THE REACTIONS OF 1,2,3,4-TETRAHYDROPHENAZINE-DI-N-OXIDE WITH ACETIC ANHYDRIDE

BY

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ABSTRACT

The reaction of 1,2,3,4-tetrahydrophenazine-di-N-oxide (XVII) with acetic anhydride at room temperature gave 1-acetoxy-2,3,4-trihydrophenazine-5-N-oxide (XVIII) and traces of phenazine (XIX). Under reflux conditions, the same reactants yielded in addition to phenazine, trans and cis 1,4-diacetoxy-2,3-dihydrophenazine in about equal amounts (XX, XXI).

The reaction of 1-acetoxy-2,3,4-trihydrophenazine-5-N-oxide (XVIII) with acetic anhydride at reflux temperature afforded XX and XXI, with no detection of phenazine.

Alkaline hydrolysis of cis and trans 1,4-diacetoxy-2,3-dihydrophenazine yielded the corresponding cis and trans 1,4-dihydroxy-2,3-dihydrophenazine (XXIII, XXII) which, upon treatment with acetic anhydride-pyridine were converted to the original diacetates (XXI, XX).

Reduction of XVIII with sodium dithionite gave 1,2,3,4-tetrahydrophenazine (XXIV).

The formation of XVIII, XIX, XX, XXI is interpreted in terms of an ion-pair mechanism.

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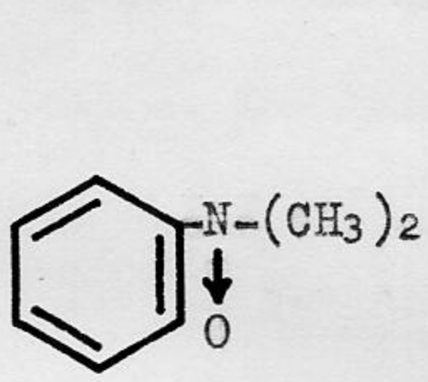
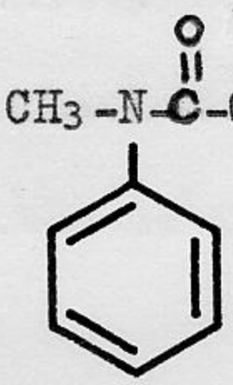
INTRODUCTION

Historical

A Polonovski type rearrangement involves the reaction of an aromatic-N-oxide with acid anhydrides.[1] For example, the base catalyzed reaction of dimethyl aniline-N-oxide (I) with acetic anhydride[2] gives N-methyl acetanilide (II) and o-acetoxy-N,N-dimethyl aniline (III).



I



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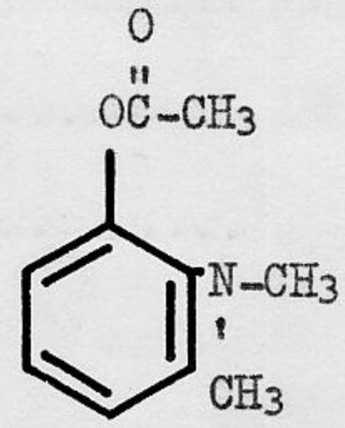
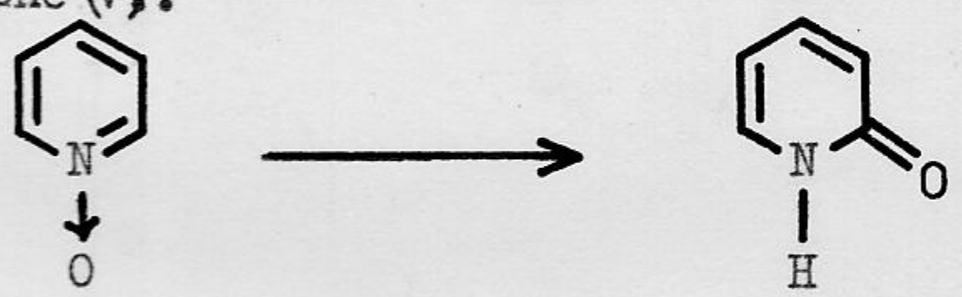


III

In 1947, Katada[3] reported that the reaction of pyridine-N-oxide (IV) with acid anhydrides (acetic or benzoic) led after hydrolysis to 2-pyridone (V).

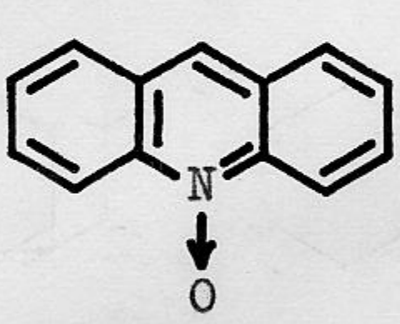


IV

V

Later, Ochiai and his collaborators, showed that the N-oxides of quinine, dihydroquinine and benzo(h)quinoline underwent re-

arrangement in a similar fashion to give the corresponding ∝ -pyridones.[4-7] If the ∝ -positions of the pyridine N-oxide are blocked, as in acridine-N-oxide VI, rearrangement takes place at the ɣ (transannular), position[8] (VII).



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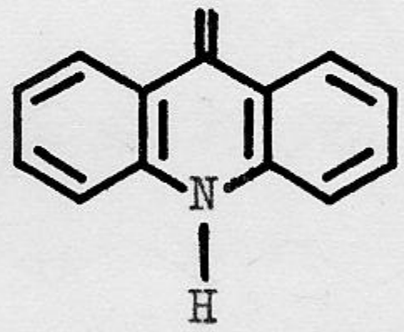
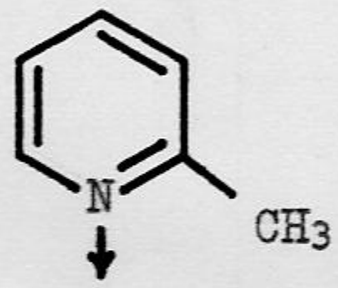
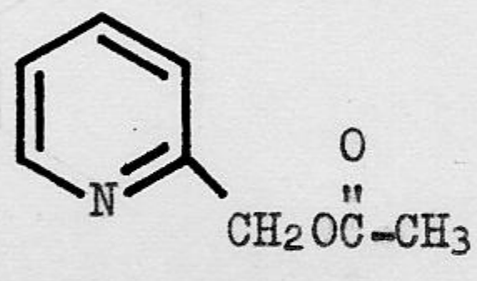


VII

Further investigations[9,10] of the above rearrangement with alkyl substituted aromatic-N-oxides namely, N-oxides of 2-, 3- and 4-picoline, 2-ethyl pyridine, 2-n-butyl pyridine, 2,6-lutidine and quinaldine, showed that with the 2- and 4-alkyl derivatives the products of the reaction were not pyridones but, pyridyl carbinol derivatives. For example, the reaction of 2-picoline-N-oxide(VIII) with acetic anhydride afforded 2-pyridine methanol acetate(IX)in 78% yield.



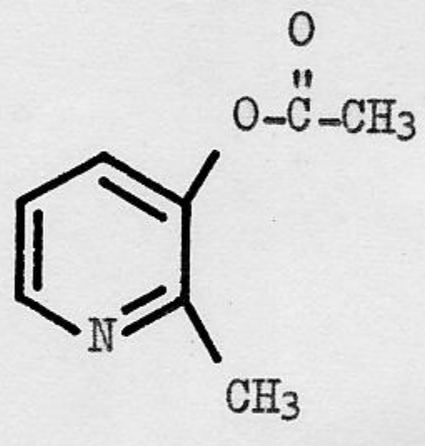
VIII



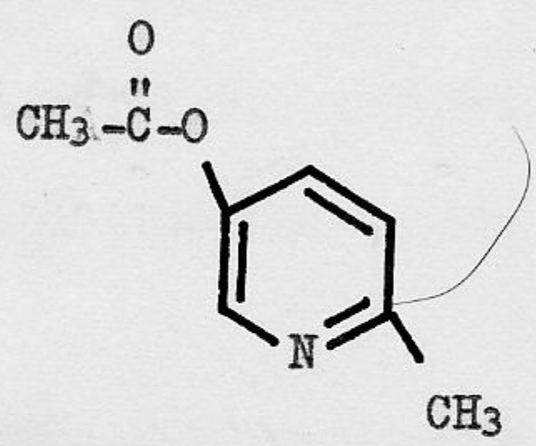
IX

Ford and Swan,[11] using gas chromatography, reported that the reaction of 2-picoline-N-oxide with acetic anhydride gives, in addition to IX (66%), two other isomeric acetoxy compounds namely,

3-acetoxy-2-picoline (X, 16%) and 5-acetoxy-2-picoline (XI, 18%).



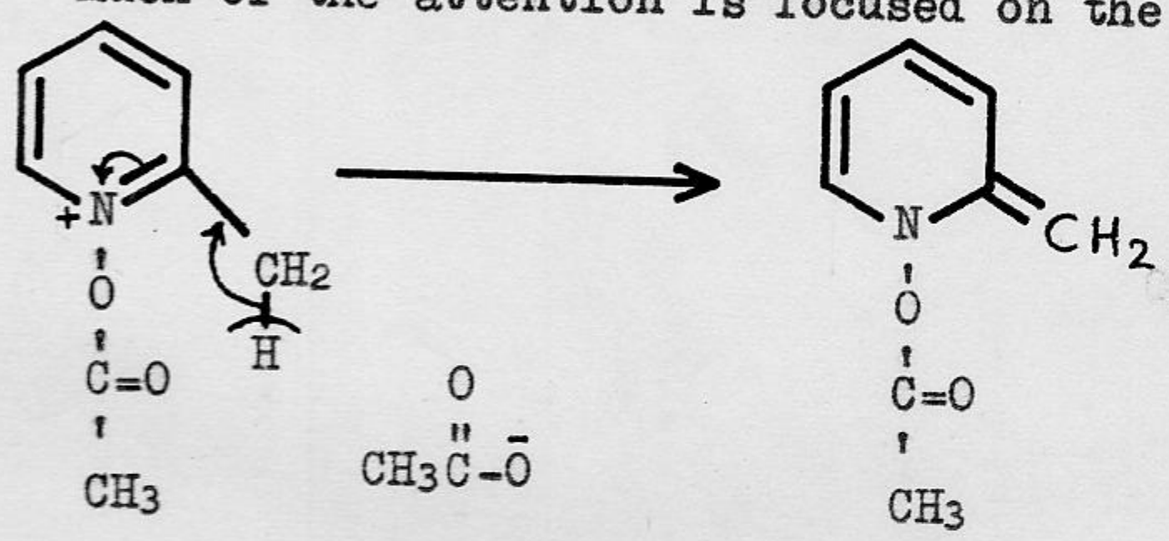
X



XI

Mechanism

The mechanism of the reaction of 2-alkyl substituted pyridine-N-oxide with acid anhydrides has been the subject of extensive studies in the last ten years.[12-16] It is generally accepted that the first step in the reaction of 2-picoline-N-oxide with acetic anhydride involves the formation of XII, the picrate[17] and perchlorate[18] salts of which have been isolated. It is also accepted that the second step involves an irreversible proton transfer and hence rate determining.[13] Much of the attention is focused on the mode of the



XII

XIII

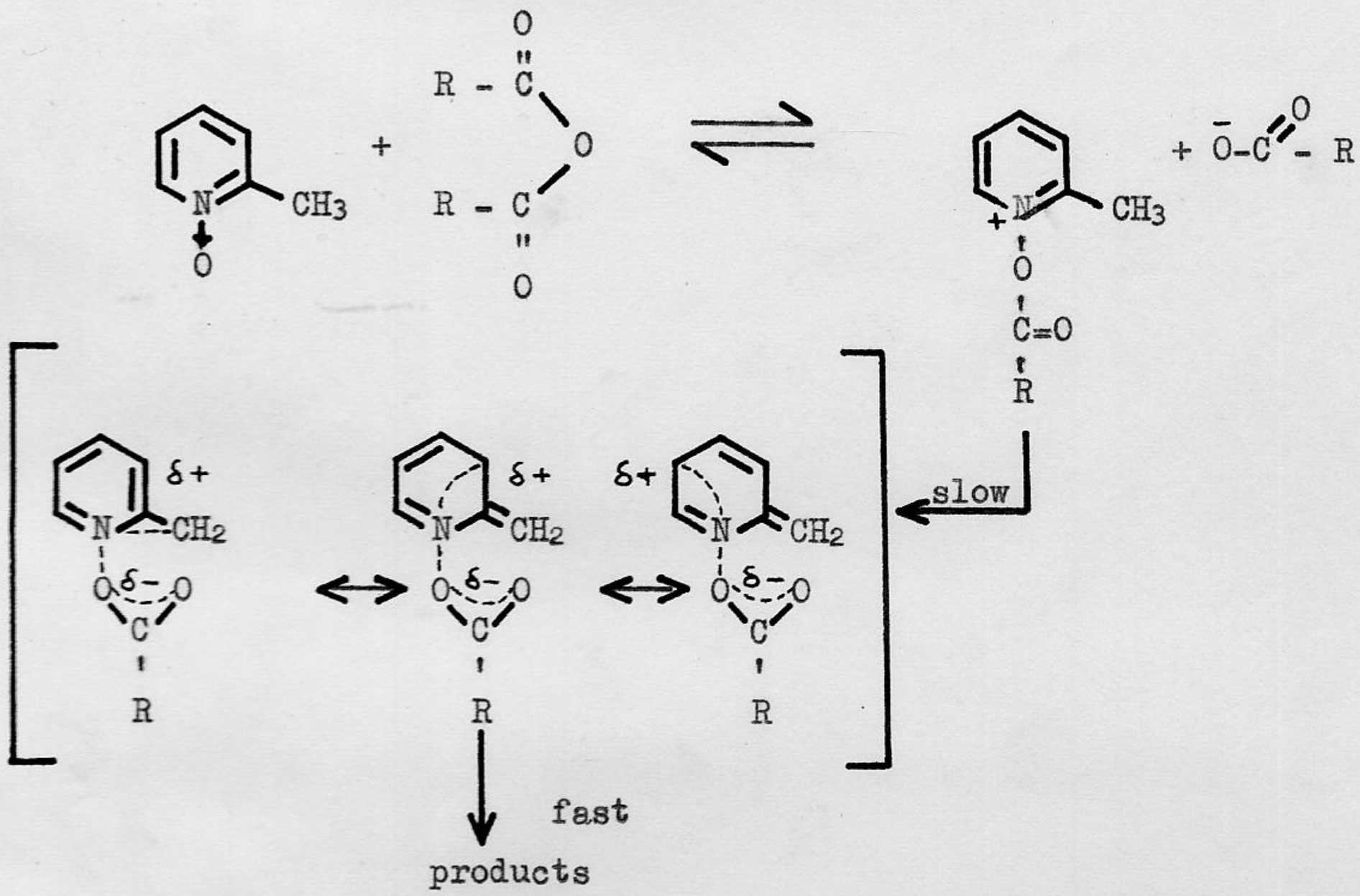
rearrangement of XIII to products. The mechanisms considered to account for this rearrangement include a concerted cyclic process,[10,12,19] an addition-elimination sequence,[9,10,12] ion pair formation[10,20] and

radical-pair formation with efficient cage recombination.[10,12]

