ylhydrazone



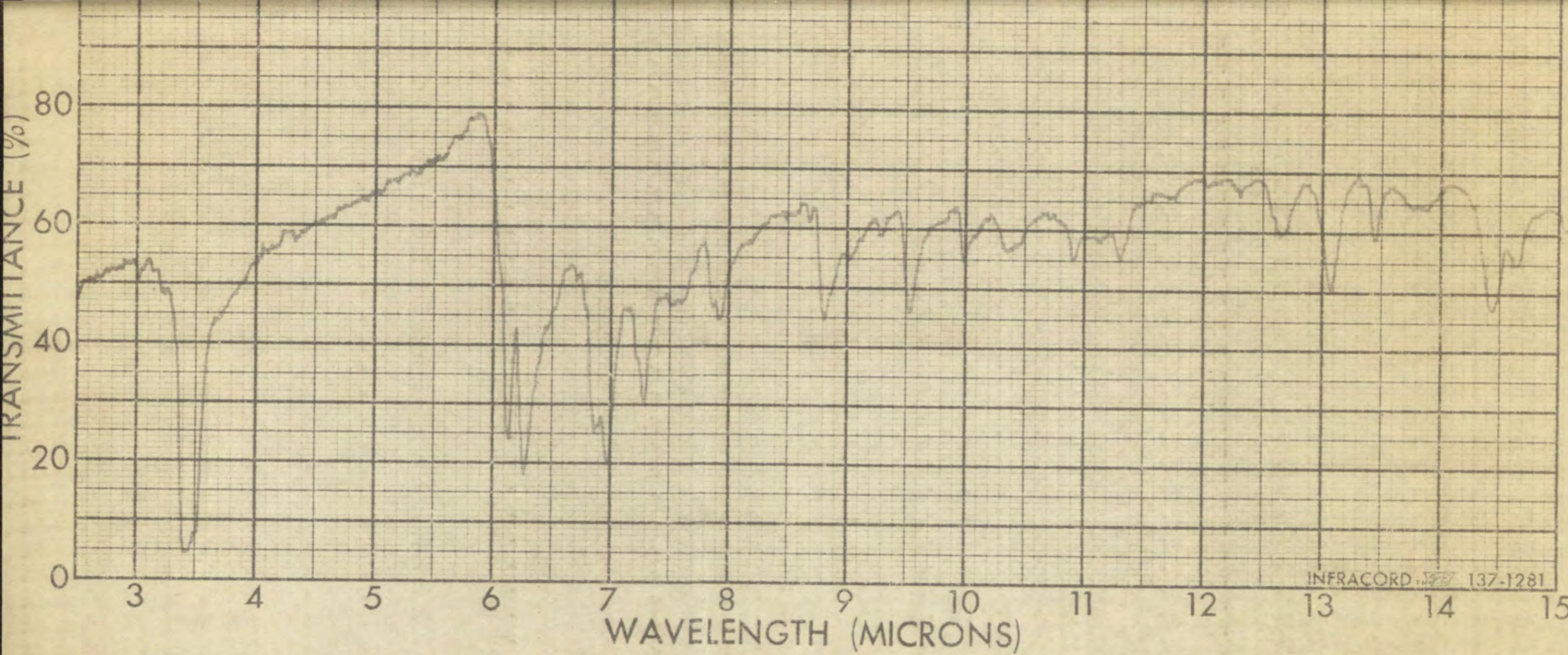
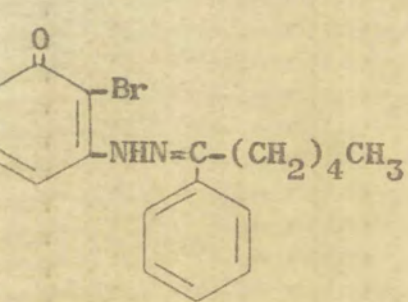


Plate XXXI: Infrared Spectrum of Hexanophenone 4-bromo-3-pyridazon-5-ylhydrazone



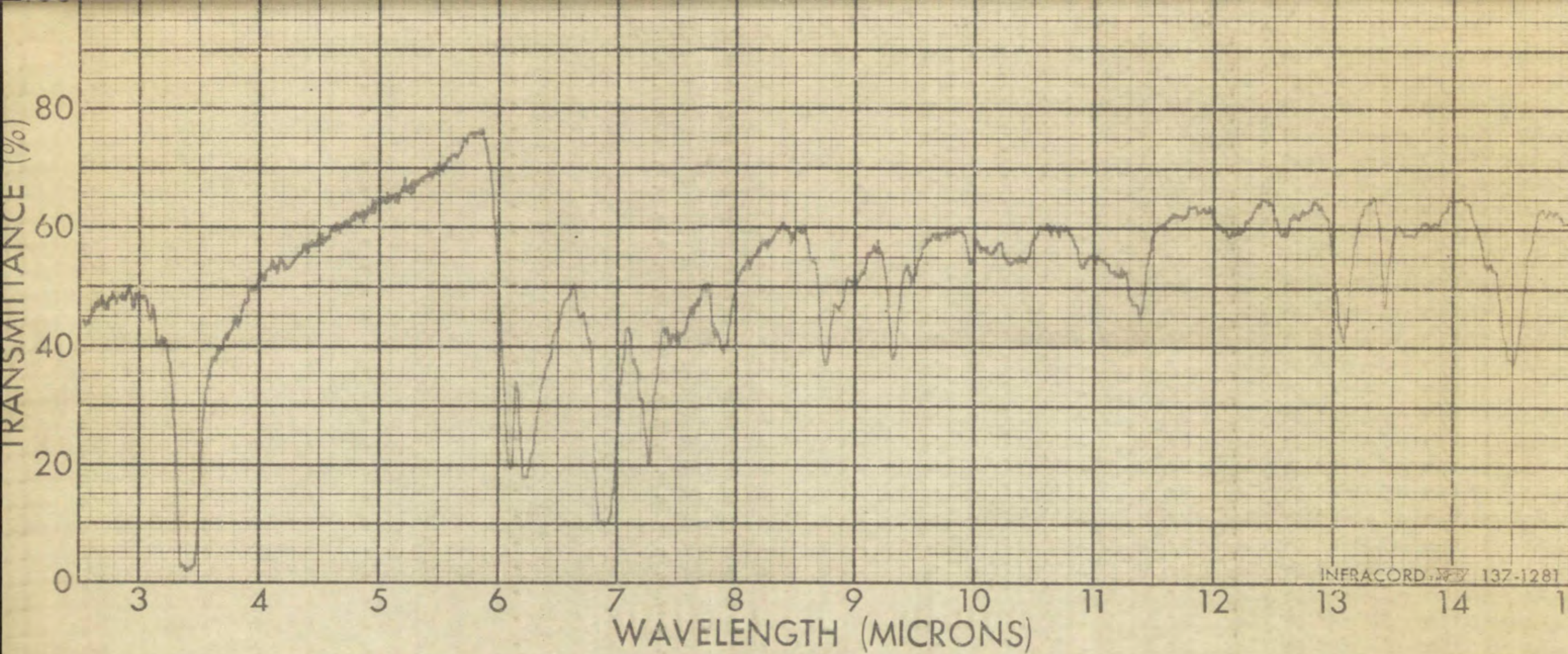
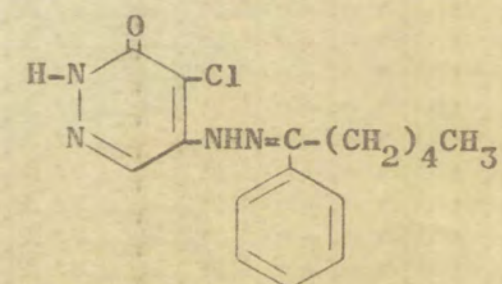


Plate XXXII: Infrared Spectrum of Hexanophenone 4-chloro-3-pyridazon-5-ylhydrozone



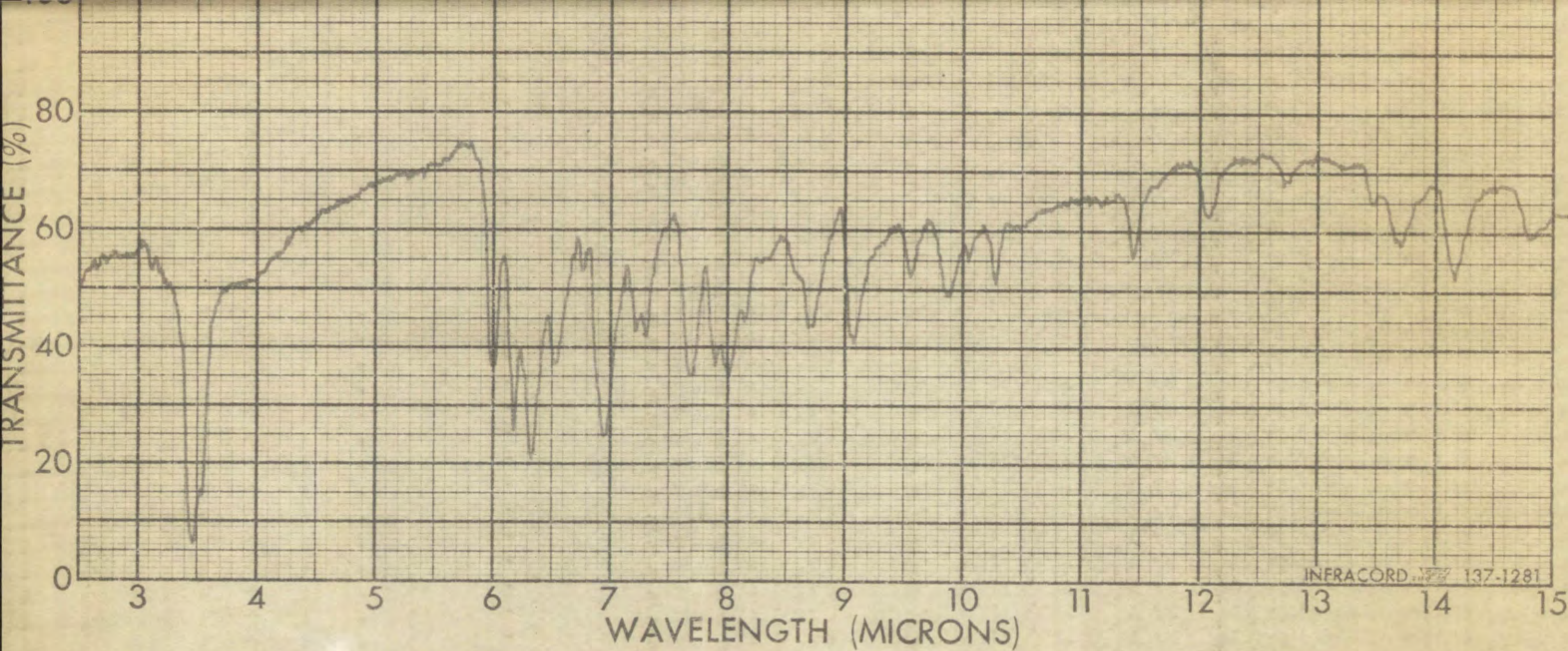
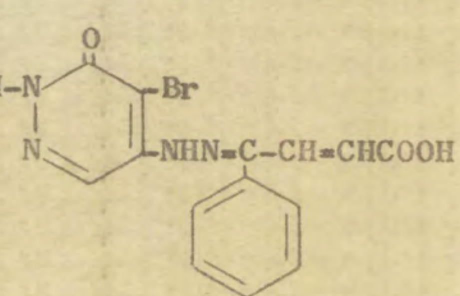


Plate XXXIII: Infrared Spectrum of β-Benzoylacrylic acid 4-bromo-3-pyridazon-5-ylhydrazone



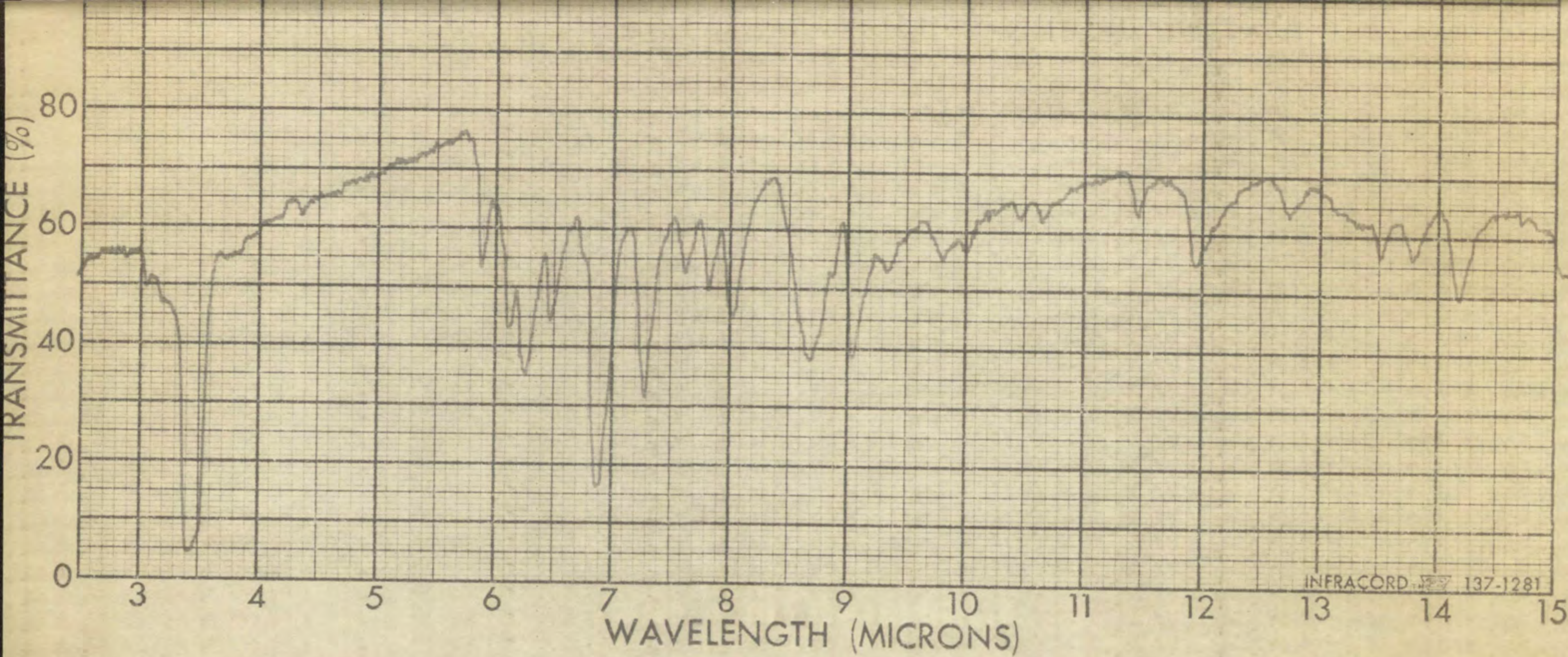
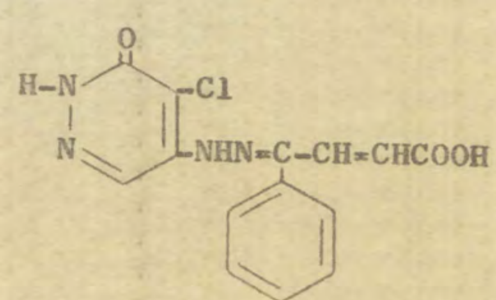


Plate XXXIV: Infrared Spectrum of β-Benzoylacrylic acid 4-chloro-3-pyridazon-5-ylhydrazone



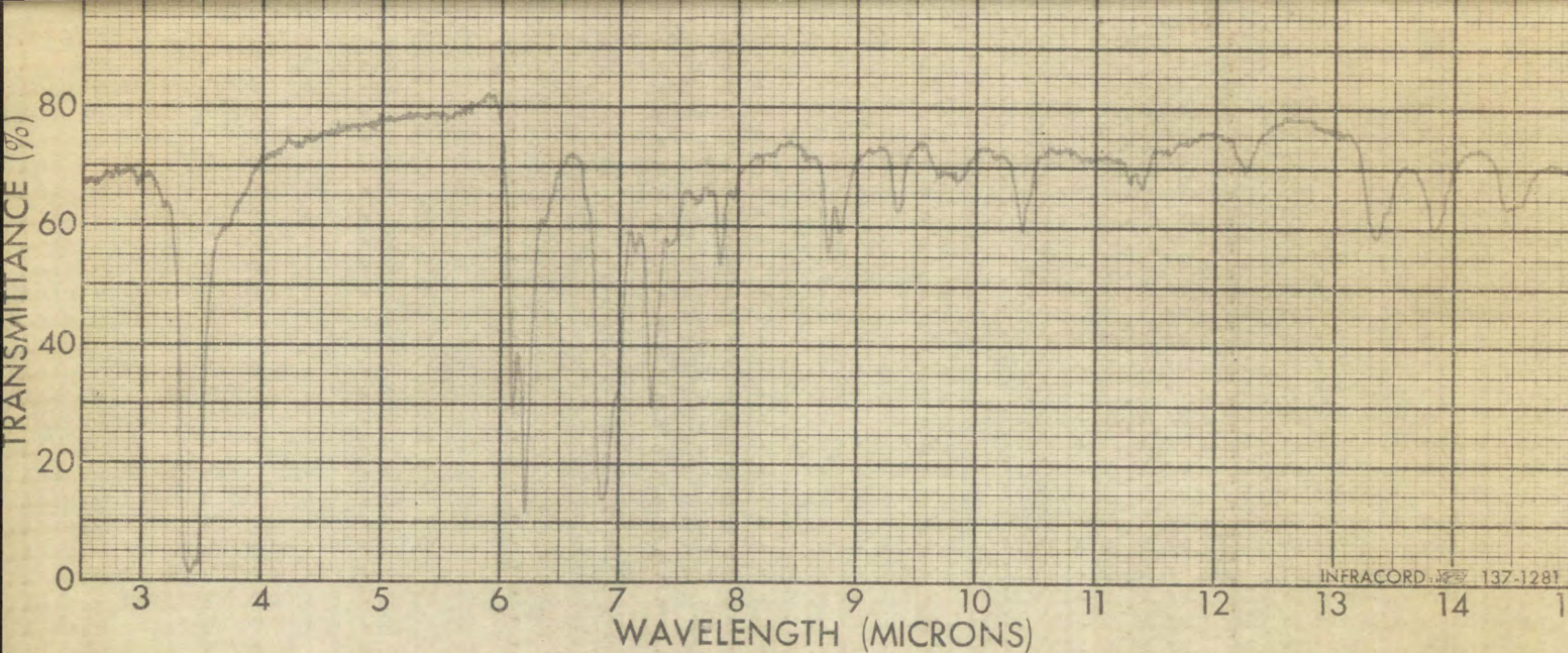
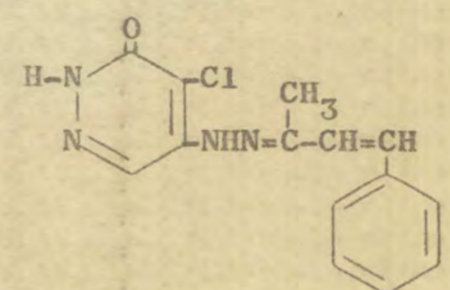


Plate XXXV: Infrared Spectrum of Methyl styryl ketone 4-chloro-3-pyridazon-5-ylhydrazone



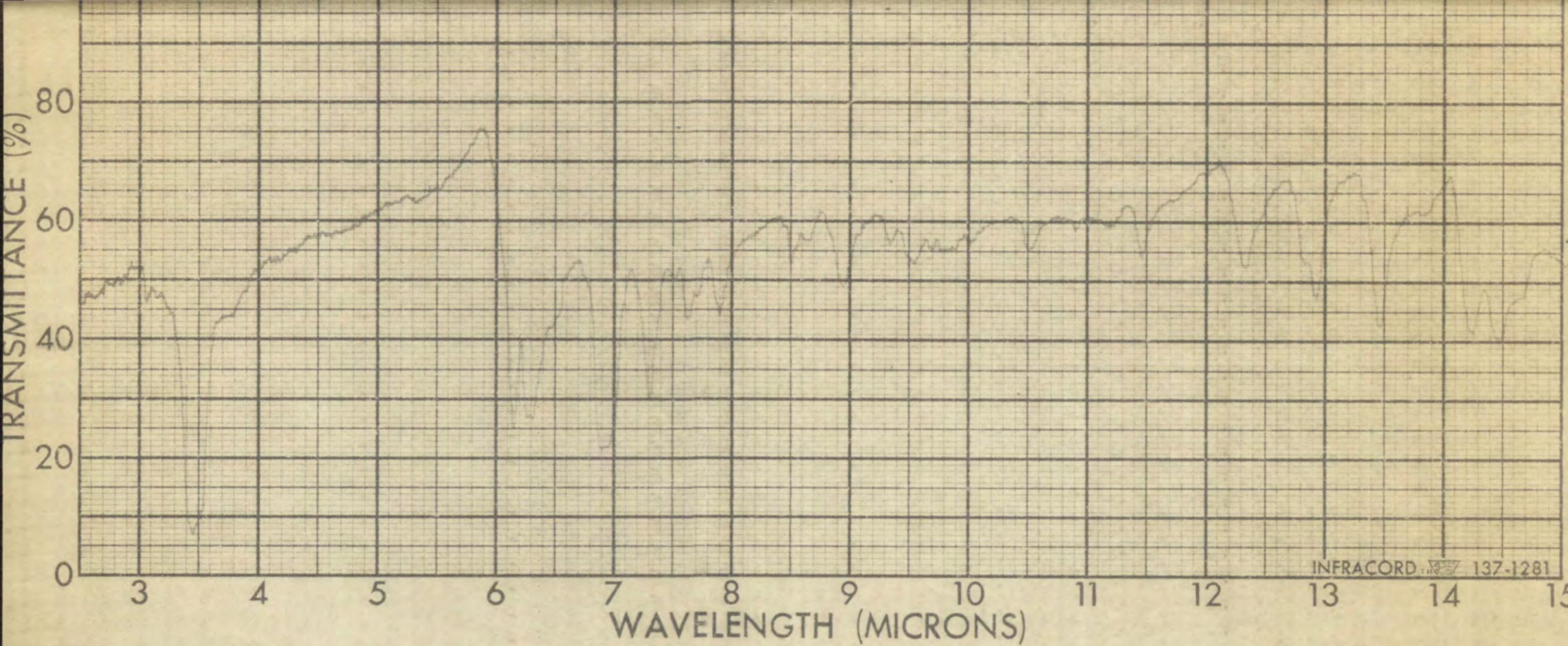
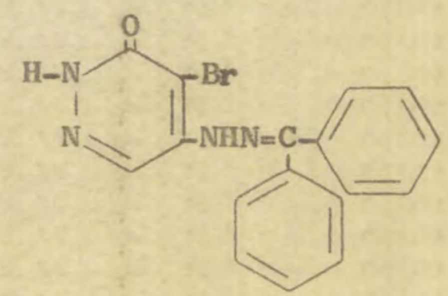


Plate XXXVI: Infrared Spectrum of Benzophenone 4-bromo-3-pyridazon-5-ylhydrazone



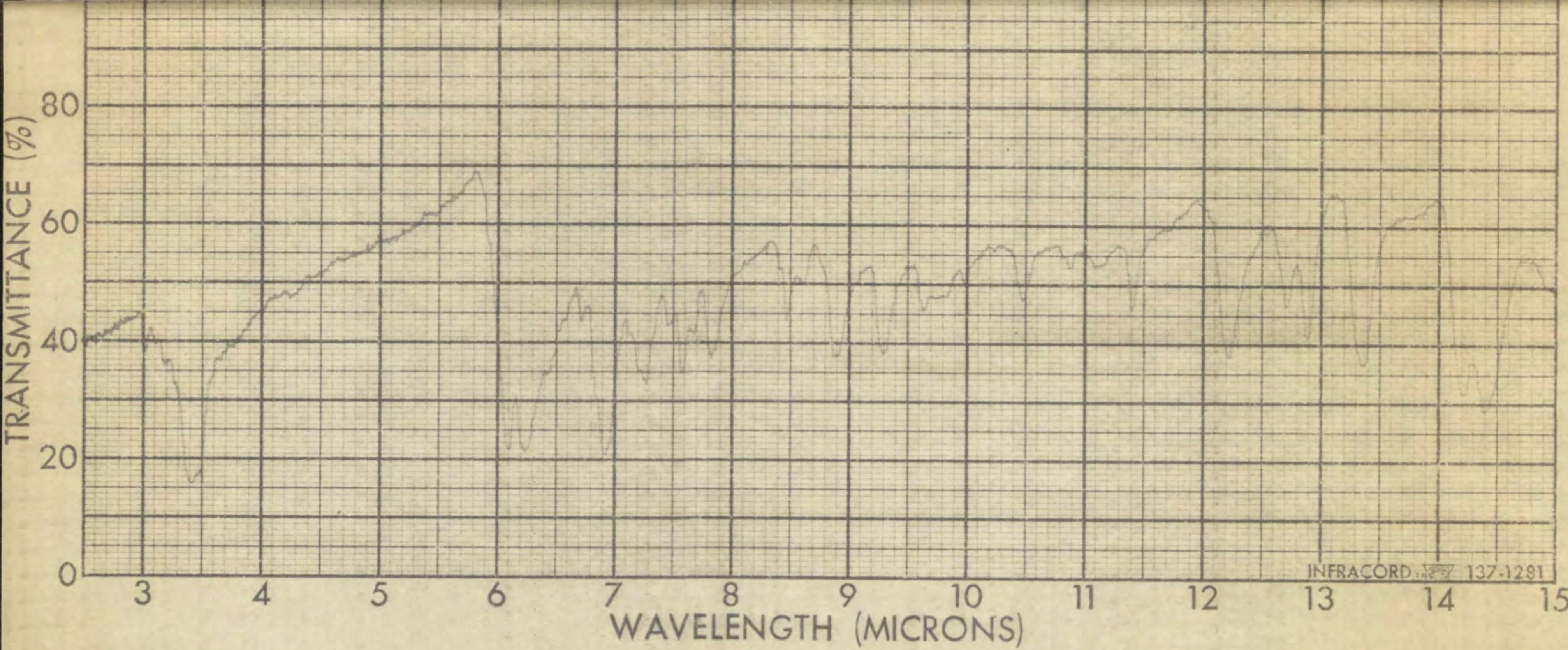
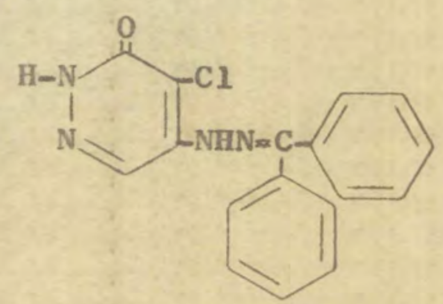


