CHEMISTRY OF HETEROCYCLIC COMPOUNDS CONTAINING NITROGEN, OXYGEN AND SULPHUR

A THESIS
SUBMITTED TO THE
UNIVERSITY OF POONA
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
(IN CHEMISTRY)

BY
AMMANAMANCHI SUBBA RAO
M. Sc.

NATIONAL CHEMICAL LABORATORY
POONA - 411 008 (India)
December, 1978

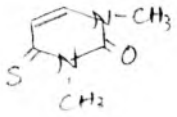
C O N T E N T S

Chapter IV

cf. the nomenclature of esters
e.g. ethyl benzoate (not ethylbenzoate)

Pages

Reaction of 1,3-dimethyl-6-~~mercapto~~thiouracil with dimethylacetylenedicarboxylate



The word "mercapto" represents a SH group, but the 1,3-dimethyl compound has no SH group.

****

GENERAL REMARKS

1. The thesis consists of four chapters and each chapter is further divided into five sections.
2. The numbers given to the structures in each chapter refer only to that particular chapter. In a particular chapter discussions and experimental sections a compound is referred by one and the same number.
3. A short summary of the present investigation is included in each chapter.
4. References are given at the end where they are combinedly serialized from all sections of the particular chapter.
5. Important NMR and IR spectra were included in discussion sections and full assignments were recorded in experimental sections.
6. General procedures were given in the experimental sections of Chapters III and IV. When the same compound was prepared by a particular method using different starting materials notations like (a), (b), (c) were used. The yield (%) with a superscript letter refers to that particular method.

CHAPTER I

SYNTHESIS OF PYRIDO[2,3-d]PYRIMIDINE-2,4-DIONES

Pyrido/2,3-d/Pyrimidines Synthesis

Review of earlier syntheses

The pioneering work of G.H. Hitchings and his co-workers resulted in the synthesis of many aromatic pyrido/2,3-d/pyrimidines. A wide variety of synthetic approaches from both pyridines and pyrimidines have been investigated.

1. From Pyridines

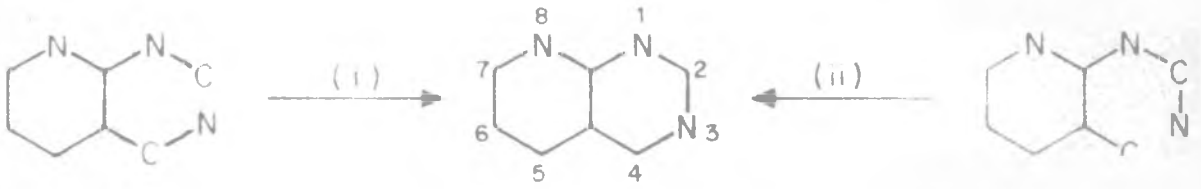
The final step in the syntheses of pyrido/2,3-d/-pyrimidines from pyridines has involved the formation of the bonds 1 - 8a, 1 - 2 and 4-4a, but the most useful methods are those which form the 2- 3 (i) and 3 - 4 (ii) bonds. The mechanism of the reactions and hence the detailed nature of the intermediates involved, are often uncertain. The syntheses which follow are, therefore, subdivided according to the starting material and not the mode of cyclization.

a) From 2-aminonicotinic acids

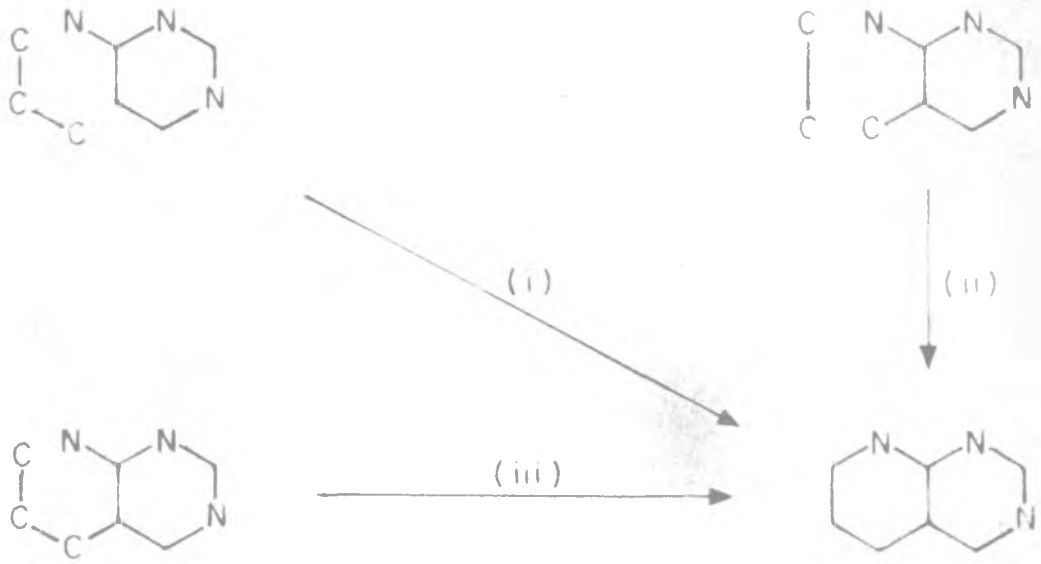
Extensions of the von Niementowski quinozolone syntheses[1-2] have proved a fruitful source of pyrido/2,3-d/pyrimidin-4(3H)-ones. This method was used by Klisiecki and Sucharda[3] in the first claimed synthesis of a pyrido/2,3-d/pyrimidine, when it was suggested that the reaction of 2-aminonicotinic acid with formamide yielded pyrido/2,3-d/pyrimidin-4(3H)-one (4). Similar reactions of 2-amino-

PYRIDO [2,3-d] PYRIMIDINES

SCHEME I FROM PYRIDINES



SCHEME II FROM PYRIMIDINES



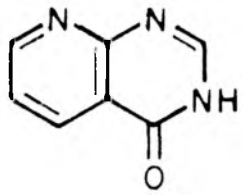
nicotinic acid with urea[4-5], thiourea[4-5], and phenyl-thiourea[6,7] yielded the 2,4-dione (5) the 2-thione analog (6) and 3-phenyl-2-thioxo pyrido[2,3-d]pyrimidin-4(1H, 3H)-one (7). The use of substituted 2-aminonicotinic acids[7,8] has enabled a series of pyrido[2,3-d]pyrimidines, which have 5,6 and 7-alkyl and aryl substituents to be obtained. These reactions seem to proceed via an intermediate ureido or thiouredo derivative as demonstrated by Dornow and Hahmann. Potassium cyanate or ammonium isothiocyanate was reacted with 2-amino-4-6 dimethyl nicotinic acid. The urea derivative of nicotinic acid gave the pyrido[2,3-d]pyrimidine-2,4 (1H, 3H)-dione (7, X = O) by the action of heat. The thiourea (7, X = S) was unchanged after similar treatment.

b) From 2-aminonicotinamides

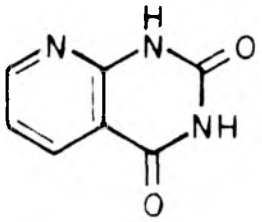
2-Aminonicotinamides have been shown to react readily with ethyl chloroformate to yield pyrido[2,3-d]pyrimidine-2-4 (1H, 3H)-diones (8)[9,10].

Tieckelmann, Mulvey and Cottis[11,12] have extended the above reaction by starting with 2-amino-5-cyanonicotinamides, with diethyl carbonate, ethylorthoacetate and ethylorthoformate, all were converted to yield 6-cyano substituted pyrido[2,3-d] pyrimidines.

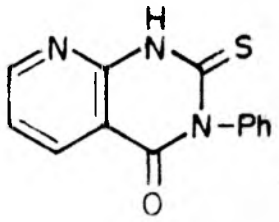
Acid chlorides[13], acetic anhydride[10], and formamide[14,15] were also reacted with 2-aminonicotinamides to give pyrido-[2,3-d]pyrimidines.



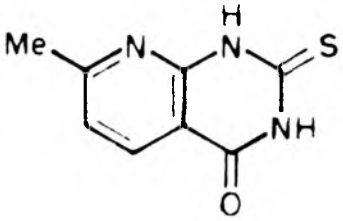
(4)



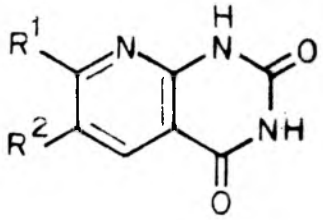
(5)



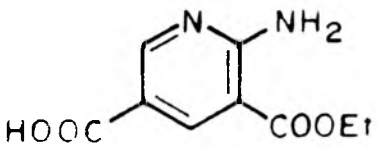
(6)



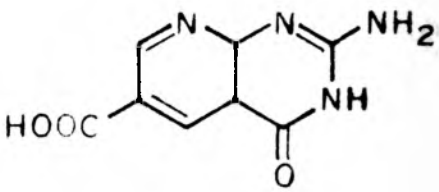
(7)



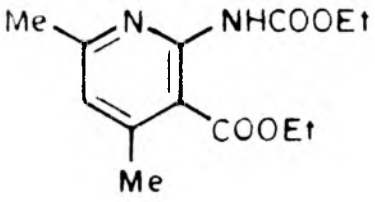
(8)



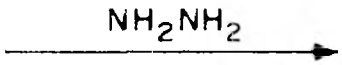
(9)

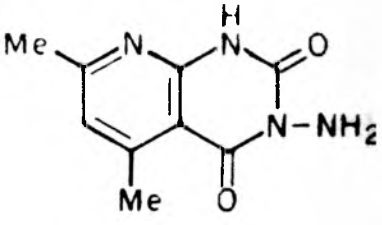


(10)



(11)





(12)

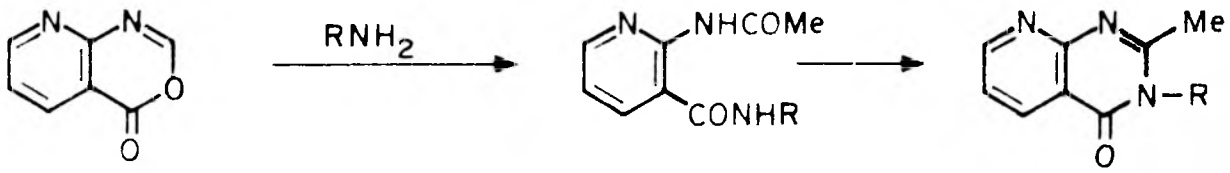
c) Ethyl 2-aminonicotinates

The reaction of guanidine with 6-amino-5-ethoxycarbonyl-nicotinic acid (9) yields 2-aminopyrido[2,3-d]pyrimidine-4(3H)-one-6-carboxylic acid[11] (10). Amino esters have also been shown[10] to yield pyrido [2,3-d]pyrimidin-4(3H)-ones when treated with isocyanates and isothiocyanates. The reactions proceed via intermediate ureido and thiouredo derivatives. The carbamate (11) reacts with hydrazine hydrate to yield 3-amino 5,7-dimethyl pyrido[2,3-d]pyrimidin-2,4 (1H,3H)-dione[10] (12).

d) From pyrido[2,3-d]-(1,3)-oxazine-4-ones

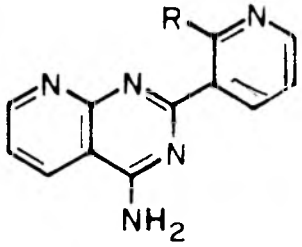
2-Methylpyrido[2,3-d] (1,3)-oxazin-4-one (13) obtained by the action of AC_2O on 2-aminonicotinic acid has been shown to be a useful intermediate in the synthesis of pyrido[2,3-d]-pyrimidin-4(3H)-ones[6]. Treatment of the pyridooxazine with various primary amines yielded a series of 3-substituted 2-methylpyrido[2,3-d]pyrimidin-4(3H)-ones (15). As in similar preparations of quinazolones[2] and pyrido[3,2-d]-pyrimidones from fused oxazin-4-ones, this reaction undoubtedly proceeds via cyclization of the amide (14).

e) From 2-aminonicotinonitrile and nicotinonitrile[16], 4-amino-2-(3-pyridyl) pyrido[2,3-d]pyrimidine (16) was obtained. Good yields of pyrido[2,3-d]pyrimidines were also obtained by the action of formamide on o-aminonitriles[11]. Reduction of 2-amino-4,6-dimethylnicotinonitrile yields ~~the 3-acyl-aminomethyl derivative (17, 18),~~ followed by cyclization, by

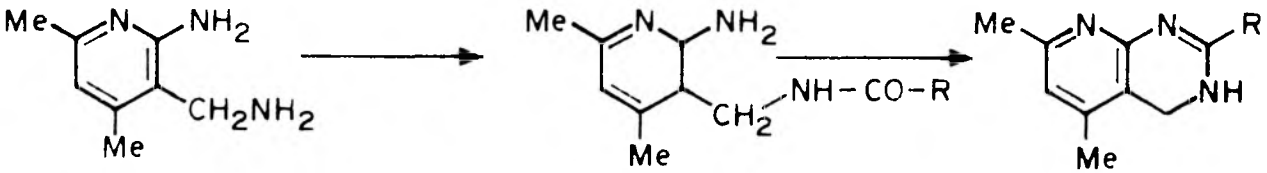


(13) (14) (15)

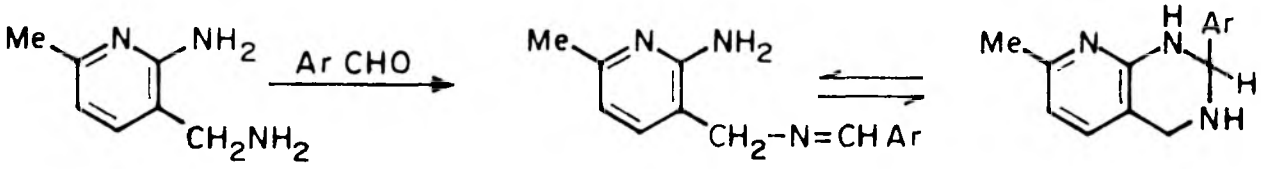
?



(16)



(17) (18) (19)



(20) (21)

means of heat or phosphoryl chloride yielded the dihydropyrido[2,3-d]pyrimidines[17] (19).

Tetrahydropyrido[2,3-d]pyrimidines (21) have been obtained via the anils (20) prepared from similar 2-amino-3-aminomethyl pyridines and aromatic aldehydes[18].

f) Pyrido [2,3-d]pyrimidines were synthesized from 2-amino-nicotinaldehydes[19,20,21] and also from 2-amino-4-picoline with CO_2[22].

g) From pyrido-2,3-dicarboxyamide

An interesting synthesis of pyrido[2,3-d]pyrimidin-2,4(1H,3H)-dione[(24)] is afforded by the reaction of quinolinamide (22) with HoBr[23]. The reaction is noteworthy in that only the pyrido[2,3-d]pyrimidine isomer[(24)] was isolated although it is conceivable that pyrido[3,2-d]pyrimidine-2-4 (1H,3H)-dione might be produced simultaneously.

h) From nicotinic acid

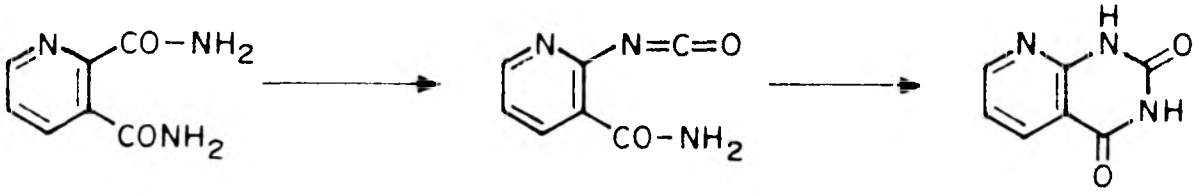
Amidation of nicotinic acid yielded 2-(3-pyridyl)pyrido[2,3-d]pyrimidine in addition to the expected nicotinamide[24].

i) From piperidines

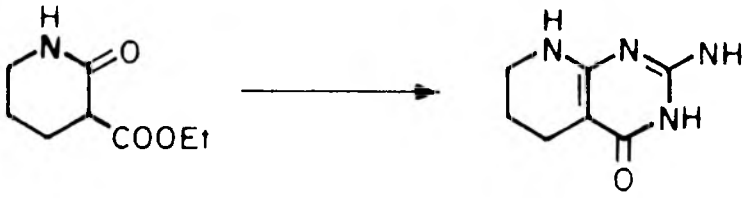
The reaction of 3-ethoxy carbonylpiperidine-2-one (25) with guanidine gave 2-amino-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-4(3H)-one[25](26).

2. From pyrimidines

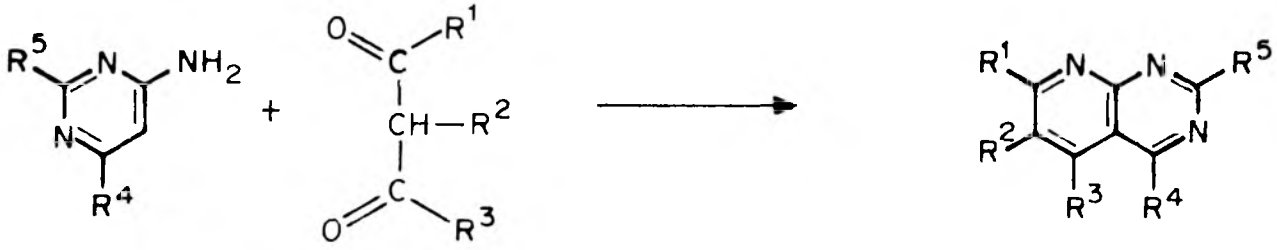
Three general approaches to the synthesis of pyrido[2,3-d]pyrimidines are available, all of which utilize an



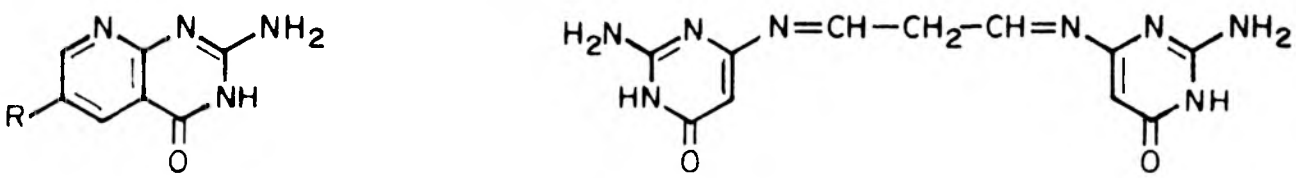
(22) (23) (24)



(25) (26)



(27) (28) (29)



(30) (31)

appropriately substituted 4-aminopyrimidine. The pyridine ring may be formed by the addition of three (route i), or two (route ii) carbon atoms, or by the intramolecular cyclization of a propionyl derivative (route iii).

a) Route (i) syntheses

The major synthetic route to pyrido[2,3-d]pyrimidines bearing amino, oxo, or thioxo substituents in the pyrimidine ring is the reaction of 4-aminopyrimidines (27) with 1,3-dicarbonyl compounds (28). The reactions are frequently carried out in the presence of phosphoric acid, sulfuric acid, or phosphorus pentoxide and the pyrido[2,3-d]pyrimidines (29) are usually obtained directly from the reaction mixture. The reaction involves an electrophilic attack of a carbonium ion into the 5-position of the pyrimidine ring and the resultant pyrimidines that are activated towards electrophilic substitution[26] by the presence of electron donating substituents at the 2- and 4-positions undergo the cyclization. 2,4,6-Triaminopyrimidine, 6-aminouracil, 6-amino-2-thiouracil, 4-amino-2,4-dimercaptopyrimidine, 2,4-diamino-pyrimidine-6(1H)-one, and various 4-amino, N-alkyl and aryl pyrimidines have all been converted into pyrido[2,3-d] pyrimidines when treated with required carbonyl compounds. 4-Amino-2-methylpyrimidin-6(1H)-one and 2,4-diamino-6-methyl-pyrimidine failed to react[27]. In view of the wide variation of carbonyl compounds which are used in this reaction, further work is reviewed on the basis of carbonyl function involved.