The addition-elimination sequence was rejected on the basis of the observation that the reaction with butyric anhydride with added acetate or chloride gave no products incorporating the external anion.[10]

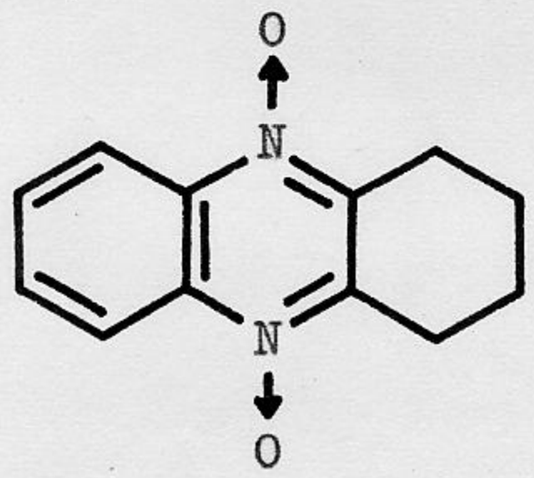
Studies of the reaction with oxygen-18-labelled acid anhydrides[12,14] confirmed the rearrangement to be intramolecular and further showed that equilibration of the two oxygen atoms of the N-acyloxyl group occurs in the process. These labeling studies ruled out the concerted cyclic process.

Recently, Koenig[16] in an investigation of the reaction of 2-picoline-N-oxide with phenylacetic, trichloroacetic and trifluoroacetic anhydrides, argues for an ion-pair mechanism against a radical-pair mechanism. Koenig's mechanism is outlinedbelow:



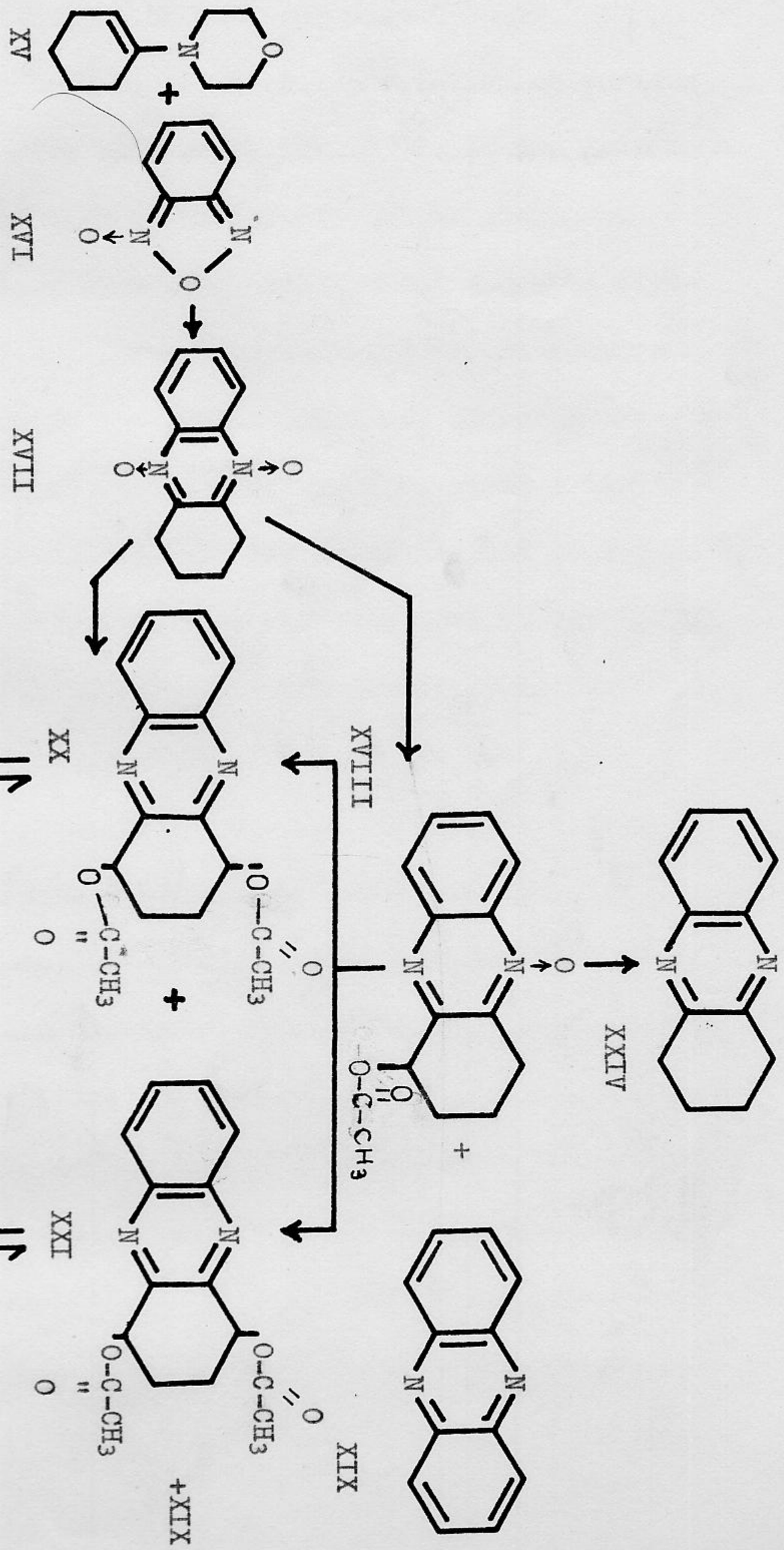
Purpose of the work

Although the reaction of various aromatic-N-oxides with acid anhydrides is extensively studied, no work has been reported on the analogous reaction of aromatic di-N-oxides and acid anhydrides. The purpose of this work was to investigate the possibility of such a reaction, and to examine its stereoselectivity using 1,2,3,4-tetrahydrophenazine-di-N-oxide(XIV) and acetic anhydride.



XIV

TRANSFORMATIONS



DISCUSSION

Intensive work has been reported on the reaction of various aromatic amine-N-oxides with acid anhydrides.[2-11] At the outset of this investigation, we knew of no reports on the analogous reaction of acid anhydrides with alkyl substituted aromatic di-N-oxides.[21] The choice of 1,2,3,4-tetrahydrophenazine-di-N-oxide (XVII) as a model di-N-oxide and acetic anhydride afforded the chance to examine the extent of the reaction i.e. whether it proceeds to give monoacetate XVIII or the diacetates XX or XXI or a mixture of all possible combinations. Furthermore it was hoped that the stereospecificity of such a rearrangement could be explored by a structural study of the reaction product(s).

1,2,3,4-tetrahydrophenazine-di-N-oxide was prepared from benzofurazan oxide (XVI) and 1-morpholino-1-cyclohexene (XV).[22] A solution of XVII and acetic anhydride, when left to stand at room temperature, gave 1-acetoxy-2,3,4-trihydrophenazine-5-N-oxide (XVIII) in 50% yield and traces of phenazine.

The structure of monooxide XVIII was assigned on the basis of elemental analysis, infrared spectra which displayed bands at 1725 (carbonyl of the acetate), 1335 (N-O) and 765 cm^{-1} (o-substituted phenyl) and n.m.r. spectra which showed a singlet at 7.8τ (7 protons, 3 for acetate and 4 for protons at carbons 2 and 3),

multiplet at 6.96 τ (2 protons at carbon 4), unsymmetrical doublet at 3.96 τ (1 proton at carbon 1) and multiplets at 2.9, 2.08 and 1.6 τ (4 aromatic protons). Phenazine was identified by comparison with an authentic sample using thin layer chromatography.

When the above reaction was repeated at reflux temperature, the resulting crude product was recrystallized several times with appreciable loss in weight and a crystalline colorless product melting at 164 - 165^{0} was recovered. This product is considered to be trans 1,4-diacetoxy-2,3-dihydrophenazine (XX). Diacetate XX gives the correct elemental analysis and shows bands at 1700, 1680 cm^{-1} (carbonyl of the acetate) and 765 cm^{-1} (o-substituted phenyl) and no N-O absorption in the 1330 cm^{-1} region. The n.m.r. spectrum of XX exhibits a singlet at 7.87 τ (6 protons for two acetates), a multiplet at 7.68 τ (4 protons at carbons 2 and 3), a multiplet at 3.76 τ (2 protons at carbons 1 and 4) and an A_2B_2 system at 2.3 and 1.9 τ (4 aromatic protons).

Differences in the infrared spectra of the crude acetylation product and that of diacetate XX, especially in the 760 cm^{-1} region, indicated that the reaction yields more than one product. Chromatography of the crude reaction product on a neutral alumina column gave, in addition to the trans diacetate XX, phenazine (XIX) and cis 1,4-diacetoxy-2,3-dihydrophenazine (XXI). The structure of XIX was confirmed by mixture melting point, infrared and ultraviolet spectra, all of which were identical to those of authentic phenazine. The structure of the cis diacetate XXI was inferred from elemental

analysis, infrared spectra which displayed an absorption band at 1720 (carbonyl of the acetate) and 765 cm^{-1} (o-substituted phenyl), and n.m.r. spectra which showed a singlet at 7.86 τ (6 protons for two acetates), multiplet at 7.70 τ (4 protons at carbons 2 and 3), a multiplet at 3.84 τ (2 protons at carbons 1 and 4) and symmetrical multiplets at 2.3 and 1.9 τ (A_2B_2 system for 4 aromatic protons). The ultraviolet spectra of the diacetates XX and XXI are consistent with those of quinoxaline derivatives.[23]

Alkaline hydrolysis of XX and XXI separately yielded the expected corresponding diols XXII and XXIII. Treatment of XXII and XXIII with acetic anhydride-pyridine yielded the original diacetates (XX, XXI) which indicates that no epimerization occurred during hydrolysis.

Attempted oxidation of the trans diol XXIII to the known 1,4-dihydroxyphenazine (XXVII)[24] resulted in intractable tars.

The factors presented above that establish the structures of XX and XXI do not constitute a conclusive evidence for the cis and trans assignment. Diacetate XX has a higher melting point (164 - 165°) than diacetate XXI (158°). Similarly diol XXII derived from diacetate XX melts at a higher temperature than diol XXIII obtained from diacetate XXI. In chromatography, when conformational differences between two substances are not pronounced as in diacetates XX and XXI where substituents on either carbon 1 or 4 are quasi axial and quasi equatorial, it is expected that polar effects dominate over conformational effects. Consequently, if diacetate XX is trans

in structure it should be less polar than diacetate XXI and hence should emerge before the latter from the chromatography column, which it does (see experimental). Low polarity and higher melting point are consistent with a trans structure for diacetate XX and accordingly a cis configuration for diacetate XXI.

The infrared spectrum of trans diacetate XX in nujol shows a doublet in the 1700 cm^{-1} region that collapses into a singlet in chloroform. This behaviour in nujol is probably due to crystal effects*. Cis diacetate XXI shows a singlet in the infrared carbonyl region in nujol and chloroform.

An interesting feature of this work is the formation of phenazine (XIX) as a by-product of the acetylation of XVII. Phenazine could arise through the elimination of the trans and / or cis diacetates XX, XXI under reflux conditions. Such a possibility was rejected because XX and XXI separately gave no phenazine under the reaction conditions (XVII $\longrightarrow$ XX + XXI). Another source of phenazine could be the monoacetate-mono-N-oxide XVIII. Treatment of the latter with acetic anhydride-acetic acid at reflux temperature gave XX and XXI in about equal amounts and no phenazine, as shown by column and thin layer chromatography.

It has been stated that phenazine-free di-N-oxide XVII and acetic anhydride gave phenazine at both room and reflux temperatures in addition to the acetylated products. As an explanation for the

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* We are thankful to Professor C. Brooks of the University of Glasgow for this suggestion.