Plate XXXVII: Infrared Spectrum of Benzophenone 4-chloro-3-pyridazon-5-ylhydrazone



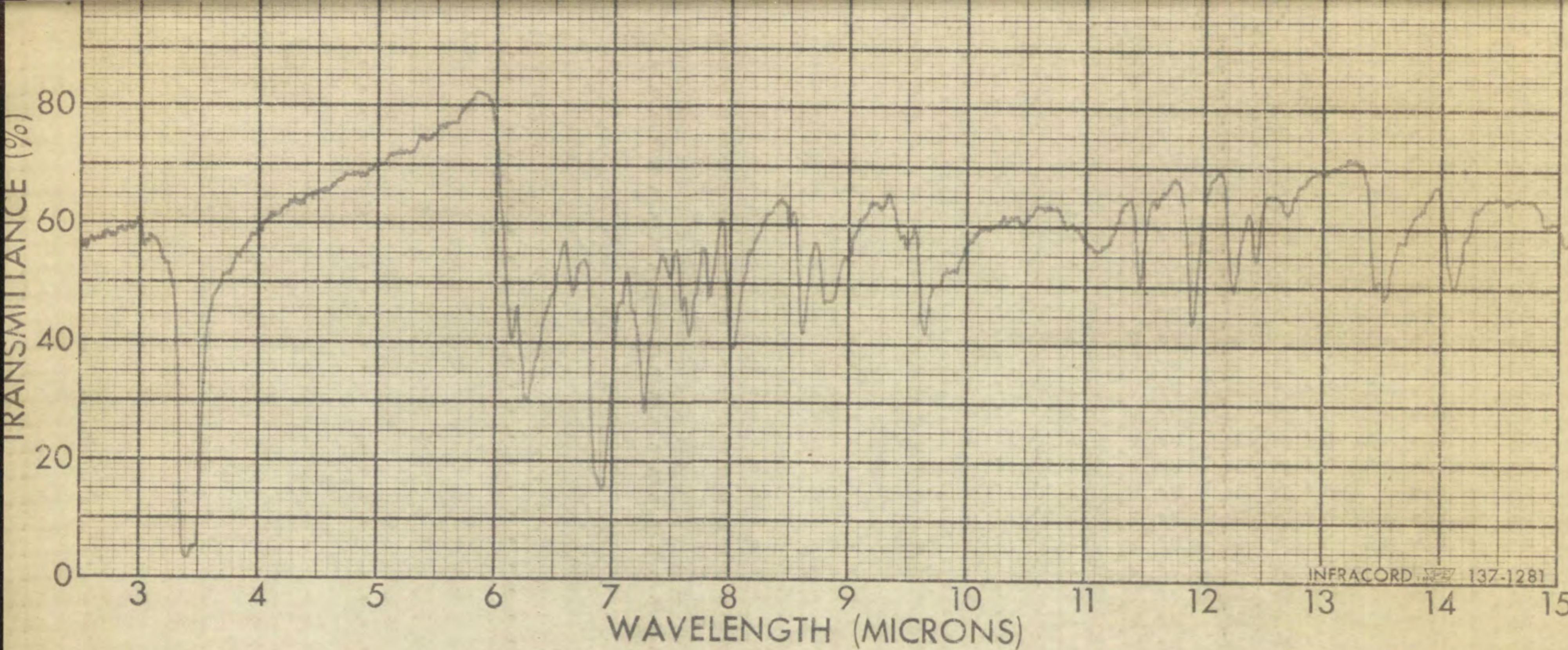
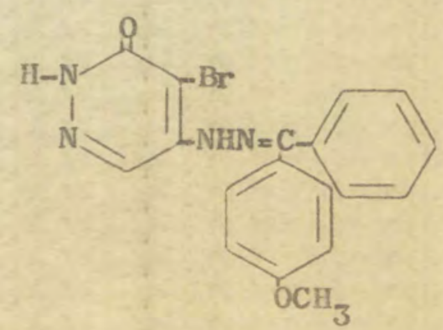


Plate XXXVIII: Infrared Spectrum of p-Methoxybenzophenone 4-bromo-3-pyridazon-5-ylhydrazone



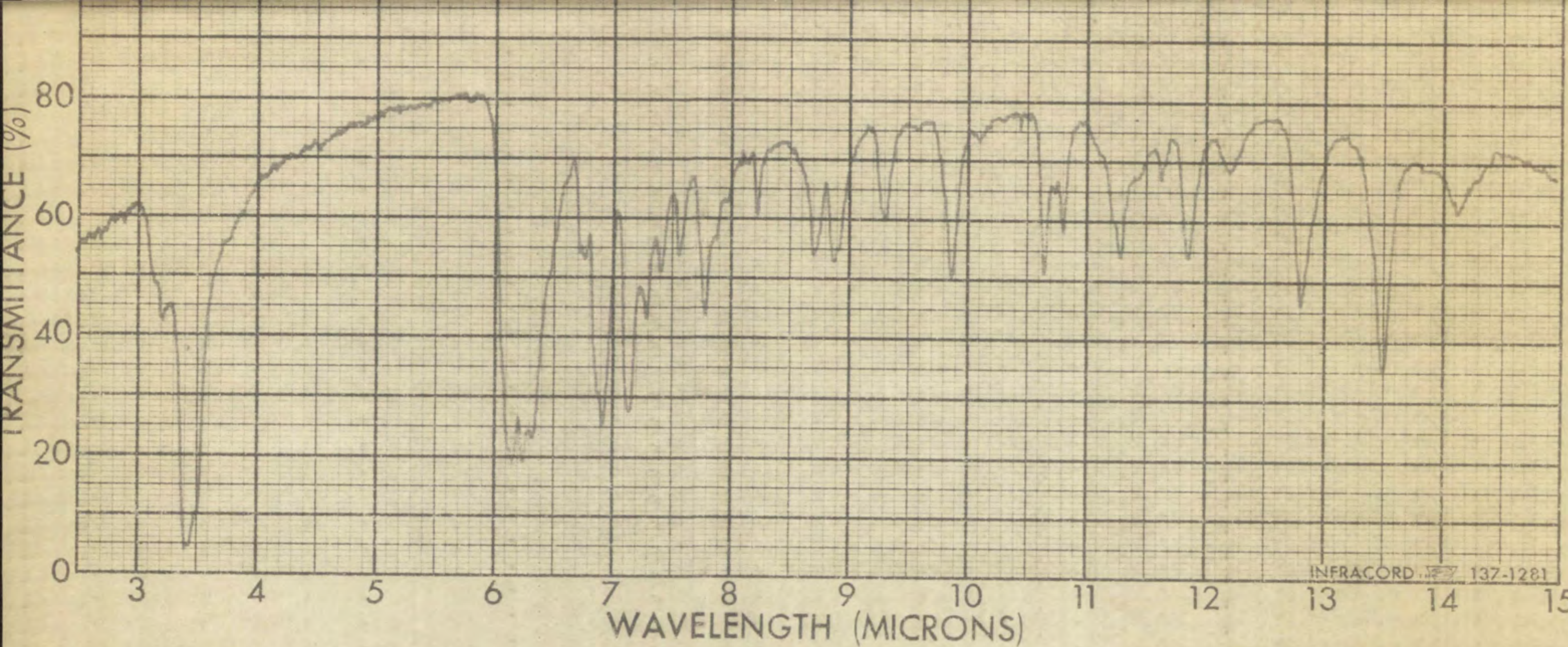
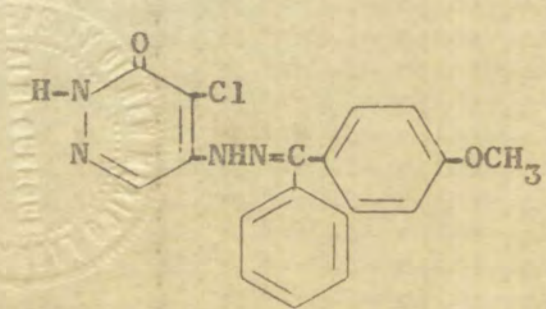


Plate XXXIX: Infrared Spectrum of p-Methoxybenzophenone 4-chloro-3-pyridazon-5-ylhydrazone



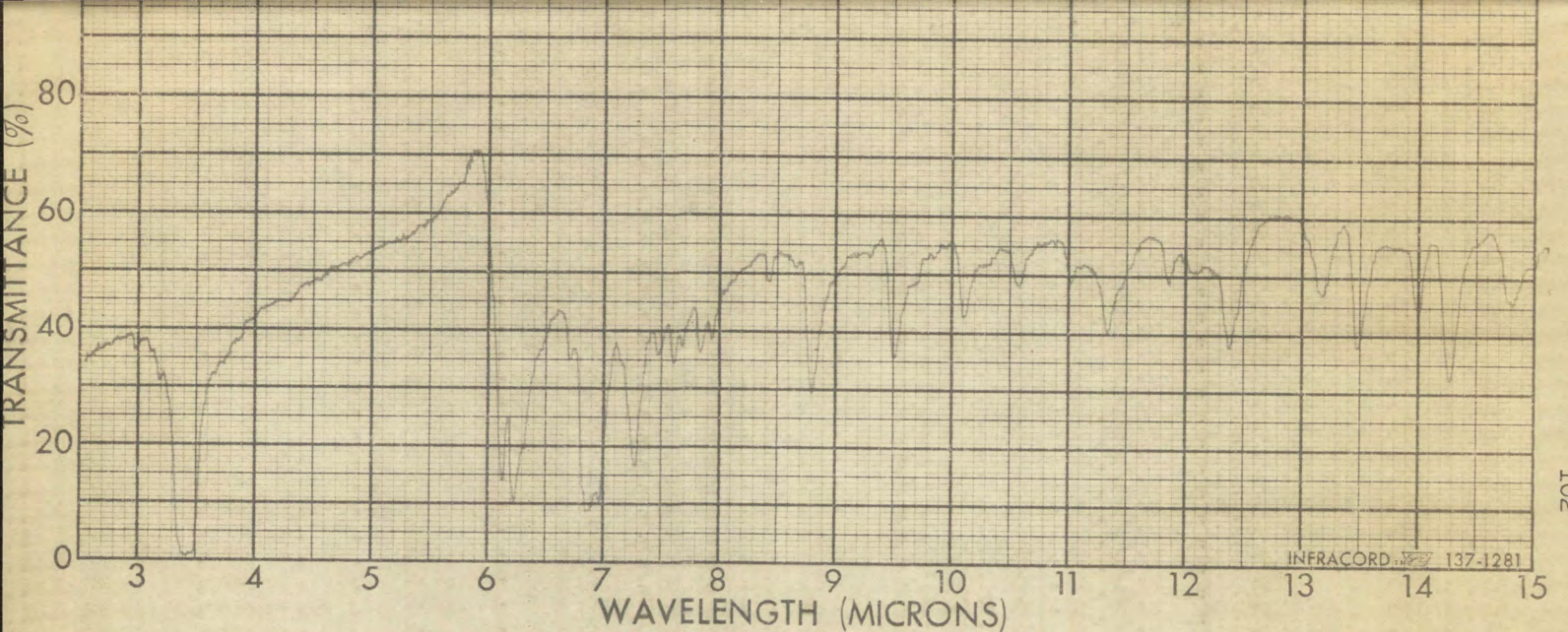
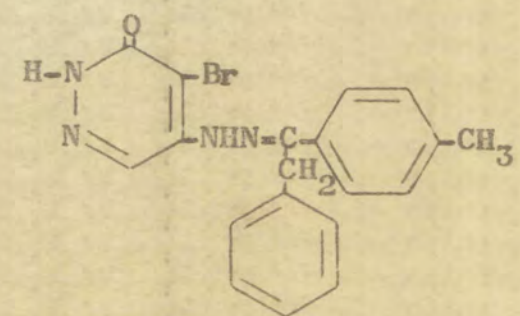


Plate XL: Infrared Spectrum of p-Methylphenyl benzyl ketone 4-bromo-3-pyridazon-5-ylhydrazone



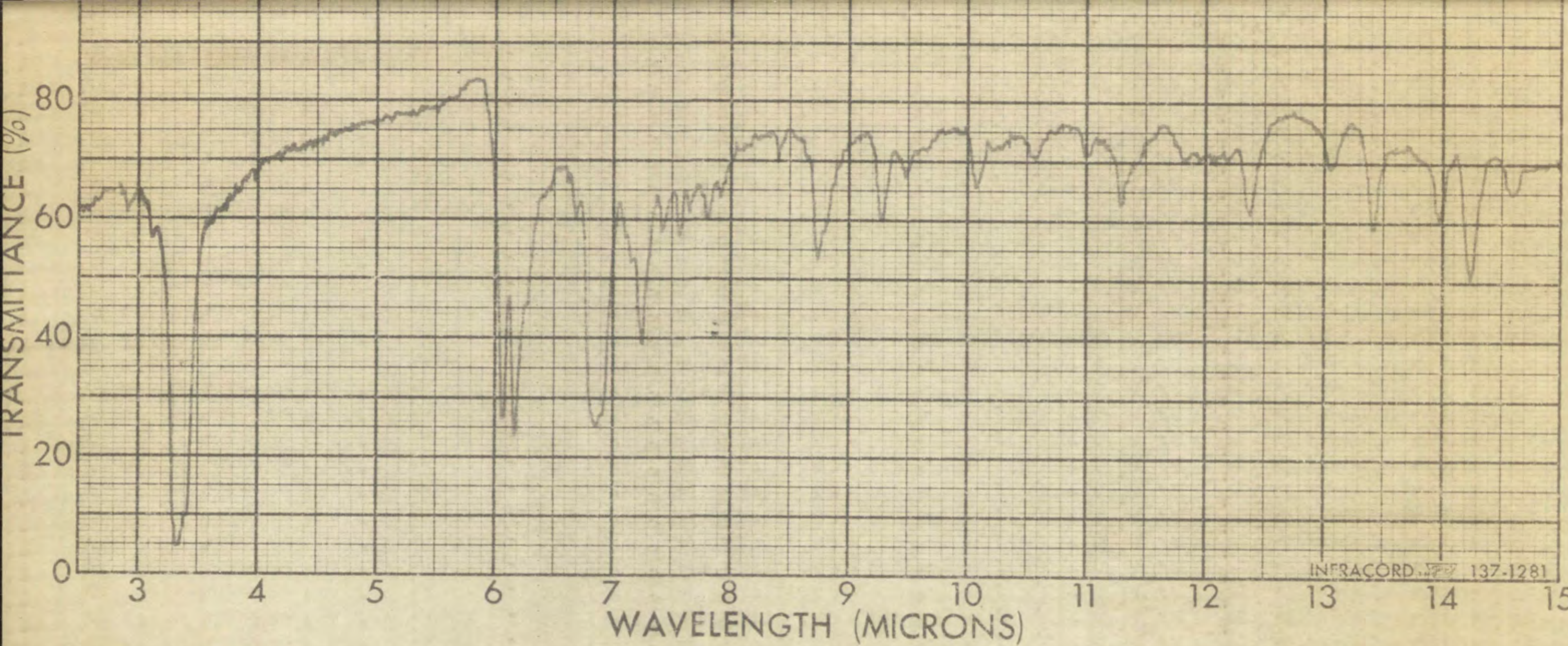
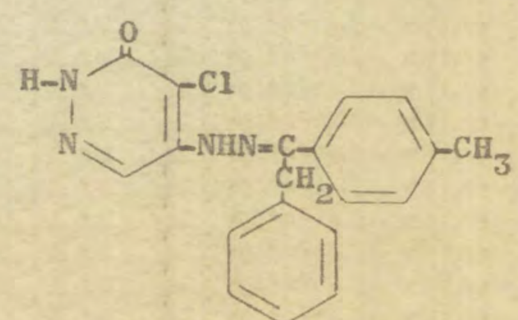


Plate XLI: Infrared Spectrum of p-Methylphenyl benzyl ketone 4-chloro-3-pyridazon-5-ylhydrazone



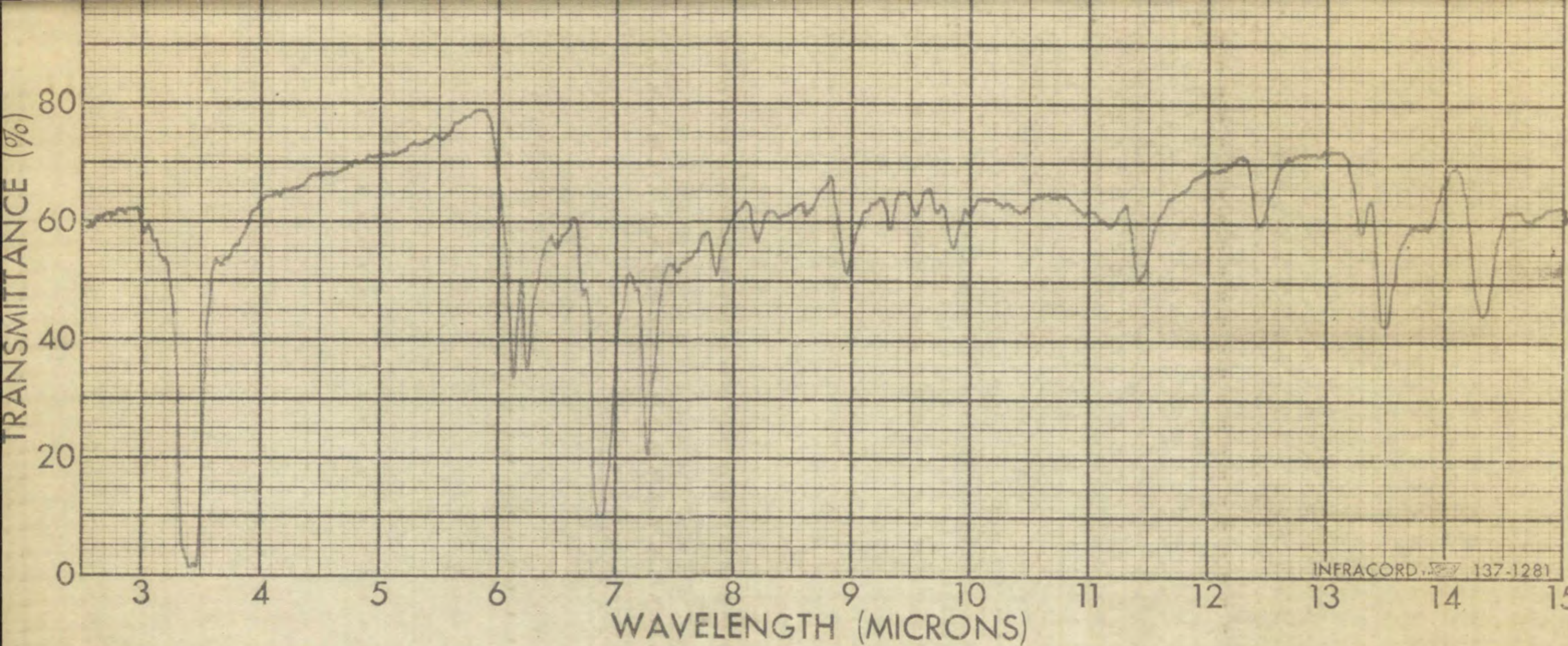
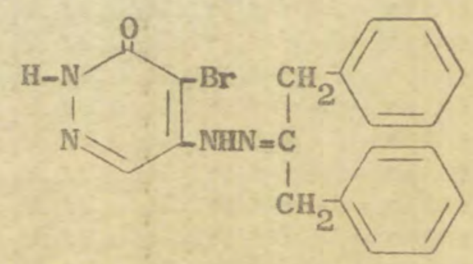


Plate XLII: Infrared Spectrum of Dibenzyl ketone 4-bromo-3-pyridazon-5-ylhydrazone



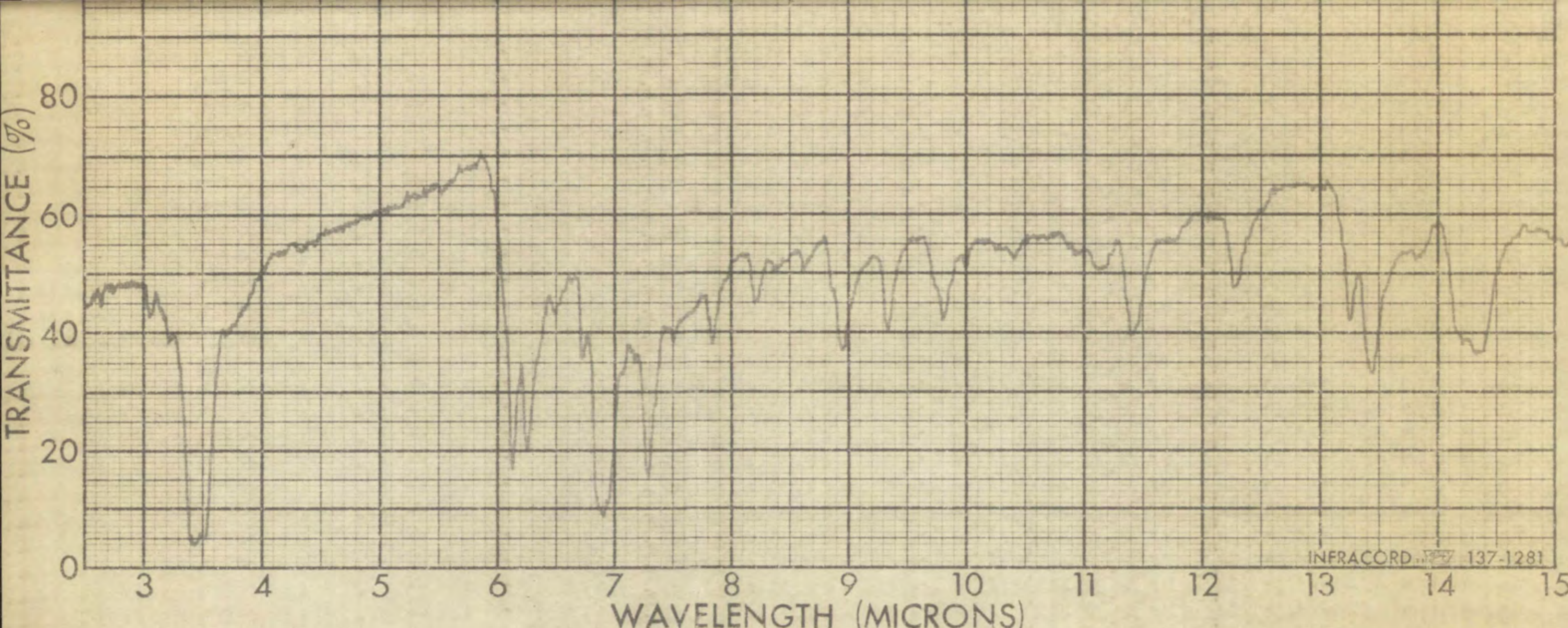
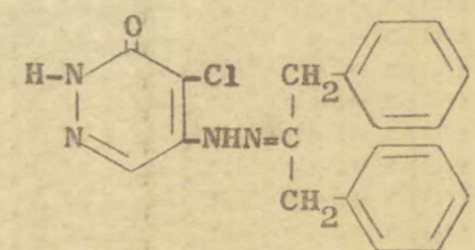
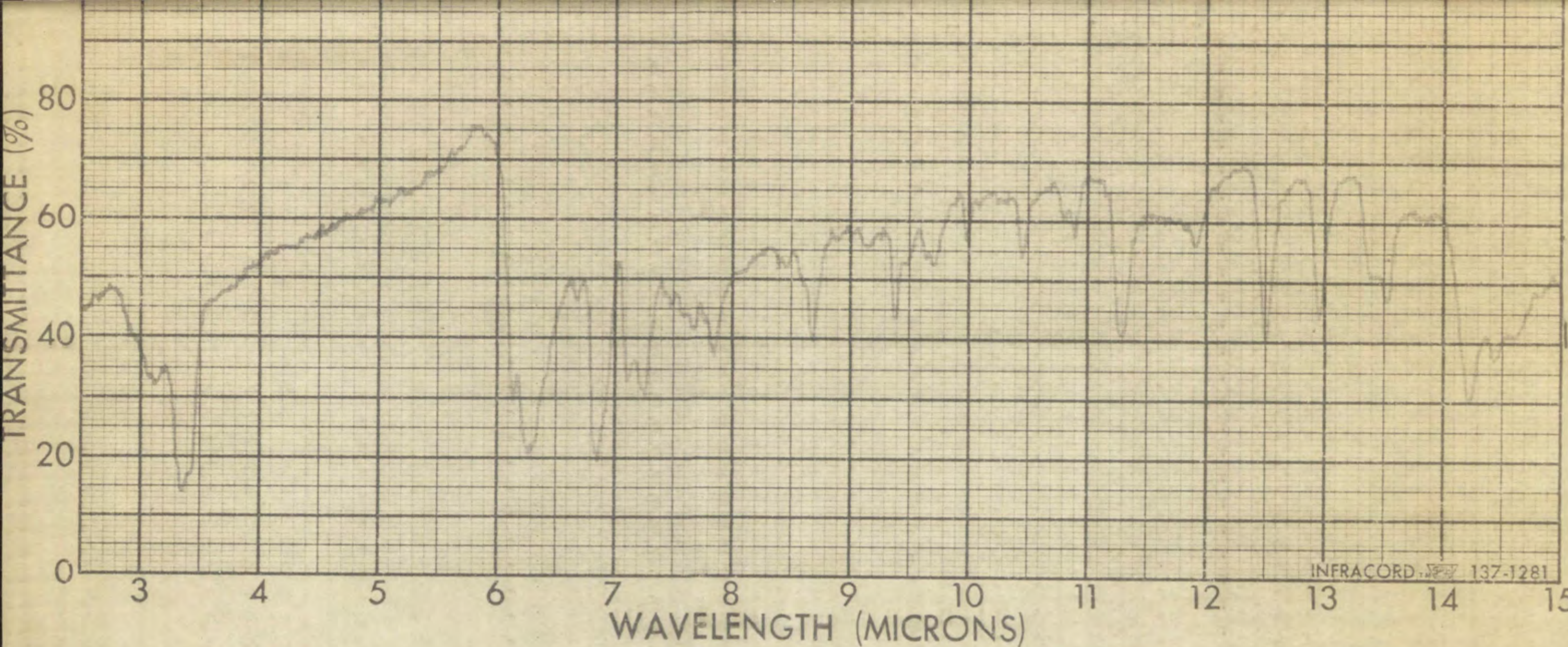