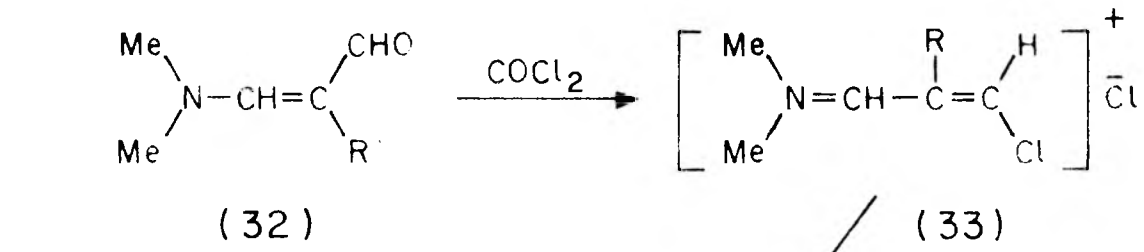
i) Dialdehydes

Sodium nitromalondialdehyde and 2,4-diamino-pyrimidin-6 (1H)-one yielded 2-amino-6-nitro pyrido[2,3-d]pyrimidin-4(3H)-one (30 R = NO_2) when heated under reflux with aqueous alkali[28,29]. Malondialdehyde tetramethylacetal, however gave the dianil (31) initially which cyclized to yield the pyrido[2,3-d]pyrimidine (30, R = H) on treatment with sulfuric acid[28]. If the structure of the dianil is as shown (31) this is a rare example of initial attack taking place at the 4-amino substituent.

An interesting variation of this procedure relies upon the formation of malondialdehyde precursors in situ (30-32). Vinylogs of Vilsmeier Haack intermediates (33) formed from dimethylaminoacroleins (32) and phosgene, undergo reaction with 2,4,6-triaminopyrimidine (34) to yield 6-alkyl and 6-aryl-substituted 2,4-diaminopyrido[2,3-d]pyrimidines (35). Dimethylaminoacroleine were found to be unsatisfactory[30].

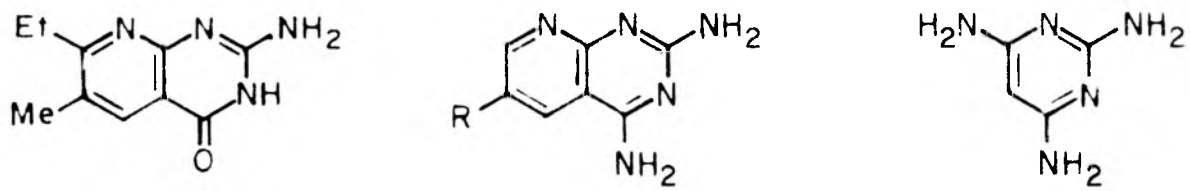
ii) Keto-aldehydes

Ketoaldehydes have proved useful for the synthesis of pyrido[2,3-d]pyrimidines which are disubstituted in the pyridine ring. The reaction is complicated by the fact that two isomeric pyridopyrimidines may be formed. Thus, 2,4-diamino-pyrimidin-6(1H)-one and 2-methyl-3-oxopentanal could theoretically produce either the 5-ethyl (35) or the 7-ethyl(36) isomer. In fact 2-amino-7-ethyl-6-methyl pyrido[2,3-d] pyrimidin-4(3H)-one (36) is the only product isolated and in all cases examined it has ben found that only one isomer is



(32)

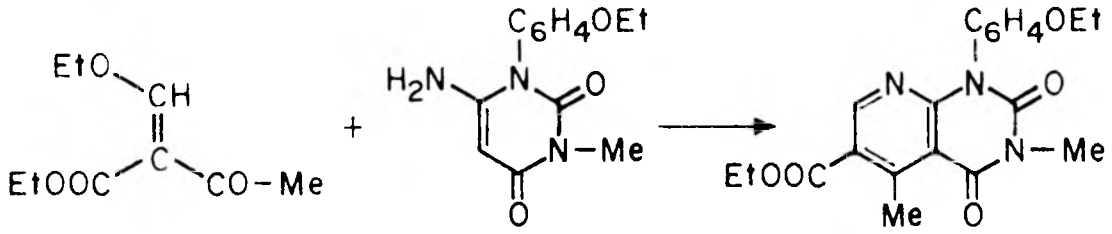
(33)



(36)

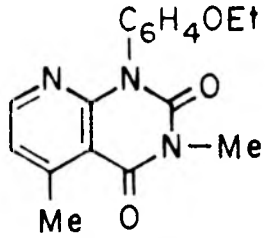
(35)

(34)



(37)

(38)



(39)

obtained[27,34-36], in every instance the pyridopyrimidine which was isolated was the one produced by reaction of the aldehyde function with the 5-position of the pyrimidine ring.

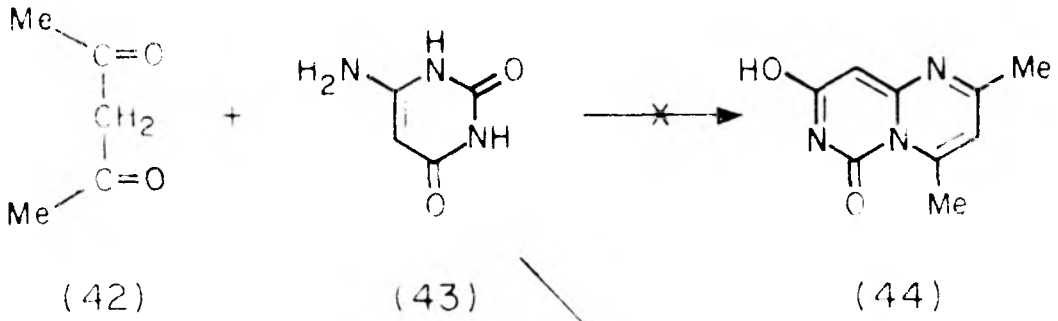
The yield of the pyrido[2,3-d]pyrimidine has been shown to be significantly reduced when unsubstituted keto-aldehydes are used. This has been attributed[27] to the self-condensation reactions of these compounds[37,38] e.g. acetyl-acetaldehyde yields s-triacetylbenzene[39].

iii) Ethoxymethylene compounds

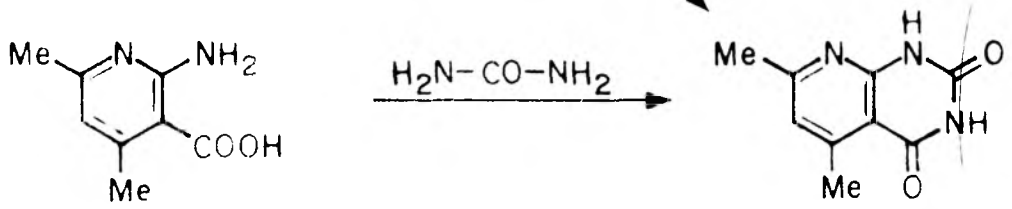
Ethoxymethylene acetoacetates and ethoxymethylene acetyl-acetones[37,38] have been used to prepare pyrido[2,3-d]pyrimidines containing 6-ethoxycarbonyl or 6-acetyl substituents. Thus, the substituted uracil (37) and ethyl ethoxymethylene aceto-acetate yielded the pyrido[2,3-d]pyrimidine (38). Hydrolysis and decarboxylation gave 3,5-dimethyl-1-(4-ethoxyphenyl) pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (39) which was not identical with the other possible isomer (41) prepared by decarboxylation of the known acid (40).

iv) Diketones

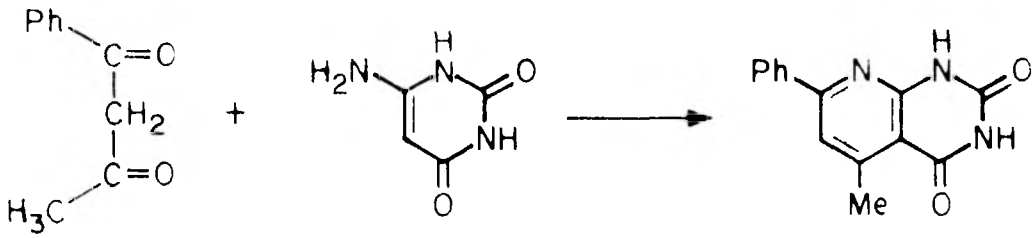
4-Aminopyrimidines also react readily with 1,3-diketones to yield various 5,6 and 7-substituted pyrido [2,3-d]-pyrimidines[27,34-36]. Acetylacetone and 6-aminouracil for example yielded 5,7-dimethyl pyrido[2,3-d]pyrimidine-2-4 (1H, 3H)-dione (46) when heated together in phosphoric acid. The alternative pathway, to yield the pyrimido (1,2-c)-pyrimidine (44) was discounted by a second synthesis from



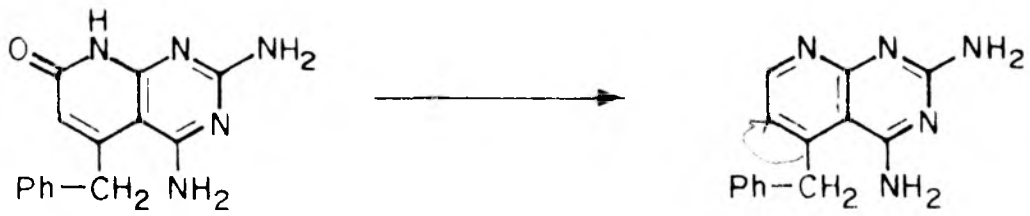
(42) (43) (44)



(45) (46)



(47)



(48) (49)

2-amino-4-6-dimethylnicotinic acid (45).

With unsymmetrical diketones the orientation of the reaction is again controlled by the reaction of the most reactive carbonyl group with the 5-position of the pyrimidine ring. Thus benzoylacetone and 6-aminouracil gave 5-methyl-7-phenyl-pyrido [2,3-d]pyrimidine-2,4-(1H,3H)-dione (47) in preference to the 5-phenyl isomer[27].

Acylacetates

β-Ketoesters have proved useful for the preparation of pyrido[2,3-d]pyrimidin-7(8H)-ones bearing alkyl and aryl substituents in the 5- and 6-positions[40-44]. Again the reaction proceeds so that the most reactive carbonyl group (i.e. the ketone) attacks the 5-position of the pyrimidine ring. Thus, ethyl α-benzylacetoacetate and 2,4,6-triaminopyrimidine, in diphenyl ether, yield 2,4-diamino-5-benzylpyrido [2,3-d] pyrimidin-7 (8H)-one (48)[41]. Structural proof has been offered by chlorination, thionation, and reduction to yield the pyrido-[2,3-d]pyrimidine (49) which has been subjected to NMR analysis[4].

vi) Malonates

A further variation of the carbonyl reagent which is useful for 7-substituted 6-hydroxy pyrido[2,3-d]pyrimidin-7(8H)-ones is the use of malonic acid derivatives[45-47]. Thus methylmalonic acid and 4-amino-1,3-dimethyl uracil, with acetic anhydride as catalyst, yielded the pyrido[2,3-d]pyrimidine (50). The trione formulation (50) was supported by NMR measurements[45].

vii) Acylpyruvates

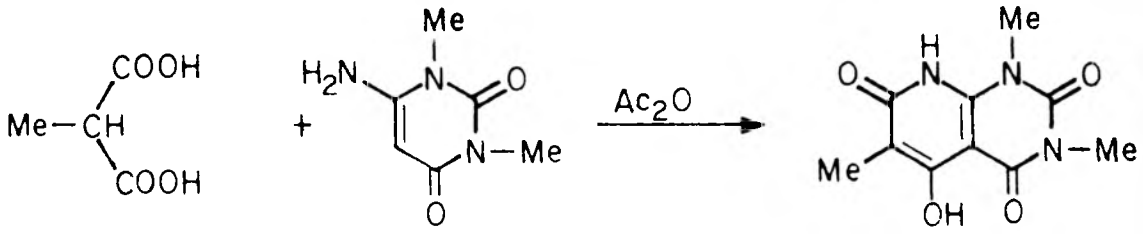
As in previous cases the unsymmetrical carbonyl compounds, the most reactive carbonyl (i.e. the pyruvate ketone) undergoes reaction at the pyrimidine nucleus, leading to 5-ethoxy carbonyl derivatives[37-38,48-50]. Ethyl pyruvate and 6-amino-3-methyl-1-phenyluracil yielded the pyrido[2,3-d]pyrimidine (51) when treated with phosphorus pentoxide. The orientation of the 5-ethoxy carbonyl group has been proved by the conversion of the pyrido[2,3-d]pyrimidine into the penta-azaphenalene (52) on treatment with hydrazine hydrate.

viii) Acetylenic ketones

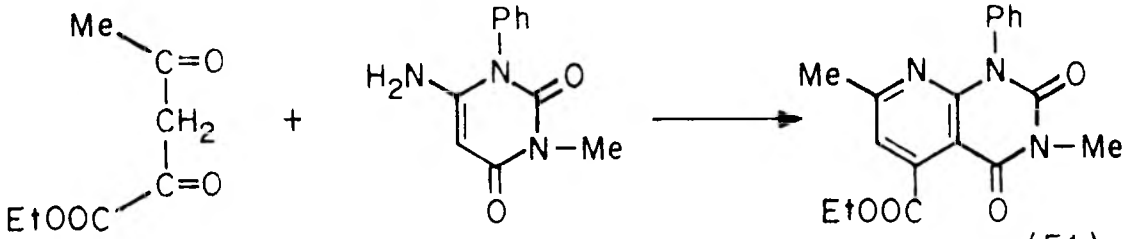
6-Amino uracil has been shown to react with propargyl aldehyde, 3-phenyl prop-1-yn-3-one or halogen acid adducts of acetylenic ketones such as 1-chlorobut-1-en-3-one to yield pyrido[2,3-d]pyrimidines[51]. Thus, 3-phenyl prop-1-yn-3-one and 6-aminouracil yielded 7-phenyl pyrido [2,3-d]pyrimidine-2,4 (1H, 3H)-dione (53).

b) Route (ii) Syntheses

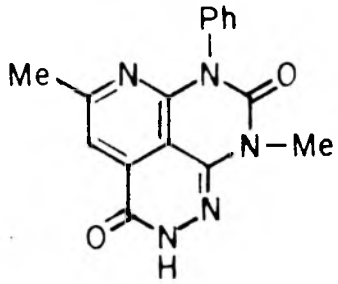
This mode of synthesis is typified by the reaction of an active methylene compound, containing an adjacent functional group capable of cyclization with 5-acyl or 5-ethoxy-carbonyl-4-aminopyrimidines. Cyclizations of this type are of



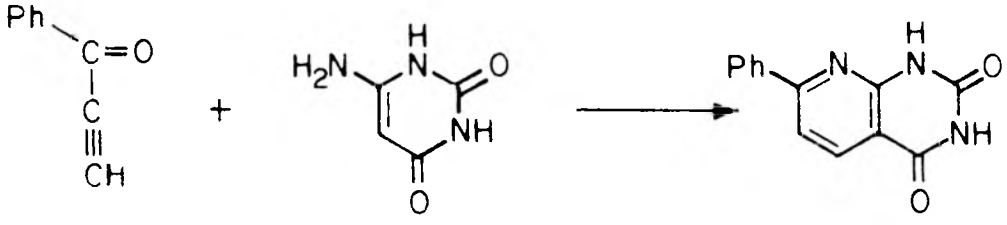
(50)



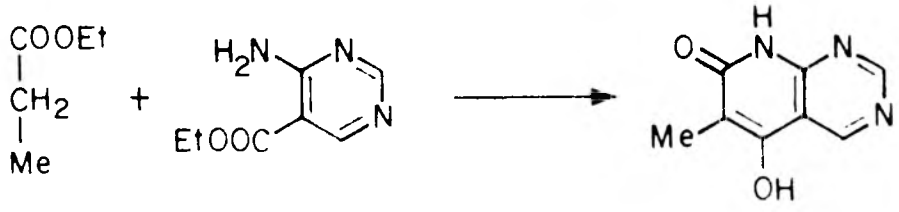
(51)



(52)



(53)



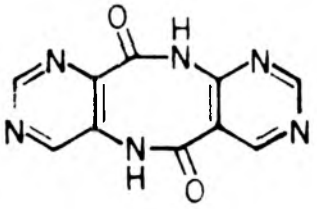
(54)

importance because, although the required pyridines are generally more difficult to prepare than those encountered in the previous section, the pyrido [2,3-d] pyrimidines which are obtained need not be substituted in the pyrimidine ring. 4-Amino-5-ethoxycarbonyl pyrimidine[52] and the 2-methyl derivative[53] have been shown to undergo reaction with α-methylene esters[52,53], ketones[52] and nitriles[52] to yield, 5-hydroxy-pyrido [2,3-d] pyrimidines variously substituted at the 6- and 7-positions. 4-Amino-5-ethoxycarbonyl pyrimidine and ethyl propionate, for example, yield 5-hydroxy-6-methyl pyrido-[2,3-d] pyrimidin-7(8H)-one when heated ~~text~~ together with metalic sodium. Ethyl acetate, however yielded the diamide (55) under similar conditions, and the pyrido [2,3-d] pyrimidine (56) was obtained only when sodium ethoxide was used as the catalyst[52]. A further convenient synthesis is that developed by Taylor and Garcia[54] who showed that pyrido [2,3-d] pyrimidines (57,58) were obtained by the action of malononitrile on 5-acetyl-4-amino-pyrimidin-6(1H)-one or 4-amino-5-benzoyl-1-methyl pyrimidin-6(1H)-one.