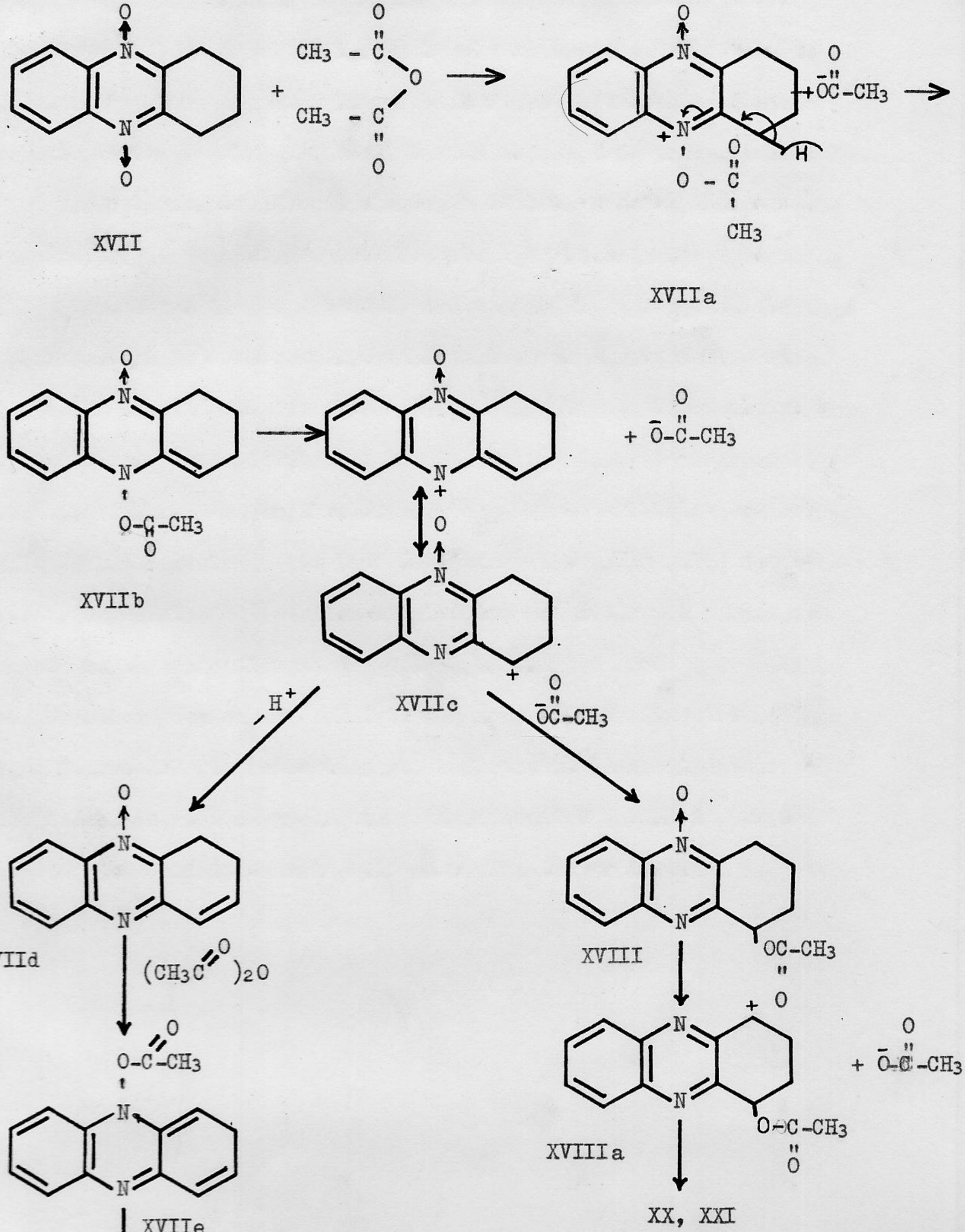
formation of these products (scheme I) it is reasonable to assume that products XVIII, XIX, XX and XXI have the common intermediate XVIIc which arises from a heterolytic cleavage of the N-O bond, and subsequently either reacts with an acetate ion to yield XVIII or loses a proton to give intermediate XVIId. The latter could also arise through a 1,4-elimination process of intermediate XVIIb, this being facilitated by the relatively acidic proton at carbon 2.

By analogy, the reaction of acetic anhydride with XVIII is believed to yield carbonium ion XVIIIa which can be attacked from either side of the ring to give a mixture of cis and trans diacetate (XXI and XX).

Similarly, the reaction of acetic anhydride with intermediate XVIId could be envisaged to lead to intermediate XVIIe which undergoes 1,2(carbonium ion) or 1,4-elimination of acetic acid and results in the formation of phenazine (XIX).

The intermediacy of XVIII in the formation of diacetates XX and XXI from XVII is supported by the fact that these diacetates are obtained in about the same ratio when monoacetate XVIII is treated with acetic anhydride-acetic acid at reflux temperature.

Scheme I



The above mechanism is suggested in the light of Koenig's recent work,[16] who convincingly dismissed a free radical mechanism involving a homolytic cleavage of the N-O bond in intermediates analogous to XVIIa. It should be stated that, in our case, although an ionic mechanism is most likely, a dual mechanism cannot be entirely excluded.

Reduction of XVIII with aqueous sodium dithionite did not lead to 1-acetoxy-2,3,4-trihydrophenazine but to 1,2,3,4-tetrahydrophenazine (XXIV), identified by m.p., mixture melting point, and by its infrared spectrum which was superimposable on that of authentic XXIV. This unexpected result probably involves an elimination of the acetate ion followed by reduction of the N-O bond. Further work is required to establish the path of this reaction.

In conclusion, it has been shown that the reaction of 1,2,3,4-tetrahydrophenazine-di-N-oxide with acetic anhydride can be used to prepare monoacetate XVIII and diacetates XX and XXI not easily obtainable by other methods, and that the formation of a mixture of cis and trans diacetates has shown that the reaction is nonstereoselective.

Moreover, the suggested ionic mechanism in scheme I presents an elimination reaction not observed before and implies the formation of other side products and therefore calls for further investigation.

EXPERIMENTAL*

1. Morpholino-1-cyclohexene (XV)[25]

A solution of 147 g of cyclohexanone, 157 g of morpholine, and 1.5 g of p-toluenesulfonic acid in 300 ml of toluene was placed in a 1 liter round bottomed flask equipped with a reflux condenser and a Dean-Stark water separator. The solution was refluxed until no separation of water was observed (6 hrs.). Boiling chips and short glass tubings were introduced into the solution to minimize bumping and foaming during distillation. An indented Claisen Still-head was attached to the flask, and after the removal of toluene (b.p. 111°), the product, 1-morpholino-1-cyclohexene (XV) was collected as a colorless liquid at 118 - 120°/10 mm. in 77.6% yield (194 g). The

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* Melting points are uncorrected. Alumina used for chromatography was neutral, Grade I "Woelm" to which 3% water was added. Solvents for chromatography are indicated thus; P.E. = 30 - 75° pet. ether, B = Benzene, E = Ether. Elemental analysis were performed by F. Pascher, Bonn, Germany. Ultraviolet spectra were measured in methanol solution, in a Perkin-Elmer Ultraviolet-Visible spectrophotometer Model 202. Unless specified otherwise, infrared spectra were determined in nujol using a Perkin-Elmer infracord spectrophotometer Model 137G. Nuclear magnetic resonance spectra were run in deuterated chloroform on a Varian A 60 spectrometer.

product was kept under nitrogen and stored in the refrigerator.

Benzofurazan oxide (XVI)[26]

a) Sodium hypochlorite solution

An aqueous solution of sodium hydroxide (50 g in 200 ml of water) was cooled to 0°. After the addition of crushed ice (100 g), the solution was placed in an ice-salt bath and chlorine gas (41 g) was bubbled into it. The hypochlorite solution was used immediately.

b) Benzofurazan oxide

o-Nitroaniline (40 g) was dissolved in a warm solution of alcoholic potassium hydroxide (21 g in 250 ml of ethanol). The deep red solution was cooled to 0°. The above hypochlorite solution was slowly added to it with stirring over the course of ten minutes at 0 - 5°. The flocculent yellow precipitate was collected on a Buchner funnel, washed with water (200 ml) and air dried. The crude product was purified by recrystallization from ethanol (45 ml) and water (15 ml). The yield of benzofurazan oxide (XVI) was 31 g (80%). m.p. 72 - 73°.

1,2,3,4-tetrahydrophenazine-di-N-oxide (XVII)[22]

To a warm methanolic solution of benzofurazan oxide (XVI, 13 g), 1-morpholino-1-cyclohexene(XV, 17 g) was added in portions with stirring. A deep red coloration developed with a rise in the temperature of the reaction mixture. Concentration of the methanolic solution under water-aspirator reduced pressure resulted in the precipitation of a pale red solid which was collected by suction filtration. Recrystallization from methanol gave yellow prisms of 1,2,3,4-tetrahydro-

phenazine-di-N-oxide (XVII, 11 g, 51%) m.p. 183 - 184°.

The reaction of 1,2,3,4-tetrahydrophenazine-di-N-oxide (XVII) with acetic anhydride

a) At room temperature

In a 10 ml Erlenmeyer flask, 1,2,3,4-tetrahydrophenazine-di-N-oxide (XVII, 1 g) was dissolved in a mixture of acetic anhydride (4 ml) and glacial acetic acid (1 ml) with gentle warming. The reaction mixture, after being allowed to stand at room temperature for 48 hours, was poured into crushed ice (10 g) with stirring. A pale yellow solid precipitated which was collected by suction filtration, washed with water (3 ml) and air dried (0.8 g). Thin layer chromatography of the crude product on silica gel, with benzene or benzene-chloroform 1:1 as solvent indicated the presence of traces of phenazine (XIX, detected by comparison with an authentic sample and by its deep red coloration with concentrated sulfuric acid)[27] and 1-acetoxy-2,3,4-trihydrophenazine-5-N-oxide (XVIII) as the major component. The latter was obtained pure after two recrystallizations from methanol. (0.6 g, 50% yield), m.p. 140 - 141°. I.R. ν_{max}: 1725, 1560, 1475, 1335, 1225, 1050, 965, 910, 850, 765 cm^{-1}. U.V. λ_{max}: 214, 244.5, 329, 344 mμ (ε : 1.6×10^4, $41. \times 10^3$, 7.7×10^3, 6.9×10^3 respectively). N.m.r.: singlet at 7.8 τ (7 protons, 3 for acetate and 4 for protons at carbons 2 and 3), multiplet at 6.96 τ (2 protons at carbon 4), unsymmetrical doublet at 3.96 τ (1 proton at carbon 1) and multiplets at 2.9, 2.08 and 1.6 τ (4 aromatic protons).

Anal. Calcd. for $C_{14}H_{14}O_3N_2$ (258.27): C, 65.10; H, 5.46, N. 10.85.

Found: C, 65.12, H, 5.50, N, 10.70.

b) <u>At reflux temperature</u>

A mixture of 1,2,3,4-tetrahydrophenazine-di-N-oxide (XVII, 11 g), acetic anhydride (44 ml) and glacial acetic acid (11 ml), was refluxed for 75 minutes. The cold tan-colored solution was poured into crushed ice (50 g) with stirring. A greenish yellow solid precipitated, collected by suction filtration, washed with cold water (60 ml) and dried (8.5 g).

A sample of 6.8 g of the crude acetylation product was dissolved in the minimum amount of benzene and chromatographed on a neutral alumina column (290 g of alumina in a column 40 mm in diameter and 250 mm in height). Elution with: P.E. - B: 8:2, 7:3, 3:2, 2:3, 1:4 (400, 400, 450, 800, 800 ml respectively) B (650 ml); B - E: 8.5:1.5, 4:1, 7:3, 3:2, 1:1 (250, 350, 100, 100, 300 ml respectively) and evaporation of the fractions yielded:

Phenazine (XIX, 125 mg) which was confirmed by m.p. 171 - 173° (lit.[28] 171 - 173), mixture melting point with authentic phenazine. The infrared and ultraviolet spectra of XIX were superimposable with those of authentic phenazine.

Trans 1,4-diacetoxy-2,3-dihydrophenazine (XX, 1.83 g). Recrystallization from methanol gave colorless needles m.p. 164 - 165°. N.m.r.: singlet at 7.87 τ (6 protons for 2 acetates), multiplet at 7.68 τ (4 protons at carbons 2 and 3), multiplet at 3.76 τ (2 protons at carbons 1 and 4) and symmetrical multiplet at 2.3 and 1.9 τ (A_2 B_2 system for 4 aromatic protons). I.R. ν_{max}: 1700, 1685, 1220, 1190, 1145, 1080, 1025, 965, 765 cm^{-1}. ν_{max} ($CHCl_3$): 1745, 1360, 1225,

1020, 965 cm^{-1}. U.V. λ_{max}: 209, 239, 315, 325 mμ (ε: 1.4 x 10^4, 3.3 x 10^4, 5.7 x 10^3, 7.5 x 10^3 respectively).

Anal. Calcd: for $C_{16}H_{16}O_4N_2$ (300.30): C, 63.99; H, 5.37; N, 9.33. Found: C, 63.94; H, 5.35; N, 9.47.

Cis 1,4-diacetoxy-2,3-dihydrophenazine (XXI, 1.50 g). Recrystallization from methanol yielded needles melting at 158°. N.m.r.: singlet at 7.86 τ (6 protons for 2 acetates), multiplet at 7.70 τ (4 protons at carbons 2 and 3), multiplet at 3.84 τ (2 protons at carbons 1 and 4) and symmetrical multiplets at 2.3 and 1.9 τ (A_2 B_2 system for 4 aromatic protons). I.R. ν_{max}: 1720, 1250, 1220, 1040, 970, 765 cm^{-1}. I.R. ν_{max}: ($CHCl_3$): 1745, 1360, 1225, 1040, 965 cm^{-1}. U.V. λ_{max}: 208, 238.5, 317, 325 mμ (ε: 1.2 x 10^4, 2.7 x 10^4, 4.6 x 10^3, 5.5 x 10^3 respectively).