Plate XLIII: Infrared Spectrum of Dibenzyl ketone 4-chloro-3-pyridazon-5-ylhydrazone





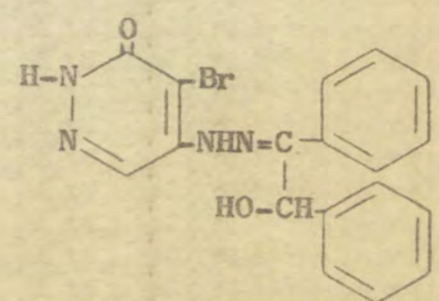


Plate XLIV: Infrared Spectrum of Benzoin 4-bromo-3-pyridazon-5-ylhydrazone

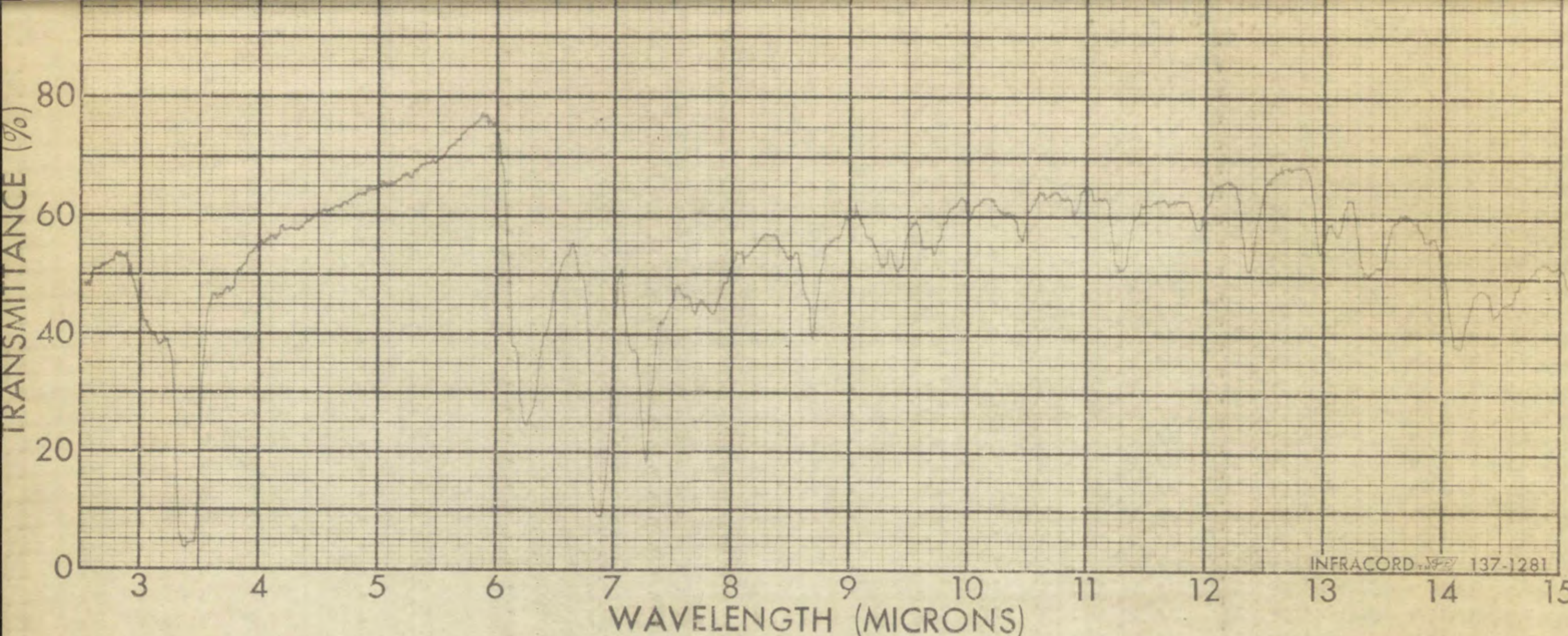
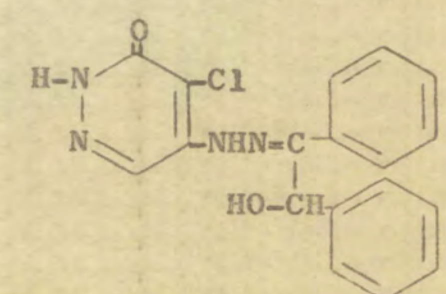


Plate XLV: Infrared Spectrum of Benzoin 4-chloro-3-pyridazon-5-ylhydrazone



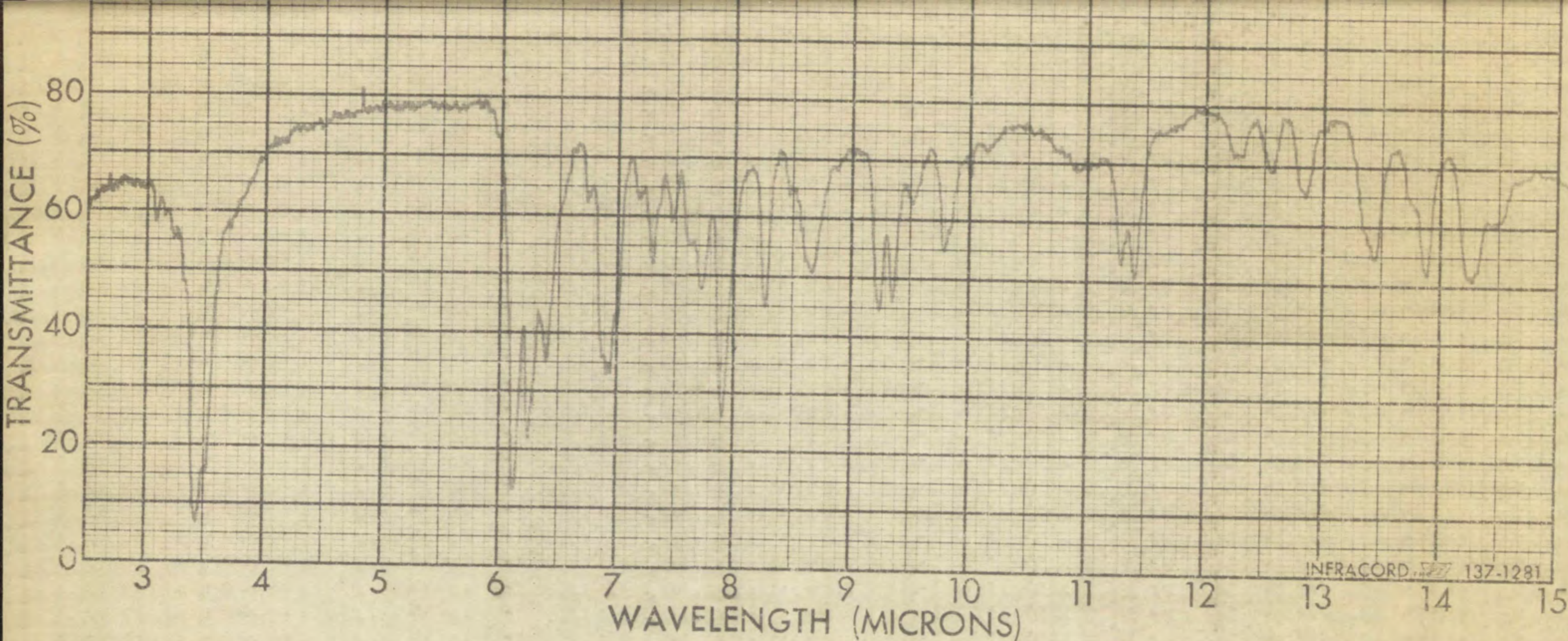
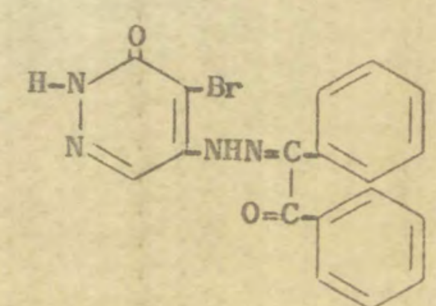


Plate XLVI: Infrared Spectrum of Benzil mono-(4-bromo-3-pyridazon-5-ylhydrazone)



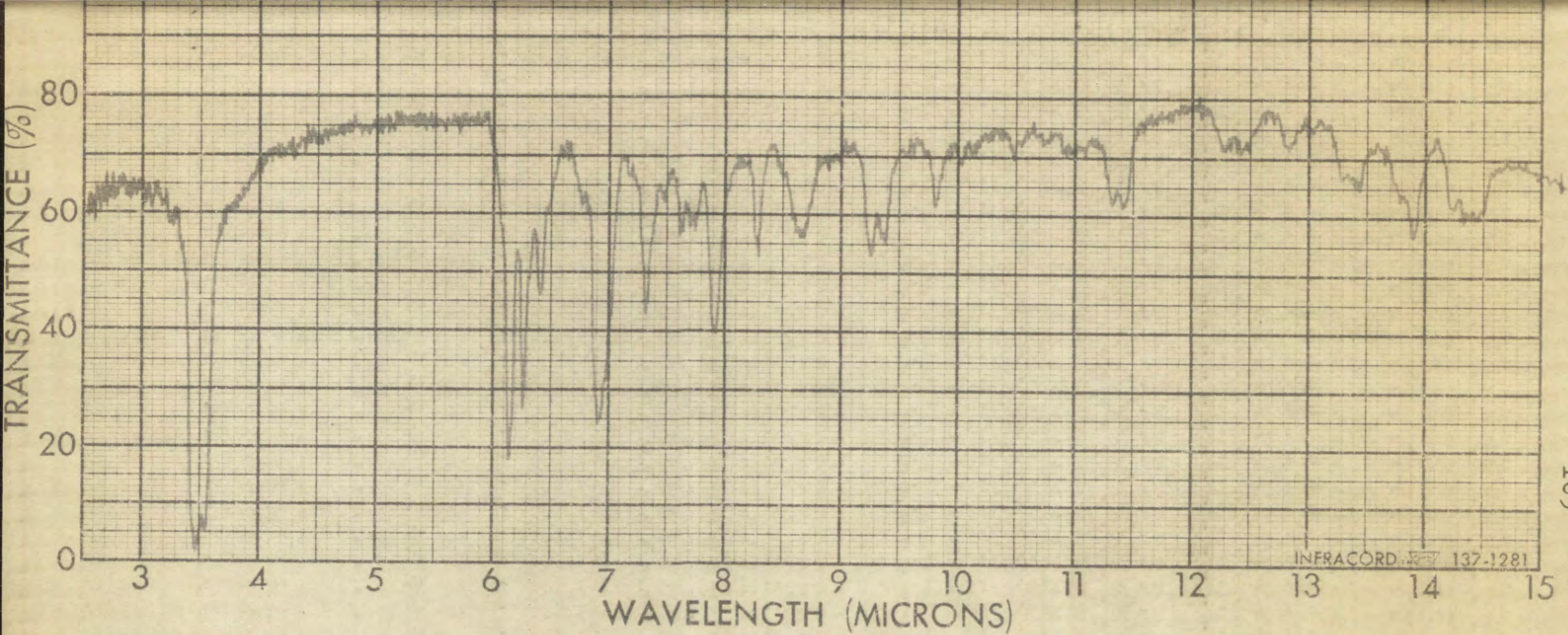
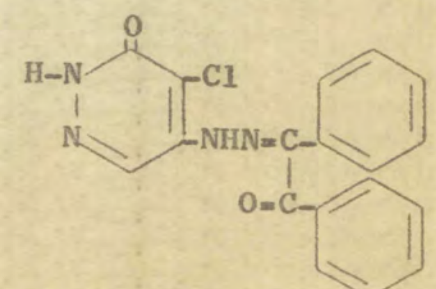


Plate XLVII: Infrared Spectrum of Benzil mono-(4-chloro-3-pyridazon-5-ylhydrazone)



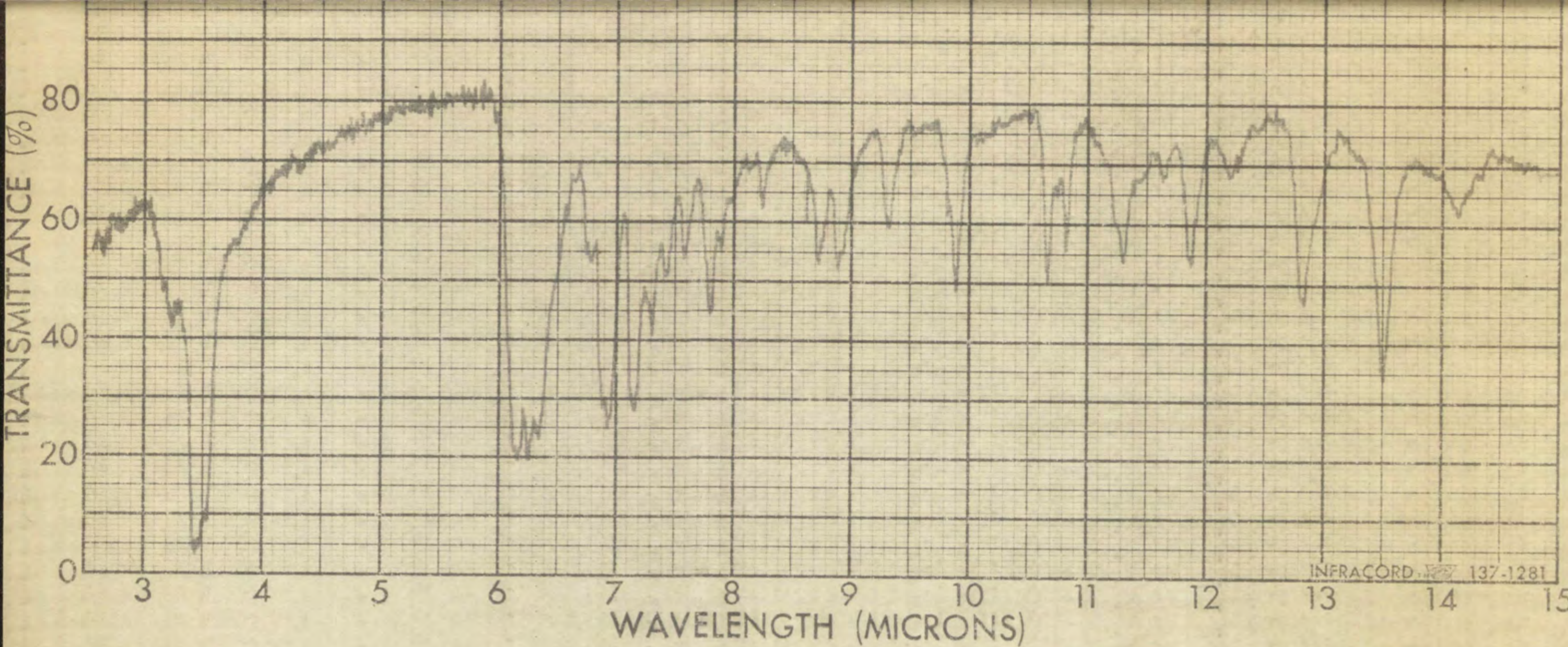
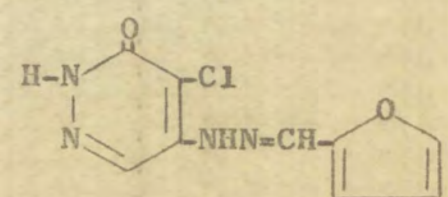


Plate XLVIII: Infrared Spectrum of 2-Furanaldehyde 4-chloro-3-pyridazon-5-ylhydrazone



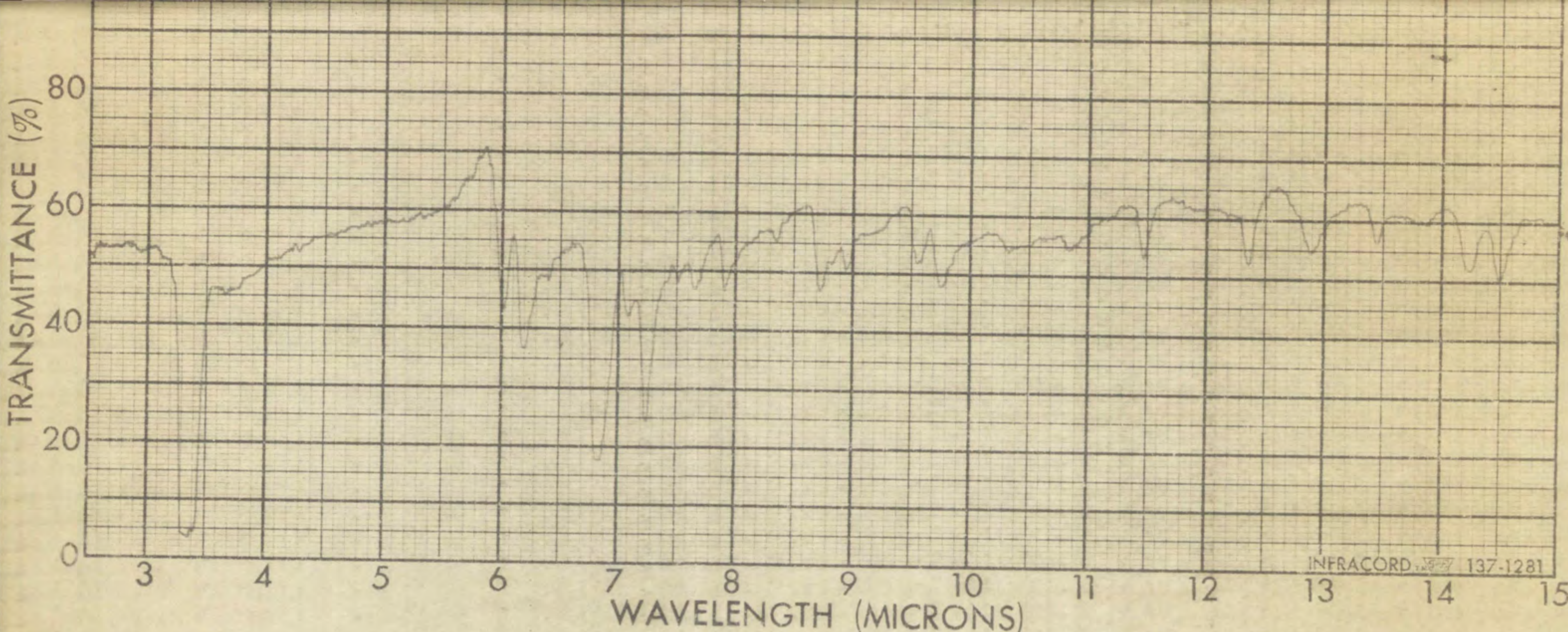
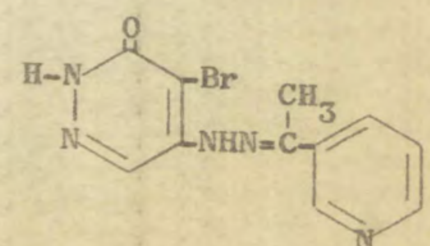


Plate XLIX: Infrared Spectrum of 3-Acetylpyridine 4-bromo-3-pyridazon-5-ylhydrazone



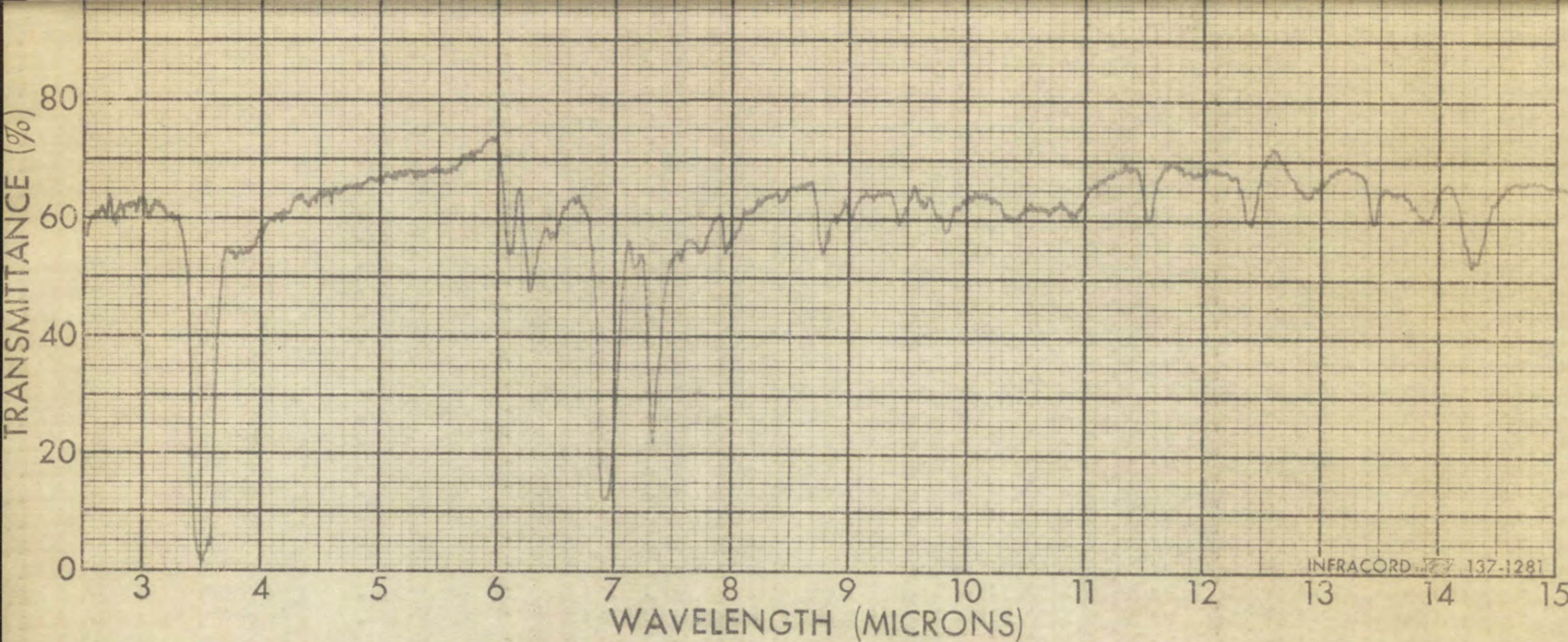
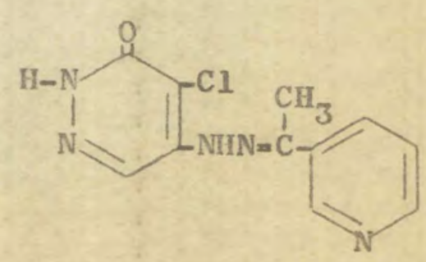


Plate L: Infrared Spectrum of 3-Acetylpyridine 4-chloro-3-pyridazon-5-ylhydrazone



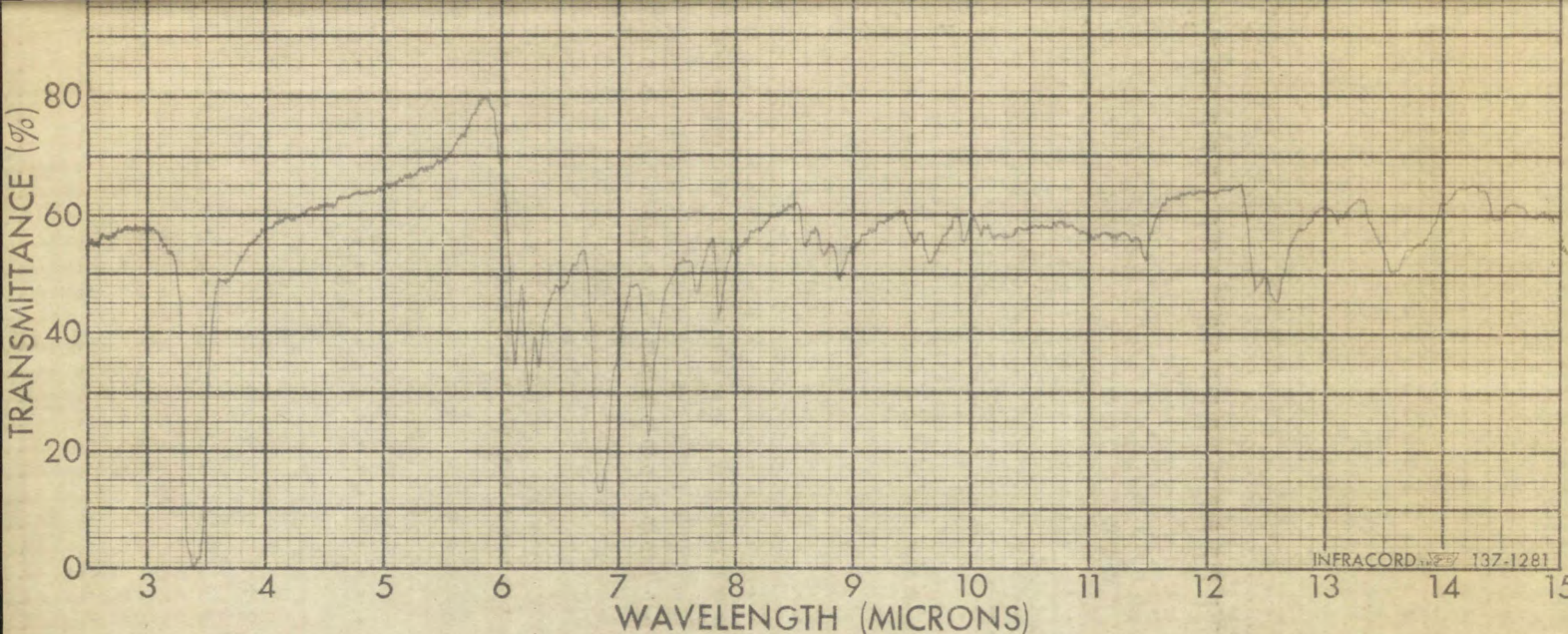
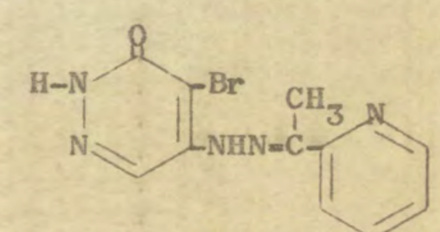