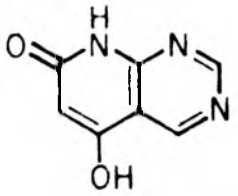
Phenyl acetonitrile, ethyl cyanoacetate and cyanoacetamide failed to yield pyrido [2,3-d] pyrimidines[54].

c) Route (iii) Syntheses

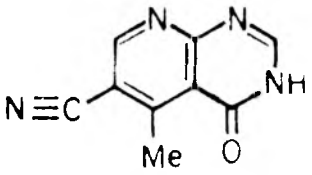
In contrast to the previous syntheses which have been described, pyrido [2,3-d] pyrimidines prepared by this route are not completely aromatic compounds and are obtained by cyclization of an aliphatic propionyl derivative. Alkylation



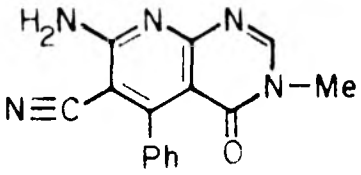
(55)



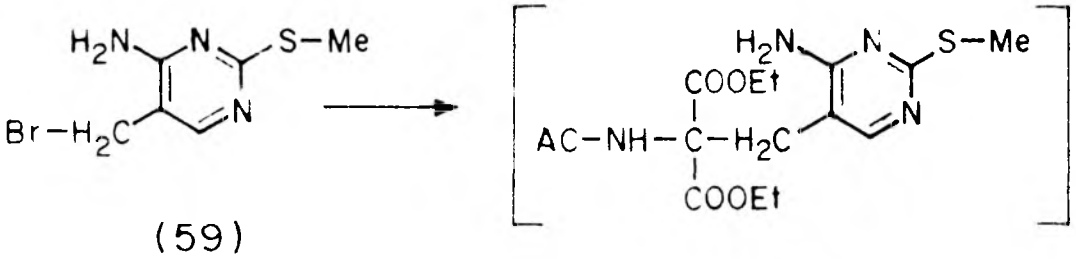
(56)



(57)

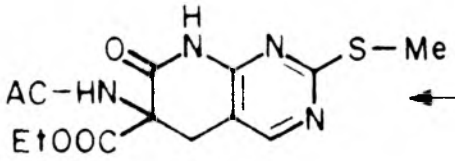


(58)



(59)

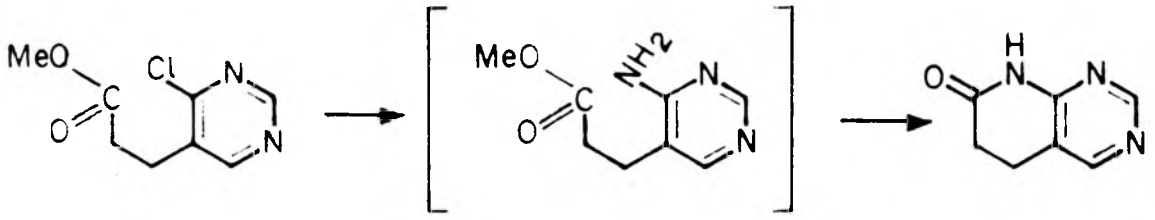
(60)



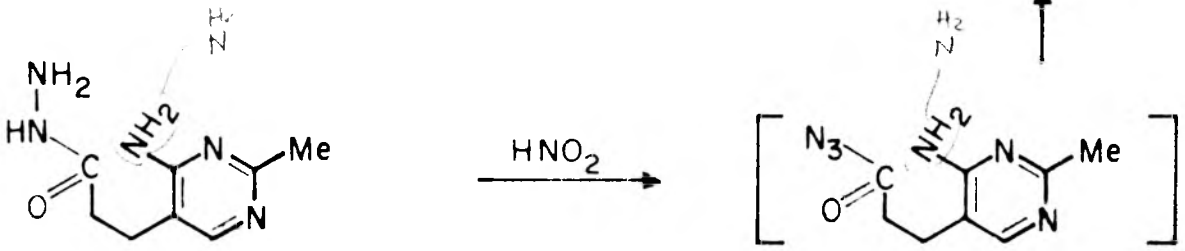
(61)

of diethyl acetamidomalonate with bromomethyl pyrimidine (59) yielded 6-acetamido-6-ethoxy carbonyl-5,6-dihydro-2-methyl thiopyrido [2,3-d] pyrimidin-7 (8)-one (61) via the cyclization of the intermediate ester (60)[55]. Similar ready cyclizations of propionyl derivatives are exemplified by the cyclizations of the chloro ester (62) to yield the pyrido [2,3-d] pyrimidine(63) when treated with ammonia[56,56a]. This pyrido [2,3-d] pyrimidine was also obtained by the action of nitrous acid on the hydrazide (64).

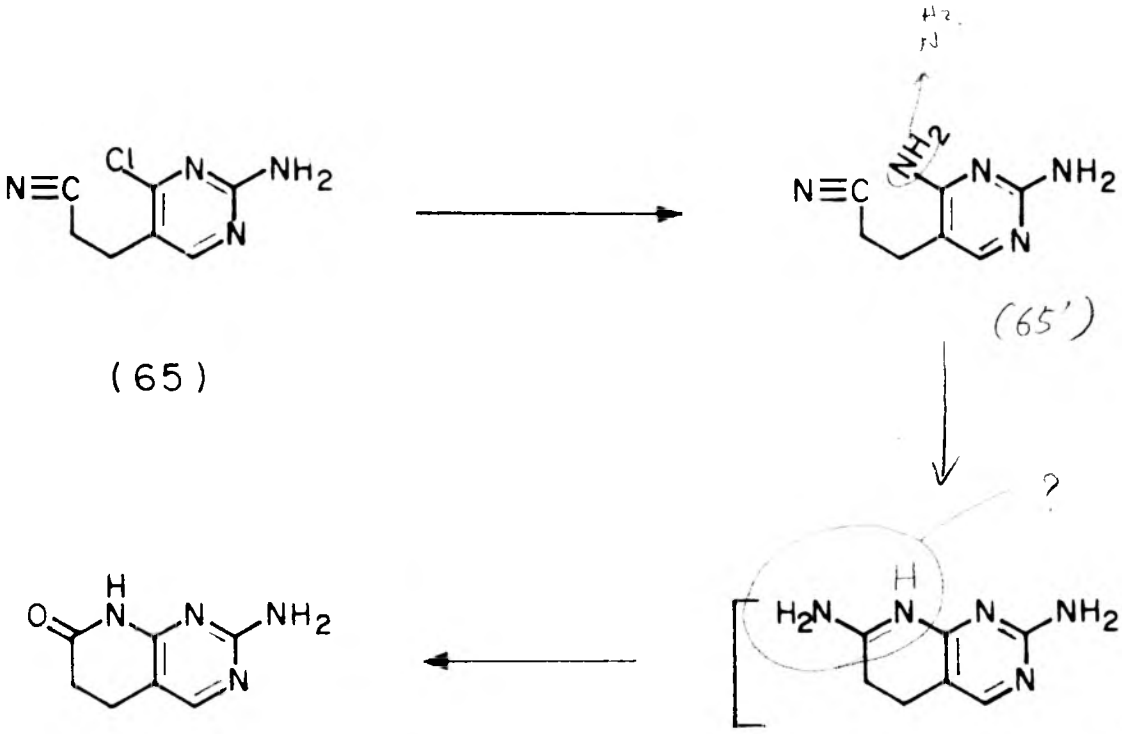
The chloro-propionitrile (65) also yielded a pyrido [2,3-d] pyrimidine (66) when treated with ammonia or methylamine, the intermediate amidine (65) undergoing hydrolysis during the reaction[57]. Amination was shown to be a rate determing step. A novel synthesis of 5-oxo and 7-oxo-pyrido [2,3-d] pyrimidines was reported recently by Haruo Ogura and Masakazu Sakaguchi[58]. Reaction of 6-amino and 6-(substituted) amino-1,3-dimethyl uracil (68a-d) with dimethyl acetylene dicarboxylate in methanol (protic solvent) afforded four ~~compounds~~ open chain compounds (69, 70a-d), 5-oxo-compound (71a-d) and 7-oxo-compound (72a-d). Treatment of (67a) with dimethylacetylene-dicarboxylate in methanol at room temperature gave an open chain compound (68a), which showed strong bands at 3370, and 3225 cm^{-1} due to an amino group in IR and did not show C-6 proton as cyclized compound (71a) in its NMR spectrum. Cyclization to (71a-d) occurred on heating of (69a) in DMF. From this result compound (71a) should have 7-oxo group in the molecule.



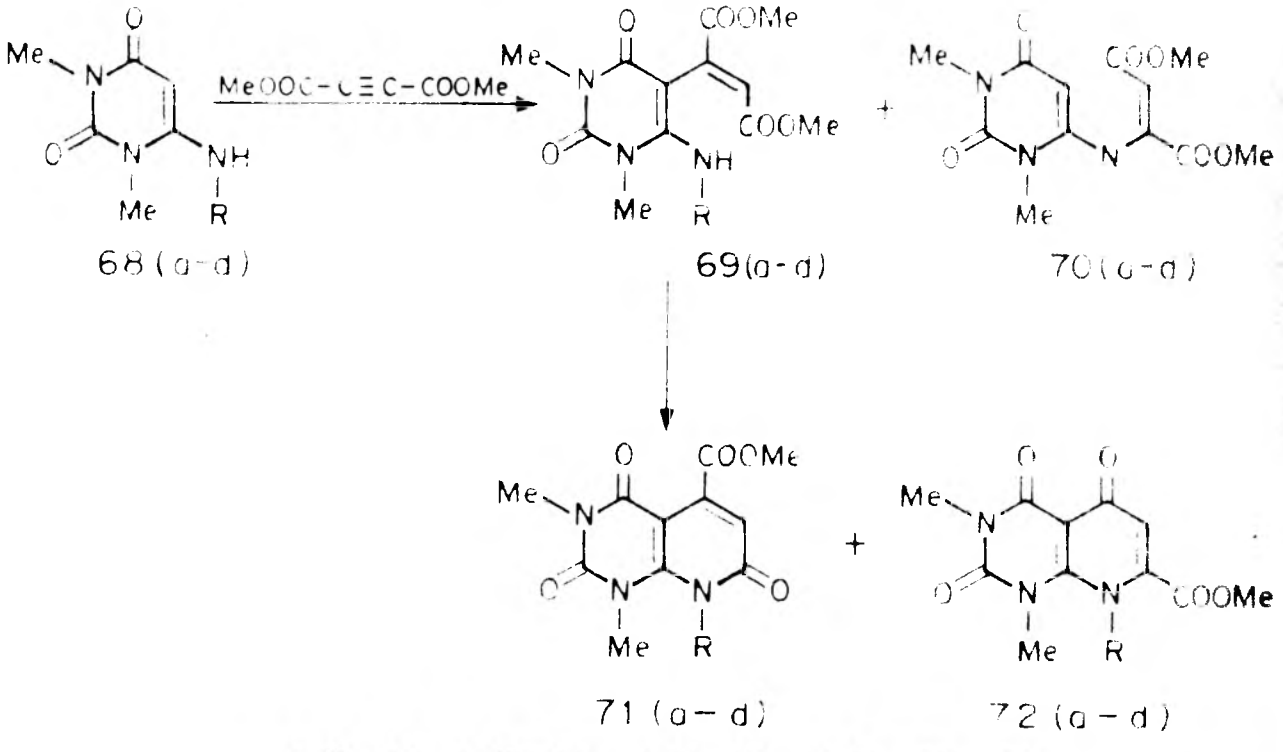
(62) (63)



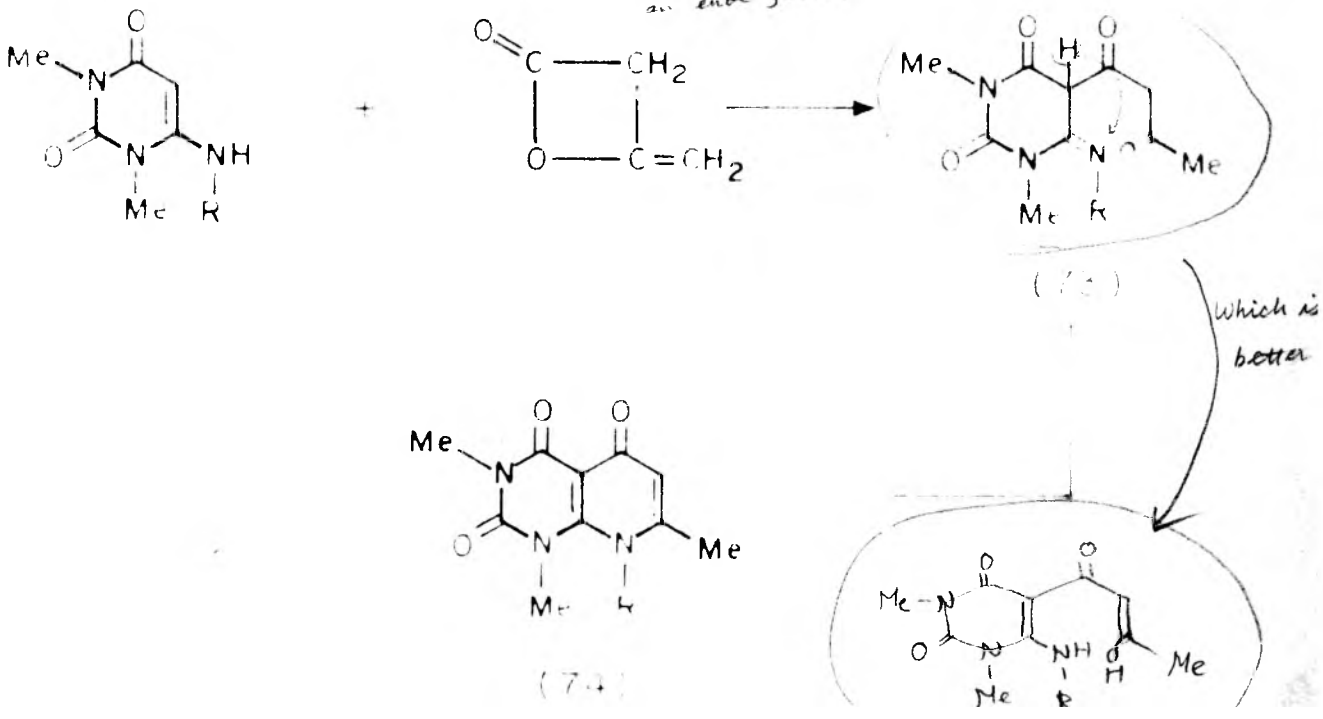
(64)



(65) (65') (66) (67)



Are there any evidences to express the structure in this form. Isn't one enamine structure favorable Further, the acetoacetyl group, in general, exists in an enol form.



Heating of (68a) with dimethyl acetylene dicarboxylate under reflux in MeOH produced directly cyclized 7-oxo compound (71a) and a small amount of 5-oxo compound (72a). In contrast the 68a,b,c,d reacted with diketene and gave 5-oxopyrido [2,3-d] pyrimidines (72a,b,c,d) and not 7-oxo-compound. The position of an oxo group was confirmed by the reaction of (67a) with ethylacetoacetate to yield 6-amino-1,3-dimethyl-2,4-dihydro-5-acetoacetyl pyrimidine (73 R = H). This intermediate easily formed 5-oxopyrido [2,3-d] pyrimidine (74) which was obtained from 68a and diketene.

DISCUSSION OF PRESENT WORK

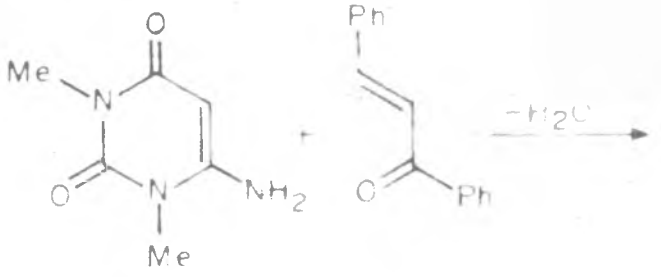
Synthesis of pyrido[2,3-d]pyrimidine 2,4-diones

Discussion of Present Work

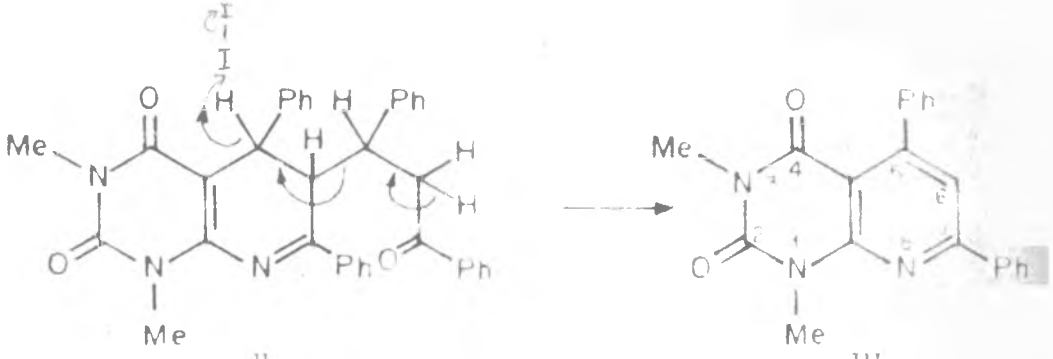
Pyrido[2,3-d]pyrimidine derivatives have shown biological and pharmacological properties such as antifolic acid, antibacterial[1] and antitumor action[58]. They have been synthesized earlier by reacting 4-aminopyrimidine or (1) with 1,3-diketones[26,27] methylmalonic acid[50], β-ketoesters[40,41] and enaminoketones[59]. With the object of synthesizing potential pharmacologically active new compounds in this series, base catalysed condensation of (1) with α,β-unsaturated ketones or dimethylacetylene dicarboxylate leading to the title compounds was carried out. The reaction involves Michael addition of the activated C-5[26] position of the amino uracil (1) to α-enones or acetylenic ester and cyclodehydration and dehydrogenation of the adducts so formed in the subsequent steps. This method of synthesis is advantageous for preparing a wide variety of 5,7-disubstituted pyrido[2,3-d]pyrimidine-2:4-diones since α-enones and acetylene esters are readily accessible.