Anal. Calcd. for $C_{16}H_{16}O_4N_2$ (300.30): C, 63.99; H, 5.37; N, 9.33. Found: C, 63.78; H, 5.33; N, 9.52.

Examination of the infrared spectrum of the crude, especially in the 760 cm^{-1} region indicated that both, trans and cis isomers (XX, XXI), were formed in about equal amounts.

<u>The reaction of 1-acetoxy-2,3,4-trihydrophenazine-5-N-oxide (XVIII) with acetic anhydride</u>

1-acetoxy-2,3,4-trihydrophenazine-5-N-oxide (XVIII, 2 g), acetic anhydride (8 ml) and glacial acetic acid (2 ml) were placed in a 25 ml round bottommed flask. The reaction mixture was refluxed for 75 minutes, cooled to room temperature and poured with stirring into crushed ice (15 g). The resulting precipitate was collected, washed with water

(30 ml) and dried. (1.62 g). The product was dissolved in the minimum amount of benzene and chromatographed on a neutral alumina column (125 g of alumina in a column 33 mm in diameter and 220 mm in height). Elution with P.E. (250 ml); P.E. - B: 9:1, 17:3, 4:1, 7:3, 3:2, 1:1, 2:3, 3:7, 1:4 (250, 200, 200, 350, 500, 350, 400, 950, 100 ml respectively) B - (1300 ml) and evaporation of the fractions yielded; trans 1,4-diacetoxy-2,3 dihydrophenazine (XX) and cis 1,4-diacetoxy-2,3-dihydrophenazine (XXI), identical with the trans and cis diacetates obtained in procedure (b) (m.p. mixture melting point, infrared and ultraviolet spectra). Thin layer chromatography of the crude product on silica gel, with benzene or benzene-chloroform 1:1 as solvents indicated the absence of phenazine (XIX, compared with authentic phenazine).

Cis and trans 1,4-diacetoxy-2,3-dihydrophenazine (XXI, XX) with acetic anhydride

a) Cis 1,4-diacetoxy-2,3-dihydrophenazine (XXI)

A mixture of cis 1,4-diacetoxy-2,3-dihydrophenazine (XXI, 100 mg), acetic anhydride (0.4 ml) and glacial acetic acid (0.1 ml) was refluxed for 75 minutes. The cold solution was poured into crushed ice with stirring. A white solid was collected by suction filtration, washed with water (5 ml) and air dried. Unchanged cis 1,4-diacetoxy-2,3-dihydrophenazine (XXI) was collected. (78 mg, 78% recovery) identified by m.p., mixture melting point and infrared spectrum. Thin layer chromatography of the crude product on silica gel, using chloroform or benzene-chloroform 1:1 as solvents indicated

the presence of the cis diacetate (XXI) and the absence of phenazine (XIX, compared with authentic samples of both, XXI, XIX).

b) Trans 1,4-diacetoxy-2,3-dihydrophenazine (XX)

The same procedure (a) was applied to trans 1,4-diacetoxy-2,3-dihydrophenazine (XX, 100 mg), and unchanged trans diacetate XX was obtained in (89 mg) 89% recovery identified by m.p., mixture melting point and infrared spectrum. Thin layer chromatography of the crude product on silica gel, using chloroform or benzene-chloroform 1:1 as solvents, indicated the presence of the trans diacetate XX and no detectable phenazine (compared with authentic samples of both XX, XIX).

Hydrolysis of 1,4-diacetoxy-2,3-dihydrophenazine

(a) Cis 1,4-diacetoxy-2,3-dihydrophenazine (XXI)

To a methanolic solution of cis 1,4-diacetoxy-2,3-dihydrophenazine (XXI, 250 mg in 10 ml), 5% sodium bicarbonate (5 ml) was added in portions and with shaking. A solid precipitated and was dissolved by the addition of water (5 ml) and methanol (5 ml). The reaction mixture was allowed to stand at room temperature for 4 hours. Upon concentration of the aqueous methanolic solution, cis 1,4-dihydroxy-2,3-dihydrophenazine (XXIII) precipitated and was collected by suction filtration, washed with water (2 ml) and methanol (2 ml) and air dried. (125 mg, 70% yield). Colorless plates (80 mg, 45% yield) were obtained from methanol. On heating, the diol XXIII develops a pale red color at 147° and melts with decomposition at 167.5 - 169° giving a dark red coloration. I.R. ν_{max}: 3030, 1480, 1275, 1080,

1065, 1055, 1000, 965, 785 cm^{-1}. U.V. λ_{max}: 215, 238.5, 315, 324 mμ (ε : $1.2x10^4$, $2.3x10^4$, $4.4x10^3$, $5.4x10^3$ respectively).

A sample of the cis diol XXIII (50 mg) was dissolved in pyridine (0.8 ml) and acetic anhydride (0.8 ml) was added. After standing for 24 hours, at room temperature, the reaction mixture was poured into crushed ice. The cis diacetate XXI was collected by suction filtration, washed with water and air dried. (42 mg, 61% yield). It was identified by m.p., mixture melting point and infrared spectrum (identical with authentic cis 1,4-diacetoxy-2,3-dihydrophenazine, XXI).

b) Trans 1,4-diacetoxy-2,3-dihydrophenazine (XX)

To a methanolic solution of trans 1,4-diacetoxy-2,3-dihydrophenazine (XX, 0.4 g in 27 ml), water (5 ml) was added followed by 5% sodium bicarbonate (8 ml). The base was added slowly with shaking. The reaction mixture was allowed to stand at room temperature for 4 hours. Concentration of the aqueous methanolic solution resulted in the precipitation of trans 1,4-dihydroxy-2,3-dihydrophenazine (XXII). The product was collected by suction filtration, washed with water (3 ml) and methanol (3 ml) and air dried (225 mg, 78% yield). The trans diol XXII was recrystallized from methanol to give hard needles (180 mg, 62% yield), which on heating became pale red at 165° and melted with decomposition at 182 - 183° giving a dark red coloration. I.R. ν_{max}: 3028, 1050, 1420, 1065, 990, 925, 915, 785 cm^{-1}. U.V λ_{max}: 215.5, 239, 315, 323.5 mμ (ε : 1.2×10^4, 2.6×10^4, 5.4×10^3, 7.2×10^3 respectively).

A sample of the trans diol XXII (50 mg) was dissolved in pyridine

(0.8 ml) and acetic anhydride (0.8 ml) was added. The reaction mixture after 24 hours at room temperature, was poured into crushed ice. The product was collected by suction filtration, washed with water and dried (45 mg, 65% yield) and was shown to be identical to trans 1,4-diacetoxy-2,3-dihydrophenazine (mixture melting point, superimposable infrared spectra).

The reaction of 1-acetoxy-2,3,4-trihydrophenazine-5-N-oxide XVIII with sodium dithionite

To 1-acetoxy-2,3,4-trihydrophenazine-5-N-oxide (XVIII, 0.4 g) indioxane (10 ml), anaqueous solution of sodium dithionite (0.6 g in 5 ml) was added in portions and with shaking. The reaction mixture was refluxed for $6\frac{1}{2}$ hours, cooled and diluted with water (5 ml). Extraction with three portions of ether (10 ml each) and evaporation of the dried ether gave 1,2,3,4-tetrahydrophenazine (XXIV), which was recrystallized twice from petroleum ether 30 - 75° (60 mg, 21%). The product was identified by m.p. 89 - 90 (lit.[29] 92.5), mixture melting point and superimposable infrared spectrum with that of authentic 1,2,3,4-tetrahydrophenazine.

ATTEMPTED REACTIONS:

Oxidation of 1-acetoxy-2,3,4-trihydrophenazine-5-N-oxide (XVIII)

with:

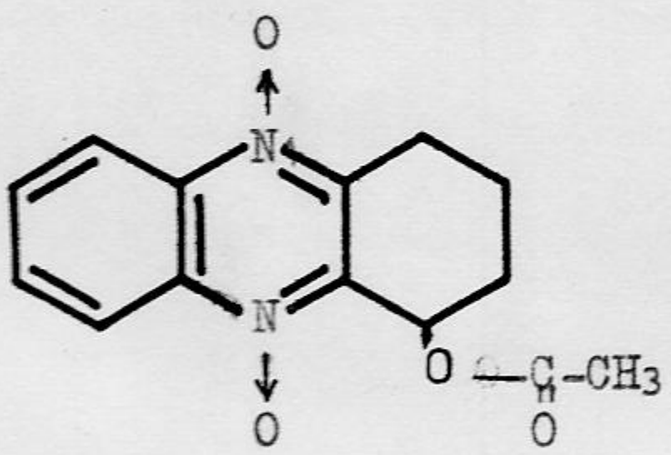
a) Peracetic acid

In three separate attempts, 1-acetoxy-2,3,4-trihydrophenazine-5-N-oxide(XVIII)was dissolved in 40% peracetic acid and the acid solution was allowed to stand at 40° for 2 hours, 4 hours, and an overnight. After dilution with water and extraction with ether, the ethereal part was washed with a 5% sodium bicarbonate solution and dried over anhydrous calcium chloride. Evaporation of ether gave unchanged 1-acetoxy-2,3,4-trihydrophenazine-5-N-oxide (XVIII).

b) Hydrogen peroxide - acetic acid

The procedure described above in (a) was repeated using hydrogen peroxide - acetic acid for 20 hours. 1-acetoxy-2,3,4-trihydrophenazine-5-N-oxide (XVIII) was recovered unchanged.

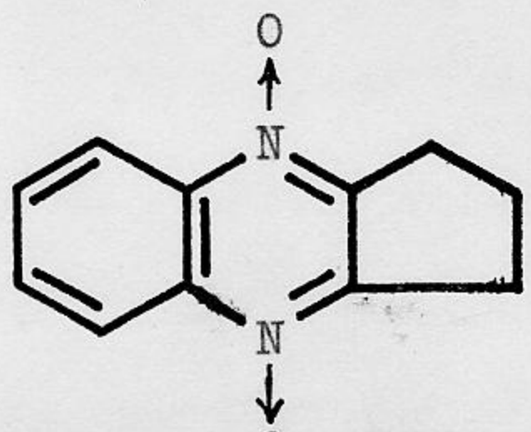
No 1-acetoxy,2,3,4-trihydrophenazine-di-N-oxide (XXV) was detected in both procedures (a) and (b).



XXV

The reaction of 1,2-cyclopentene-quinoxaline-di-N-oxide (XXVI) with acetic anhydride

The reaction of 1,2-cyclopentene-quinoxaline-di-N-oxide (XXVI, 1 g) with acetic anhydride (4 ml) and glacial acetic acid (1 ml) was attempted in four separate runs (a) at room temperature for 72, 48 and $1\frac{1}{2}$ hours respectively and (b) at reflux temperature for 15 minutes. In all attempts, after pouring the reaction mixture into crushed ice a black tarry material was obtained.



XXVI

Oxidation of trans 1,4-dihydroxy-2,3-dihydrophenazine (XXII)

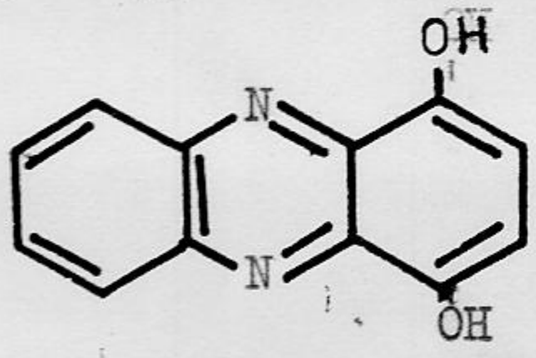
The oxidation of trans 1,4-dihydroxy-2,3-dihydrophenazine (XXII, 100 mg) was attempted using

a) chromium trioxide - pyridine[30]

b) freshly prepared manganese dioxide[31]

c) neutral potassium permanganate[32]

as oxidizing agents. In all attempts, tarry products were obtained and no 1,4-dihydroxyphenazine (XXVII) was detected.