Plate LI: Infrared Spectrum of 2-Acetylpyridine 4-bromo-3-pyridazon-5-ylhydrazone



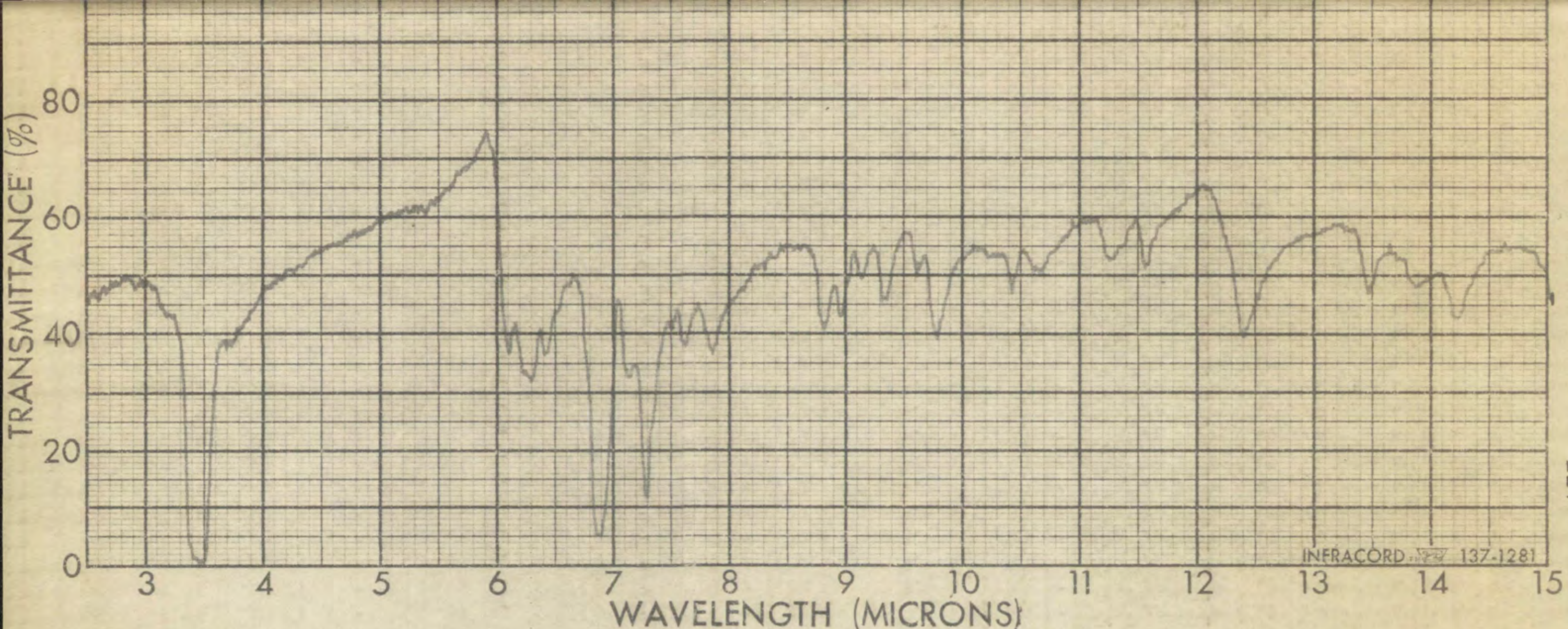
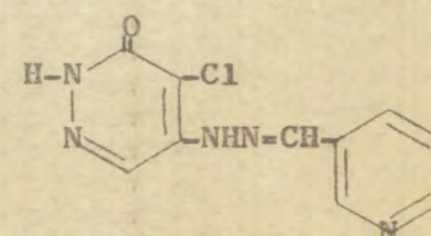
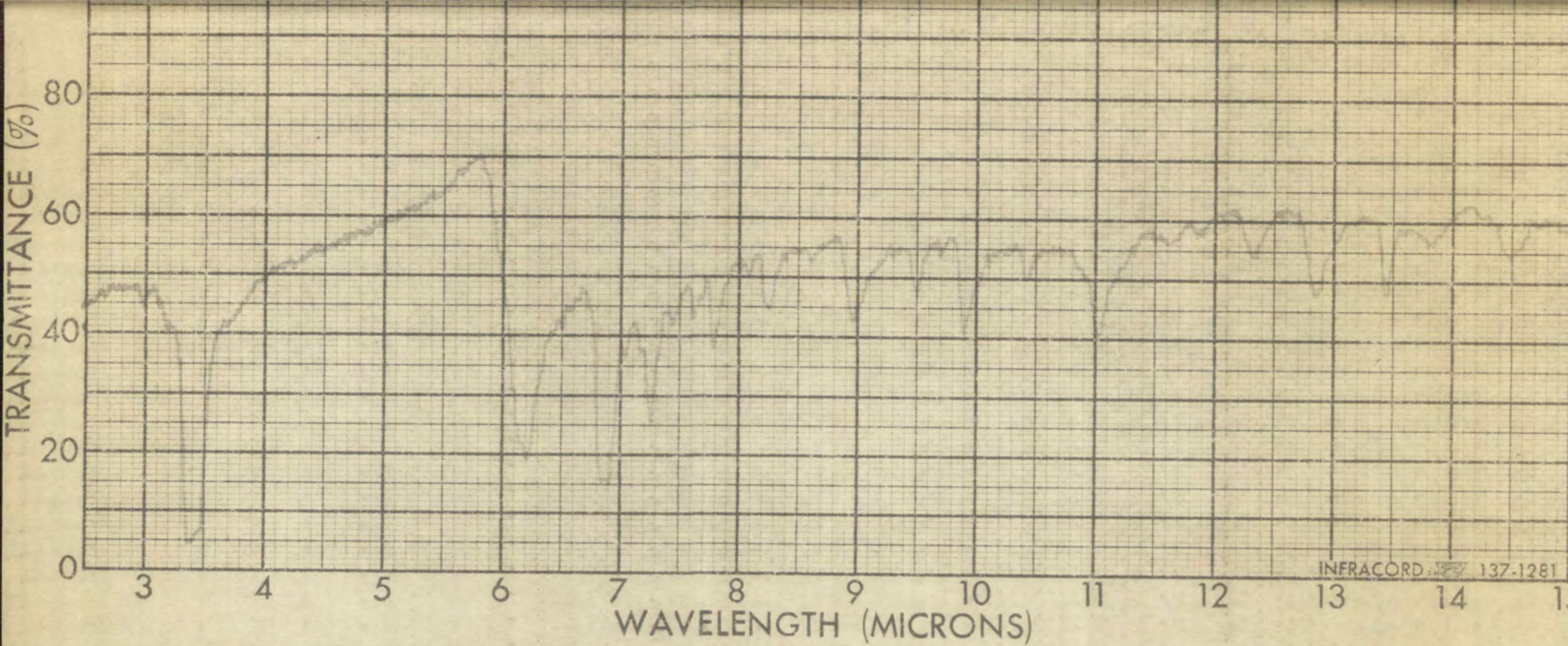


Plate LII: Infrared Spectrum of 3-Pyridinaldehyde 4-chloro-3-pyridazon-5-ylhydrazone





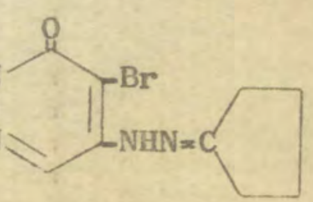


Plate LIII: Infrared Spectrum of Cyclopentanone 4-bromo-3-pyridazon-5-ylhydrazone

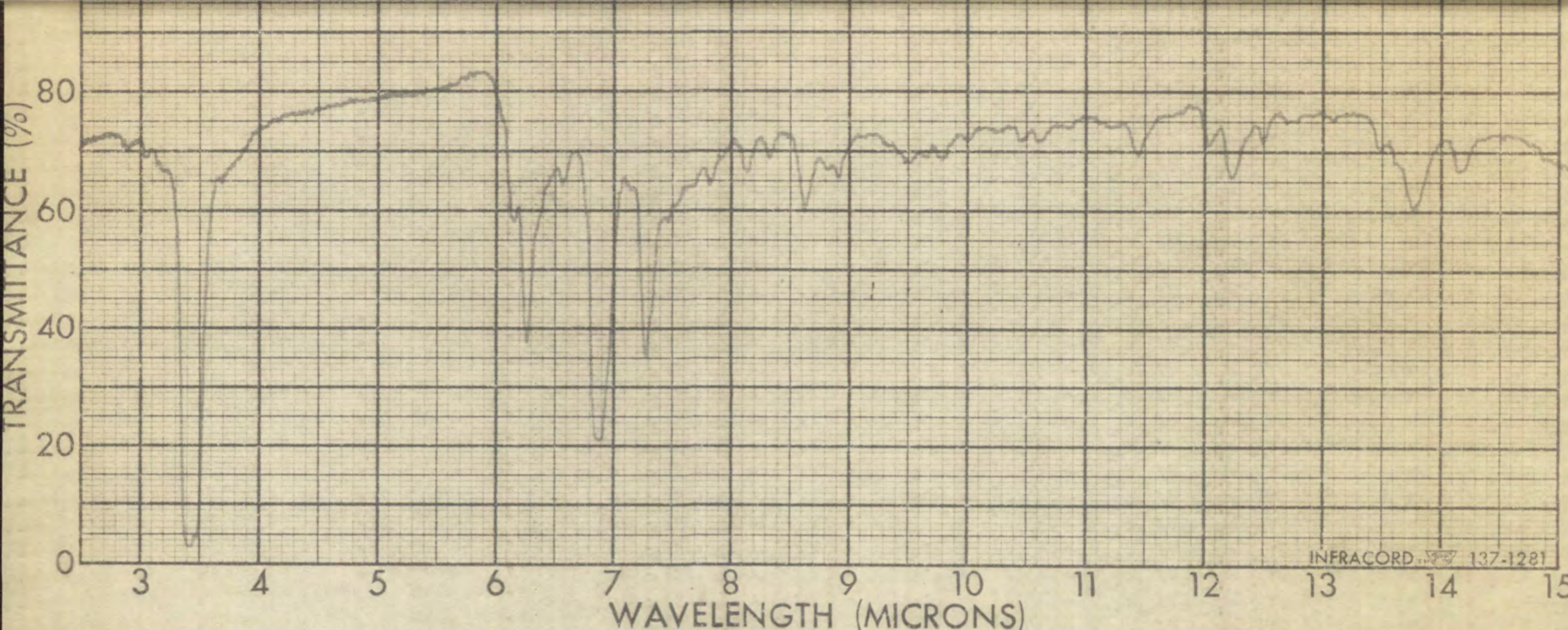
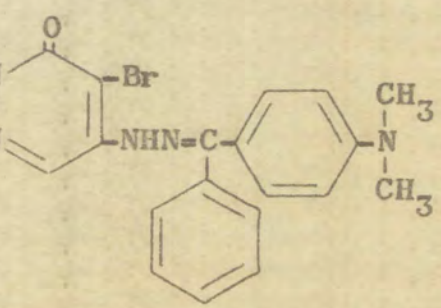


Plate LIV: Infrared Spectrum of p-Dimethylaminobenzophenone 4-bromo-3-pyridazon-5-ylhydrazone



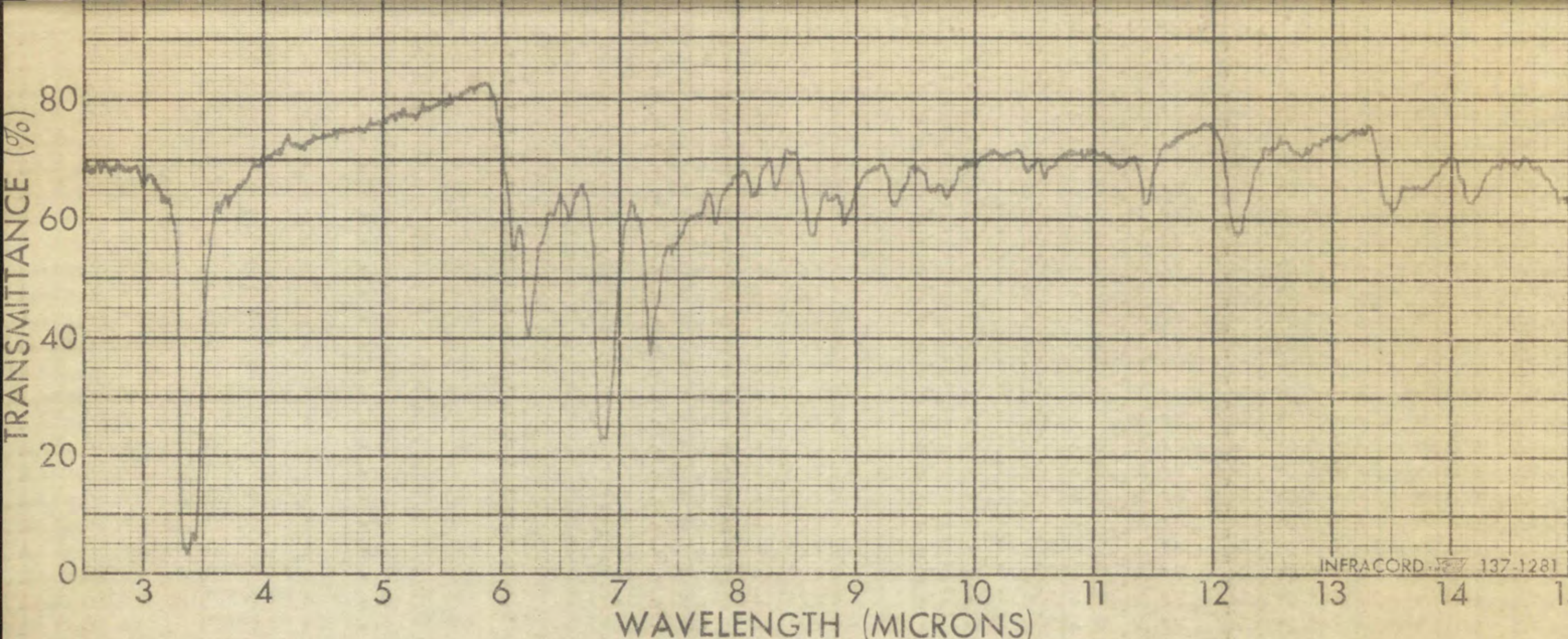
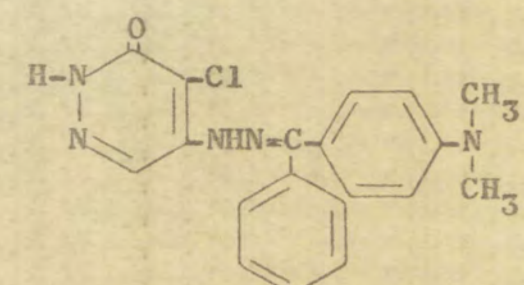


Plate LV: Infrared Spectrum of p-Dimethylaminobenzophenone 4-chloro-3-pyridazon-5-ylhydrazone



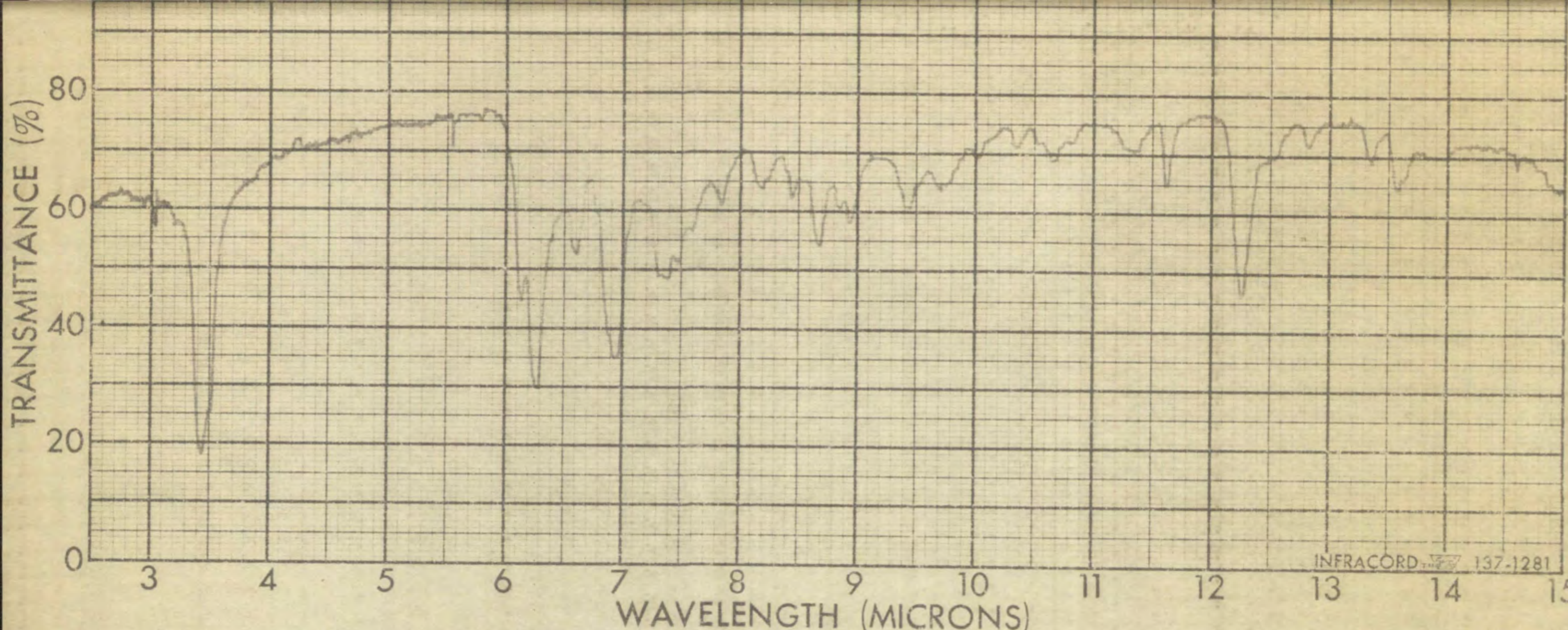
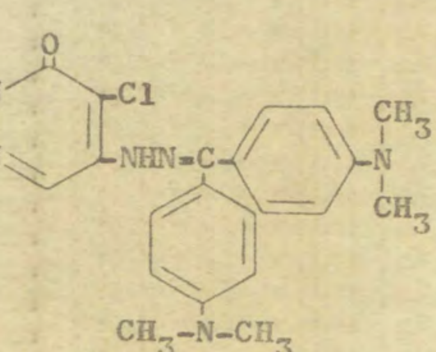


Plate LVI: Infrared Spectrum of 4,4'-Bis (dimethylamino)-benzophenone 4-chloro-3-pyridazon-5-ylhydrazone



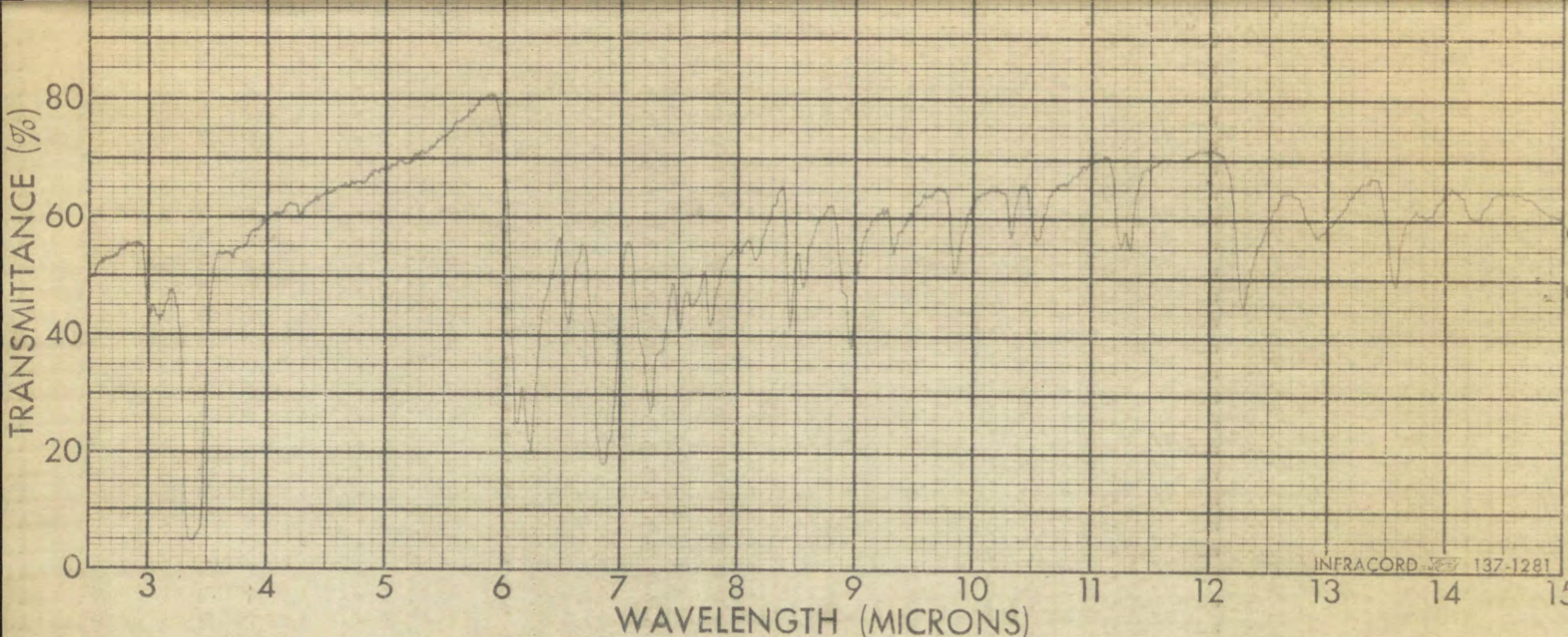
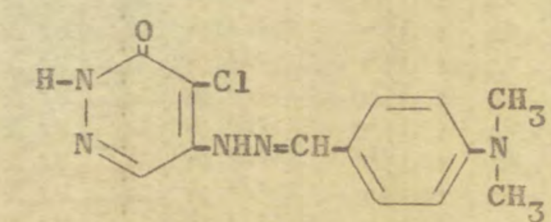


Plate LVII: Infrared Spectrum of p-Dimethylaminobenzaldehyde 4-chloro-3-pyridazon-5-ylhydrazone



IV. THE EFFECT OF SELECTED PYRIDAZONES ON THE RESPIRATION OF BACTERIA

A. Introduction

Such a wide variety of pharmacological activities has been discovered among the pyridazones[22-36] and compounds containing the hydrazino moiety[35] that any hydrazinopyridazone may be considered potentially active. The blind screening of compounds for effect on the respiration and growth of microorganisms is a reasonable first step for the determination of activity.

The oxidation of glucose is a reaction common to most forms of plant and animal life. The Embden-Meyerhoff scheme for the dissimilation of glucose is among the best known and understood biochemical sequences and is for this reason chosen for preliminary screening studies.

The determination of oxygen uptake does not in itself define a specific activity, for many biochemical reactions are integrated in the respiration cycle. Similarly, oxygen consumption cannot be directly related to growth of the organisms. However, any compound that affects respiration either by stimulation or depression warrants further investigation.

[illegible]

[illegible]

[illegible]

[illegible] has been [illegible]

[illegible]

[illegible]

compounds potentially active. The first step [illegible]

[illegible]

[illegible] first step for [illegible] activity

[illegible]

[illegible]

[illegible]

[illegible]

[illegible] screening studies.

[illegible]

a specific activity, for [illegible] questions are interest[illegible]

[illegible]

[illegible] However, [illegible]

suggest that [illegible]

[illegible] further investigation.

B. Materials and Methods

Standard Warburg respirometry[41] was used to test the effect of some 4-halo-3-pyridazon-5-ylhydrazones on the respiration of certain bacteria.

Each of the compounds was tested with the following three organisms:[42]

Escherichia coli, a Gram negative rod. Facultative anaerobe. Produces CO_2 and H_2 in almost equal amounts from glucose.

Staphylococcus aureus, a Gram positive coccus. Facultative anaerobe. Produces only acid from glucose and can ferment glucose under anaerobic conditions.

Bacillus subtilis, a Gram positive, spore-forming rod. Aerobe. Generally ferments carbohydrates with the production of acid.

The organisms were grown in Kolle flasks on nutrient agar at 37°C for 18 hours. The bacteria were harvested by being washed from the surface of the agar with 20 ml. of Sorensen's phosphate buffer (pH 6.8). After thorough agitation, this buffer suspension of the organisms was measured by pipette directly into the Warburg reaction flasks.

Because of the extreme insolubility of the compounds, they were used as finely powdered suspensions in the buffer to obtain maximum concentration. The mass of the organisms and the

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41. Umbreit, Burris and Stauffer, Manometric Techniques, 3rd Edition.

42. Bergey's Manual of Determinative Bacteriology, 7th Edition, 1957.

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible] Produces only acid from [illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible] (Table [illegible])

[illegible] of the organisms was measured [illegible]

[illegible] (Table [illegible])

Because of the extreme [illegible] of the [illegible]

used as finely powdered suspensions in the [illegible]

[illegible]

41. [illegible]

42. [illegible]

compound was determined by the dry weight method and corrected for the buffer.