An equimolar proportion of (1) and benzalacetophenone in aqueous ethanol int the presence of piperidine as a catalyst gave a good yield of a yellow compound to which structure II was assigned based on the following analytical and spectral data. It gave a molecular formula $C_{36}H_{21}N_3O_3$ and molecular

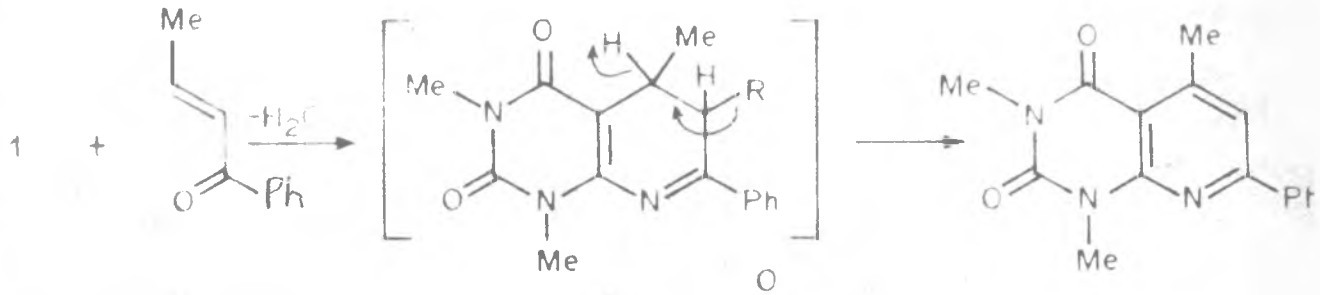
weight 553. Its IR spectrum showed the presence of amide and benzoyl carbonyls at 1695-1650$^{cm^{-1}}$ and aromatic C=C stretching at 1580-1600$^{cm^{-1}}$ region. The n.m.r. spectrum of the compound gave two singlets at 3.28 and 3.40 for the two N-CH_3 groups. A broad multiplet peak of four protons at 3.80 was assigned to methylene and methine protons of the side-chain and also for the ring C_6-H. A broad peak at 4.36 of one proton intensity was assigned to C_5-H of the ring. There were altogether twenty protons in the aromatic region. A ten proton broad peak at 7.01 was attributed to C_5 and C_6-side chain phenyl protons. The ortho protons of C_7-phenyl and the side-chain benzoyl group appeared deshielded at 8.03 as four protons. The meta and para protons of the phenyl rings appeared at 7.43 as a six proton multiplet. The mass spectral fragmentation and appearance of m/e at 553 (M^+), 344 (dihydropyrido[2,3-d]pyrimidine), 276.5($M^+/2$), 105 (benzoyl) and 77 (phenyl) cations also support the structure of the compound as a condensed diadduct (II). Michael addition of α-picoline or 2-methylquinoline[60] to chalcone (benzalacetophenone) is known to give diadducts involving one molecule of donor and two of acceptor molecules. Similarly one molecule of (1) and two molecules of chalcone gave the compound II. The dihydropyrido[2,3-d]pyrimidine (II) has three asymmetric centres at C_5, C_6 and side-chain C_1 and hence a mixture of four racemic diesteromers are possible. No attempt was made to separate and distinguish them. Stereoisomerism of groups at C_5 and



1

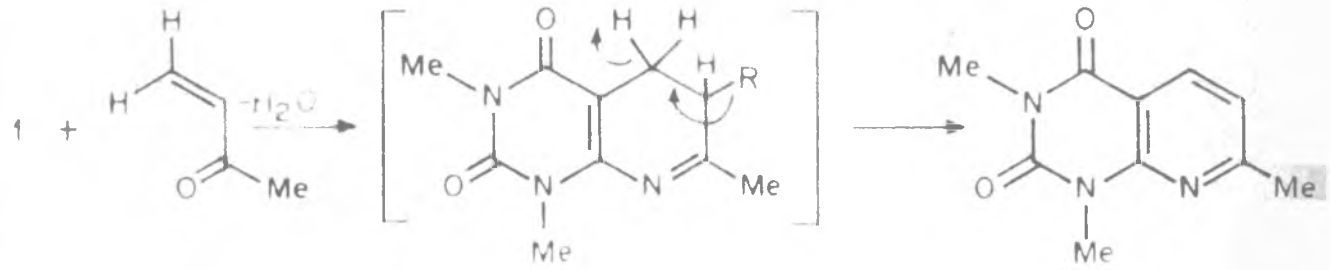


II III



R = H or $Me-CH-CH_2-C-Ph$ (O)

IV



V

R = H or $-CH_2-CH_2-C-Me$ (O)

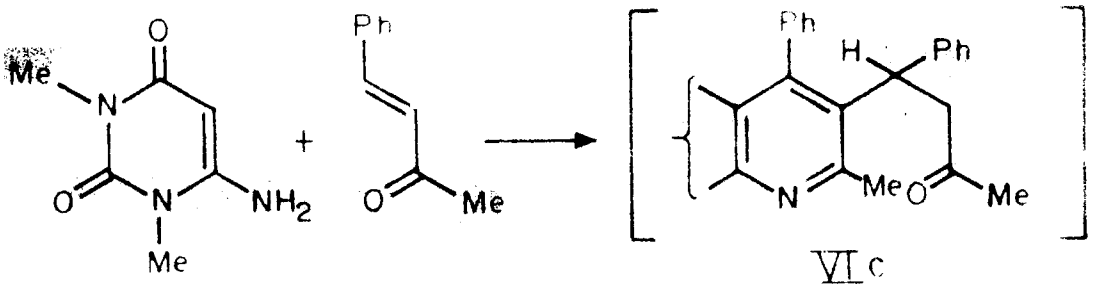
C_6 is possible. The C-5 proton in the n.m.r. appeared as a broad singlet indicating very little coupling with adjacent C_6 proton. If they are trans diequatorial one would have expected a large coupling (8-12 Hz) between C_5 and C_6 protons which is not so, molecular models indicate the C-5 phenyl ring and the C_6-side-chain must be equatorial and axially oriented in a cis configuration respectively to avoid steric interaction. The adduct (II) was refluxed with glacial acetic acid and iodine as catalyst and from the reaction mixture pyrido[2,3-d]pyrimidine (III) in 46% yield and benzalacetophenone were isolated. The n.m.r. of III showed two N-CH_3 as singlets at 3.36 and 3.86 region. The two ortho protons of phenyl at C_7 appeared at 8.01. The other three protons (2 meta, 1 para) of phenyl at C_7, the five protons of phenyl at C_5 and the proton at C_6-position of the ring appeared at 7.41 as a multiplet of nine protons. This and the molecular weight 343 confirmed the structure III. The benzalacetophenone isolated agreed in its m.p., i.r., n.m.r. with an authentic sample. Hence elimination of benzalacetophenone from II as depicted in the scheme (II) led to the formation of III.

Refluxing (1) and phenylpropenylketone in methanol with piperidine as a catalyst furnished directly the 5-methyl-7-phenyl-pyrido[2,3-d]pyrimidine-2,4-dione (IV). Reaction of (1) and methylvinylketone under similar experimental

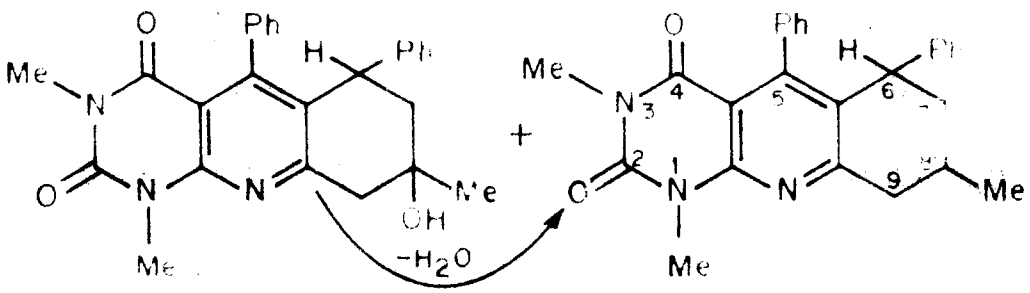
conditions also gave 7-methyl-pyrido[2,3-d]pyrimidine 2,4-dione (V). The analytical and spectral data such as n.m.r., IR, mass of these compounds are in good agreement with the structures (IV, V) assigned to them. Although no intermediates were isolated to support the actual pathway leading to the pyrido[2,3-d]pyrimidine ring system (IV, V), as it was already reported on similar reactions[61], that tetrahydropyrido[2,3-d]pyrimidines formed as intermediates undergo autooxidations under the experimental conditions to give aromatised pyrido[2,3-d]pyrimidines. However the other alternative route, a diadduct eliminating one molecule of phenylpropenylketone or methylvinyl ketone to give pyrido [2,3-d]pyrimidine (as in II → III) cannot be ruled out in the absence of experimental evidence.

Refluxing aminouracil (1) and benzalacetone in aqueous ethanol with piperidine as a catalyst furnished two compounds (VI, VII). The IR spectrum of the compound VI showed -OH at 3420^{cm-1} and amide carbonyls at 1695^{cm-1}. The molecular weight obtained was 427. The structure as a linear tricyclic tertiary alcohol (VI) was confirmed from its n.m.r. spectrum which showed apart from two N-CH_3 groups a singlet of three protons at 1.40 corresponding to methyl group at C_8-position. The -OH proton at C_8 and non-equivalent methylene protons at C_7 appeared as a three proton multiplet peak at 2.00 region. The -OH proton exchanged

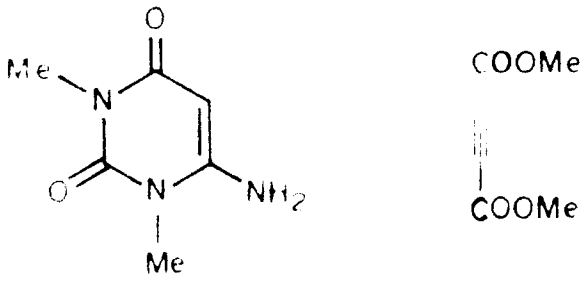
with D_2O. A non-equivalent broad two peaks centred at 2.86 with J = 13 Hz, 1.5 Hz were assigned to C_9-methylene protons. The multiplet centre at 2.96 - 3.33 was attributed to benzylic proton at C_6 position. The C_5-phenyl and the C_6-phenyl protons appeared at 6.75, 7.20 and at 7.36 as multiplets. Since C_6 and C_8 are chiral centres stereoisomeric mixtures are possible for (VI). Models constructed for the compound showed that the C_6-phenyl should be in axial position for if it is in equatorial position severe steric interation will be there between C_6-phenyl and C_5-phenyl groups. In a boat form conformation two stereoisomers (axial, equatorial) are possible for the methyl at C_8-position. However, no attempt was made to distinguish the isomeric protons in the n.m.r. spectrum. This alcohol (VI) on refluxing with glacial acetic acid with conc. H_2SO_4 as a catalyst gave a dehydration product for which structure VII was assigned. The dehydration product (VII) gave molecular weight 409. Its n.m.r. showed a broad singlet of three protons at 1.86 corresponding to C_8- methyl group on a double bond. A doublet at 6.26 with J 8Hz vicinal coupling and 2-3 Hz allylic coupling with C_9-protons suggested the presence of an olefinic proton which was assigned the C_7-position. A doublet partially merged in the N-methyl signal at 3.88 was assigned to the benzylic proton at C_6-position adjacent to olefinic proton. The non-equivalent C_9-methylene protons appeared at 2.30 - 2.78 as a multiplet with geminal coupling

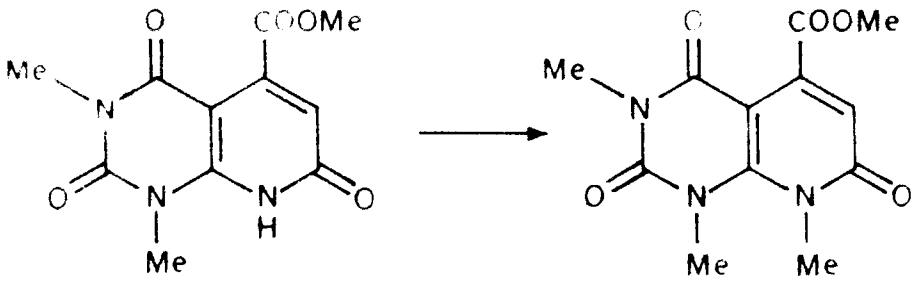


VI c



VI VII





VIII IX

18 Hz[62] and 2-3 Hz for the long range allylic coupling[62] with olefinic proton at C_7 position. The doublet nature of the olefinic proton established that during the dehydration process a proton from C_7-position is lost and not from C_9-position. Models of the dehydrated product (VII) revealed that the C_6-phenyl as in the case of alcohol (VI) must be in axial position for the reasons already mentioned The C_6-proton in equatorial position makes a dihedral angle 30° with the olefinic proton at C_7-position. The observed J value is in agreement with the theoretical value[63] reported for such a situation. The spectral and stereoisomeric characteristics presented above, the molecular weight and its formation from VI justify the structure as 5,6-diphenyl-8-methyl-pyrimido[4,5-b]-3H-quinoline (VII). The formation of this ring system may be explained via an intermediate (VIa) a condensed diadduct (like II). A carbanion derived out of the C_7-methyl group of the adduct can undergo aldol condensation with the carbonyl group of the side chain (VII) to give the tertiary alcohol (VI) and loss of H_2O from this results in the pyrimido [4,5-b]quinoline ring system.

As an extension of the synthesis of title compounds reaction of 6-amino-1,3-dimethyluracil (1) and dimethyl-acetylenedicarboxylate in refluxing methanol was carried out. A yellow crystalline product was isolated in good yield to which structure VIII was assigned based on the following data.

The IR spectrum of it gave -NH at 3300^{cm-1}, amide and ester carbonyls at 1710-1740^{cm-1} region. The n.m.r. spectrum showed an olefinic proton as a singlet at 6.45^{64} besides the N-methyl and methyl ester signals in the up-field region. Methylation of VIII with diazomethane in ether furnished an N-methyl derivative (IX) which showed the extra N-methyl at 4.00 and an olefinic proton in n.m.r. at 6.53 as singlets. Thus the above information confirmed the structures (VIII and IX) as 5-carbomethoxy-7-oxopyrido[2,3-d]pyrimidine derivatives. long after the above work was completed but not published, Ogura and Sakaguchi published a paper[58] in which the synthesis of compounds VIII and IX by the same route has been described. The N-methyl derivatives IX was synthesised by them directly from 1,3-dimethyl-6-methyl-aminouracil and dimethylacetylene dicarboxylate in a one step reaction. Mention has been made of their work in the literature survey section.

E X P E R I M E N T A L

EXPERIMENTAL

Pyrido[2,3-d]pyrimidine-2,4-diones

All melting points are uncorrected. IR spectra were taken on Perkin-Elmer infracord-137 and UV spectra on Beckman DK-2 instruments. NMR spectra were recorded on A-60 or T-60 instruments with TMS as internal standard. The chemical shift values were expressed as δ(ppm) and the J values in Hz. Mass spectra were recorded on CEC-2-110B double focussing instrument with a direct inlet system. Only significant m/e peaks were given as percentages of base peak taken as 100%.

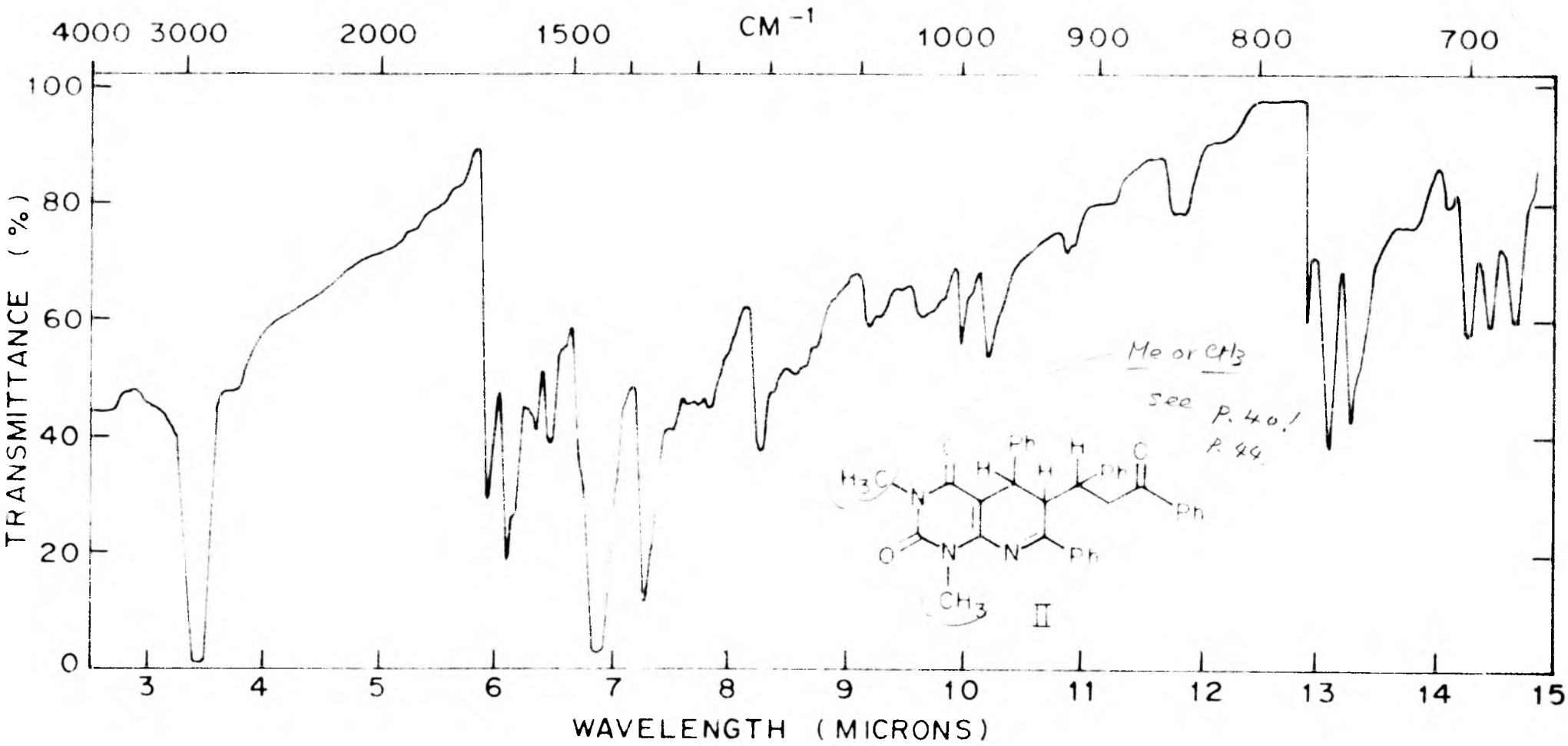
1,3-Dimethyl-2,4-dioxo-5,7-diphenyl-6 (1-benzoyl-2-phenylethane) 1,2,3,4,5,6-hexahydro-pyrido[2,3-d]pyrimidine (II).

A solution of 6-amino-1,3-dimethyluracil (1,5g,0.032 mol) in rectified spirit (50 ml) was stirred at room temperature with piperidine (0.3 ml) for 5 minutes. To this solution benzal-acetophenone (6.6 g, 0.032 mol) was added and refluxed at 85° for 5 hrs. A bright yellow solid separated on cooling the reaction mixture was filtered. The product was recrystallised from rectified spirit. Yield 8 g (44.8%) m.p. 206-208°.