XXVII

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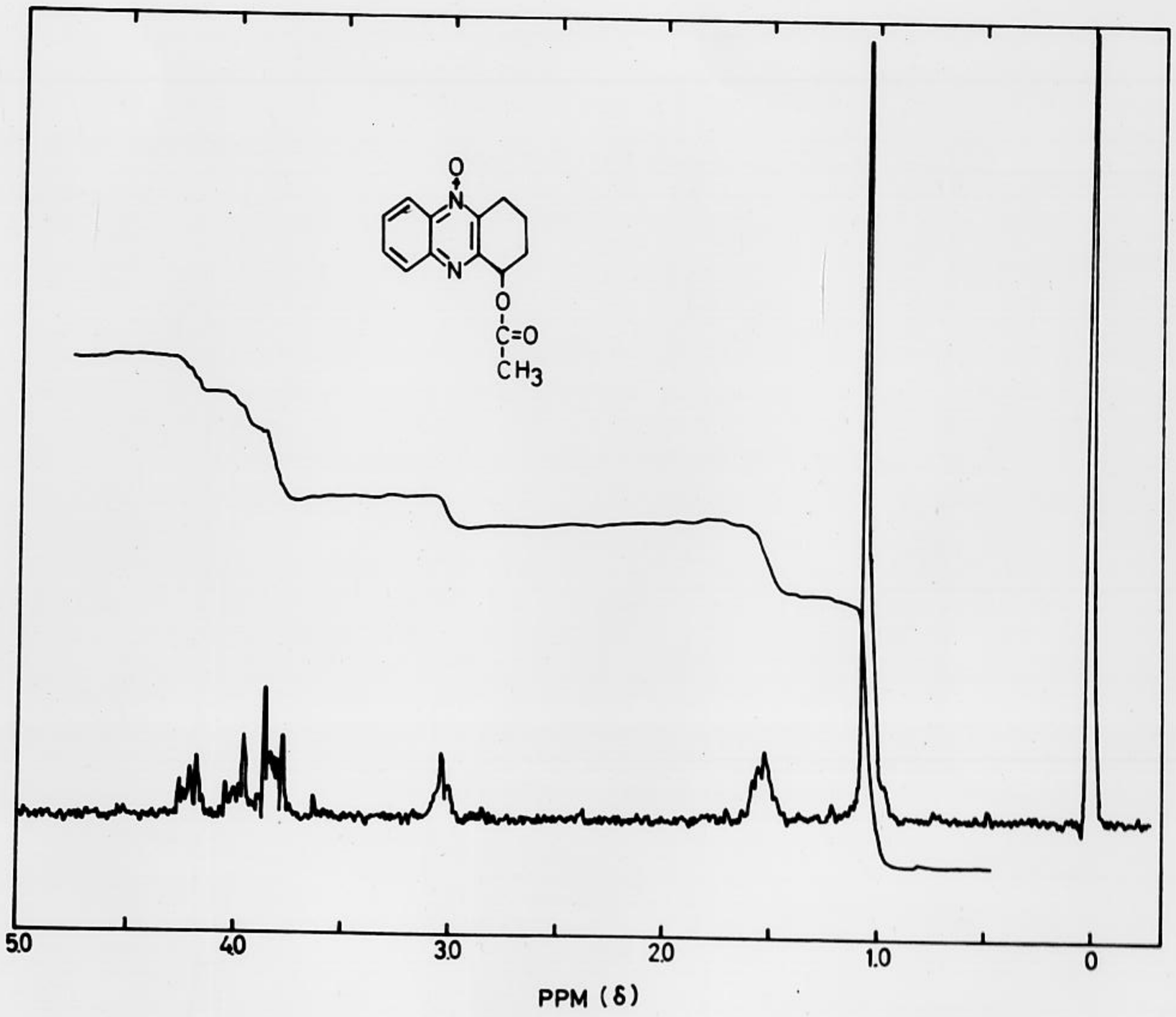
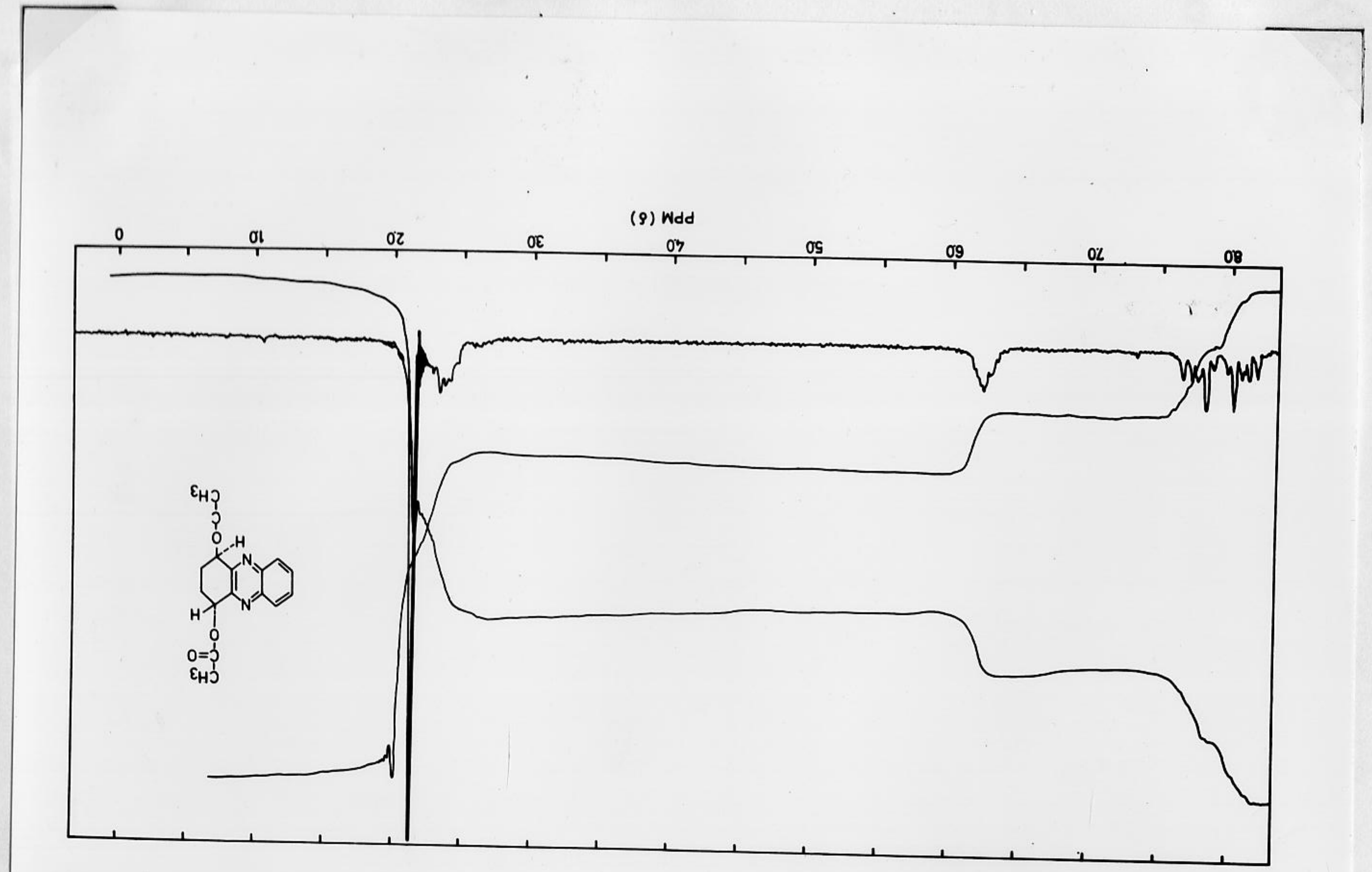

O
N
N
O
C=O
CH3
5.0
4.0
3.0
2.0
1.0
0
PPM (δ)


PPM (δ)
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7.0
6.0
5.0
4.0
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2.0
1.0
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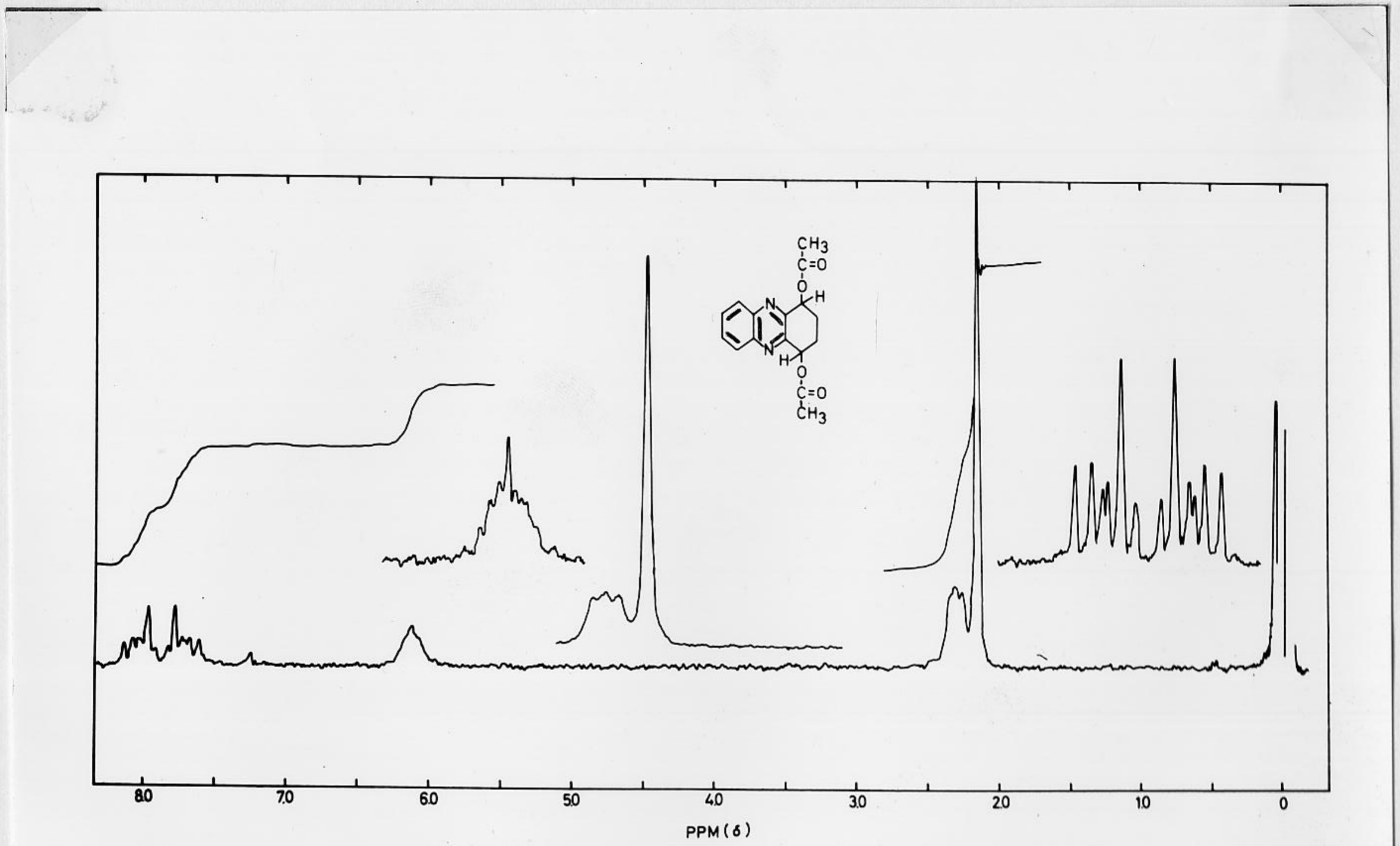
O
C=O
O
H
N
N
H
O
C
CH3


CH3
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O
H
N
N
H
O
C=O
CH3
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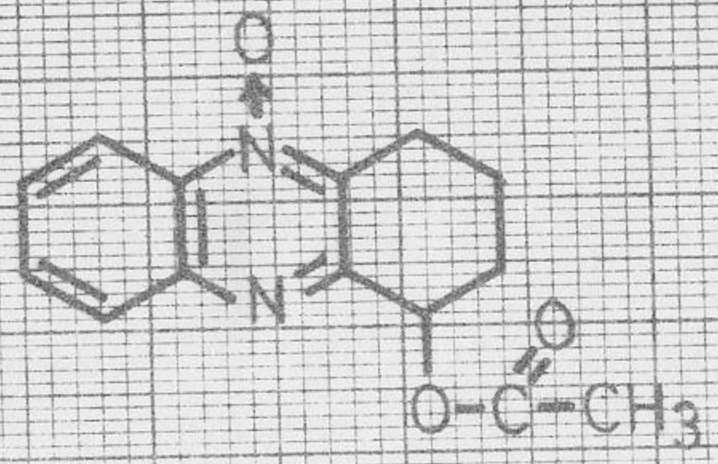
0
PPM (δ)

WAVENUMBER (CM^{-1})

4000 3000 2000 1500 1000 900 800 700



1-acetoxy-2,3,4-trihydrophenazine-5-N-oxide

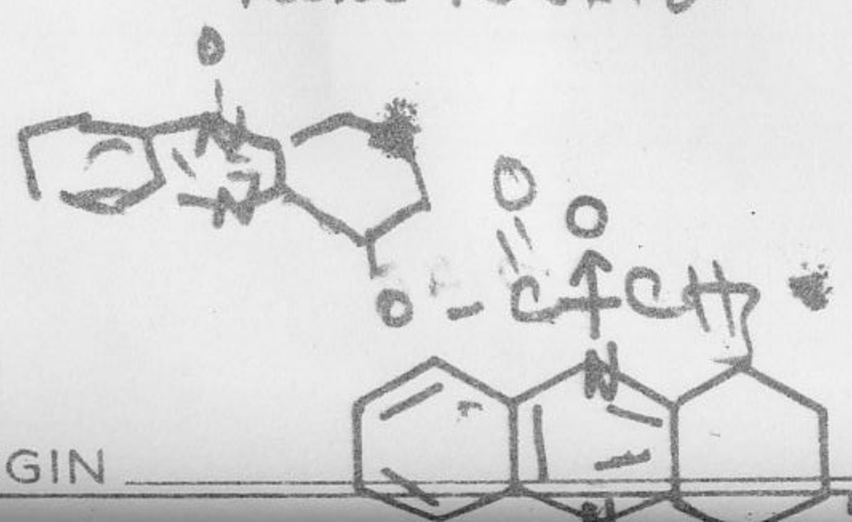
TRANSMITTANCE (%)

100 80 60 40 20 0

3 4 5 6 7 8 9 10 11 12 13 14 15

WAVELENGTH (MICRONS)

SAMPLE Monoacetate Mono N Oxide



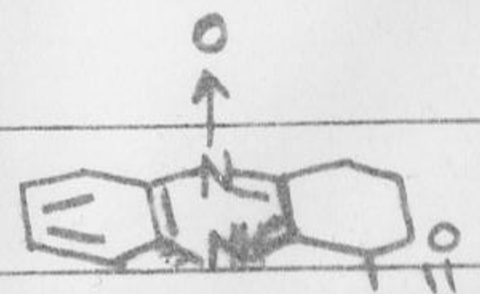
ORIGIN

PHASE Nujol

SOLVENT

CONC.