A M/20 solution of glucose was used as the substrate. A 20% potassium hydroxide solution served to absorb carbon dioxide in some of the flasks, while concentrated sulfuric acid was used in others to release bound carbon dioxide at the end of the reaction period.

The flasks were each filled to a total volume of 2.4 ml. Following a twenty minute equilibration period, manometer readings were recorded every ten minutes for a total of seventy minutes. Table VIII indicates the experimental design used with twenty flasks.

The effect of benzophenone 4-bromo-3-pyridazon-5-ylhydrazone (LIV) on the growth of E. coli was also studied. Twelve sterile control flasks containing 20 ml. of nutrient agar and twelve sterile experimental flasks containing 20 ml. of nutrient broth with compound were inoculated with 0.2 ml. each of a suspension of the bacteria. The flasks were incubated at 37°C. Two control and two experimental flasks were removed from the incubator every four hours and the contents transferred aseptically to centrifuge tubes. The cells were washed three times with distilled water. After the final washing, the cells were resuspended in distilled water to give a final volume of 10 ml. The optical density of the suspension was recorded using a Bausch and Lomb Spectronic 20. The plot of optical density versus time is shown in Fig. 2.

compound was determined by the dry weight, [illegible] and [illegible] [illegible]

the medium.

A N/20 solution of [illegible] was used [illegible]

potassium hydroxide solution served to absorb [illegible]

some of the flasks, while [illegible]

oxygen [illegible] carbon dioxide [illegible]

flasks.

The flasks were then filled to a [illegible]

Following a twenty minute equilibration [illegible]

[illegible] ten [illegible] for a total of [illegible]

minutes. Table VIII indicates the experimental [illegible] for [illegible]

Warburg flasks.

The effect of [illegible]

[illegible] in the growth of [illegible] was also [illegible]

product. Flasks containing 100 ml. of [illegible]

sterile [illegible] containing 2.0 ml. of [illegible]

[illegible] were [illegible] with 0.2 ml. [illegible]

[illegible] The flasks were [illegible]

[illegible] flasks were [illegible]

four hours and the contents transferred [illegible]

tubes. The cells were [illegible]

After the final washing, the cells were [illegible]

water to give a final volume of 10 ml. The [illegible]

the suspension was [illegible] using a Bausch and Lomb Spectronic

20. The plot of optical density versus [illegible]

Table VIII

Warburg Experimental Design

	Exogenous Respiration			
	Control	Experimental		R. Q. Control
Flask	1 | 2 | 3 | 4	5 | 6 | 7 | 8	9	10 | 11 | 12
Chamber	1.6 ml. Buffer 0.2 ml. Glucose 0.4 ml. Cells	1.6 ml. Compound 0.2 ml. Glucose 0.4 ml. Cells	Thermo- barometer	1.6 ml. Buffer 0.2 ml. Glucose 0.4 ml. Cells
Well	0.2 ml. KOH	0.2 ml. KOH		
Side Arm				0.2 ml. H_2SO_4

				Endogenous Respiration	
	R. Q. Experimental	Bound Carbon Dioxide		Control	Experimental
Flask	13 | 14 | 15 | 16	17	18	19	20
Chamber	1.6 ml. Compound 0.2 ml. Glucose 0.4 ml. Cells	2.0 ml. Buffer 0.2 ml. Glucose	2.0 ml. Compound 0.2 ml. Glucose	1.8 ml. Buffer 0.4 ml. Cells	1.8 ml. Compound 0.4 ml. Cells
Well				0.2 ml. KOH	0.2 ml. KOH
Side Arm	0.2 ml. H_2SO_4	0.2 ml. H_2SO_4	0.2 ml. H_2SO_4		

C. Results

The following compounds were observed to stimulate respiration in B. subtilis: benzophenone 4-bromo-3-pyridazon-5-ylhydrazone (LIV) (Fig. 4) and 3,4-dimethoxybenzaldehyde 4-chloro-3-pyridazon-5-ylhydrazone (LVII) (Fig. 13). Benzophenone 4-chloro-3-pyridazon-5-ylhydrazone (LIII) (Fig. 1) depressed respiration in this same organism. E. coli was found to respond to only one compound. Dibenzyl ketone 4-bromo-3-pyridazon-5-ylhydrazone (LVI) stimulated respiration in this organism (Fig. 11). The greatest response to the compounds was seen with S. aureus. Both dibenzyl ketone 4-chloro-3-pyridazon-5-ylhydrazone (LV) (Fig. 9) and its bromo isomer (LVI) stimulated respiration and to about the same degree (Fig. 12). However, compounds LIII and LVII caused a definite depression of respiration (Figs. 3 and 15). Neither 4-bromo-5-hydrazino-3-pyridazone (XLIV) nor 4-chloro-5-hydrazino-2-phenyl-3-pyridazone (XLVI) affected the respiration of the organisms tested (Figs. 16, 17, 18, and 19).

These data are listed in Table IX as per cent stimulation or depression of respiration. Plots of oxygen consumption in terms of microliters of oxygen per milligram of cells versus time are shown in Figs. 1 through 19. Though exogenous respiration was the principal concern in these studies, endogenous respiration was also observed (Table VIII). Since the values for endogenous respiration were so low, they were not included on the plots.

The following compounds were found to [illegible]

[illegible]

[illegible] (LIV) (Fig. 4) and [illegible]

[illegible] (LVII) (Fig. 5) [illegible]

[illegible] (LVII) (Fig. 8) [illegible]

[illegible] in this test organism. [illegible] was found to [illegible]

to only one compound. [illegible]

[illegible] (LVI) [illegible] respiration in this organism [illegible]

[illegible] The greatest response to the [illegible]

[illegible]. Both [illegible]

(LVI) (Fig. 7) and [illegible]

[illegible] about the same degree (Fig. [illegible]

[illegible] a definite depression of respiration

(Figs. [illegible]

[illegible]

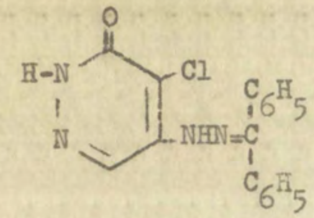
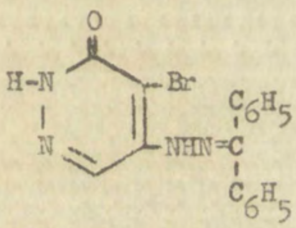
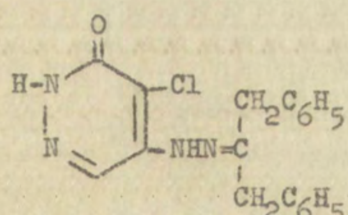
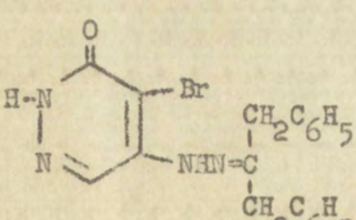
affected the respiration of the organisms tested (Figs. 10, 11, 12, and 13).

These data are presented in Table IX as per cent stimulation or depression of respiration. Plots of oxygen consumption [illegible] of [illegible] of oxygen [illegible] are shown in Figs. 4 through 13. [illegible] the [illegible] in these studies [illegible] was also computed (Table VIII). Since the [illegible] not [illegible]

Table IX

Per Cent Stimulation or Depression of Respiration in

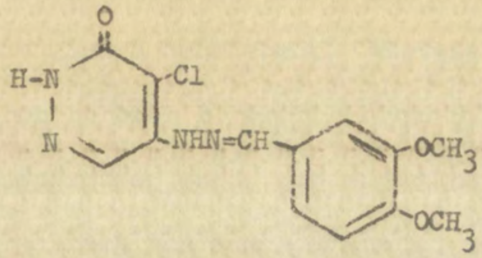
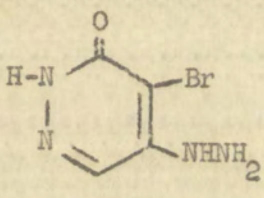
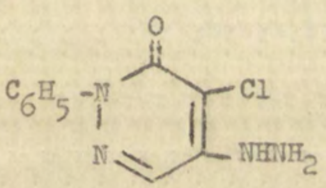
the Presence of the Compound for 70 Minutes Cumulative

Compound	*B. subtilis*	*E. coli*	*S. aureus*
 LIII	-12.2*	+ 0.03	-17.1
 LIV	+ 29.3**	- 0.01	+ 0.01
 LV	0.00	+ 1.06	+ 13.3
 LVI	- 0.07	+ 11.5	+ 12.8

* Minus indicates depression.

** Plus indicates stimulation.

Table IX Continued

Compound	B. subtilis	E. coli	S. aureus
 LVII	+12.7	+0.06	-14.3
 XLIV		0.00	- 0.02
 XLVI		- 0.01	+ 0.02

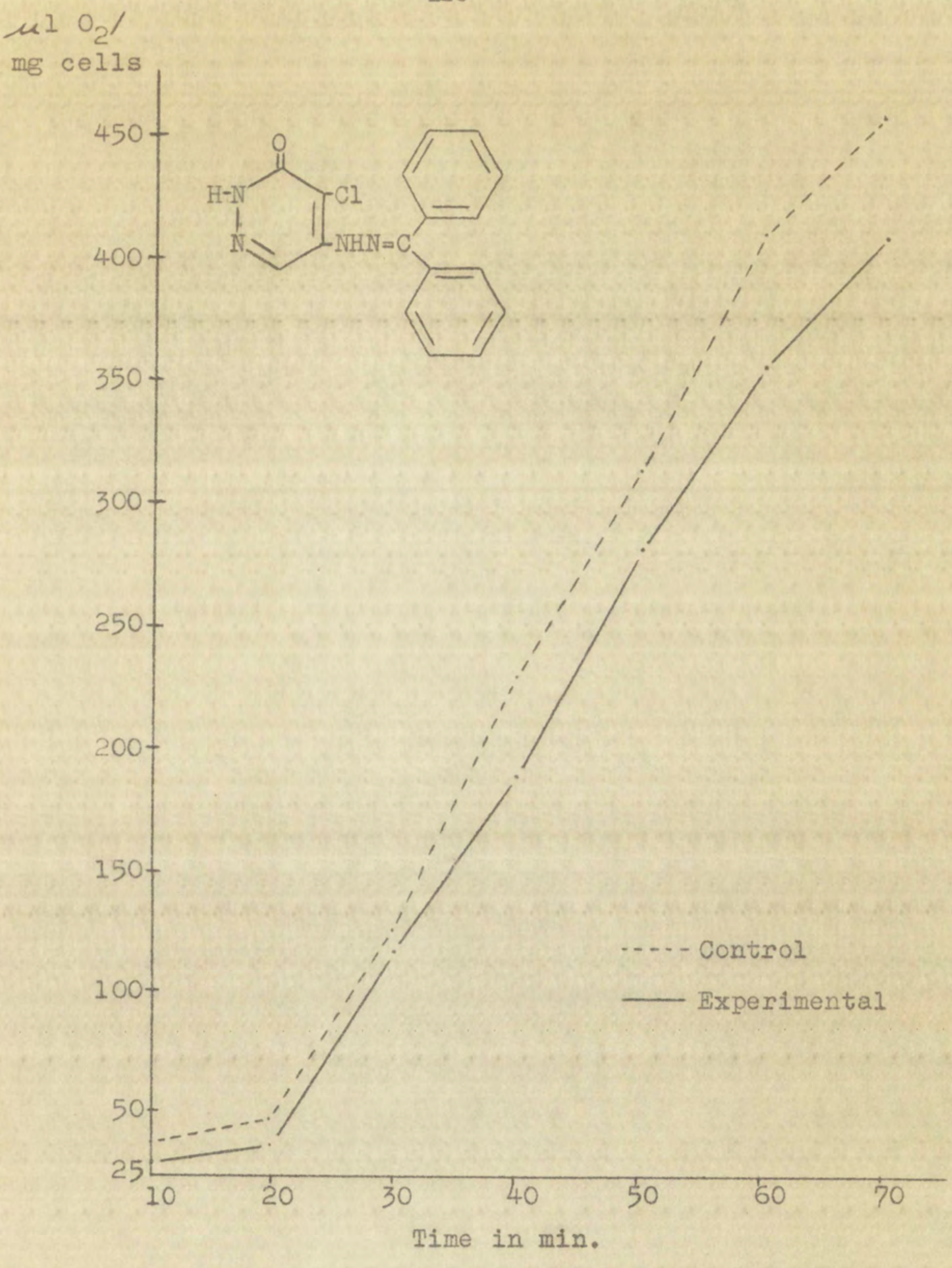


Fig.1. The influence of benzophenone 4-chloro-3-pyridazon-5-ylhydrazone on the exogenous respiration of B. subtilis. The cells were suspended in M/15 phosphate buffer, pH 6.80, 37°C.

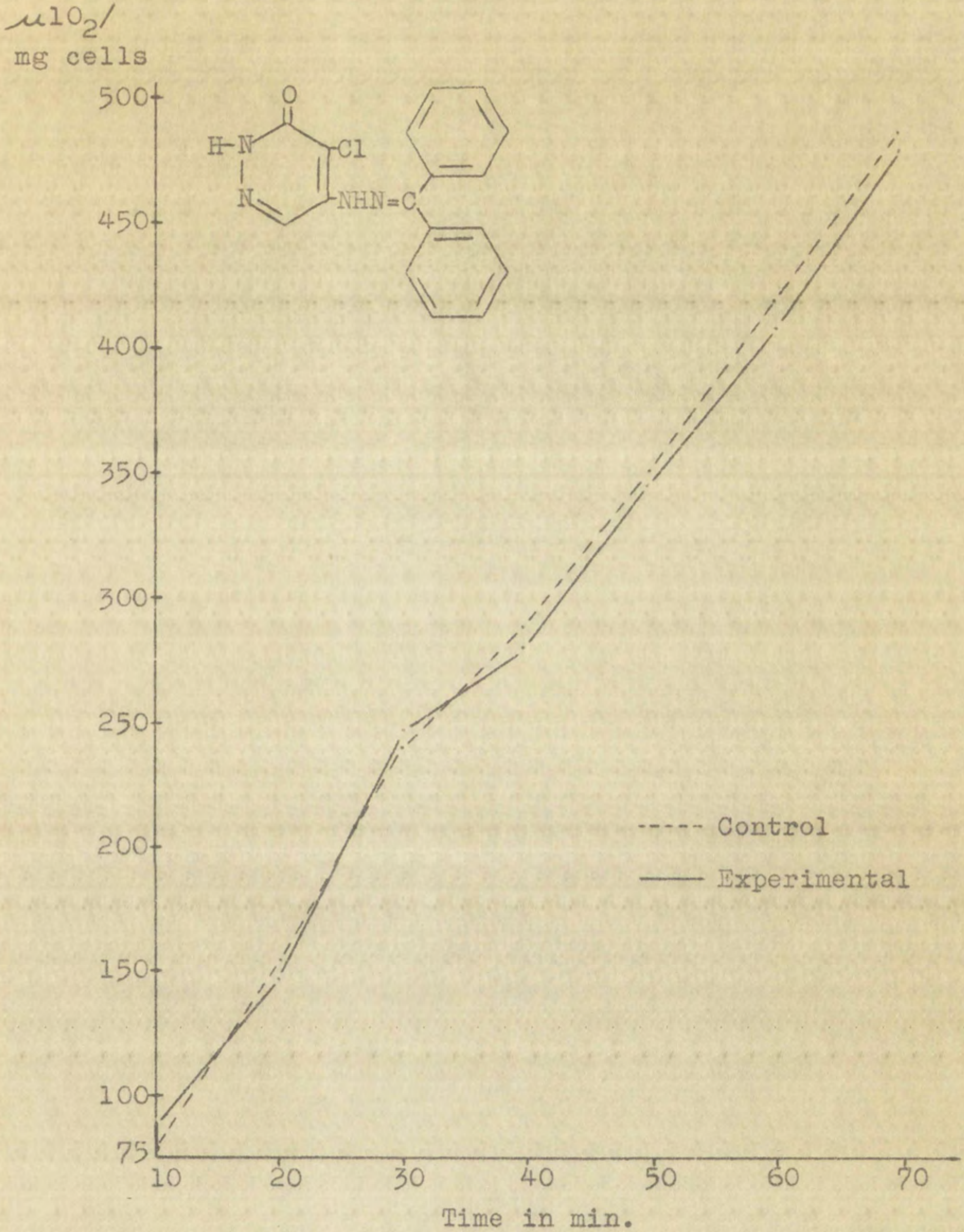


Fig. 2. The influence of benzophenone 4-chloro-3-pyridazon-5-ylhydrazone on the exogenous respiration of *E. coli*. The cells were suspended in M/15 phosphate buffer, pH 6.80, 37°C.

D. Discussion of Results

More cases of stimulation of respiration were observed than of depression by the compounds tested; however, the effect was not always consistent. Whereas compound LIII depressed respiration in both B. subtilis and S. aureus, compound LVII depressed respiration in S. aureus but caused a stimulation in B. subtilis by almost the same per cent. A very marked stimulation of respiration of B. subtilis was brought about by the presence of compound LIV, but neither of the other organisms was affected. The chloro isomer of LIV, compound LV, stimulated the respiration of S. aureus but had no effect on B. subtilis or E. coli. In fact, E. coli was influenced only by compound LVI and then the stimulation was not great.

Two unsubstituted hydrazino derivatives, XLIV and XLVI, were tested. Neither compound affected the respiration of the organisms used.

In the twenty-four hour growth study using E. coli and compound LIV, a definite stimulation of growth was observed (Fig. 20). However, no effect on respiration was noted for this organism using the same compound (Fig. 5).

Though no conclusions can be drawn with so few structures and only one type of test, it is nevertheless interesting to note that the benzophenone derivatives LIII and LIV caused both stimulation and depression of respiration; whereas the dibenzyl ketone derivatives in which the phenyl groups are each removed from the carbonyl carbon by a methylene group caused only stimulation.

[illegible]

[illegible] and decreased, but the mechanisms [illegible] however, [illegible] [illegible]

[illegible]

[illegible] (Fig. [illegible]). [illegible]

[illegible] was not [illegible].

[illegible]

In the [illegible] E. coli and [illegible] of growth was observed (Fig. [illegible]). However, no effect on [illegible] was seen for this [illegible] with the same compound (Fig. 5).

Thus, the conclusions can be drawn with so few substances [illegible]

[illegible]

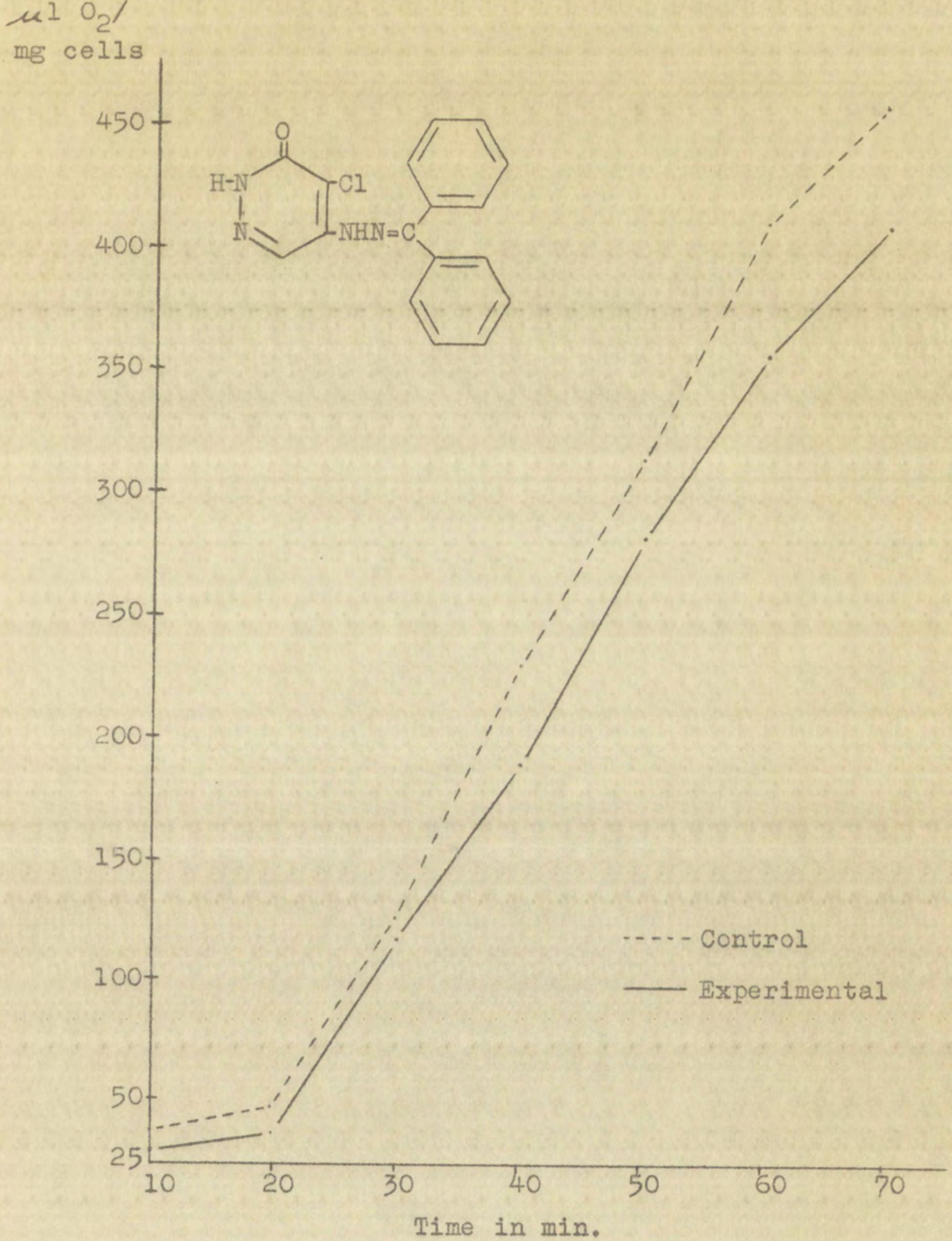


Fig.1. The influence of benzophenone 4-chloro-3-pyridazon-5-ylhydrazone on the exogenous respiration of <u>B. subtilis</u>. The cells were suspended in M/15 phosphate buffer, pH 6.80, 37°C.

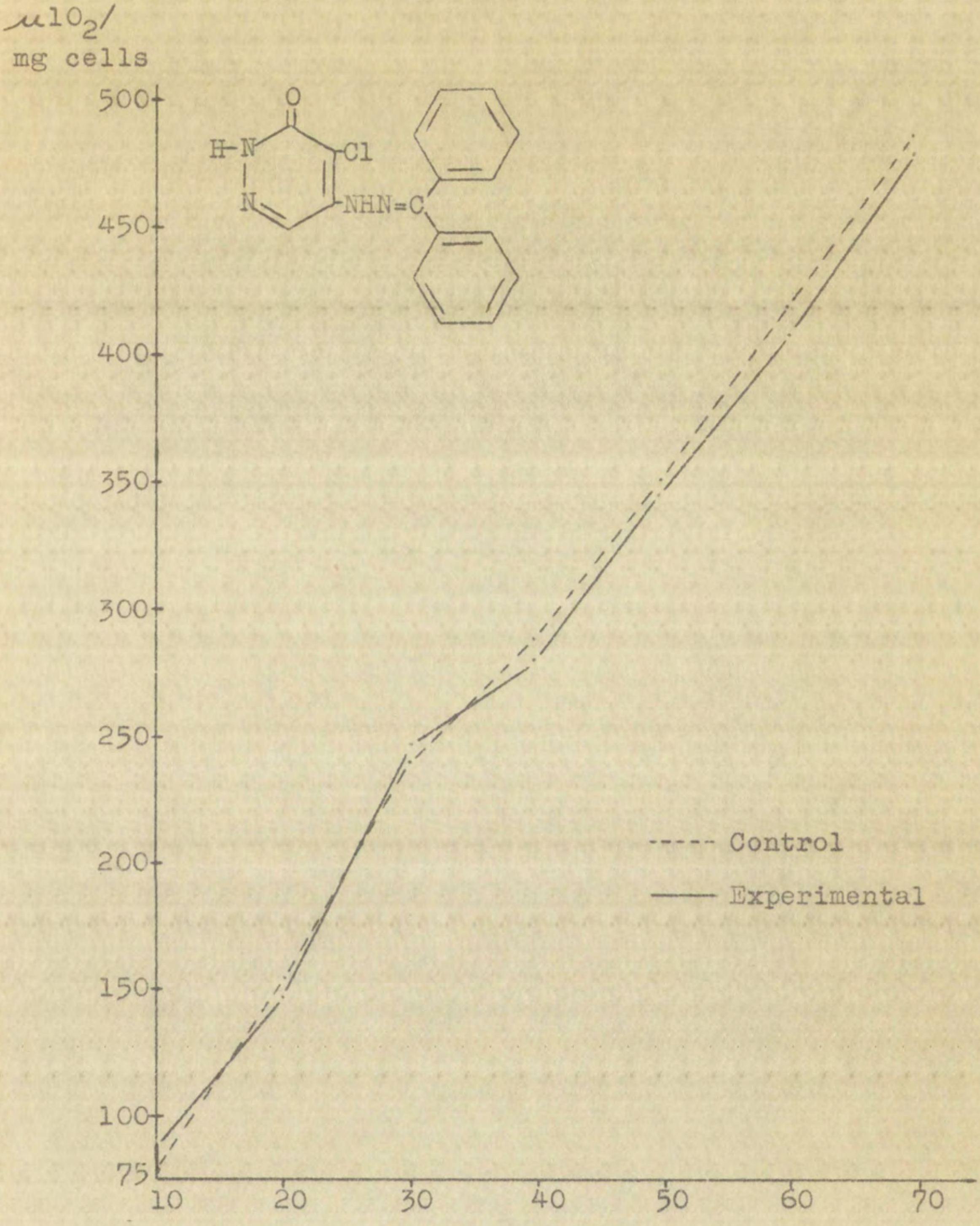


Fig. 2. The influence of benzophenone 4-chloro-3-pyridazon-5-ylhydrazone on the exogenous respiration of <u>E. coli</u>. The cells were suspended in M/15 phosphate buffer, pH 6.86, 37°C.