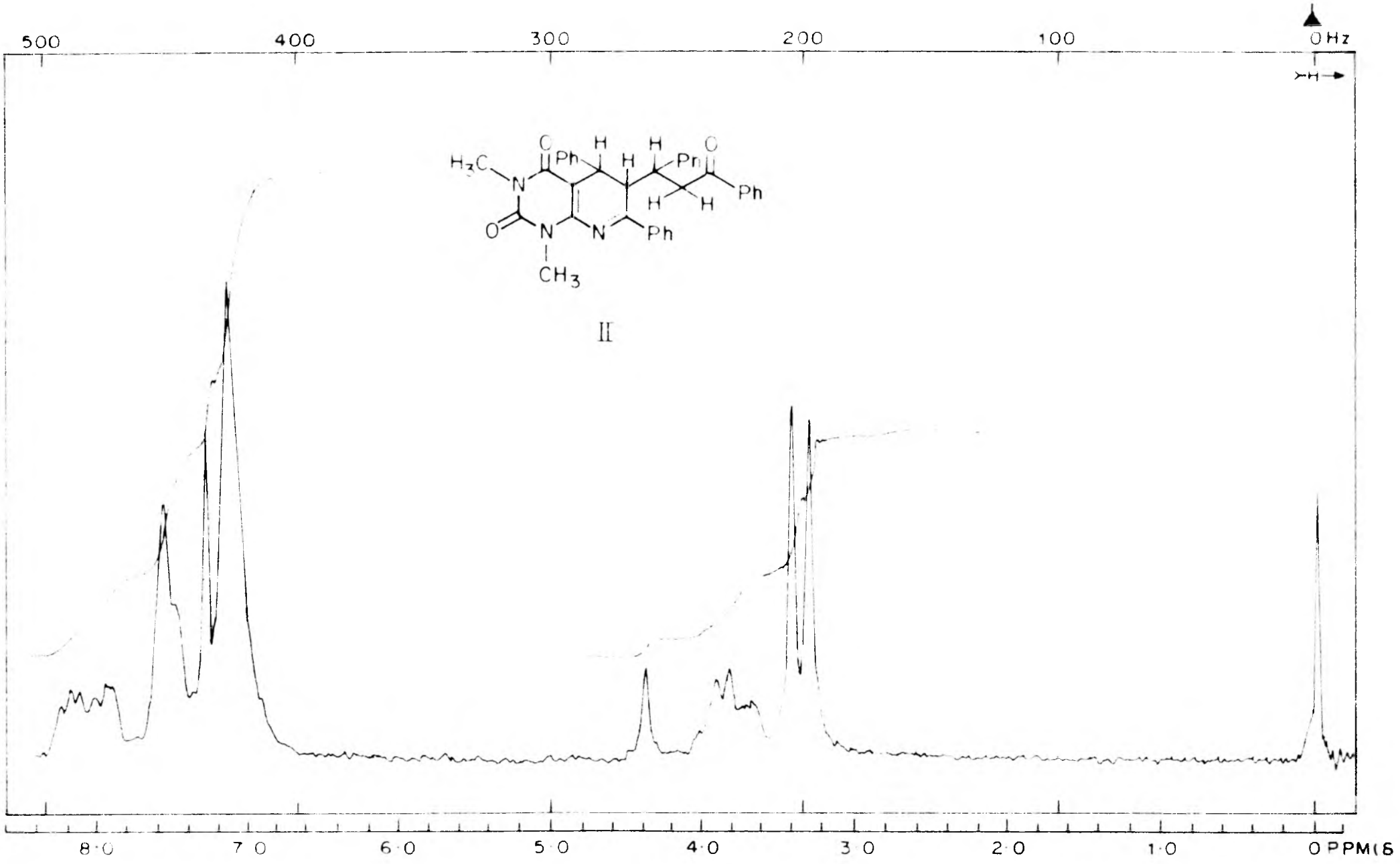
Elemental analysis: Found: C, 78.29; H, 5.66, N, 7.43

$C_{36}H_{31}N_3O_3$ requires C, 78.10; H, 5.64; N, 7.59%.

IR (nujol): 2950 (CH stretch), 1695, 1645 cm^{-1} (amide and benzoyl C=O's).


4000 3000
2000
1500
CM -1
1000
900
800
700
100
80
60
40
20
0
TRANSMITTANCE (%)
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
Me or CH3
See P. 40 / P. 44
II

IR OF II



II

N.M.R. OF II

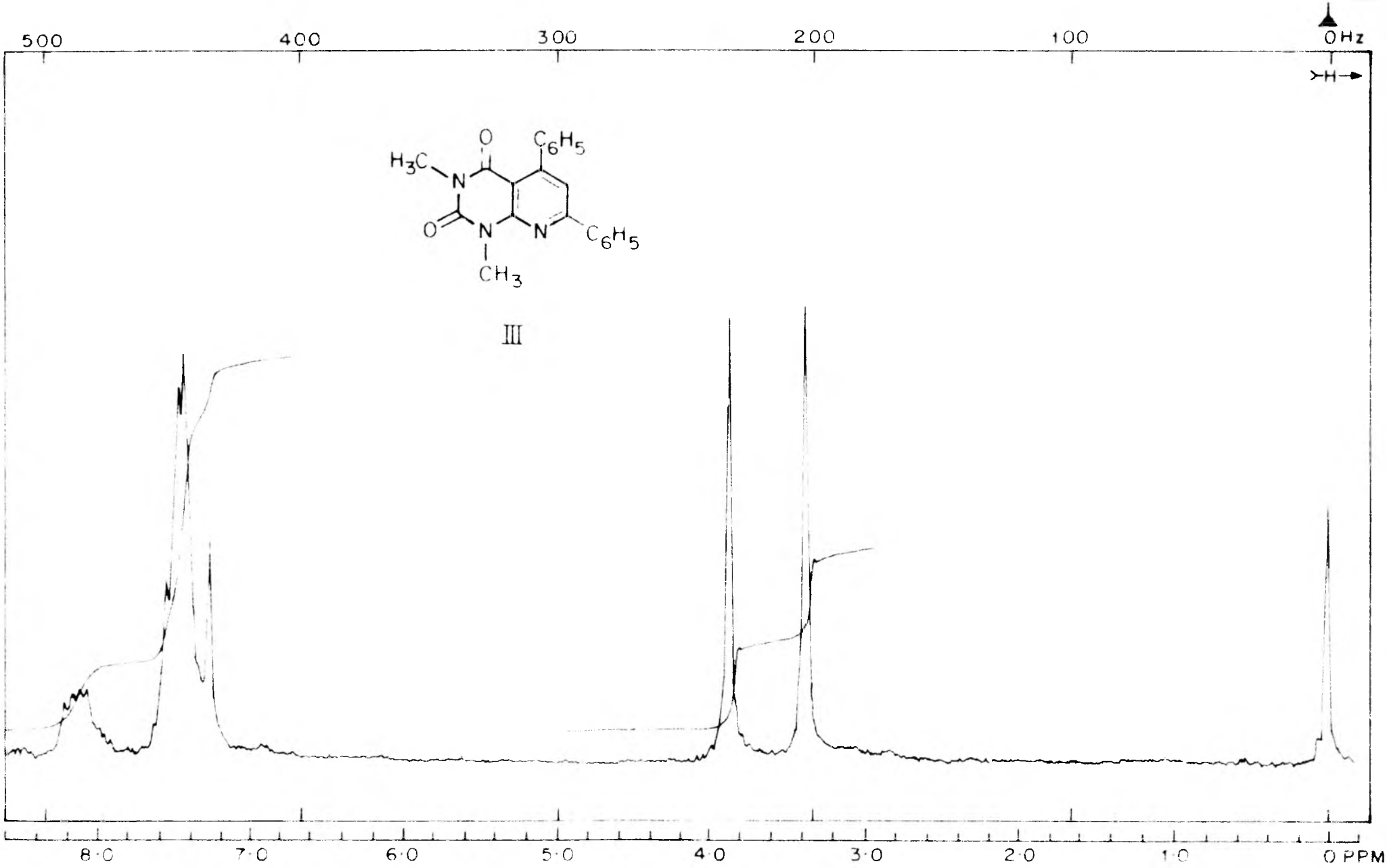
UV λ(ε): 242 (4.01), 276 (3.98) in EtOH.

NMR ($CDCl_3$): 3.28 (s, 3H, N-CH_3), 3.40 (s, 3H, N-CH_3), 3.80 (m.c. 4H, methylene and methine protons of side-chain and ring C_6-H) 4.36 (b.s. 1H, ring C_5-H) 7.01 (b.s. 10H, arom), 7.43 (b.s. 6H, arom), 8.03 (m.c. 4H, arom).

Mass spectrum : m/e(%) 553(2), 476(2), 448(11), 435(6), 344(96), 343(96), 287(23), 276.5, 268(88), 239(19), 230(42), 209(45), 208(45), 207(46), 155(45), 154(24), 131(15), 105(98), 77(100), 51(10).

1,3-Dimethyl-5,7-diphenyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido-[2,3-d]pyrimidine (III)

A solution of II (1 g) in glacial acetic acid (25 ml) with and iodine (3 mg) as a catalyst was refluxed at 120° for 4 hrs. Acetic acid was distilled from the reaction mixture at 40 mm and at 50-60° temperature. The residue was taken up over a silicagel column (30 x 2.4 cm) and was chromatographed using pet-ether(60-80°), benzene, benzene:chloroform (4:1), benzene, chloroform (7:3) for elutions. The pet.-ether elutions (250 ml) gave pure benzalacetophenone (30 mg, m.p. 49-50°). The benzene $CHCl_3$(4:1) fractions (600 ml) gave impure (III). This was recrystallised from rectified spirit to furnish pure compound yield 0.21 g (46%), m.p. 242-243°C. Benzene:chloroform (7:3) elutions gave unchanged II (0.3 gms.).



III

N. M. R. OF III

Elemental analysis: Found: C, 73.52; H, 4.83
N, 12.84; $C_{21}H_{17}N_3O_2$ requires C, 73.45,
H, 4.99, N, 12.24%.

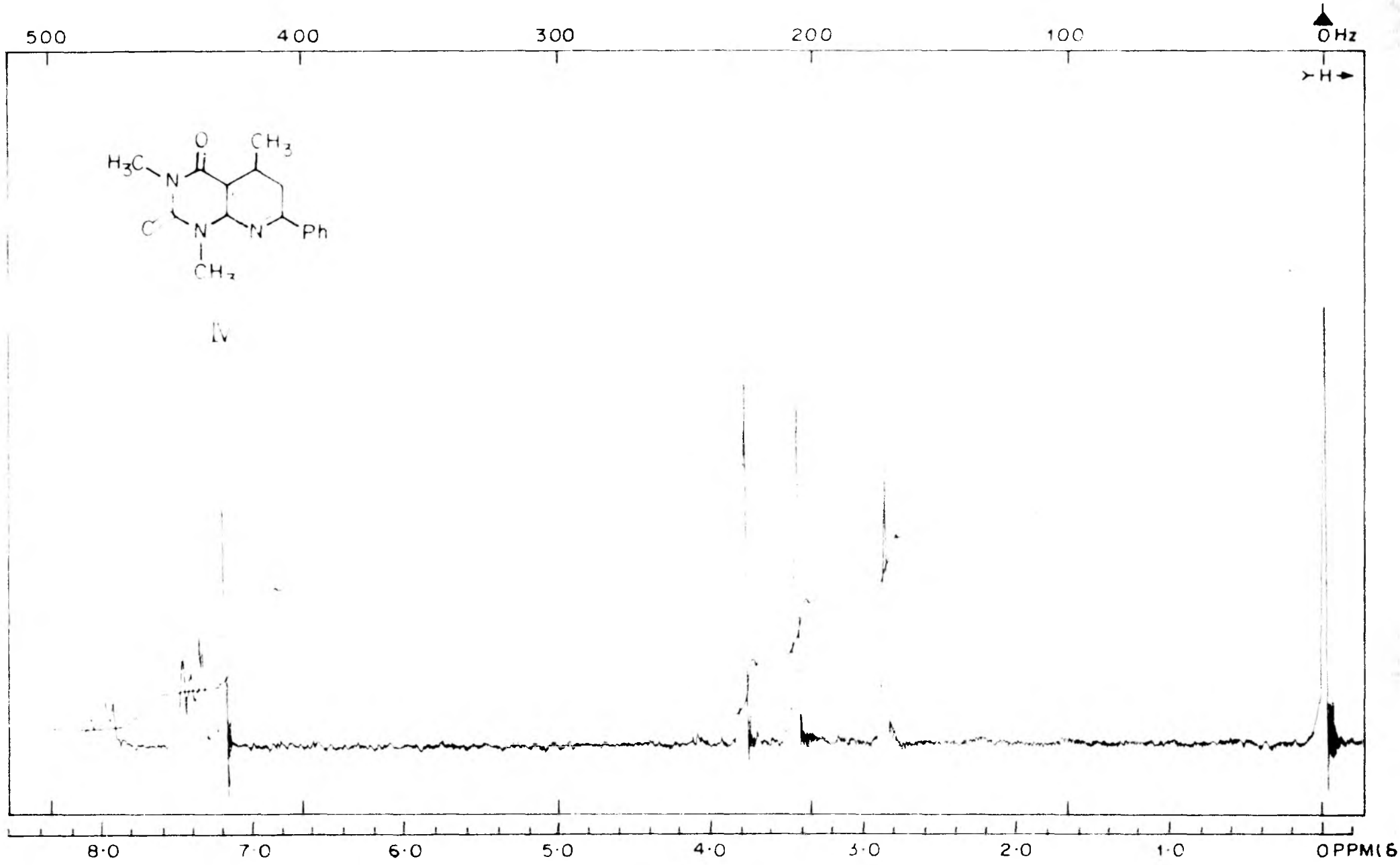
IR (nujol): 1720 - 1675 cm^{-1} (Amide C=O's).

NMR ($CDCl_3$): 3.36 (s, 3H, N-CH_3), 3.86 (s, 3H, NCH_3),
7.41 (m.c., 9H, Arom), 8.01 (m.c. 2H, Arom).

Mass spectrum: m/e(%) 343(100), 315(66.5), 268(27),
266(17), 256(18), 231(58), 230(54),
216(33), 202(39), 189(22), 165(16),
154(21), 140(31), 127(22), 115(32),
104(37), 103(36), 91(33), 89(22), 77(27),
50(36), 51(37), 43(29), 39(22), 28(26).

1,3-Dimethyl-5-methyl, 7-phenyl, 2:4-dioxo, 1,2,3,4-tetrahydro-pyrido/2,3-d/pyrimidine (IV)

To a solution of 1,3-dimethyl, 6-aminouracil (1, 0.78 g, 0.005 mol), phenyl propenyl ketone (0.73 g, 0.005 mol) in methanol (15 ml) piperidine (0.2 ml) was added and refluxed at 85° for 24 hrs. Methanol was distilled off from the reaction mixture. The residue was treated with boiling chloroform twice each time with 10 ml and was filtered. The solid amorphous compound (0.3 g, m.p. 290°C) obtained corresponded with aminouracil (1). The filtrate was distilled to dryness and the residue was recrystallised from methanol gave yellowish needles of m.p. 193° yield 0.26 g (30%).


500
400
300
200
100
0 Hz
H
O
CH3
H3C
N
C
N
N
Ph
CH3
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM (δ

IV

N.M.R. OF IV

Experimental analysis: Found: C, 68.15; H, 5.42; N, 15.30; $C_{16}H_{15}N_3O_2$ requires C, 68.32; H, 5.33; N, 14.95%.

IR (nujol): 1695-1720 cm^{-1} (amide C=O), 1600-1580^{cm-1} (Arom C=C).

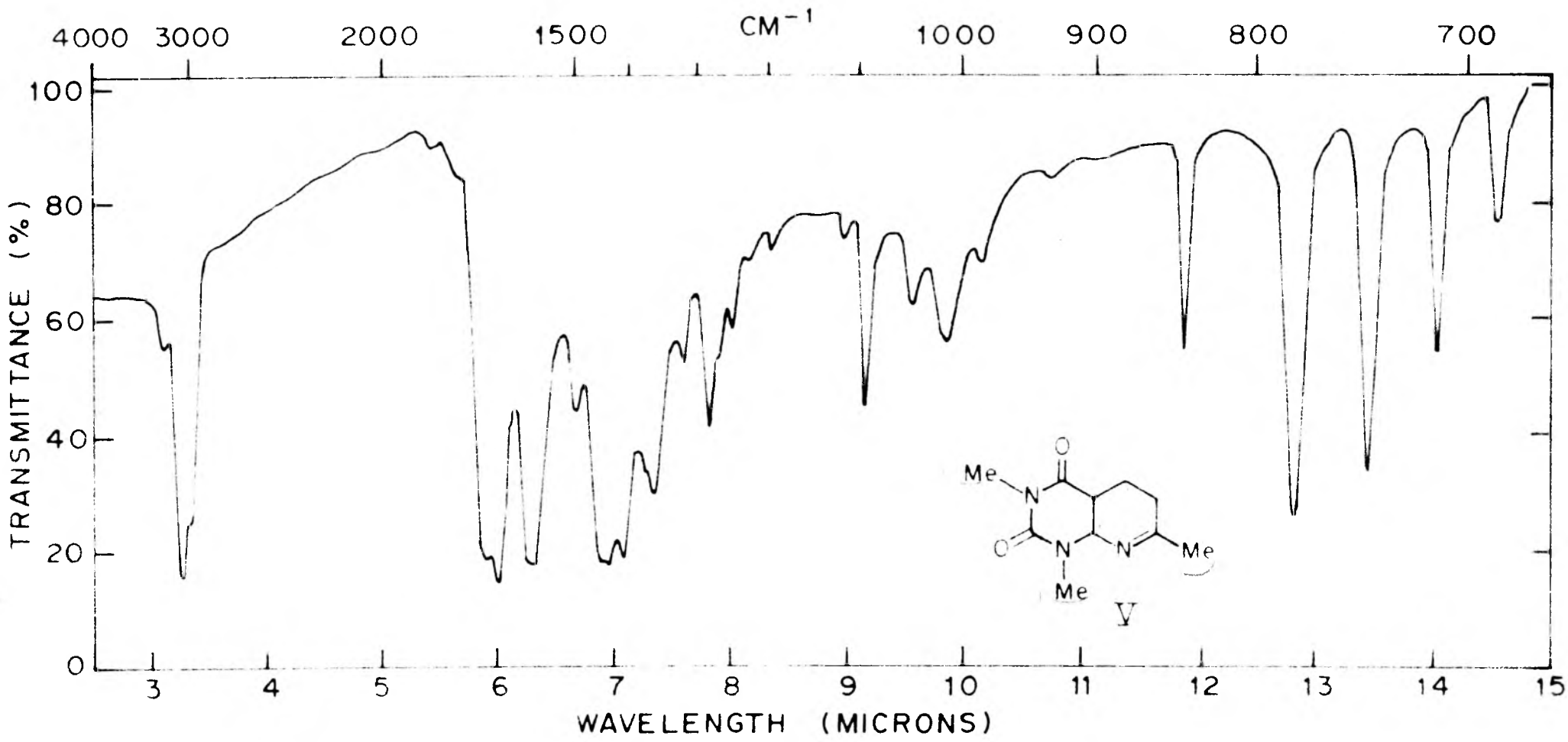
Mass spectrum: M^+ 281.