CELL PATH



REFERENCE 1-acetoxy-2,3,4-trihydrophenazine-5-N-oxide

SCAN SPEED SLIT

OPERATOR DATE 13/4/67

REMARKS

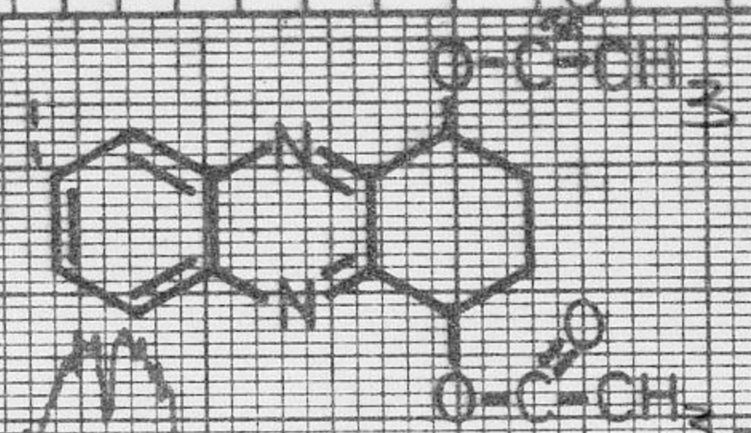
N.O.

WAVENUMBER (CM^{-1})

4000 3000 2000 1500 1000 900 800 700

TRANSMITTANCE (%)

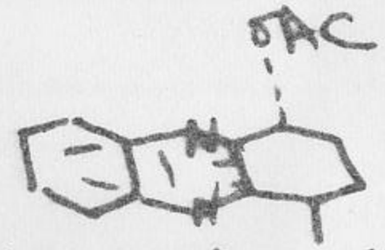
100 80 60 40 20 0



Trans 1,4-diaceloxy-2,3-dihydrophenazine

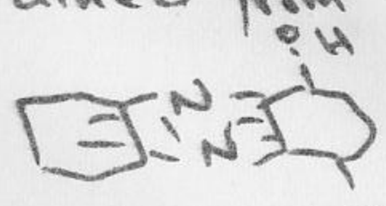
3 4 5 6 7 8 9 10 11 12 13 14 15

WAVELENGTH (MICRONS)

SAMPLE 

m.p. 164-165°. OAc

obtained from Acetylation



of R.T. for

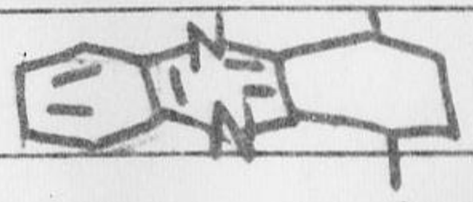
OH 2 CH3.

ORIGIN

PHASE Solid

SOLVENT Nujol

CONC.

CELL PATH 

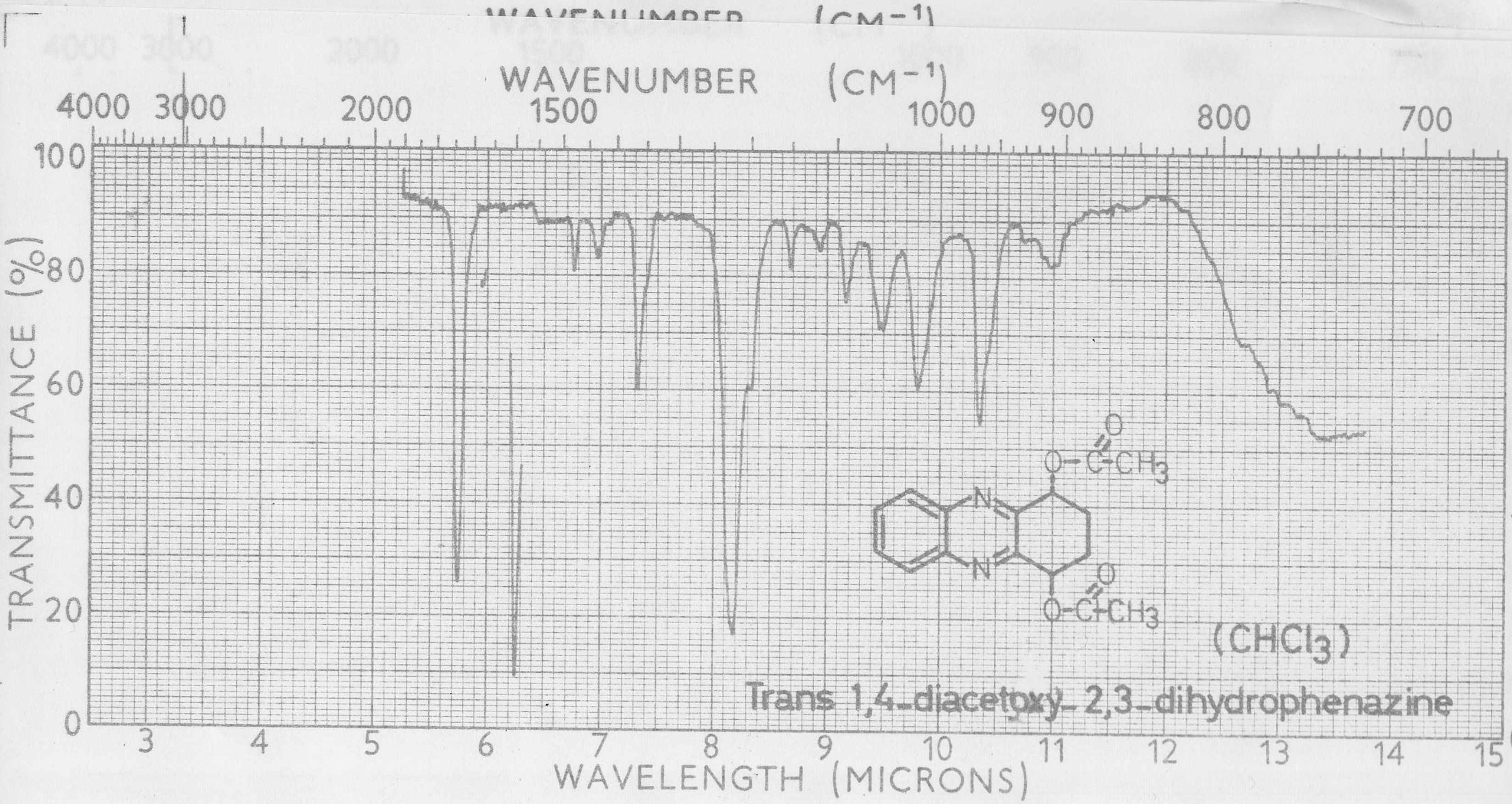
REFERENCE

SCAN SPEED SLIT

OPERATOR DATE 4/3/67

REMARKS Trans 1,4-diacetoxy -2,3-dihydrophenazine.

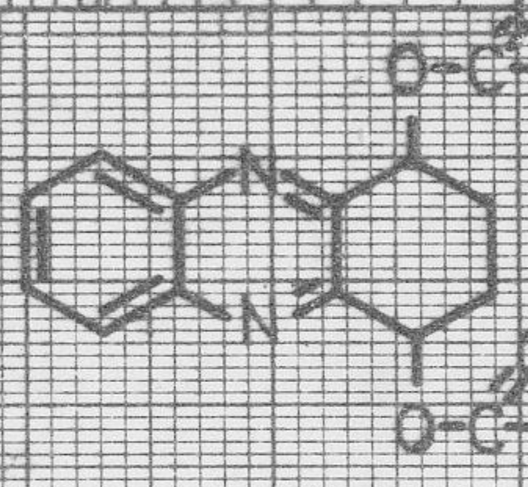
NO.



SAMPLE Trans diacetate	PHASE liquid	SCAN SPEED ____ SLIT ____
	SOLVENT Chloroform	OPERATOR ____ DATE 15/4/67
	CONC. ____	REMARKS ____
	CELL PATH ____	
ORIGIN ____	REFERENCE (CHCl3)	

WAVENUMBER (CM^{-1})

4000 3000 2000 1500 1000 900 800 700



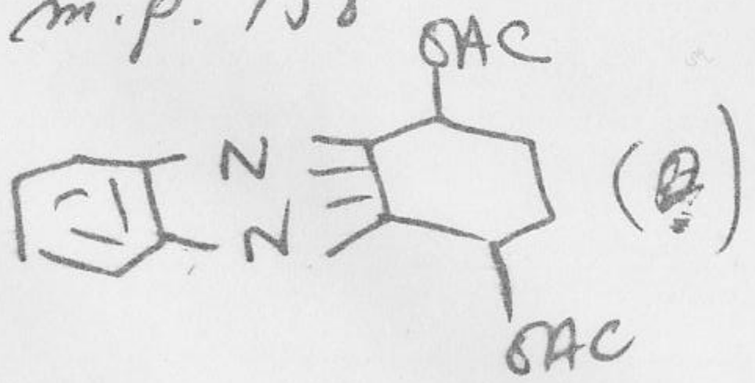
Cis 1,4-diaceloxy-2,3-dihydrophenazine

TRANSMITTANCE (%)

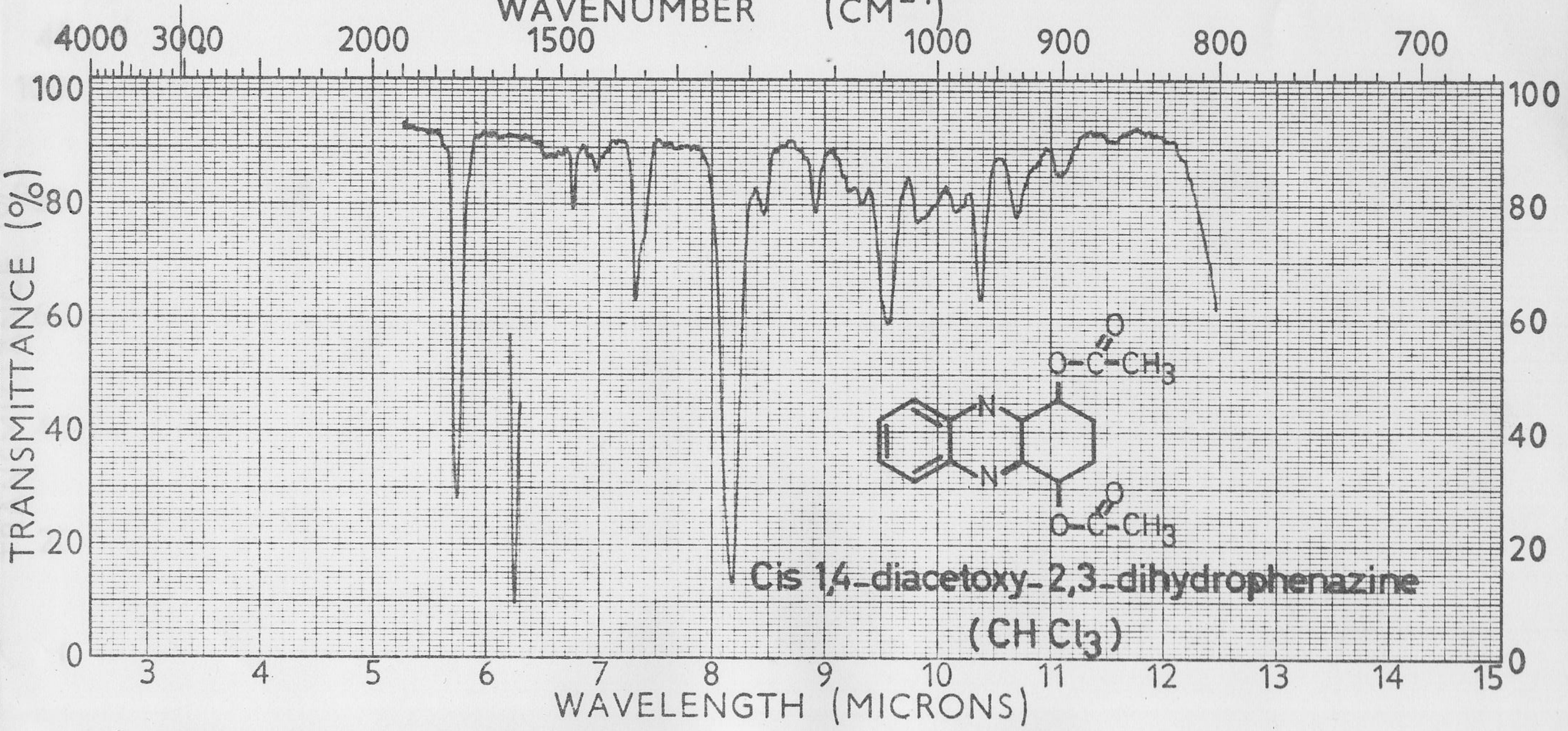
100 80 60 40 20 0

3 4 5 6 7 8 9 10 11 12 13 14 15

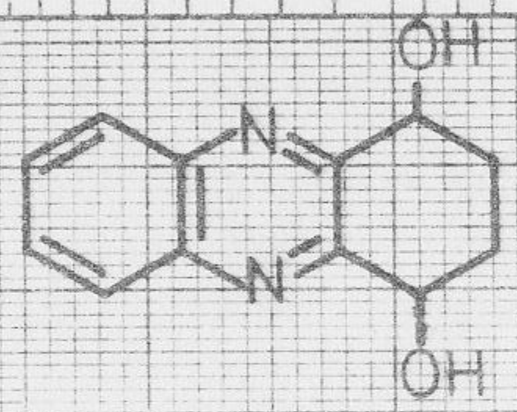
WAVELENGTH (MICRONS)

SAMPLE AS5 (Sample Sent for Analysis) m.p. 158° 	PHASE Solid	SCAN SPEED ____ SLIT ____
	SOLVENT Nujol	OPERATOR ____ DATE 9/1/67
	CONC. ____	REMARKS ____
	CELL PATH ____	Cis 1,4-diacetoxy-2,3-dihydrophenazine.
ORIGIN ____	REFERENCE ____	

NO.