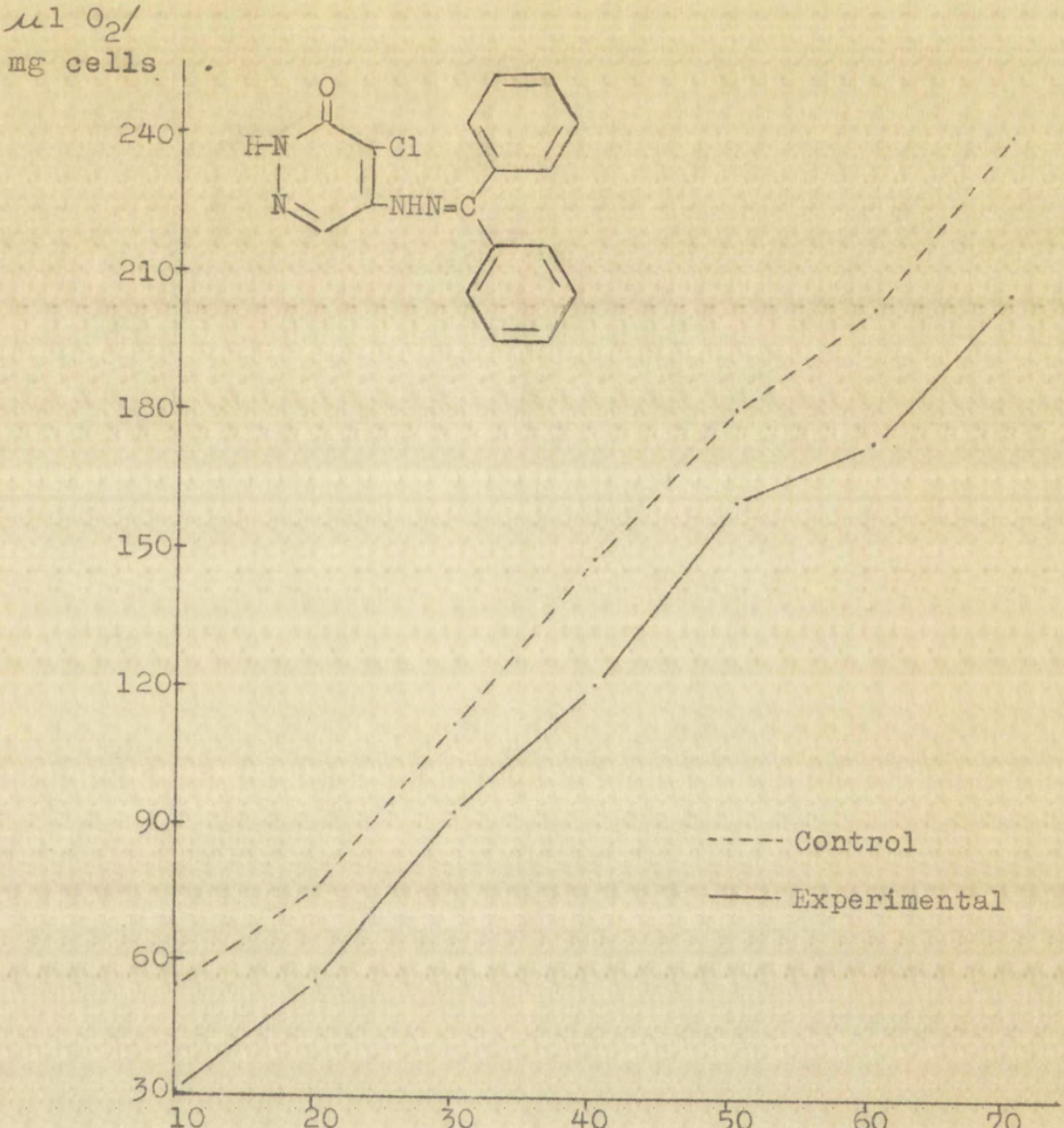


Fig. 3. The influence of benzophenone 4-chloro-3-pyridazon-5-ylhydrazone on the exogenous respiration of S. aureus. The cells were suspended in M/15 phosphate buffer, pH 6.80, 37°C.

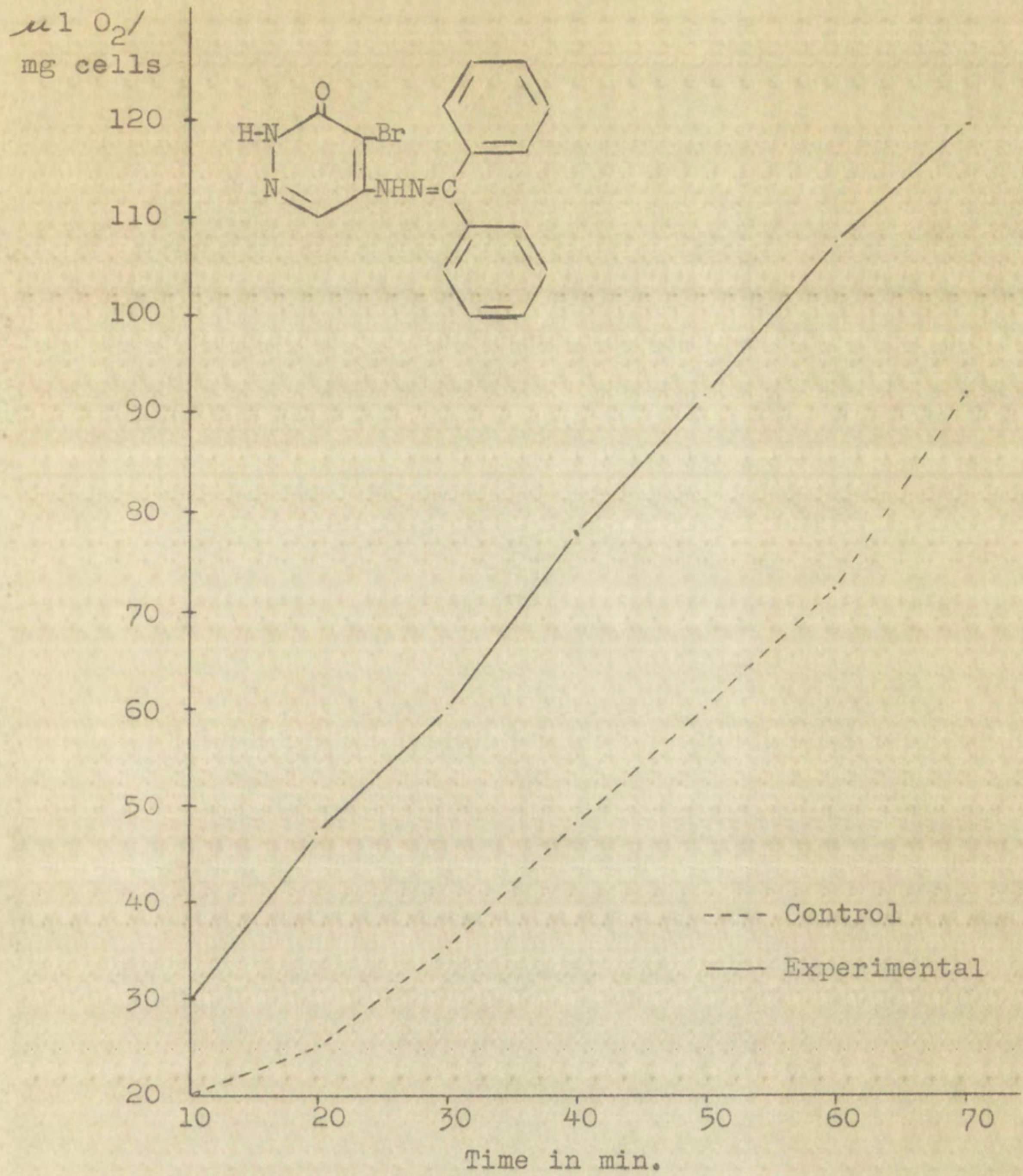


Fig. 4. The influence of benzophenone 4-bromo-3-pyridazon-5-ylhydrazone on the exogenous respiration of B. subtilis. The cells were suspended in M/15 phosphate buffer, pH 6.80, 37°C.

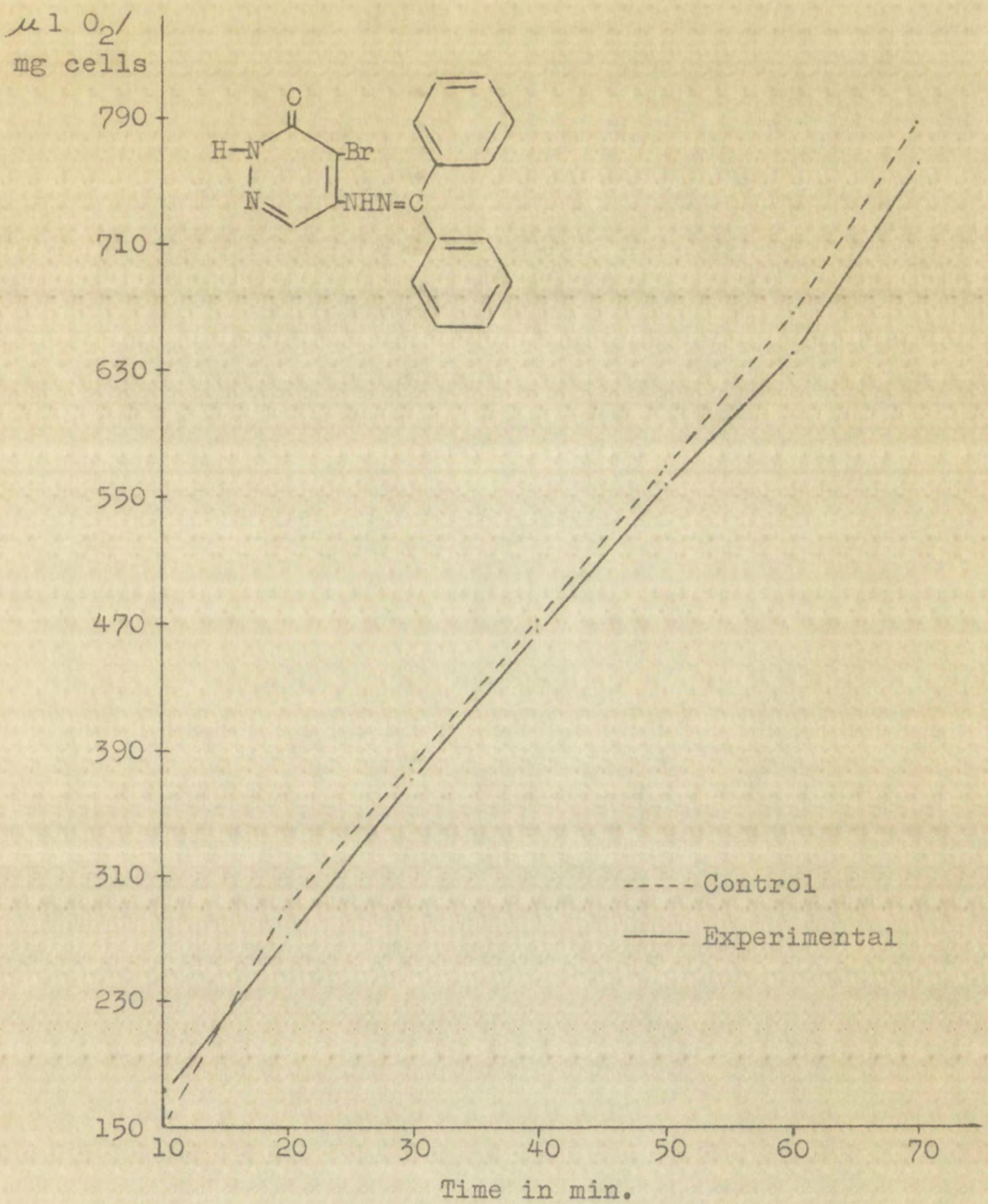


Fig. 5. The influence of benzophenone 4-bromo-3-pyridazon-5-ylhydrazone on the exogenous respiration of E. coli. The cells were suspended in M/15 phosphate buffer, pH 6.80, 37°C.

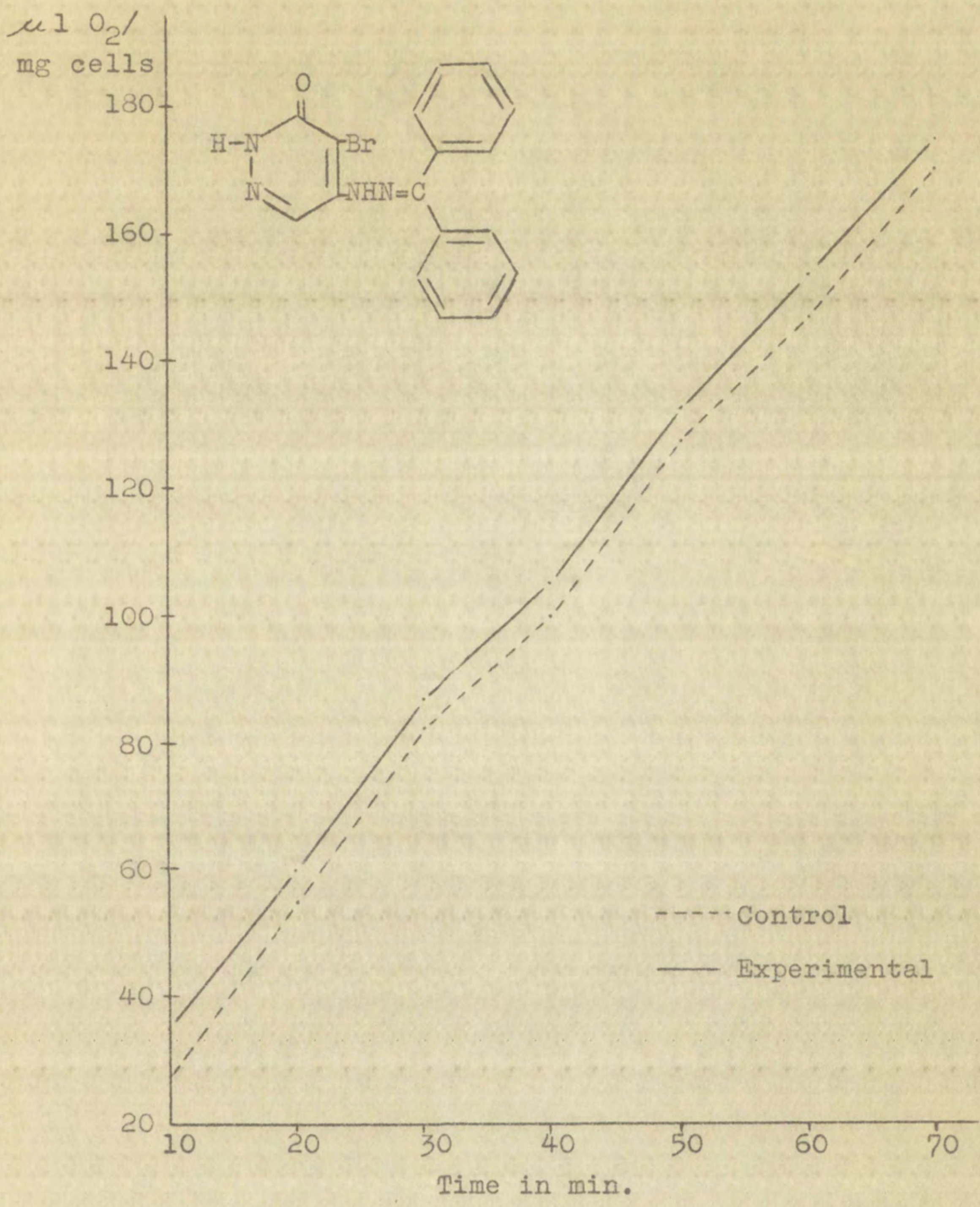


Fig. 6. The influence of benzophenone 4-bromo-3-pyridazon-5-ylhydrazone on the exogenous respiration of S. aureus. The cells were suspended in M/15 phosphate buffer, pH 6.80, 37°C.

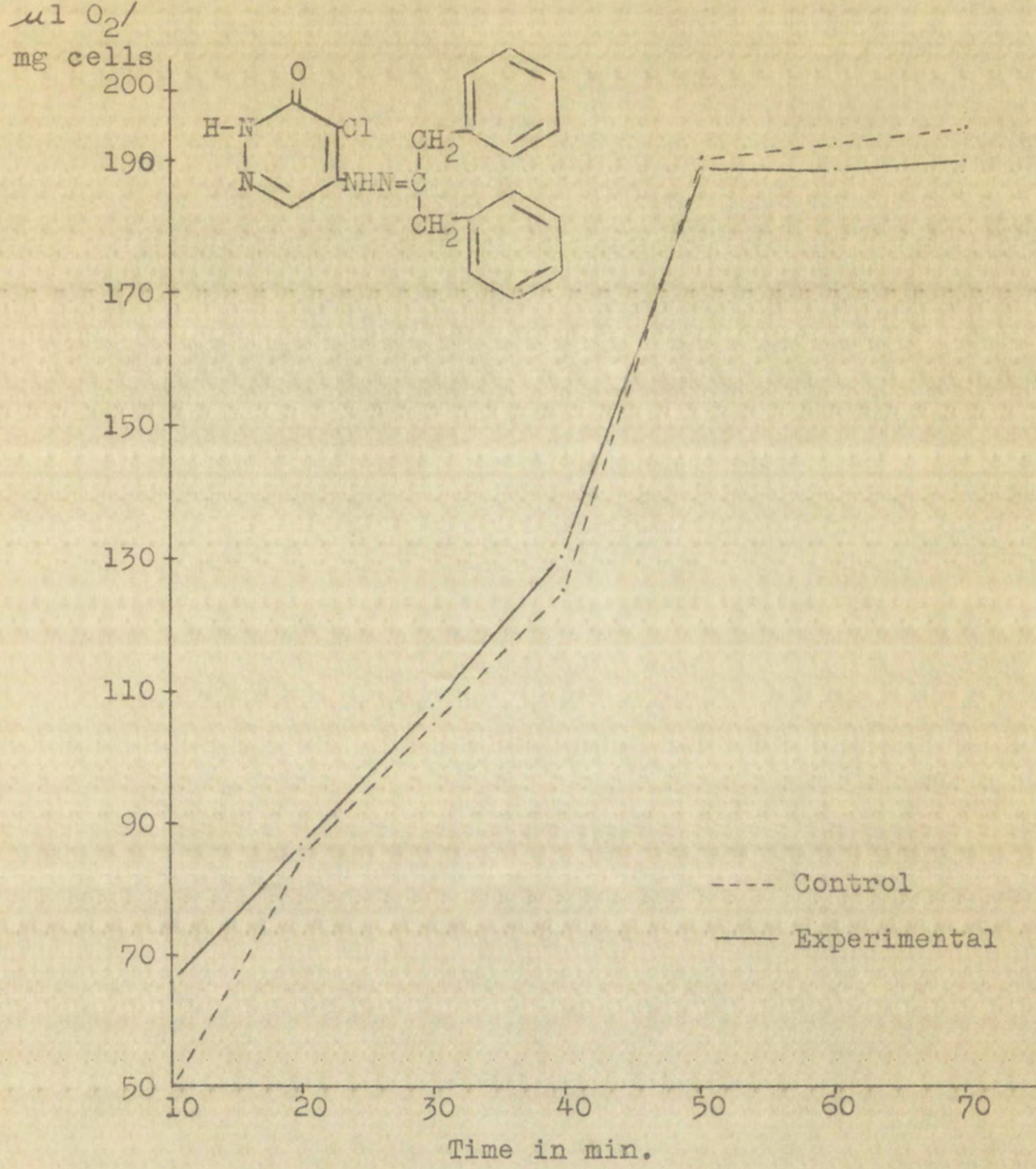


Fig. 7. The influence of dibenzyl ketone 4-chloro-3-pyridazon-5-ylhydrazone on the exogenous respiration of <u>B. subtilis</u>. The cells were suspended in M/15 phosphate buffer, pH 6.80, 37°C.

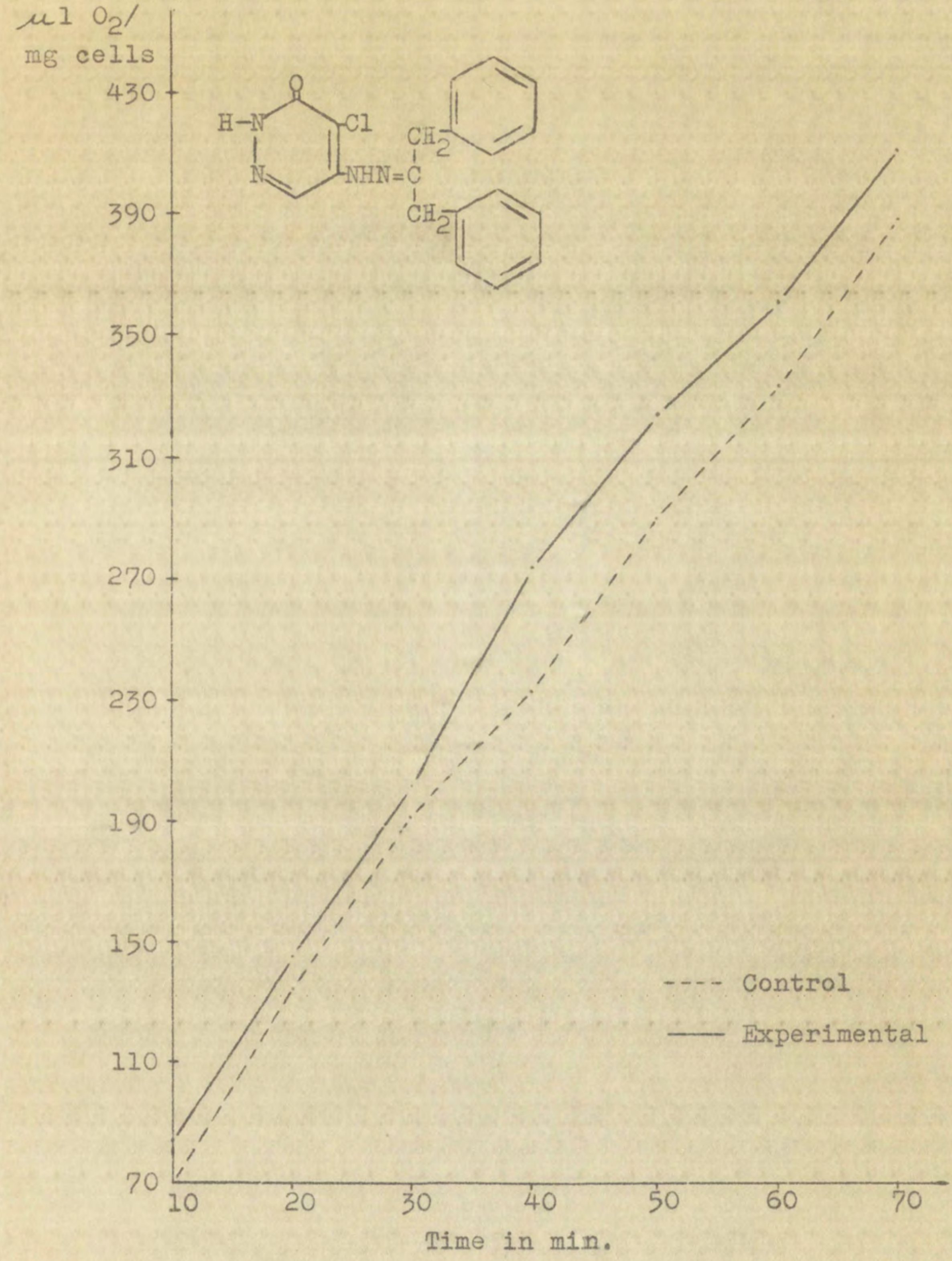


Fig. 8. The influence of dibenzyl ketone 4-chloro-3-pyridazon-5-ylhydrazone on the exogenous respiration of E. coli. The cells were suspended in M/15 phosphate buffer, pH 6.80, 37°C.

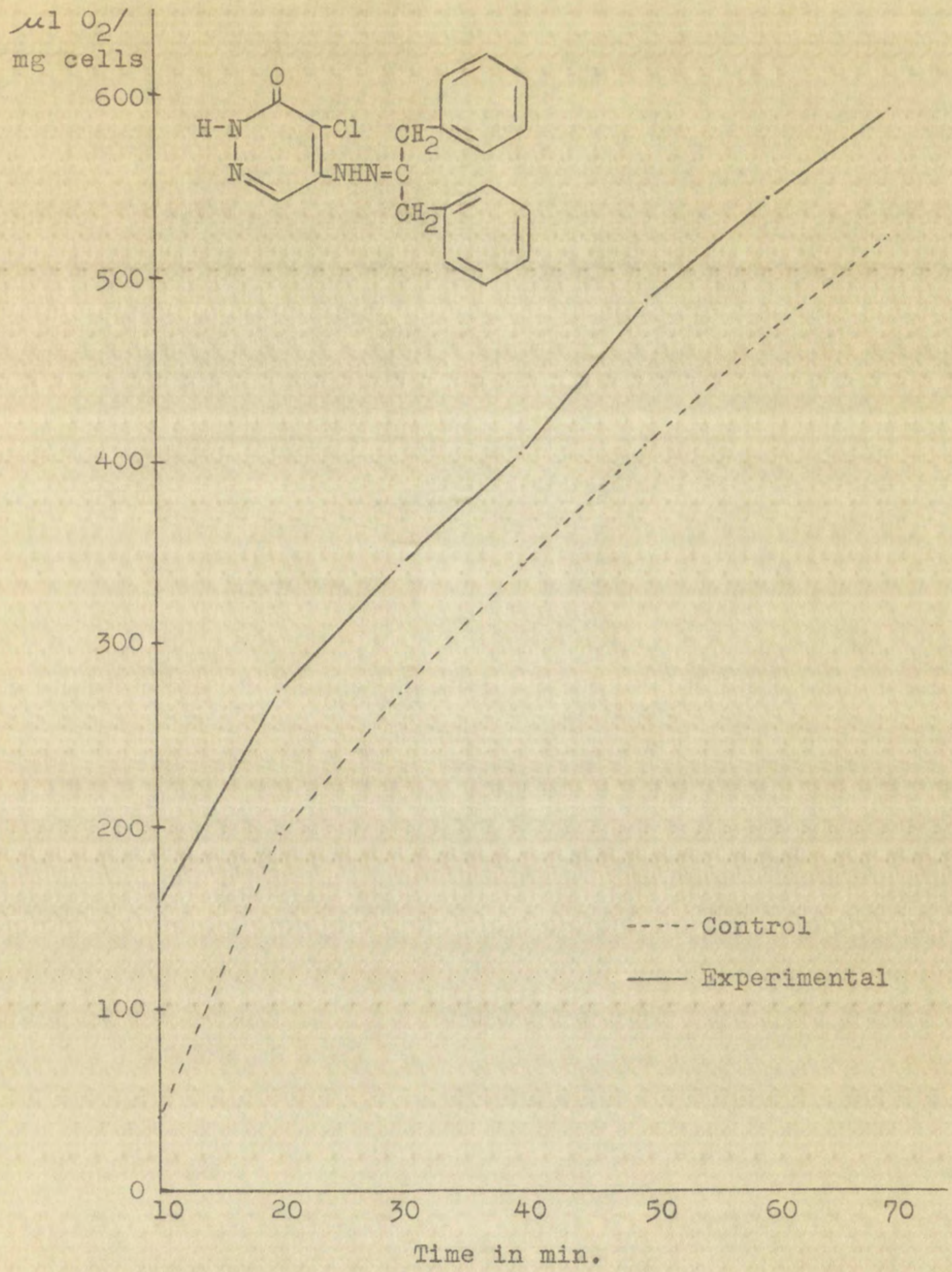


Fig. 9. The influence of dibenzyl ketone 4-chloro-3-pyridazon-5-ylhydrazone on the exogenous respiration of <u>S. aureus</u>. The cells were suspended in M/15 phosphate buffer, pH 6.80, 37°C.