NMR ($CDCl_3$): 2.85 (s, 3H, C_5-CH_3), 3.43 (s, -3H, N-CH_3), 3.78 (s, 3H, N-CH_3), 7.36 (m.c. 4H, C_6-H and arom 3H's), 7.96 (m.c., 2H, Arom).

1,3-Dimethyl, 7-methyl,2,4-dioxo-1,2,3-4-tetrahydro-pyrido[2,3-d]pyrimidine (V)

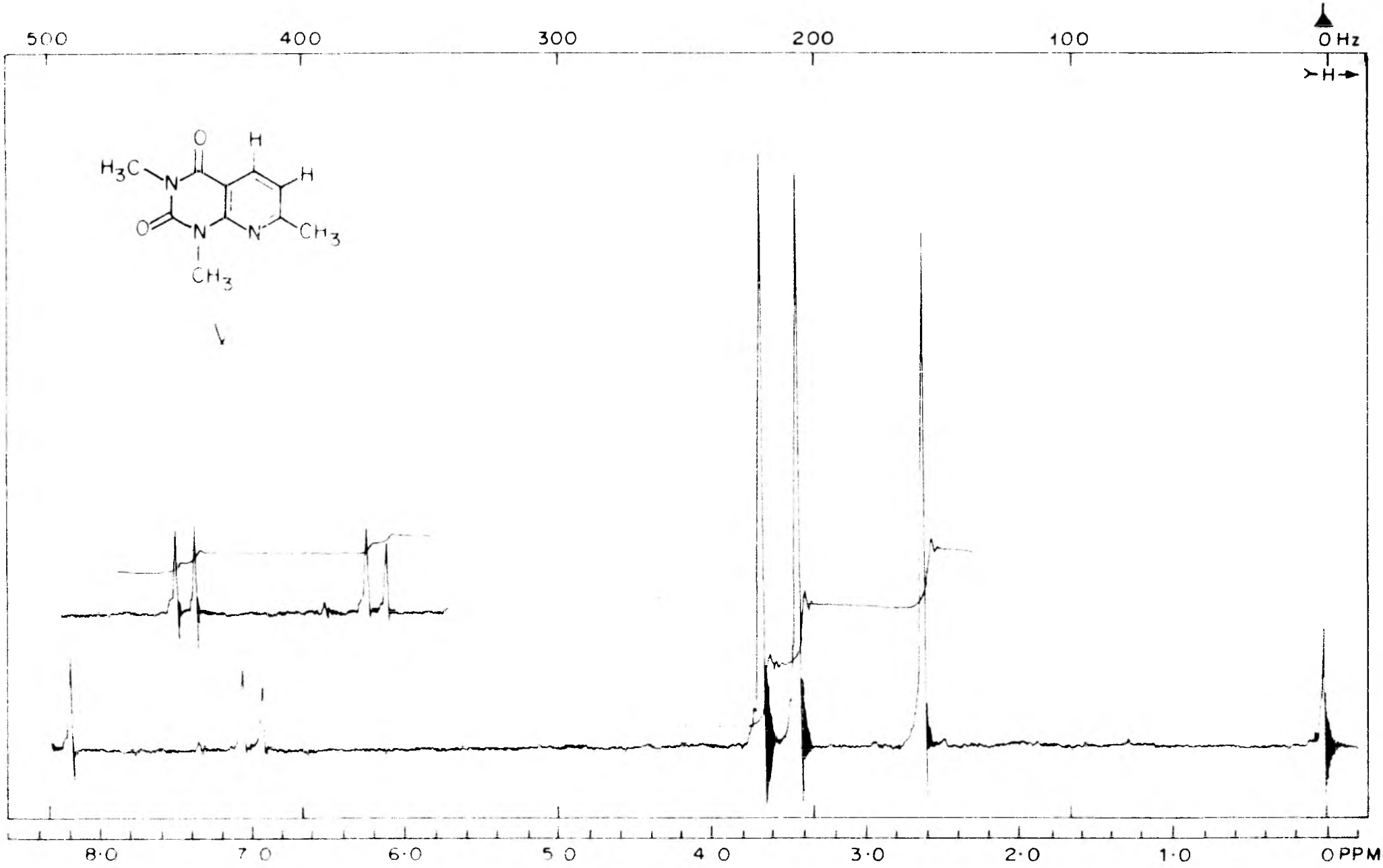
A solution of 1,3-dimethyl-6-aminouracil (1, 1.55 g, 0.01 mol) methylvinylketone (1.02 g, 0.015 mol), piperidine (0.1 ml) and rectified spirit (20 ml) was refluxed at 90°C for 4 hrs. The solvent was distilled from the reaction mixture. The residue was treated with chloroform (20 ml), warmed the solution to 70°C and filtered. The insoluble solid (0.5 g) left was the unreacted aminouracil. The filtrate was distilled to remove chloroform. The residue was chromatographed over silicagel column (30 x 2.5 cm) using benzene and chloroform for elution. Chloroform elutions gave pure (V). Yield 0.5 g (36%), m.p. 182°.

Elemental analysis: Found: C, 58.68; H, 5.50. N, 20.71. $C_{10}H_{11}N_3O_2$ requires C, 58.53; H, 5.36 N, 20.48%.


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
Me
N
O
O
N
N
Me
Me
Me

V

IR OF V


500
400
300
200
100
0 Hz
H
O
H
H_3C
N
H
O
N
N
CH_3
CH_3
V
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM (δ

N.M.R. OF V

IR (nujol): 2950-3100 (CH.stretch), 1690-1725 cm^{-1} (amide C=O's).

NMR ($CDCl_3$): 2.63 (s, 3H, C_7-CH_3), 3.41 (s, 3H, N-CH_3), 3.65 (s, 3H, N-CH_3), 6.96 (d, 1H, J = 8 Hz, C_6 or C_5-H) 8.21 (d, LH, J = 8 Hz, C_6 or C_5-H).

Mass spectrum:m/e(%) 205(100), 175(64), 176(79), 162(9), 148(27), 147(28), 133(10), 120(52), 105(28), 93(62), 78(36), 66(38), 65(39), 58(21), 57(23), 56(30), 53(36), 52(34), 51(30),42(12), 39(16).

2,4-Dioxo-8-hydroxy-5,6-diphenyl-1,2,3,4,6,7,8,9-octahydro-1, 3,8-trimethyl-pyrimido/4,5-b/quinoline and 1,2,3,4,6,9-hexa-hydropyrimido/4,5-b/quinoline derivative (VI, VII)

A solution of 6-amino-1,3-dimethyluracil (1, 1.55 g. 0.01 mol), benzalacetone (1.5 g, 0.01 mol) aqueous ethanol (20 ml, 1:1) and piperidine (0.2 ml) was refluxed at 80-85° for six hours. The solvent was distilled under vacuum and the residue was treated with chloroform (10 ml) warmed to 65° and the solution was filtered. Unreacted aminouracil (1, 0.8 g) remained undissolved in chloroform. The chloroform solution was concentrated and the product was chromatographed over silicagel column. The column was eluted with benzene, benzene:ethylacetate (9:1), and finally ethylacetate. Ethyl-acetate fractions gave pure (VI). Benzene:ethylacetate (9:1)

furnished pure (VII).

Pyrimido/4,5-b/quinoline (VI) m.p.118°C. Yield 0.25 g (12%).

Elemental analysis: Found C, 73.29; H, 5.67; N, 10.15

$C_{26}H_{25}N_3O_3$ requires C, 73.08; H, 5.85; N, 9.82%.

Mass spectrum: m/e (%) 427(100), 410(37), 409(54.6), 394(51), 384(70), 332(90), 308(25.6), 282(58), 281(35), 280(43), 268(37), 254(23), 252(16), 251(15), 218(26), 206(49), 205(20), 204(22), 203(28), 202(20), 195(16), 190(18), 189(17), 183(25.6), 169(23), 166(23), 165(24), 149(28), 129(37), 128(43), 127(37), 115(50), 105(55), 97(49), 91(60), 85(43), 84(50), 83(60), 82(43), 81(58), 77(63), 69(65), 57(74.5), 55(81.5), 43(88).

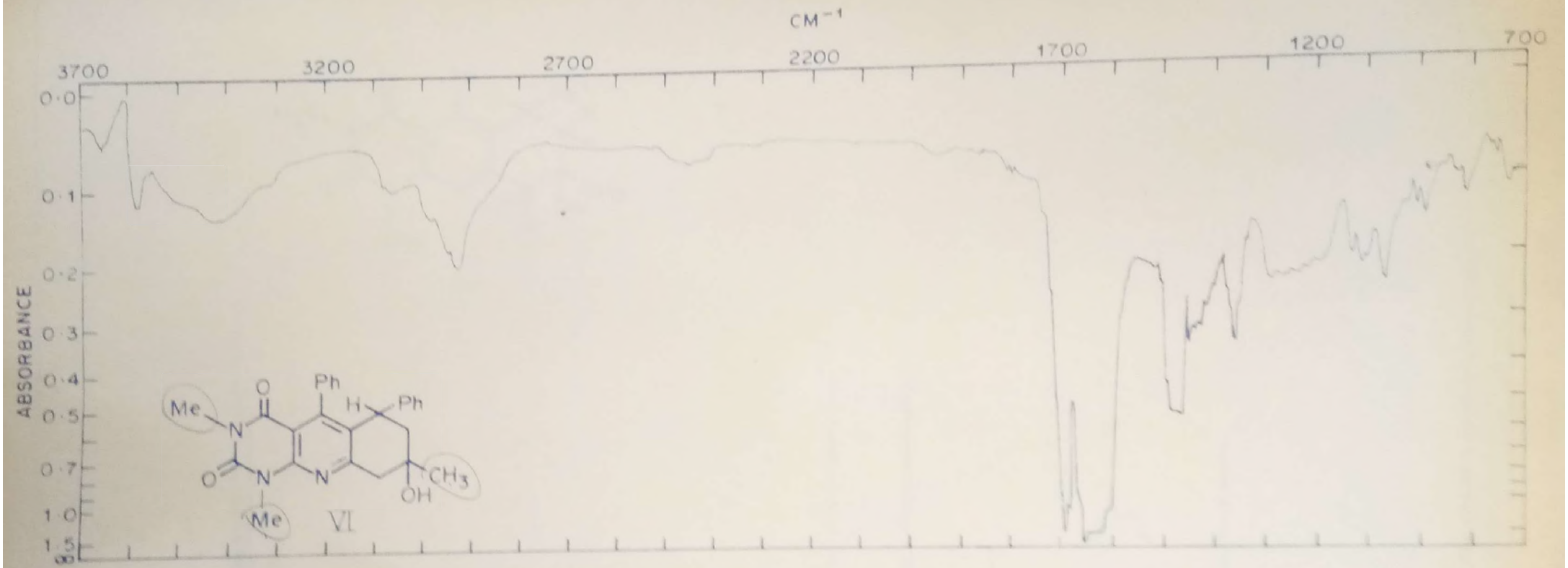
IR($CHCl_3$): 3420-3600 cm^{-1} (OH stretch), 2900-3000 cm^{-1} (CH stretch), 1600-1660 cm^{-1} (Arom C=C stretch) 1660-1700 cm^{-1} (Amide carbonyls).

NMR($CDCl_3$): 1.40 (s, 3H, C_8-CH_3), 2.00 (b,m,c, 3H, C_7-CH_2 and C_8-OH exchangeable with D_2O), 2.75 (b,s,2H, C_9-CH_2), 2.96 - 3.33 (m.c, 1H, C_6-H), 3.26 (s, 3H, N-CH_3), 3.71 (s, 3H, N-CH_3), 6.75 (m.c. 2H, J, 3 Hz Arom), 7.20 (m.c. 3H, Arom), 7.36 (s, 5H, Arom).

Pyrimido/4,5-b/quinoline(VII) m.p.195°. Yield 0.4 g (20.2%).

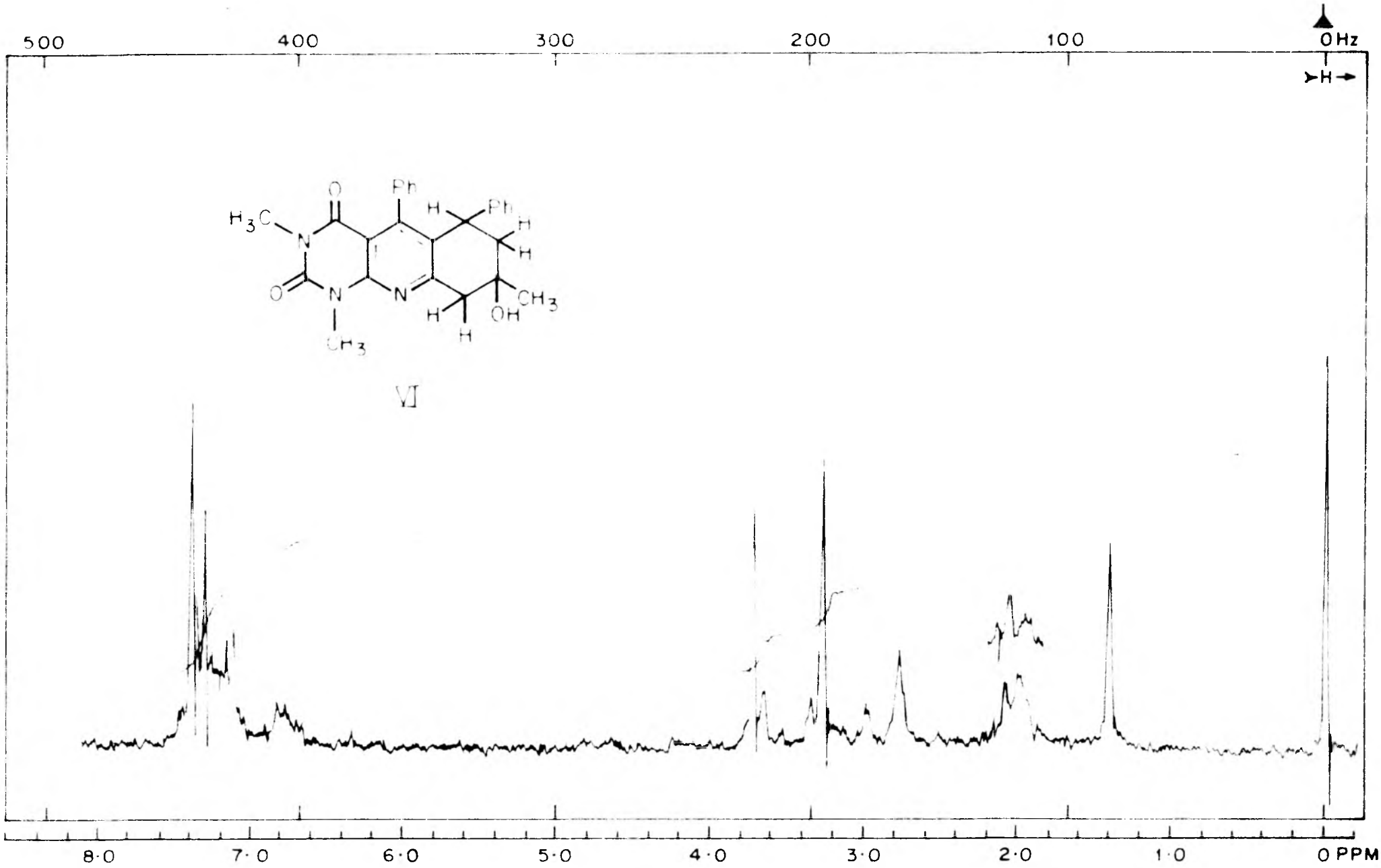
Elemental analysis: Found C, 76.45, H, 5.50, N, 10.50

$C_{26}H_{23}N_3O_2$ requires C, 76.30; H, 5.62 N, 10.24%.


CM⁻¹
3700
3200
2700
2200
1700
1200
700
0·0
0·1
0·2
0·3
0·4
0·5
0·7
1·0
1·5
ABSORBANCE
Me
O
N
O
N
Me
Ph
H
Ph
N
CH3
OH

VI

IR OF VI


500
400
300
200
100
0Hz
H
O
Ph
H
Ph
H
H
H3C
N
O
N
N
CH3
H
OH
CH3
H
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM(δ

VI

N. M. R. OF VI

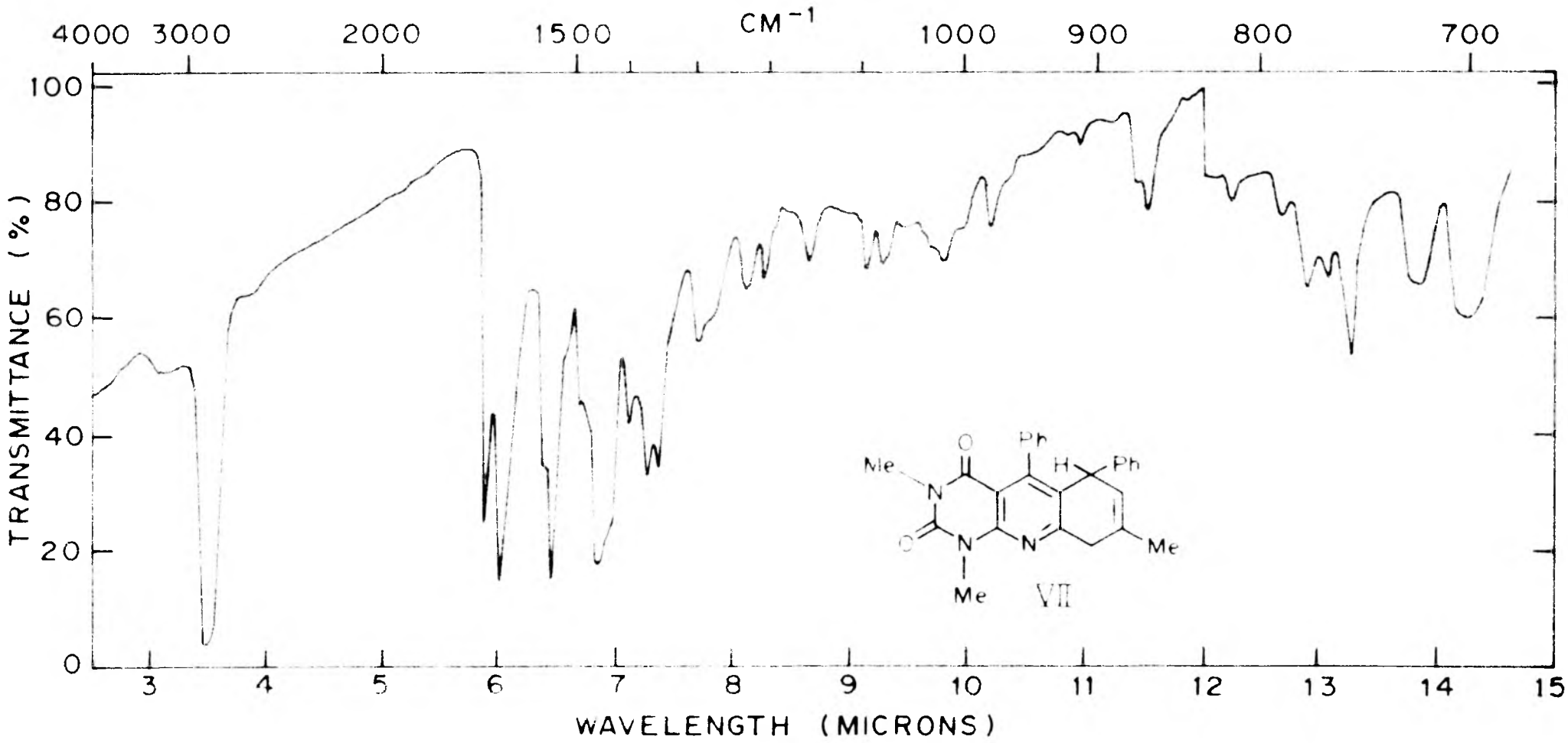
IR (nujol): 1700, 1670, 1565 cm^{-1} (Amide carbonyl and C=C conjug. stretch).