SAMPLE cis diacetate	PHASE liquid	SCAN SPEED ____ SLIT ____
	SOLVENT CHCl3	OPERATOR ____ DATE 15/4/67
	CONC. ____	REMARKS ____
	CELL PATH cis	
ORIGIN ____	REFERENCE (CHCl3)	NO. ____



Trans 1,4-dihydroxy-2,3-dihydrophenazine

WAVENUMBER (CM^{-1})

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TRANSMITTANCE (%)

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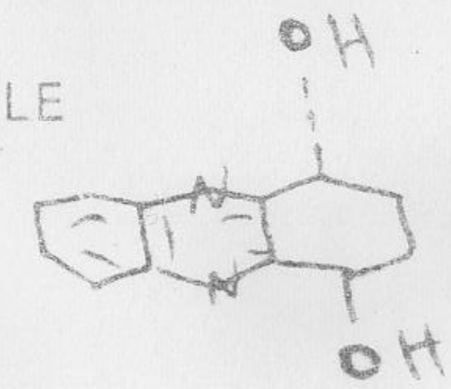
3 4 5 6 7 8 9 10 11 12 13 14 15

WAVELENGTH (MICRONS)

SAMPLE 

recrystd from MeOH

was acetylated with Ac_2O, m.p: changed color at 163° to light red at 175° melted completely with dec

ORIGIN

PHASE Solid

SOLVENT Nujol

CONC.

CELL PATH

REFERENCE

Name: Trans 1,4-dihydroxy-2,3 dihydrophenazine

SCAN SPEED SLIT

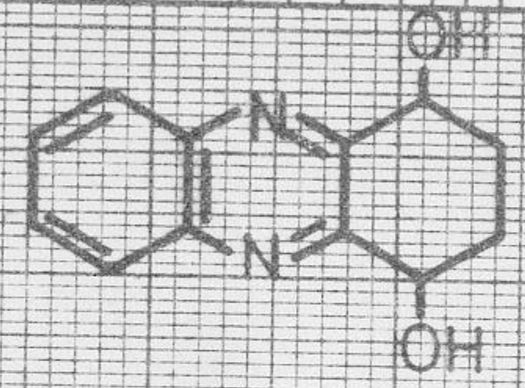
OPERATOR DATE 4/3/67

REMARKS

NO.

WAVENUMBER (CM^{-1})

4000 3000 2000 1500 1000 900 800 700



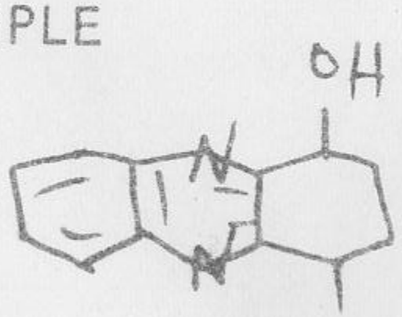
Cis 1,4-dihydroxy - 2,3-dihydrophenazine

TRANSMITTANCE (%)

100 80 60 40 20 0

3 4 5 6 7 8 9 10 11 12 13 14 15

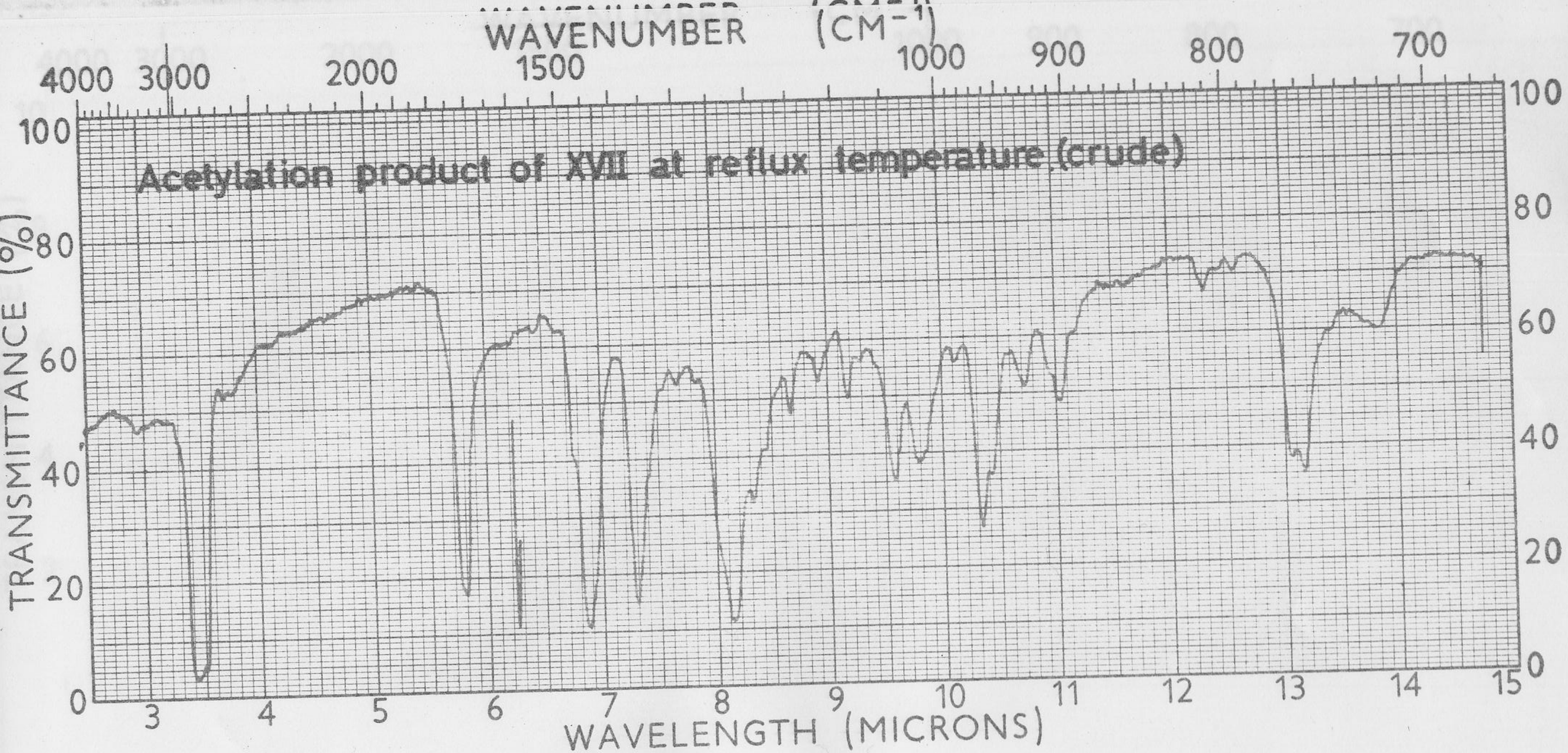
WAVELENGTH (MICRONS)

SAMPLE  recryst. from MeOH m.p. :	PHASE	SCAN SPEED SLIT
	SOLVENT	OPERATOR DATE 28/3/67
	CONC.	REMARKS
	CELL PATH Nujol	
ORIGIN	REFERENCE Cis 1,4-dihydroxy-2,3-dihydrophenazine.	

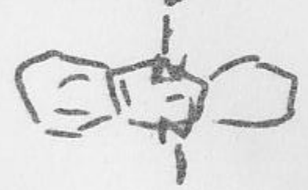
No. 1

PART NO. 137E - 1281

PERKIN - ELMER LIMITED, BEACONSFIELD, BUCKS



SAMPLE Acetylation of



with HAC Ac2O reflux at 75 min

(Crude)

ORIGIN

PHASE solid

SOLVENT Nujol

CONC.

CELL PATH Acetylation product of XVII at reflux temperature. (Crude).

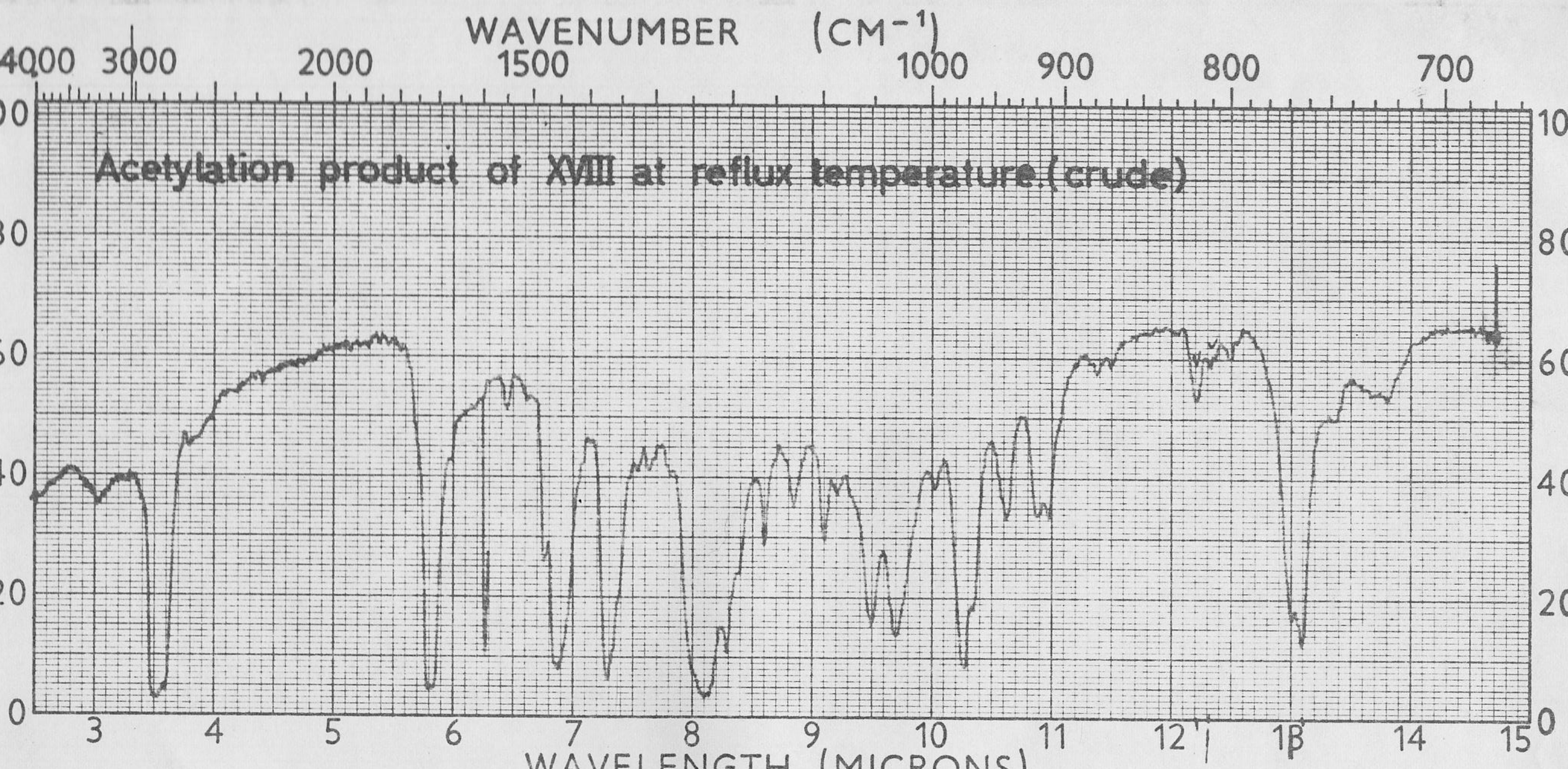
REFERENCE

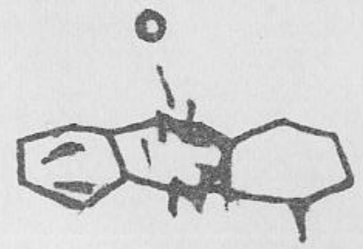
SCAN SPEED SLIT

OPERATOR DATE 17/3/87

REMARKS

NO.



SAMPLE  + HAc Ac2O

pure SAC

reflux for 75 min.

(crude product.)

ORIGIN

PHASE Solid

SOLVENT Nujol.

CONC.

CELL PATH Acetylation product of XVIII at

REFERENCE reflux temperature (crude.)