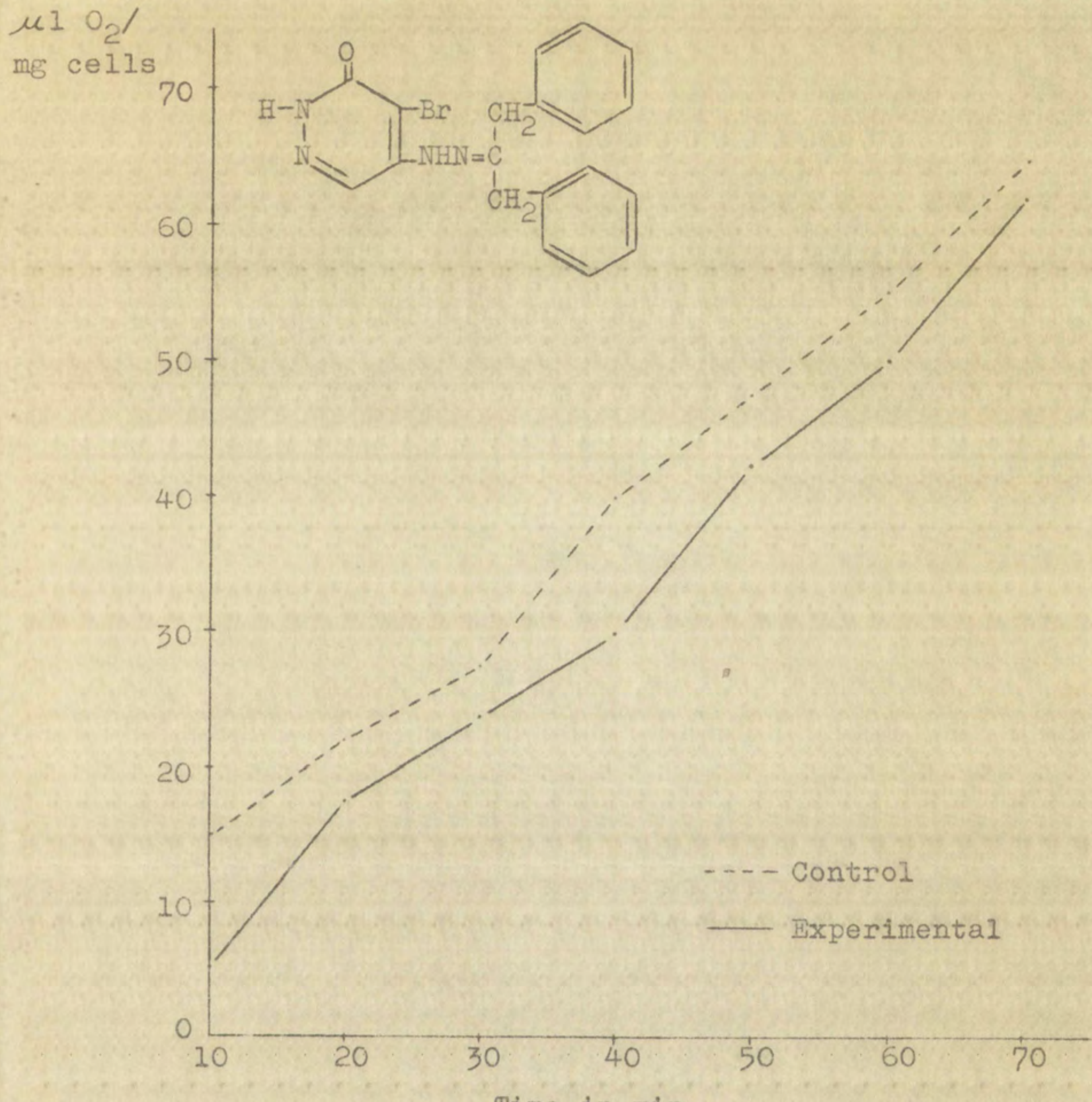


Fig. 10. The influence of dibenzyl ketone 4-bromo-3-pyridazon-5-ylhydrazone on the exogenous respiration of B. subtilis. The cells were suspended in M/15 phosphate buffer, pH 6.80, 37°C.

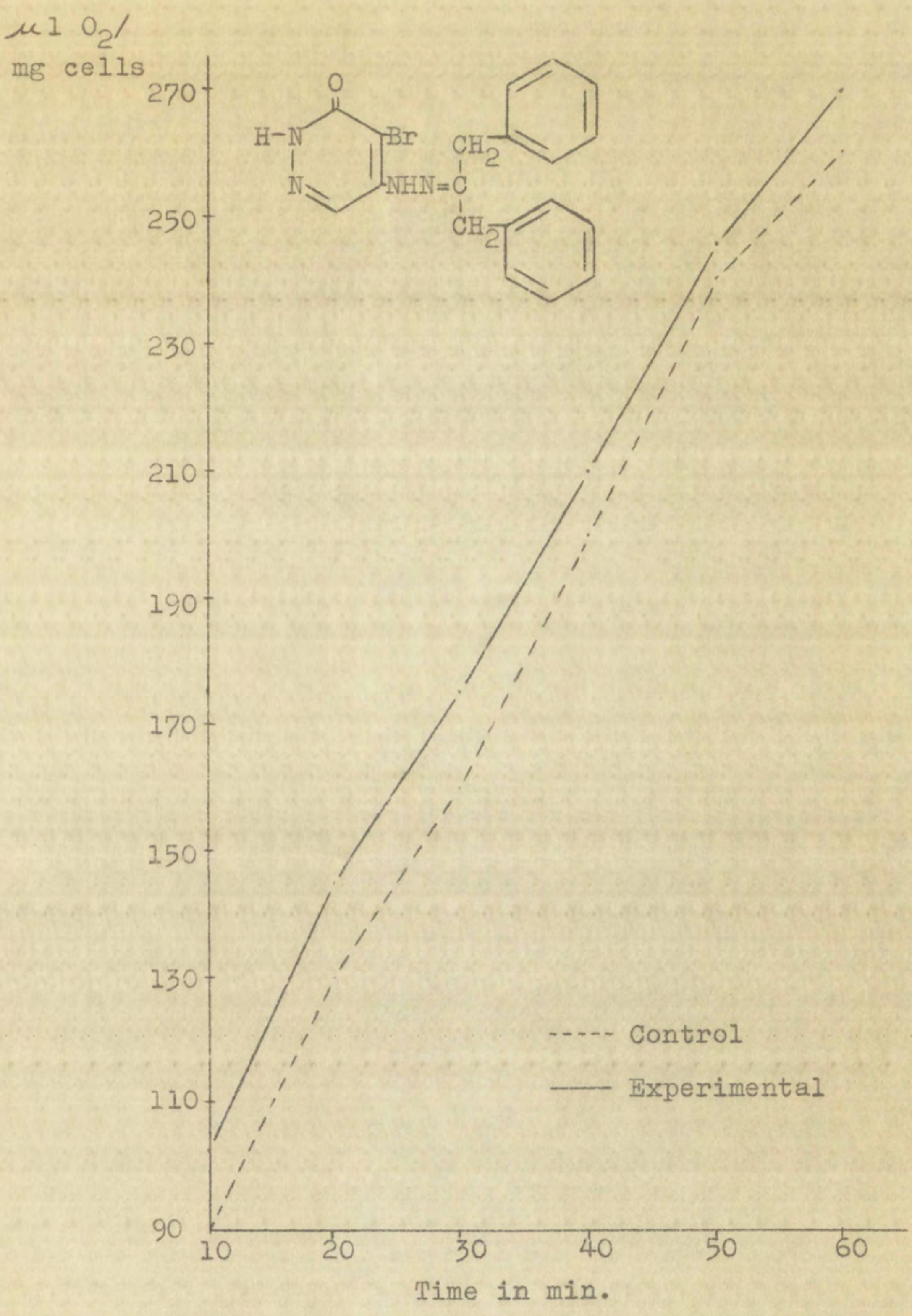


Fig. 11. The influence of dibenzyl ketone 4-bromo-3-pyridazon-5-ylhydrazone on the exogenous respiration of E. coli. The cells were suspended in M/15 phosphate buffer, pH 6.8, 37°C.

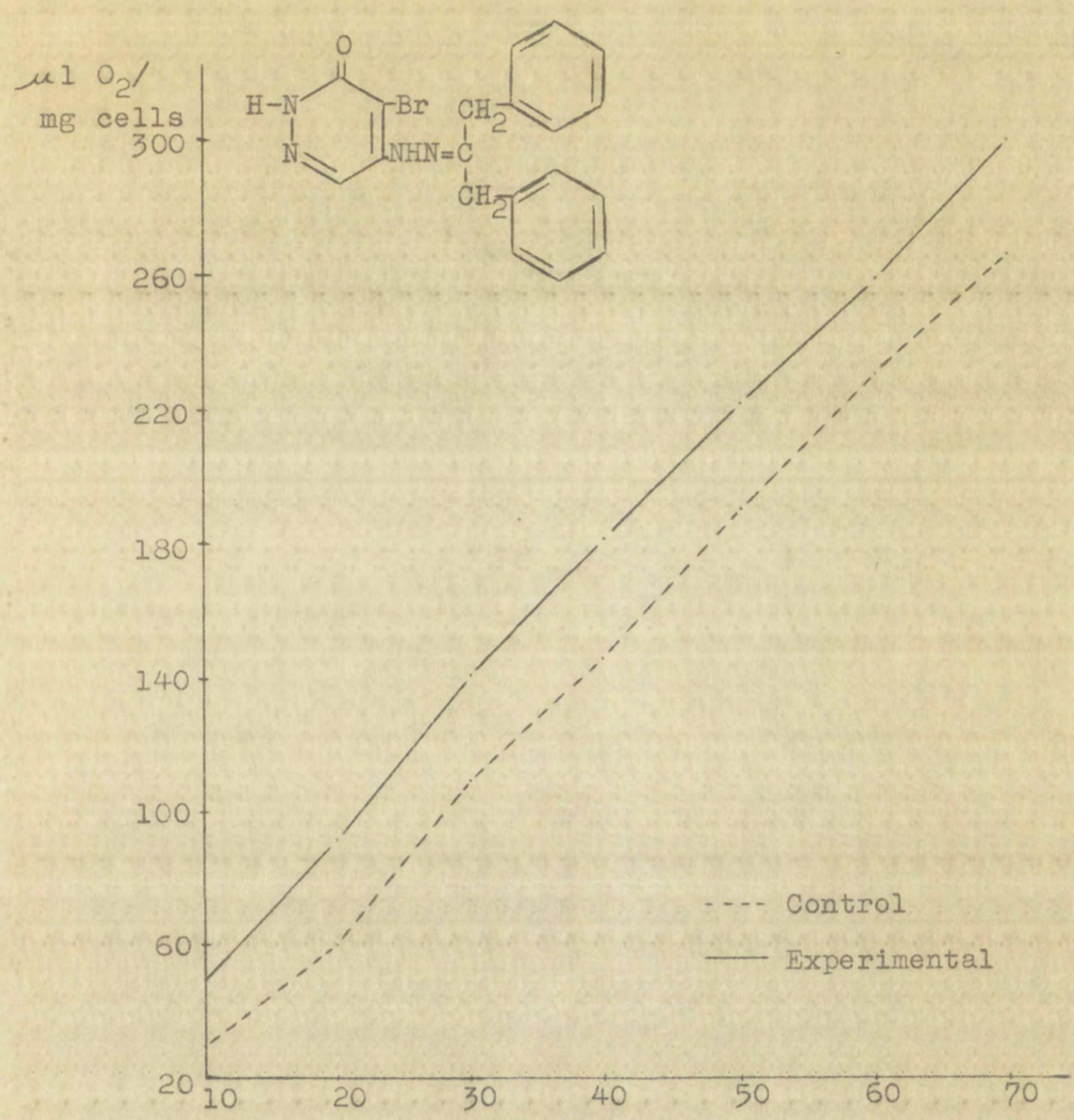


Fig. 12. The influence of dibenzyl ketone 4-bromo-3-pyridazon-5-ylhydrazone on the exogenous respiration of S. aureus. The cells were suspended in M/15 phosphate buffer, pH 6.80, 37°C.

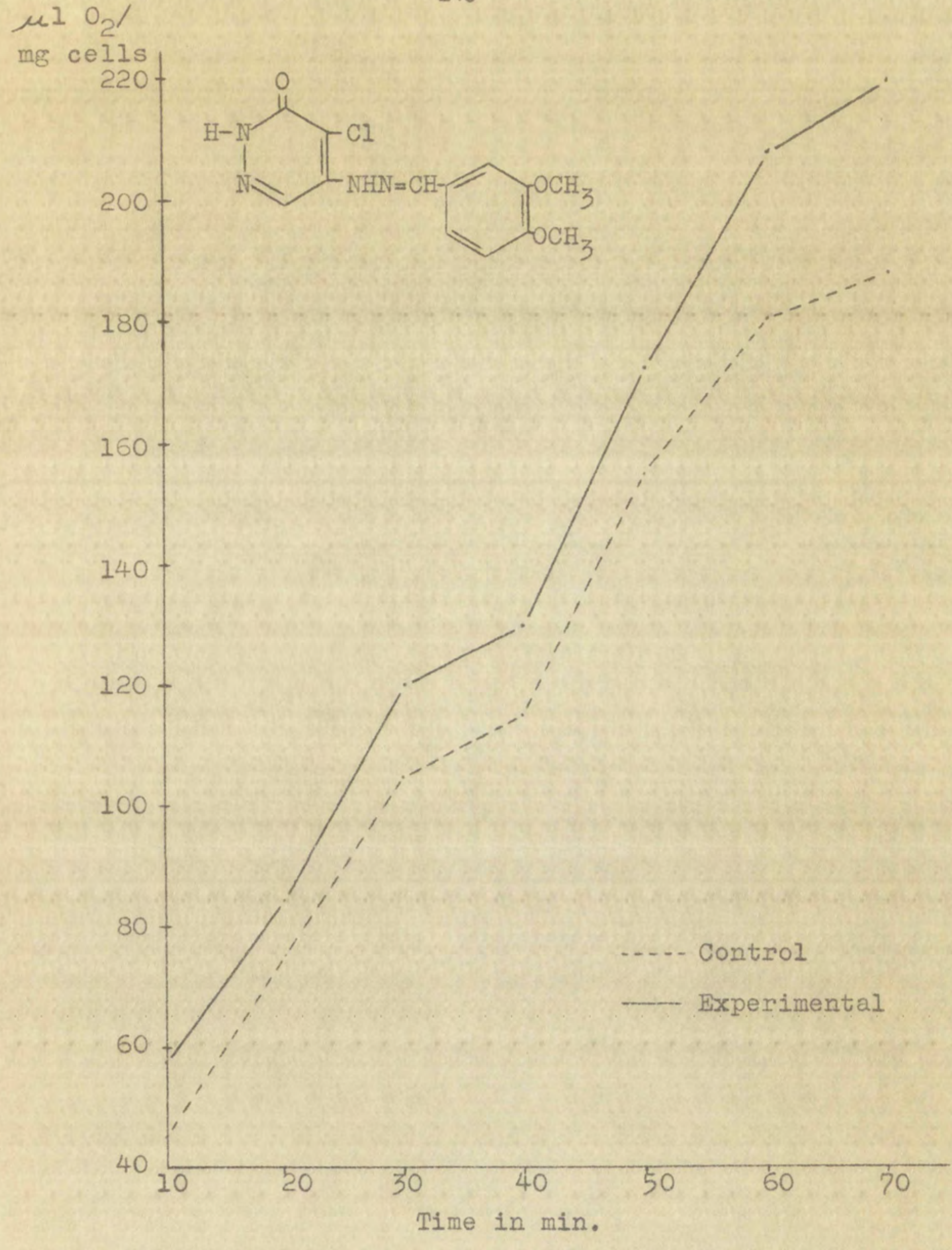


Fig. 13. The influence of 3,4-dimethoxybenzaldehyde 4-chloro-3-pyridazon-5-ylhydrazone on the exogenous respiration of B. subtilis. The cells were suspended in M/15 phosphate buffer, pH 6.80, 37°C.

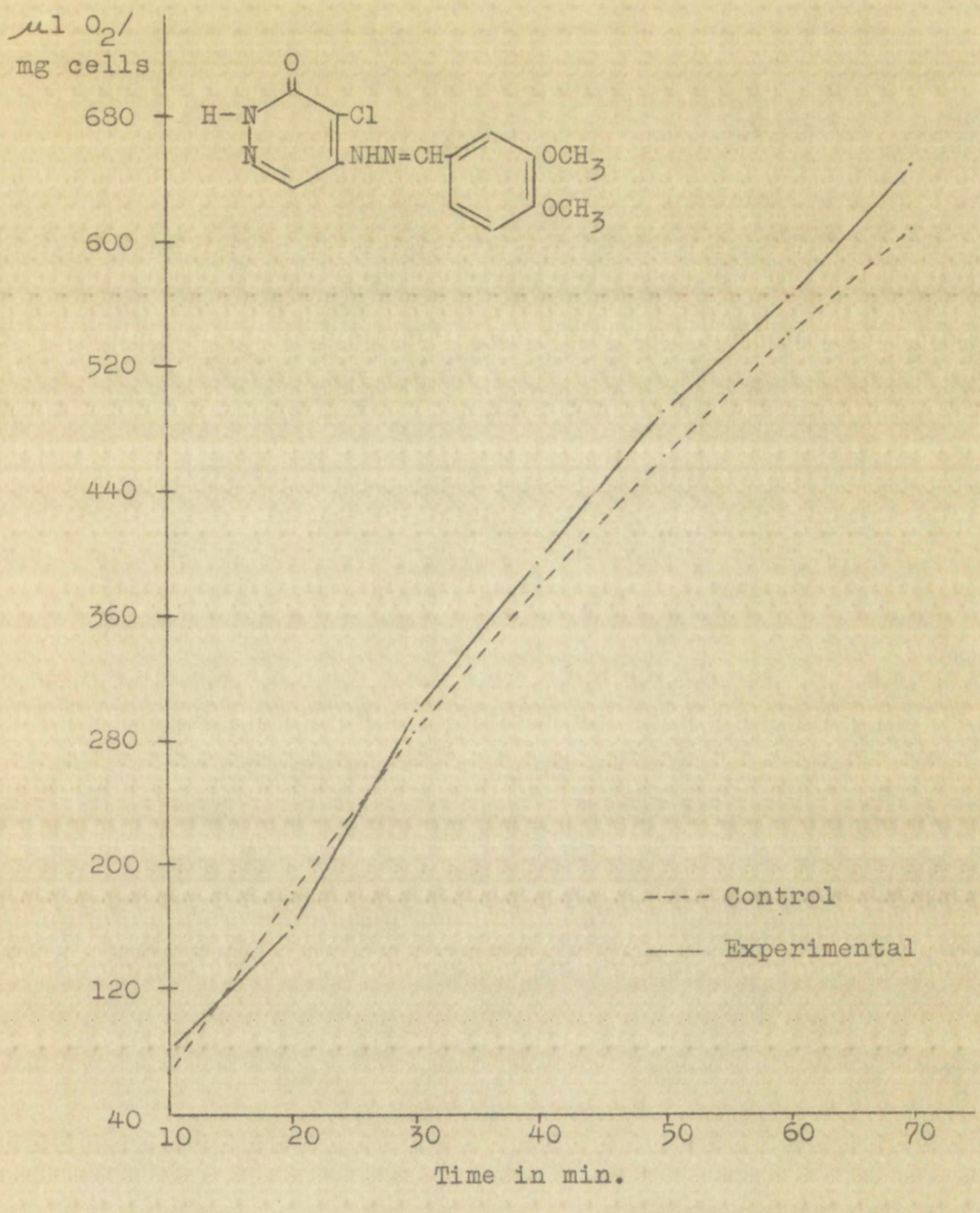


Fig. 14. The influence of 3,4-dimethoxybenzaldehyde 4-chloro-3-pyridazon-5-ylhydrazone on the exogenous respiration of E. coli. The cells were suspended in M/15 phosphate buffer, pH 6.80, 37°C.

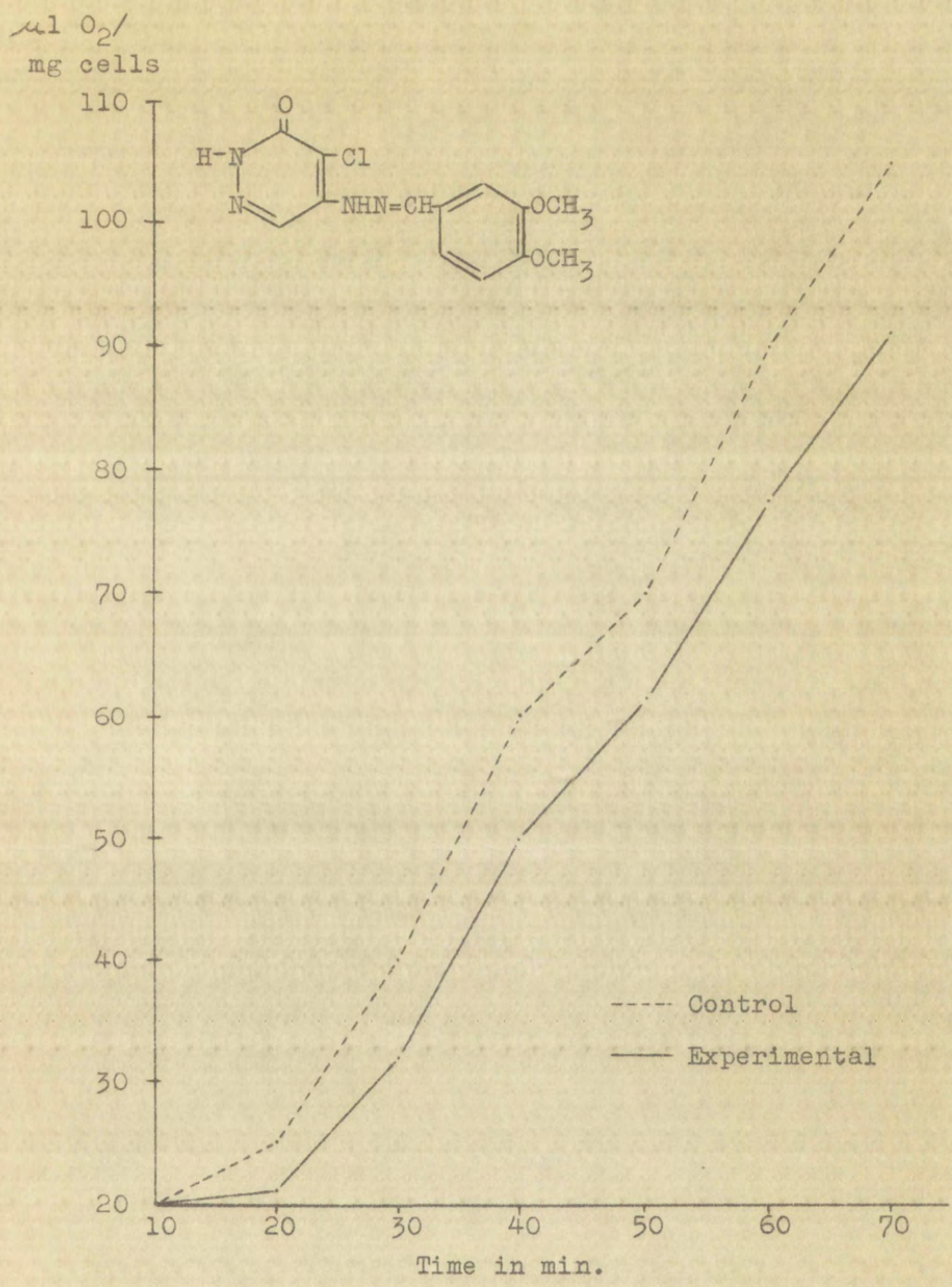


Fig. 15. The influence of 3,4-dimethoxybenzaldehyde 4-chloro-3-pyridazon-5-ylhydrazone on the exogenous respiration of S. aureus. The cells were suspended in M/15 phosphate buffer, pH 6.80, 37°C.