Mass spectrum: M^+ 409.

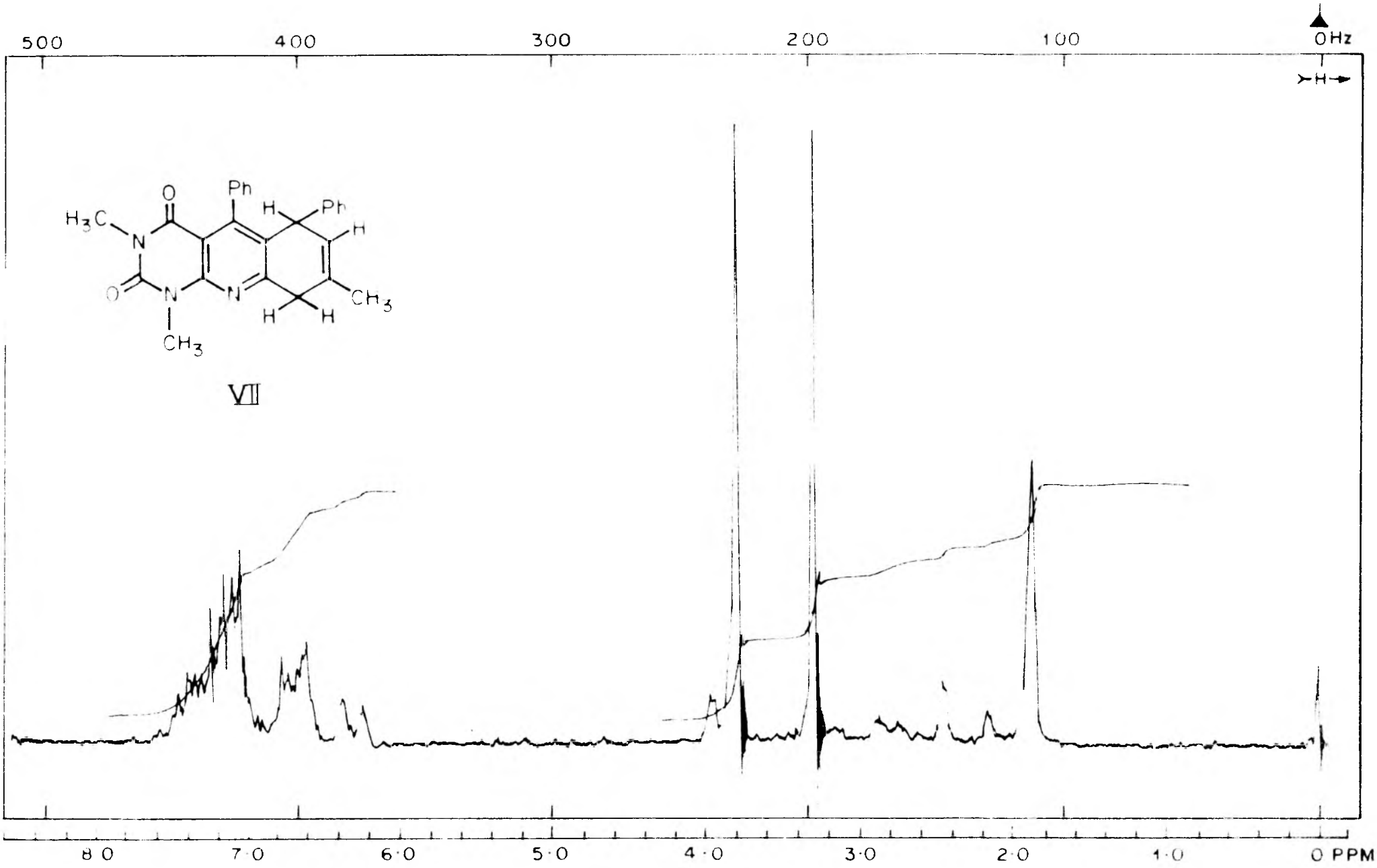
NMR ($CDCl_3$): 1.86 (s, 3H, C_8-CH_3), 2.1 - 2.78 (m.c. 2H, C_9-H's), 3.26 (s, 3H, N-CH_3), 3.76 (s, 3H, N-CH_3), 3.88 (d, 1H, J, 8 Hz, C_6-H partly merged with the signal at 3.88), 6.26(d, H, J, 8 Hz, C_7-H), 6.65 (m.c. 2H, Arom), 7.16 (m.c. 8H, Arom).

Dehydration of alcohol (VI)

A solution of the alcohol (VI, 0.2 g) in glacial acetic acid (2 ml) and one drop of concentrated sulphuric acid as a catalyst was refluxed at 136° for 2 hrs. The solvent was distilled off from the reaction mixture under reduced pressure 60-70°, 40-50 mm. The residue obtained was neutralised with Na_2CO_3 solution(5% 20 ml). Extracted with chloroform (50 ml). The chloroform solution was washed with water, dried over anhydrous Na_2SO_4 and distilled to get a pale yellow solid. It was chromatographed over silica gel column using benzene, benzene ethylacetate (9:1) for elution. The mixture solvent fractions when evaporated gave the pure compound (VII). M.p.195°, yield 0.078 (30%). Identical in n.m.r. and Mass with the earlier isolated compound (VII).


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
Me
O
Ph
H
Ph
N
O
N
N
Me
Me
VII

IR OF VII



VII

N. M. R. OF VII

5-Carbomethoxy-1,3-dimethyl-2,4,7-trioxo-1,2,3,4,7-pentahydro-8H-pyrido/2,3-d/pyrimidine (VIII)

A solution of 6-amino-1,3-dimethyluracil (1, 3.1 g, 0.02 mol) dimethylacetylene dicarboxylate (2.88 g, 0.02 mol) and methanol (50 ml) was refluxed at 80-85°C for 6 hrs. The solvent and unreacted ester were distilled under reduced pressure. The residue left after distillation was dissolved in warm methanol (20 ml) and was filtered in hot condition to separate from minor colourless impurities. The methanolic solution upon cooling gave pure yellow crystalline product (VIII) m.p. 238°. Yield 3.8 g (70%).

Elemental analysis: Found: C, 50.58; H, 4.51; N, 15.52

$C_{11}H_{11}N_3O_5$ requires C, 49.81; H, 4.18 N, 15.84%.

Mass spectrum: M^+ 265.

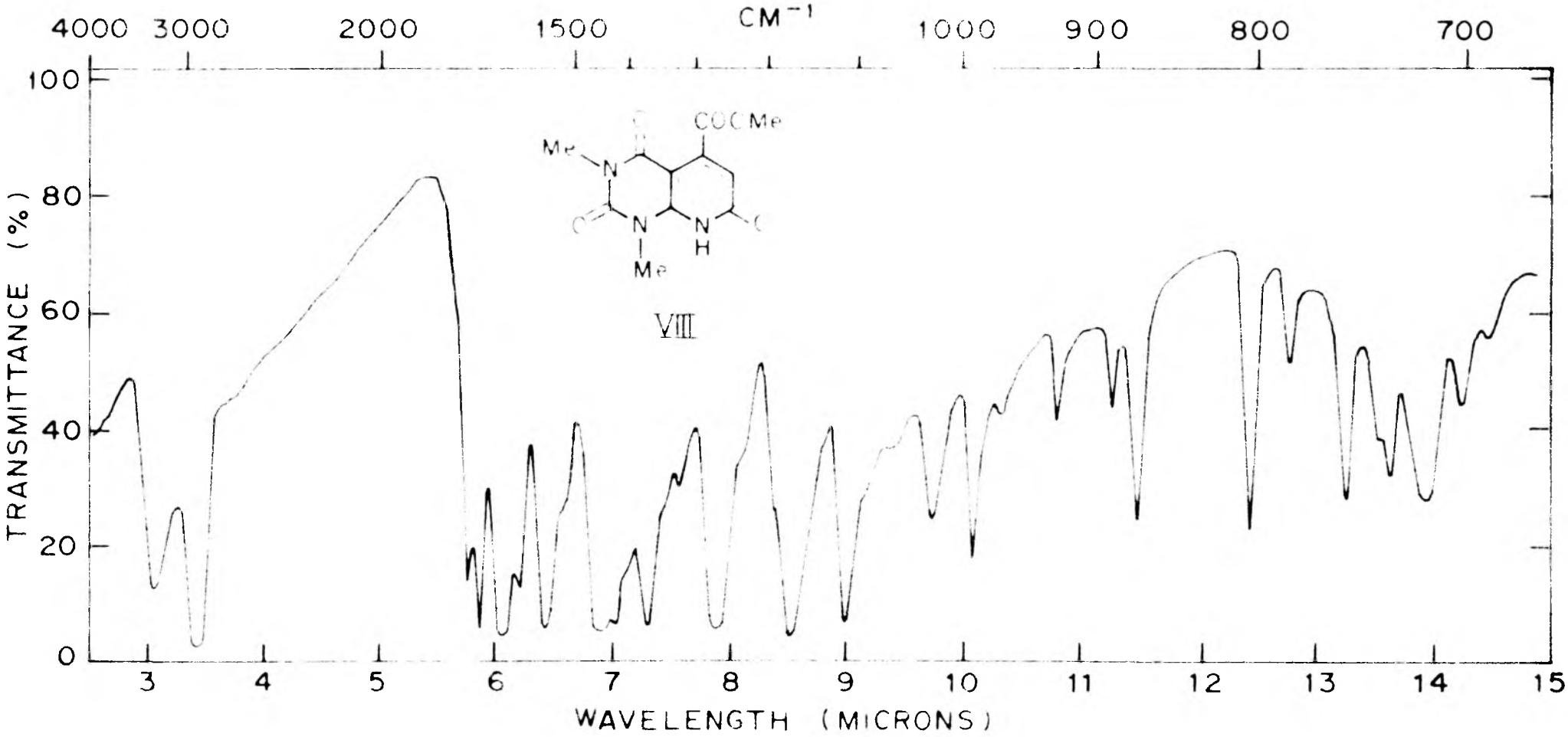
IR(nujol): 3300 (amide NH), 1748, 1675, 1620 cm^{-1} (ester C=O, amide C=O and C=C conju.)

UV λ_{max}^{EtOH} : 273(4.04), 309(4.24).

NMR(DMSO) : 3.26 (s, 3H, N-CH_3), 3.50 (s, 3H-N-CH_3), 3.83 (s, 3H, $COOCH_3$), 6.45 (s, 1H, ring C_6-H)

5-Carbomethoxy-1,3,8-trimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-pyrido/2,3-d/pyrimidine (IX)

Pyrido/2,3-d/pyrimidine (VIII, 0.11 g) was added to a solution of diazomethane in ether (20 ml, 0.2%) and the solution



VIII

IR OF VIII

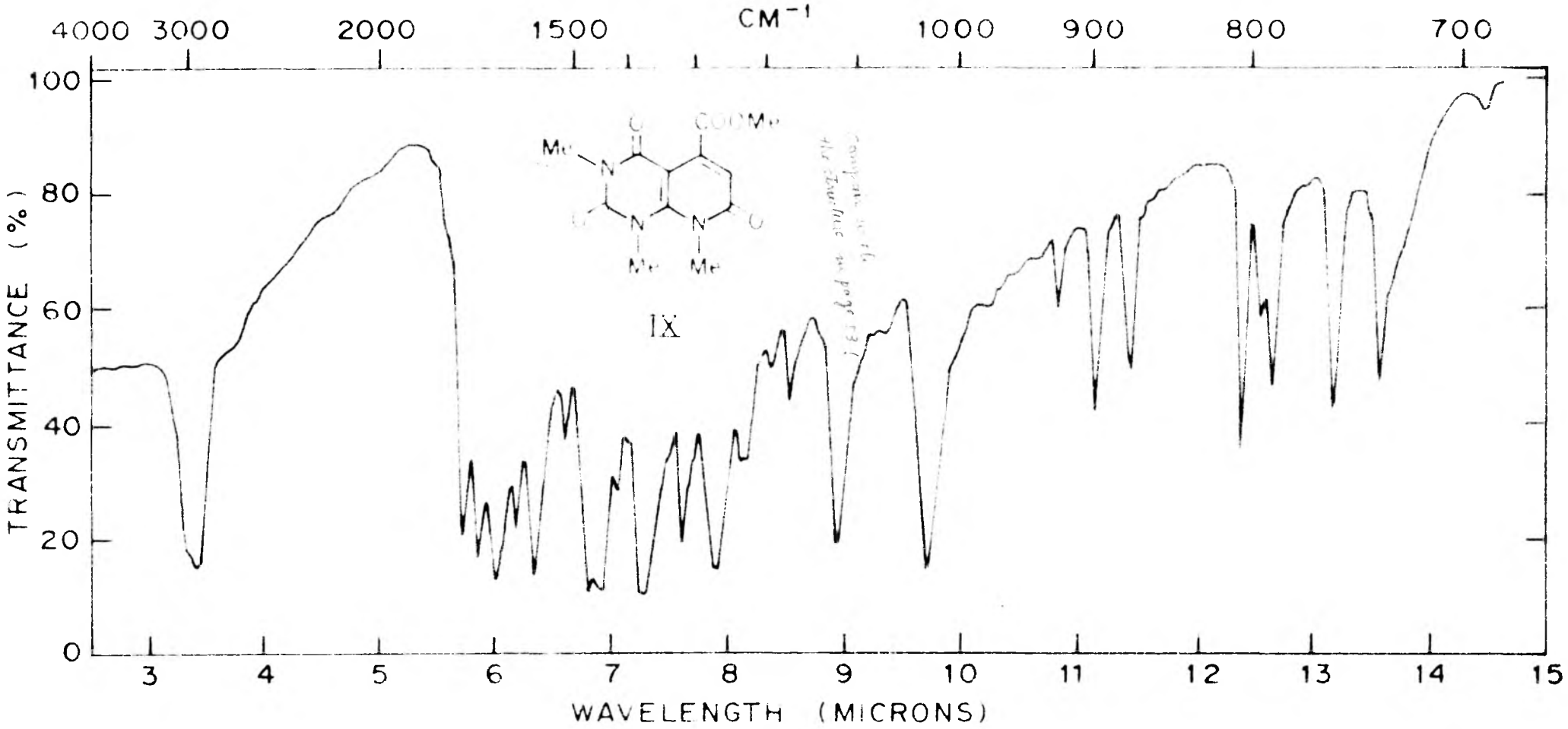
was kept at 5° with stirring for 18 hrs. Ether was evaporated and the residue was washed with sodium carbonate solution (25 ml, 5%) and filtered. The product was recrystallised from a mixture of chloroform and pet.ether (60-80°), m.p.212°, yield 0.07 g (60%).

Elemental analysis: Found: C, 51.25; H, 4.52; N, 15.30.
$C_{12}H_{13}N_3O_5$ requires C, 51.61; H, 4.69; N, 15.05%.

Mass spectrum M^+ 279.

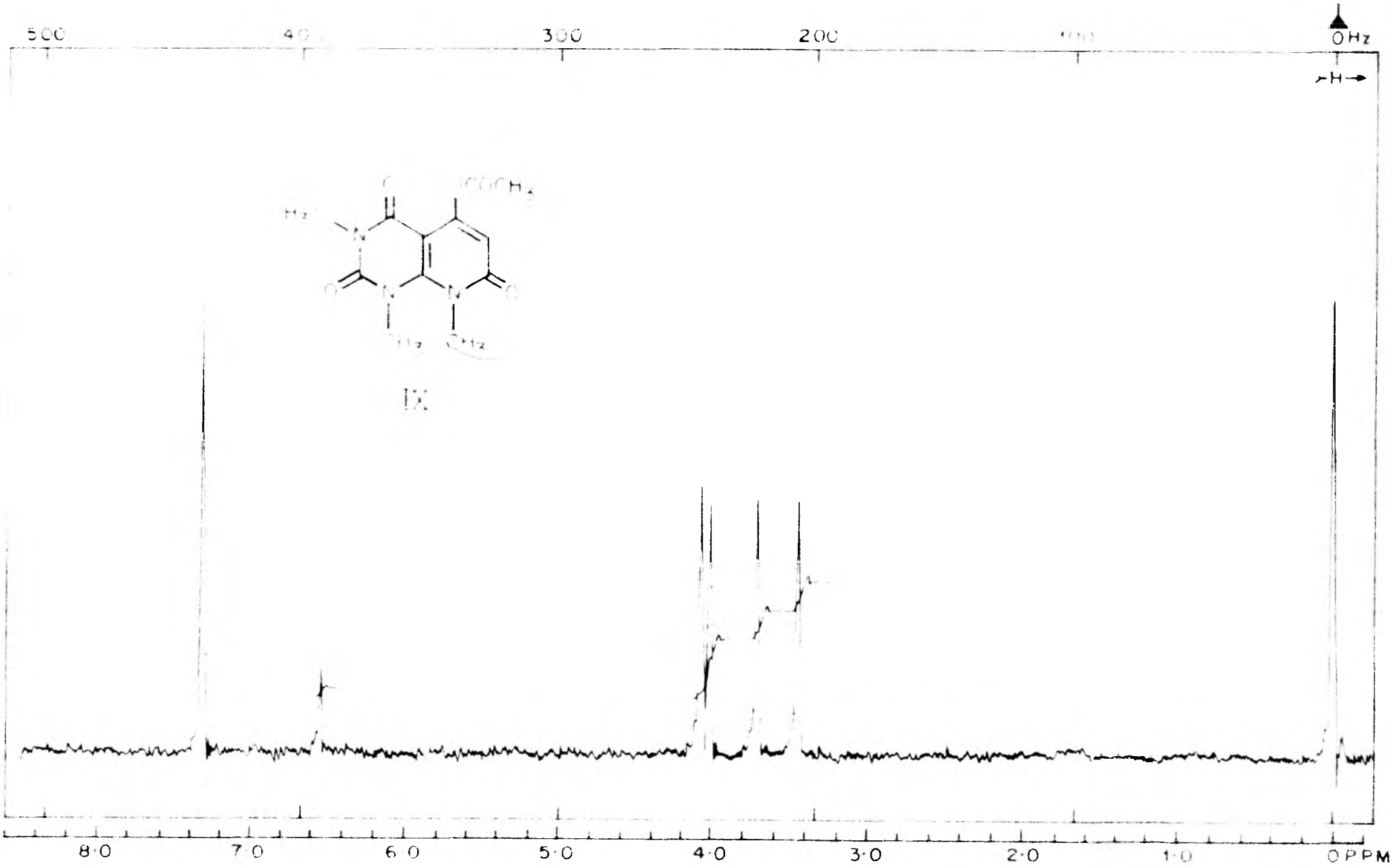
IR(Nujol): 1740, 1710 cm^{-1} (ester, amide C=O).