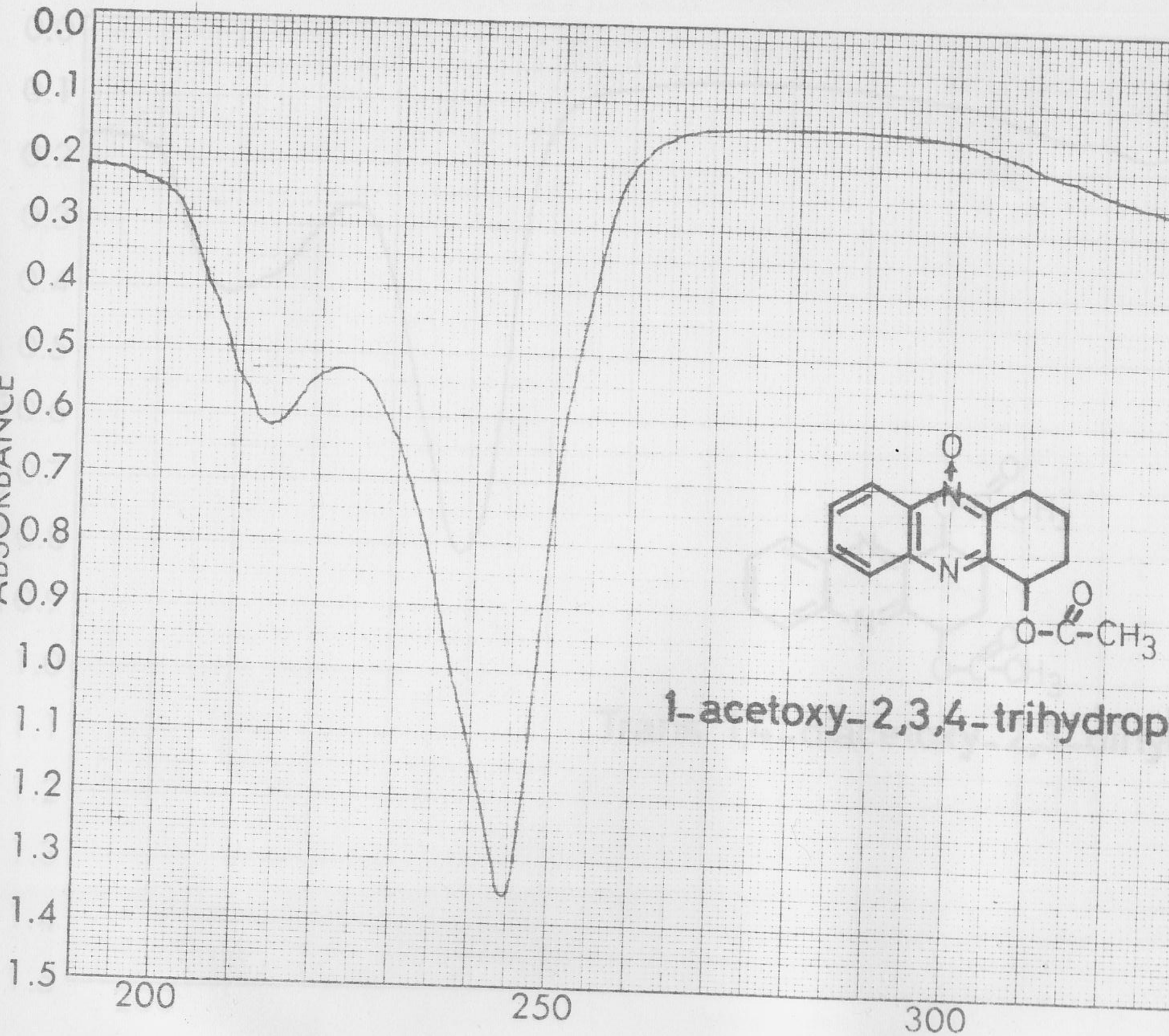
SCAN SPEED SLIT

OPERATOR DATE 16/3/67

REMARKS

NO.

UV

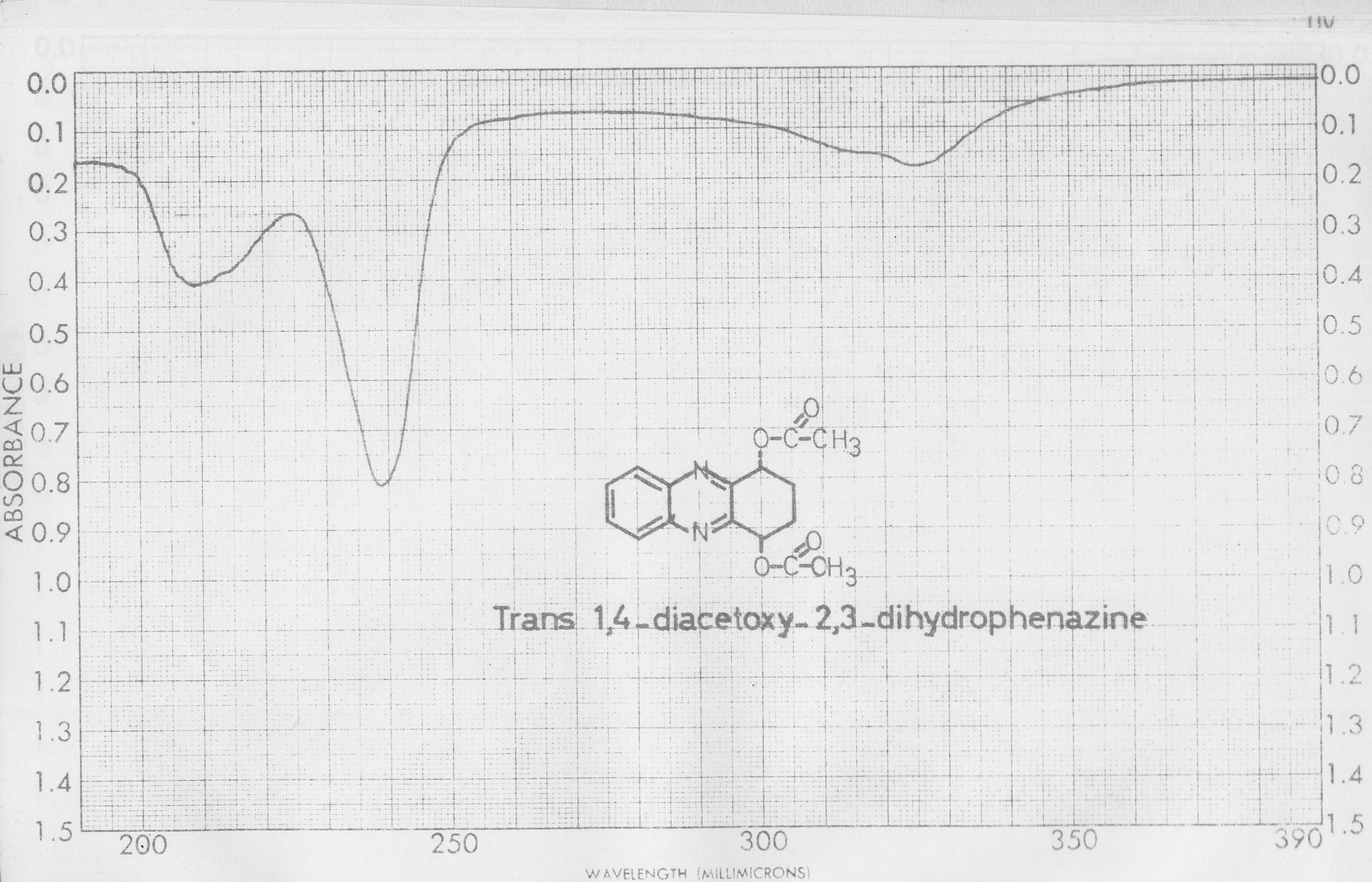


1-acetoxy-2,3,4-trihydrophenazine-5-N-oxide

SAMPLE Monoacetate	CURVE NO.	SCAN SPEED	OPERATOR
ORIGIN	CONC. 82 mg/l	SLIT	DATE
SOLVENT	CELL PATH	REMARKS	
	REFERENCE		

PART NO. 202-1511

PERKIN-ELMER

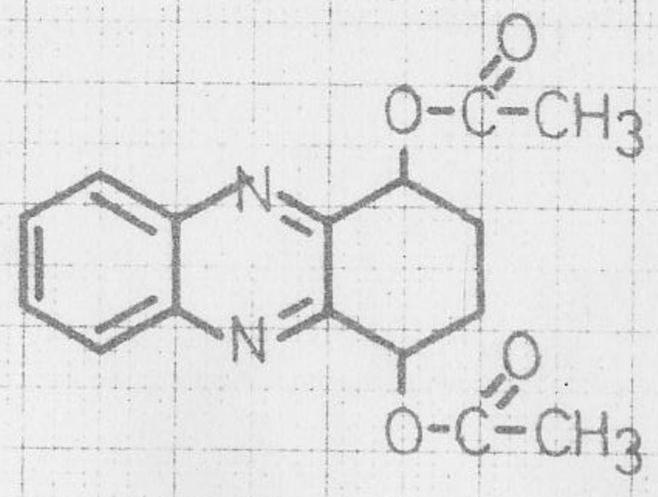


SAMPLE trans. diacetate	CURVE NO.	SCAN SPEED	OPERATOR
	CONC. 6.8 mg/l	SLIT	DATE 16/2/67
ORIGIN	CELL PATH	REMARKS	
SOLVENT MeOH	REFERENCE		

UV

ABSORBANCE

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5



Cis 1,4-diacetoxy-2,3-dihydrophenazine

200 250 300 350 390

WAVELENGTH (MILLIMICRONS)

SAMPLE cis diacetate	CURVE NO.	SCAN SPEED	OPERATOR
	CONC. 6.5 mg/l	SLIT	DATE 16/2/67
ORIGIN	CELL PATH	REMARKS	
SOLVENT MeOH	REFERENCE Cis 1,4-diacetoxy-2,3-dihydrophenazine.		

PART NO. 202-1511

PERKIN-ELMER

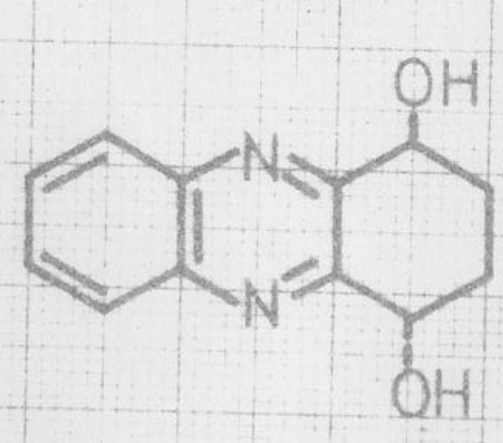
UV

ABSORBANCE

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5

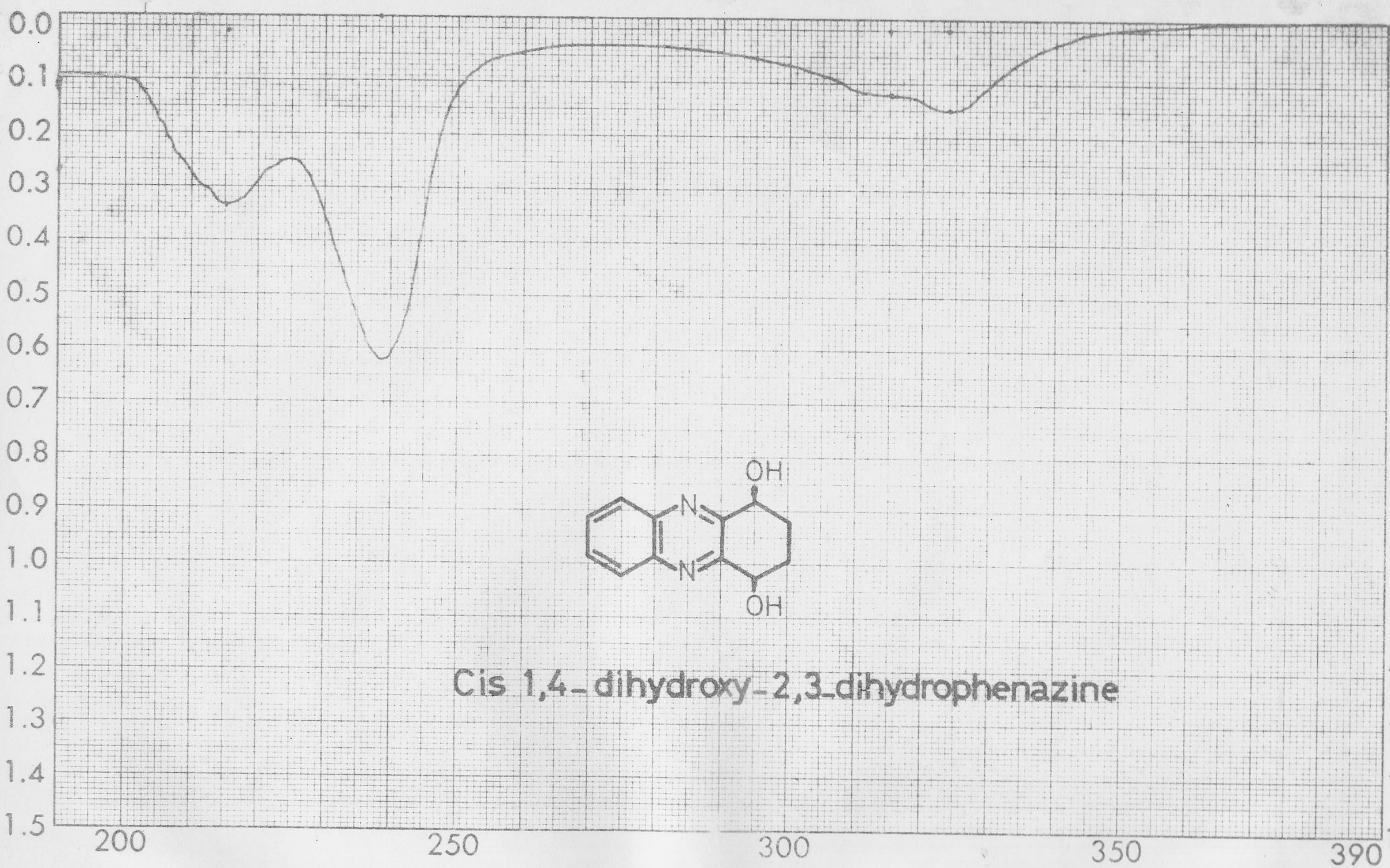
200 250 300 350 390

WAVELENGTH (MILLIMICRONS)



Trans 1,4-dihydroxy-2,3-dihydrophenazine

SAMPLE Naus diol	CURVE NO. 12mg	SCAN SPEED	OPERATOR
ORIGIN	CONC 1 in 100 ml diluted 10x.	SLIT	DATE
SOLVENT	CELL PATH 3 ml in 5 ml	REMARKS	
	REFERENCE		



SAMPLE cis diol	CURVE NO	SCAN SPEED	OPERATOR
	CONC. 6mg 1l.	SLIT	DATE
ORIGIN	CELL PATH	REMARKS	
SOLVENT	REFERENCE		