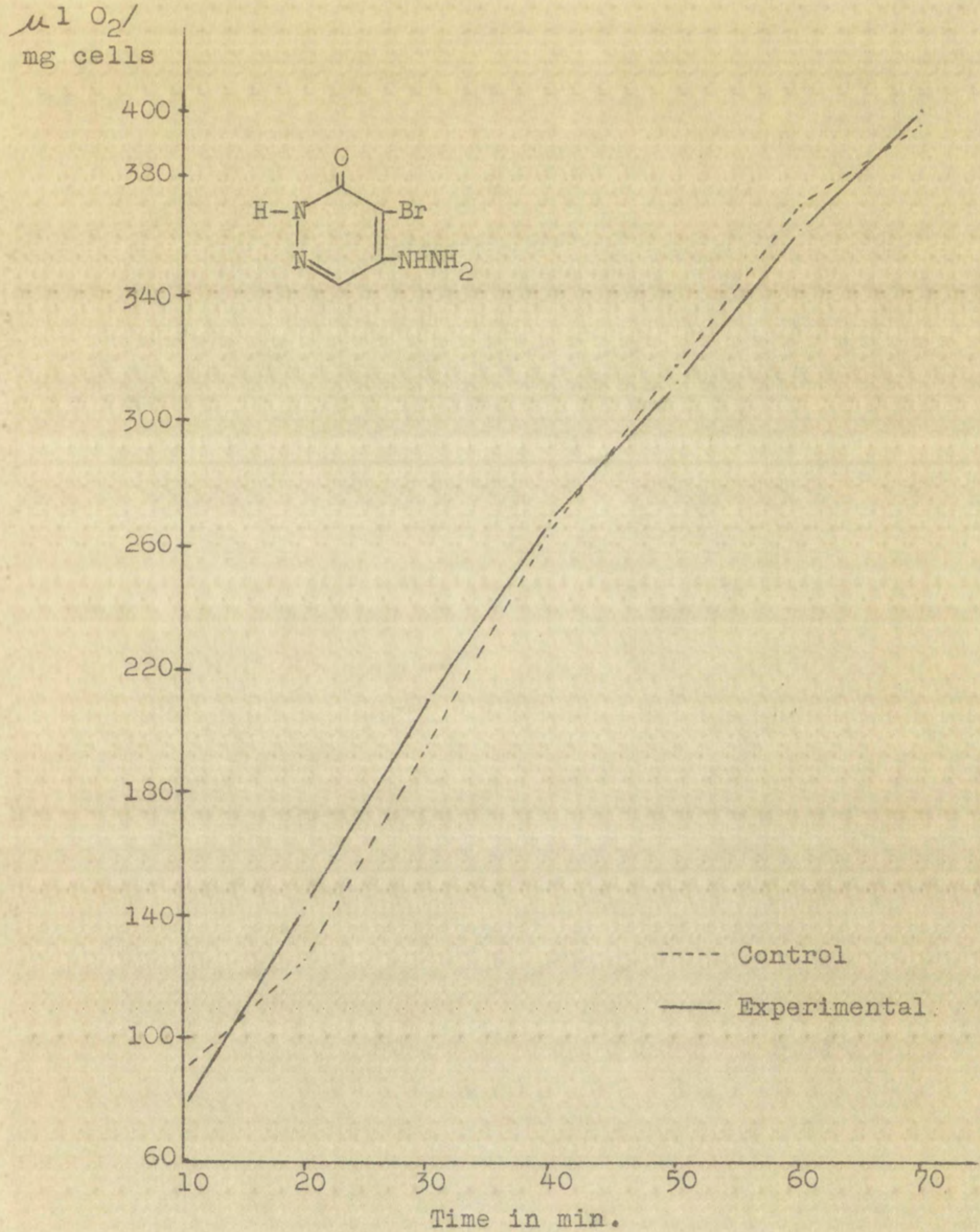


Fig. 16. The influence of 4-bromo-5-hydrazino-3-pyridazone on the exogenous respiration of E. coli. The cells were suspended in M/15 phosphate buffer, pH 6.80, 37°C.

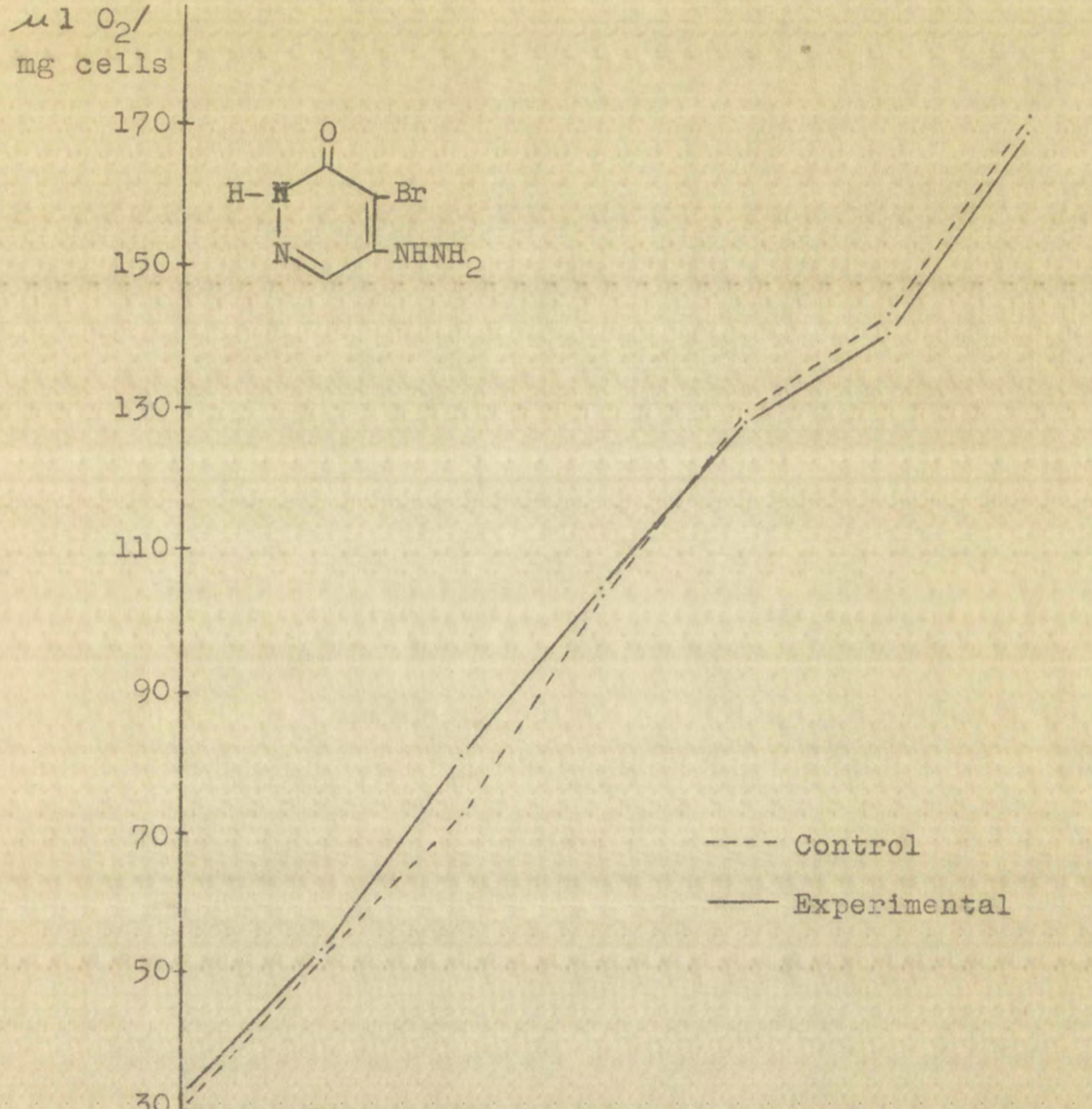


Fig. 17. The influence of 4-bromo-5-hydrazino-3-pyridazone on the exogenous respiration of S. aureus. The cells were suspended in M/15 phosphate buffer, pH 6.8, 37°C.

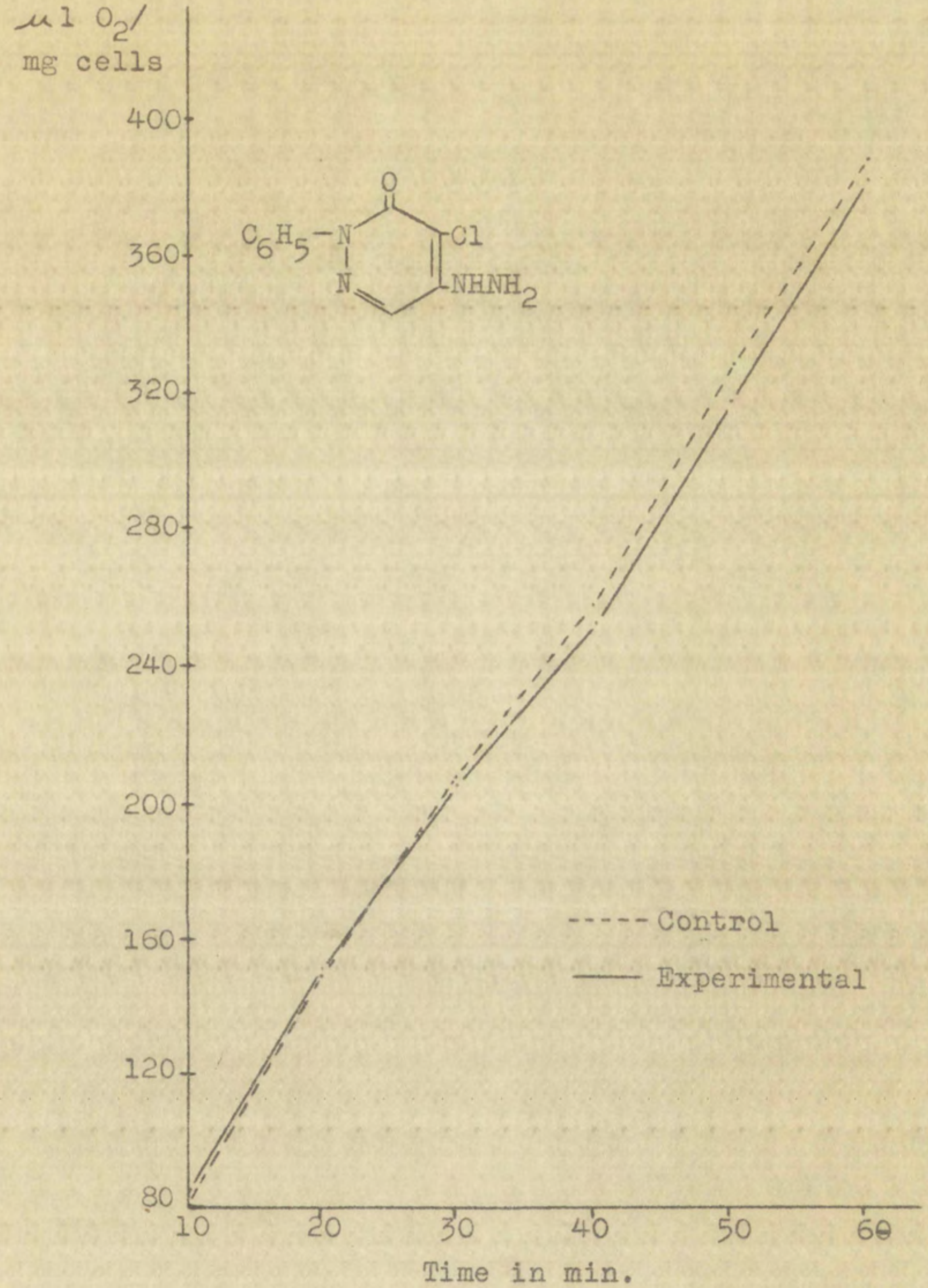


Fig. 18. The influence of 4-chloro-5-hydrazino-2-phenyl-3-pyridazone on the exogenous respiration of E. coli. The cells were suspended in M/15 phosphate buffer, pH 6.80, 37°C.

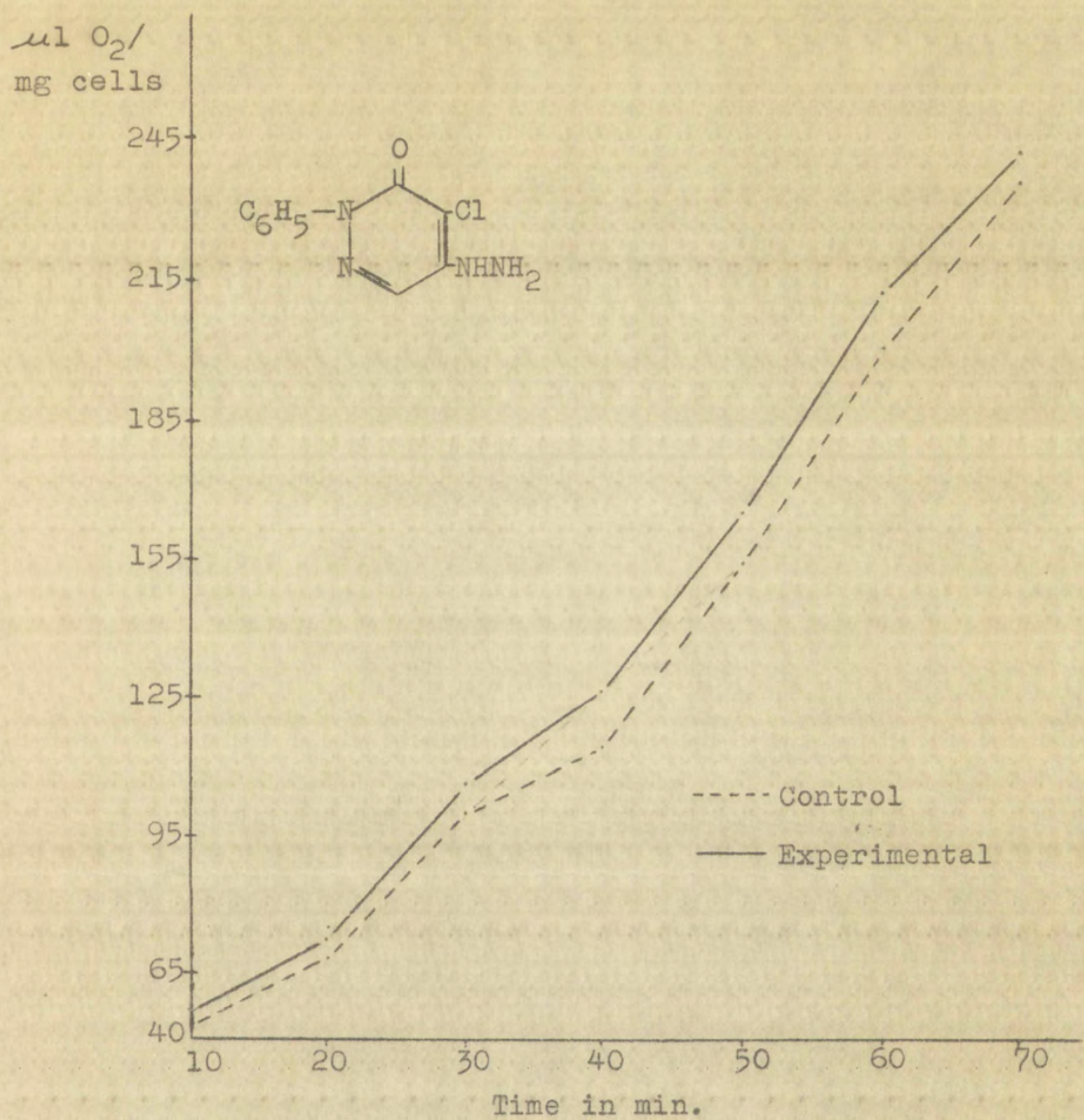


Fig. 19. The influence of 4-chloro-5-hydrazino-2-phenyl-3-pyridazone on the exogenous respiration of S. aureus. The cells were suspended in M/15 phosphate buffer, pH 6.80, 37°C.

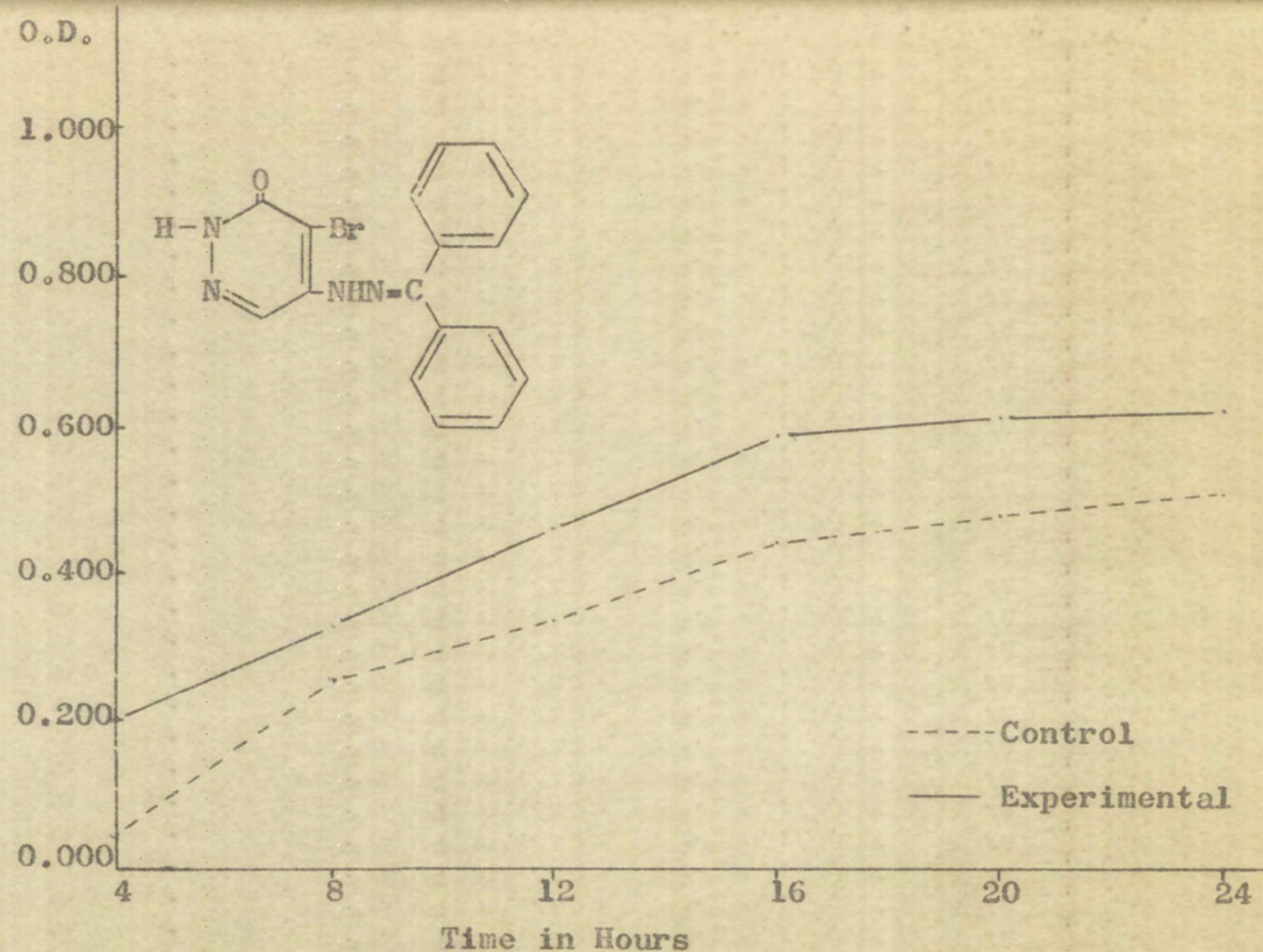


Fig. 20 . The influence of benzophenone 4-bromo-3-pyridazon-5-ylhydrazone on the growth of E. coli during twenty-four hours. The cells were grown in nutrient broth, 37°C.

V. EXPERIMENTAL

The elemental analyses were determined in this laboratory by Miss Yoko Tokashiga. All melting points were determined with a Vanderkamp "Melt-Pointer", and are uncorrected.

Mucobromic Acid. This compound was prepared by the method described in Organic Syntheses, Collective Volume III, p. 621.

4,5-Dibromo-3-pyridazone (XLIII). To a solution of 155 g. mucobromic acid (0.6 mole) dissolved in 400 ml. 95% ethanol was added all at once 66.9 g. (0.6 mole) semicarbazide hydrochloride dissolved in 200 ml. water. A solution of 41 g. potassium carbonate (0.3 mole) in 200 ml. water was added in portions with stirring. A copious evolution of CO_2 followed each addition and the semicarbazone precipitated readily. The reaction mixture was allowed to stand 4 hours; the precipitate was collected and washed with water. The semicarbazone was dissolved in 1 liter of boiling glacial acetic acid. Upon cooling, 123 g. (70%) of fine white crystals were obtained, m.p. 222-4°C.

4,5-Dichloro-3-pyridazone (XXXVI). Mucochloric acid (0.6 mole) was treated with semicarbazide hydrochloride (0.6 mole) and potassium carbonate (0.3 mole) in the manner described above. The quantitative yield of the semicarbazone was similarly decomposed in boiling glacial acetic acid and upon cooling, large white crystals (47%) were obtained, m.p. 201-3°C.

4-Bromo-5-hydrazino-3-pyridazone (XLIV). To 700 ml. of a boiling methanolic solution containing 25.4 g. (0.1 mole) of 4,5-dibromo-3-pyridazone was added in portions 10 ml. (0.3 mole) of

95% hydrazine. A yellow precipitate appeared after 10 min. After the mixture was allowed to reflux 1.5 hours, 14.9 g. (73%) of solid was obtained. Recrystallization from water afforded dark yellow needles, m.p. 180°C dec.

Anal. Calcd. for $C_4H_5N_4OBr$: C, 23.43; H, 2.46. Found: C, 23.78; H, 2.14.

4-Chloro-5-hydrazino-3-pyridazone (XXXVII). This compound was prepared in the same manner as described above for 4-bromo-5-hydrazino-3-pyridazone. Recrystallization from water produced long pale yellow needles which darkened to orange on standing, m.p. 195°C with decomposition.

This compound had previously been prepared by Castle and Aldous, unpublished report.

5-Hydrazino-3-pyridazone (XXXIX). 4-Chloro-5-hydrazino-3-pyridazone (4.8 g., 0.05 mole) dissolved in 200 ml. of 1% sodium hydroxide was treated with hydrogen in the presence of 1.2 g. 5% Pd-C catalyst at atmospheric pressure and room temperature. After the theoretical amount of hydrogen had been absorbed, the catalyst was separated and washed with 50 ml. 1% sodium hydroxide followed by methanol until washings were no longer basic. The filtrate and washings were neutralized with glacial acetic acid and the solution concentrated on a steam bath under reduced pressure. After cooling 48 hours, 2.8 g. (74%) of a dark orange solid was collected. Recrystallization from 95% ethanol (norite) afforded pale yellow needles, m.p. 267°C with decomposition.

Anal. Calcd. for $C_4H_6N_4O$: C, 38.09; H, 4.79. Found: C, 38.16; H, 4.59.

5-Amino-3-pyridazone (XL). A mixture of 1.75 g. 5-hydrazino-3-pyridazone (0.014 mole) dissolved in 85% ethanol and Raney-Ni W-2 (prepared from 15 g. of Raney-Ni alloy) was allowed to reflux 2 hours. The odor of ammonia was discernible after 15 minutes and continued throughout the reaction period. The catalyst was removed and the filtrate evaporated on a steam bath at reduced pressure to approximately one-half volume. After cooling overnite, 0.9 g. (60%) gray platelettes were collected and recrystallized from water (norite) to yield white crystals, m.p. 288°C with decomposition.

Anal. Calcd. for $C_4H_5N_3O$: C, 43.24; H, 4.54. Found: C, 42.94; H, 4.10.

The derivatives of both 4-bromo-5-hydrazino-3-pyridazone and 4-chloro-5-hydrazino-3-pyridazone were prepared by the two general procedures described below. Table II of the derivatives indicates which procedure was followed.

General Procedure A. One-tenth mole of the appropriate halo-hydrazino pyridazone was treated with 8 ml. concentrated sulfuric acid followed by 70 ml. water and the mixture heated gently just until the solid dissolved at which time the hot acidic solution was poured into a second flask containing 1 ml. carbonyl compound dissolved in 40-80 ml. 95% ethanol. The mixture was allowed to stand 12-24 hours, the solid was filtered and recrystallized, usually from ethanol.

General Procedure B. To one-tenth mole of the hydrazino pyridazone was added 10 ml. concentrated hydrochloric acid in 10 ml. water and 15 ml. 95% ethanol. The mixture was heated, then

General Procedure [illegible] [illegible] ... mixture of [illegible] [illegible] hydrazine [illegible] (0.01 mole) dissolved in [illegible] ethanol was [illegible] [illegible] [illegible] 1 g. of [illegible] [illegible] and [illegible] [illegible] 2 hours. [illegible] [illegible] ammonia was [illegible] after [illegible] minutes and continued throughout the reaction period. The catalyst was removed and the filtrate evaporated on a steam bath [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] were collected and recrystallized from water [illegible] [illegible] [illegible] crystals, [illegible] [illegible] with decomposition.

Anal. Calcd. for [illegible]: C, [illegible]; N, [illegible]. Found: C, [illegible]; N, [illegible].

The derivatives of both [illegible] [illegible] and [illegible] were prepared by the two [illegible] general procedures described below. Table II of the derivative indicates which procedure was followed.

General Procedure A. One-[illegible] mole of the appropriate [illegible] was treated with [illegible] ml. concentrated sulfuric acid followed by 10 ml. water and the mixture heated gently just until the solid dissolved at which time the hot acidic solution was poured into [illegible] [illegible] containing the carbonyl compound dissolved in [illegible] ml. of [illegible] ethanol. The mixture was allowed to stand 12-24 hours, the solid was filtered and recrystallized, usually from ethanol.

General Procedure B. One-[illegible] mole of the hydrazino [illegible] was added to [illegible] ml. concentrated hydrochloric acid in [illegible] ml. water and [illegible] ml. [illegible] ethanol. The [illegible] was [illegible], [illegible].

added to one gram of the carbonyl compound dissolved in 10 ml. of ethanol. After cooling 24 hours the precipitate was filtered and recrystallized from an appropriate solvent.