NMR($CDCl_3$): 3.43 (s, 3H, N-CH_3), 3.70 (s, 3H, N-CH_3), 4.00 (s, 3H, N-CH_3), 4.05 (s, 3H, $COOCH_3$), 6.53 (s, 1H, C_6-H).


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

IX

'R OF IX



IX

N.M.R. OF IX

SUMMARY

S U M M A R Y

Michael addition of 1,3-dimethyl-6-aminouracil (1) and benzalacetophenone in presence of piperidine gave 5,6-7-trisubstituted-pyrido[2,3-d]pyrimidine(II)which on refluxing with glacial acetic acid + I_2 was converted to 5,7-diphenylpyrido[2,3-d]pyrimidine 2:4-dione. Reaction of (1) and phenyl propenyl ketone or methyl vinyl ketone in presence of piperidine gave directly the aromatised pyrido[2,3-d] pyrimidine 2:4-diones (IV, V) in one step. Reaction of (1) with benzalacetone, however, gave pyrimido[4,5-b]quinoline derivatives (VI, VII). Condensation of (1) and dimethyl-acetylenedicarboxylate furnished a 7-oxo-pyrido[2,3-d] pyrimidine 2:4-dione(VIII) in a single step. Structural determination was based on IR, NMR and mass spectral analysis.

REFERENCES

REFERENCES

1. Armarego, W.L.F., Advan. Heterocyclic Chem., 1, 253-309 (1963).

2. Williamson, T.A., in "Heterocyclic compounds" (R.C. Elderfield, ed.) Vol. 5 .P. 324, Wiley, New York, 1957.

3. Klisiecki, L. and Sucharda, E. Roczniki, Chem. 3, 251 (1923).

4. Robins, R.K. and Hitchings, G.H., J.Am.Chem.Soc., 77, 2256 (1955).

5. V. Oakes, R. Pascoe and H.N. Rydon, J.Chem.Soc. p.1045 (1956).

6. Bhaduri, A.P. and Khanna, N.M., Indian J.Chem. 4, 447 (1966).

7. Wellcome Foundation, British Patent No.774, 094 and 774, 095 (1957); Chem.Abstr. 52, 2097 (1958).

8. Hitchings, G.H. and Robins, R.Ki U.S. Patent No.2,697,710 (1954); Chem. Abstr., 50, 1093 (1956).

9. Doronow, A, and Hahmann, Arch.Pharm. 290, 61 (1957).

10. Doronow, A. and Wille, D. Chem.Ber. 98, 1505 (1965).

11. Mulvey, D.M., Cottis, S.G. and Tieckelmann, H., J.org.Chem. 29, 2903 (1964).

12. Mulvey, D.M. Dessertation Abstr. 26, 5043 (1966).

13. Rhone,-Pouleux, S.A., Netherlands,Patent No.6,507,580 (1965); Chem.Abstr. 64, 126, 98 (1966).

14. Cottis, S.G. and Tiekelmann, H., J.org.Chem. 26, 79 (1961).

15. Cottis, S.G. Ph.D. thesis, University of Buffalo, New York (1962).

16. Taylor, E.C. and Borror, A.L., J.org.Chem., 26, 496(1961).

17. Vanderhorst, P.J. and Hamilton, C.S., J.Am.Chem.Soc. 75, 656 (1953).

18. Suter, H., Habichl, E. and Martin, H., Swiss Patent No.331, 989 (1958); Chem. Abstr. 53, 5292 (1959).

19. Albert, A. and Reich, F., J.Chem.Soc., p.1370 (1960).

20. Armarego, W.L.F., Proc.Chem.Soc., p.450 (1961).

21. Armarego, W.L.F., J.Chem.Soc., p.4094 (1962).

22. Gilbert, W.W., U.S. Pat. No. 2,680,741 (1954), Chem.Abstr., 49, 6322 (1955).

23. Mclean, A.C. and Spring, F.S., J.Chem.Soc., p.2582 (1949).

24. Jones, R.G., J.org.Chem., 25, 956 (1960).

25. DeGraw, J. and Goodman, L. Can.J.Chem., 41, 3137 (1963).

26. Lythgoe, B., Todd, A.R. and Topham, A., J.Chem.Soc. p. 316 (1944).

27. Robins, R.K. and Hitchings, G.H., J.Am.Chem.Soc., 80, 3449 (1958).

28. Bernetti, R., Manicini, F. and Price, C.C., J.org.Chem. 27, 2863 (1962).

29. Bernetti, R. Ph.D. Thesis, University of Pennsylvania, Philadelphia, Pennsylvania, 1959.

30. Hurbbert, B.S. and Valenti, B.F., J.Med.Chem., 11, 708 (1968).

31. Hitchings, G.H. and Hurbbert, B.S., U.S. Patent No.3, 288, 792 (1966); Chem.Abstr. 66, 6163 (1967).

32. Wellcome Foundation, Belgian Patent No.657,922 (1965), Chem.Abstr. 64, 15896 (1966).

33. Arnold, Z. and Sorm, F., Chem.Listy, 51, 1082 (1957).

34. Wellcome Foundation, British Patent No.774,095 (1957), Chem.Abstr. 52, 2097 (1958).

35. Hitchings, G.H. and Robins, R.K. U.S. Patent No.2,749, 344 (1956), Chem.Abstr. 51, 1304 (1957).

36. Hitchings, G.H. and Robins, R.K. U.S. Patent No.3,021,332 (1962) Chem.Abstr. 57 , 839 (1962).

37. Ridi, M. Ann.Chim.(Rome) 49,944 (1959).

38. Ridi, M. Ann.Chim.(Rome) 50,405 (1960).

39. Claisen, L. and Stylos, N. Ber.Deut.Chem.Ges. 21, 1144 (1888).

40. Ridi, M. Checchi, S. and Papini, P., Ann.Chim.(Rome) 45, 439 (1955).

41. Hulbert, B.S. Ledig, K.W., Stenbuck, P., Valenti, B.F. and Hitichings, G.H., J.Med.Chem., 11, 703 (1968).

42. Wellcome Foundation, British Patent No.913,710(1962), Chem.Abstr, 60, 1771 (1964).

43. Hitchings, G.H. and Ledig, K.W. U.S. Patent No.2,937,284 (1960); Chem.Abstr. 55, 25999 (1961).

44. Wellcome Foundation, Belgian Patent No.658,069 (1965); Chem.Abstr., 64, 5110 (1966).

45. Scarborough, H.C., J.org.Chem., 29, 219 (1964).

46. Ziegler, E. and Nolken, E., Monatsh. Chem. 92, 1184 (1961).

47. Scarborough, H.C., U.S.Patent No.3,139,432 (1964); Chem.Abstr., 61, 7024 (1964).

48. Ridi, M., Papini, P. and Checchi, S., Ann.Chim.(Rome) 46, 428 (1956).

49. Ridi, M., andChecchi, S., Ann.Chim.(Rome), 47, 728 (1957).

50. Fatutta, S. Gazz.Chim.Ital. 93, 576 (1963).

51. Pasedach, H. and Seefelder, M., German Patent No.1040,040 (1958); Chem.Abstr. 55, 6507 (1961).

52. Bredereck, H. Effenberger, F., Henseleit, E. and Schweizer, E.H., Chem.Ber., 96, 1868 (1963).

53. Dornow, A. and Hinz, E. Chem.Ber. 91, 1834 (1958).

54. Taylor, E.C. and Gracia, E., J.org.Chem., 29, 2116 (1964).

55. Blank, B. and Caldwell, W.T., J.org.Chem., 24, 1137 (1959).

56. Biggs, J. and Sykes, P., J.Chem.Soc., p.1849 (1954).

56a. Suranyi, L. and Schuler, L. Ger.Pat.No. 1,100,030 (1961), Chem.Abstr. 57, 2231 (1962).

57. Baker, B.R., and Almaula, P.I., J.Het.Chem., 1, 263 (1964).

58. Ogura, H. and Sakaguchi, M., Chem.Pharm.Bull., 21(9), 2014-2018 (1973).

59. Junek, H. and Wertilek, Ilse, Monatsh Chem., 101(4), 1130 (1970).

60. Weiss and Hauser, J.Am.Chem.Soc. 71, 2026 (1949).

61. Tamura, Yasumitsu, Sakaguchi, Toshinko, Kawasaki, Tomomi, Kita, Yasuyuki, Heterocycles, 3 (2), 183(6),(1975).

62. Bhacca, N.S. Williams, D.H., Applications of NMR Spectroscopy in organic chemistry, Edition 1964, p.45. (D.H. Williams, et al., J.Am.Chem.Soc. 85, 2810 (1963).

63. Williamson, K.L. and Johnson, W.S., J.Am.Chem.Soc. 83, 4623 (1961).

CHAPTER II

SYNTHESIS OF PYRANO[2,3-d]PYRIMIDINE-2,4-DIONES

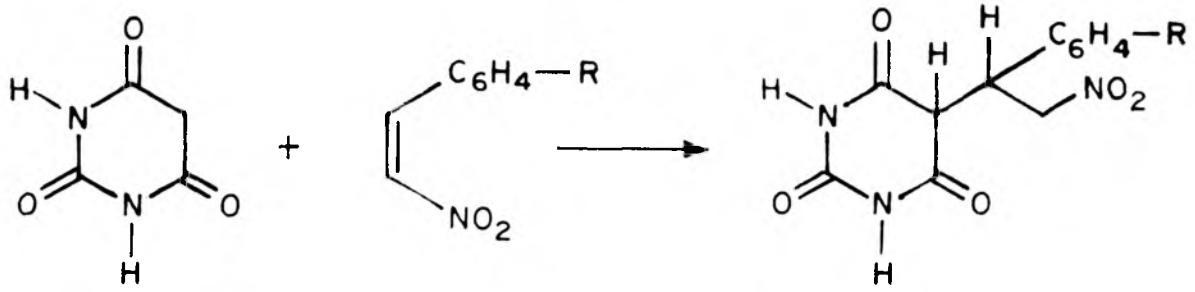
LITERATURE SURVEY

Pyrano-[2,3-d]pyrimidines

Literature survey

Barbituric acid was reacted with a series of substituted β-nitrostyrenes in the absence of catalysts to give the 5-(2-nitro-1-arylethyl)-barbiturates[1]. In the course of the study it was confirmed that where the barbituric acid adds to conjugated olefinic systems, the addition occurs quite readily in the absence of catalysts, while competing side reactions are minimised. When dissolved in minimal amounts of aqueous dioxane, aqueous methanol or aqueous acetic acid barbituric acid reacted smoothly at room temperature with β-nitrostyrene to give a 1:1 adduct (5-(2-nitro-1-phenyl ethyl)-barbituric acid in good yields. Analogous 1:1 adducts were formed with m, p-dinitro, p-chloro-β-nitro, 3,4-methylene dioxy-β-nitro, P-methoxy-β-nitro and P-dimethylamino-β-nitro-styrenes (~~Table~~ Scheme I, III). The structure of these compounds was established by oxidative degradation to dialuric acid and by conversion to the corresponding arylsuccinic acids on refluxing with concentrated hydrochloric acid. Attempts to effect similar addition reactions with cinnamic acid, acrylic acid, methylacrylate and with diethyl benzylmalonate under a variety of conditions were unsuccessful as were attempts to join 5-nitrobarbituric acid or indanedione 1,3-with the nitrostyrenes.

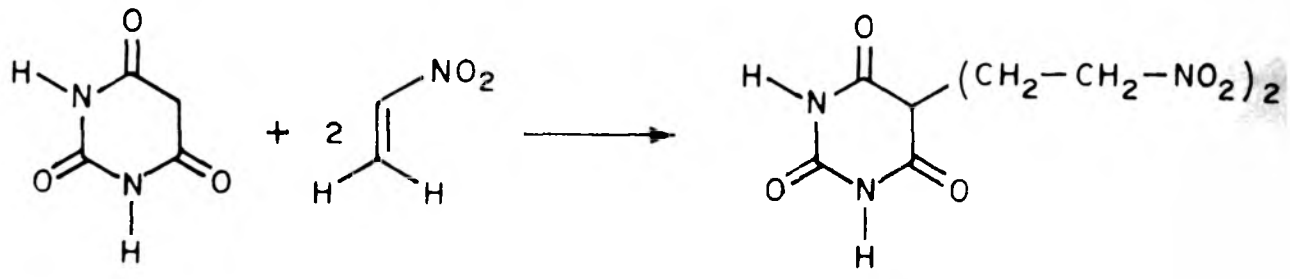
Scheme 1.



I II III

II , III R = H; P−$(CH_3)_2N$; P−CH_3O ; P−Cl;
3,4−CH_2O_2; m−NO_2

Scheme 2.

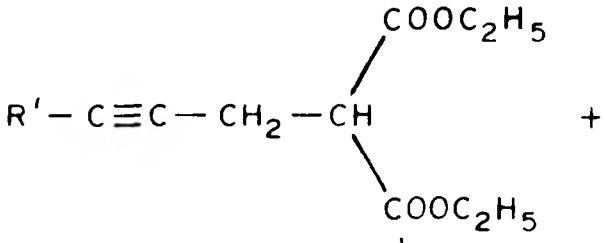


IV

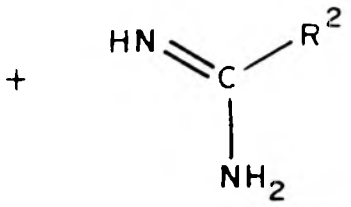
Konikova, V.A. and Perekaline V.V.[2] reported Michael addition of barbituric acid to nitroethylene in anhydrous methanol and triethylamine as a catalyst. They isolated a 5-substituted diadduct (IV, ~~table 1~~). Schulte et al.[3] have condensed propargyl or phenyl proporgyl acetoacetic esters and acetamidine or benzamidine to obtain 5-substituted-pyrimidone derivatives (VIIa-d). These pyrimidone derivatives when treated with zinc carbonate gave Furano[2,3-d]pyrimidines (VIII) and an unstable pyrano[2,3-d]pyrimidines (IX). In a hihgly acidic medium of conc. H_2SO_4, H_3PO_4, HBr/Ac_2O, the pyrimidones (VIIa-d) added elements of water to triple bond present in the side chain resulting in propiophenone derivatives (X), and the pyrano[2,3-d]pyrimidines were not obtained under these conditions. However when 5-alkinyl substituted barbituric acids (XIa-d) were treated with conc. H_2SO_4, H_3PO_4 the expected Furano[2,3-d]pyrimidines and pyrano[2,3-d] pyrimidines were obtained.

Pyrano[2,3-d]pyrimidine derivatives were also prepared by the condensation of malonic or methyl malonic acid (XV) with 1,3-dimethylbarbituric acid (XIV) in acetic anhydride[4] (scheme 5). A related 1,3-diphenyl-2-thio-pyrano[2,3-d] pyrimidine[5] has been prepared by the condensation of malonyl-dichloride with 1,3-diphenyl-2-thio-barbituric acid. Earlier workers[5] postulated the existence of a compound (XVIa) in rationalizing the isolation of (XVIIa) accompanying the synthesis of 1,3-dimethyl-barbituric acid. It was found that the lactone function of pyrano[2,3-d]pyrimidine (XVIa)

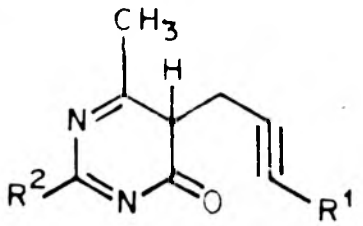
Scheme 3.



V



VI



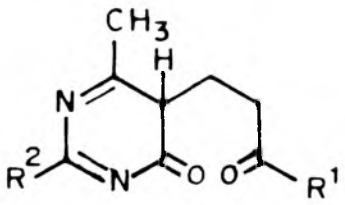
VII a – d

VII	R^1	R^2
a	H	CH_3
b	H	C_6H_5
c	C_6H_5	CH_3
d	C_6H_5	C_6H_5

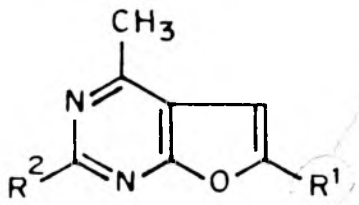
Cap.

$znCO_3$ $R^1 = H$, $R^2 = C_6H_5$

$+ H_2O$ $H^{\oplus}$

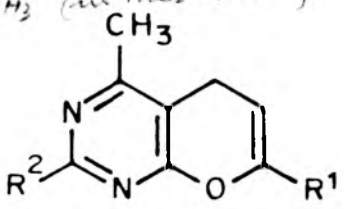


X



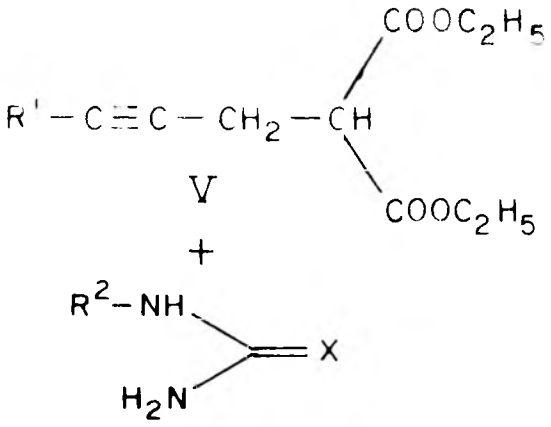
VIII

not R_1 ?
$R_1 = CH_3$ (in this case)

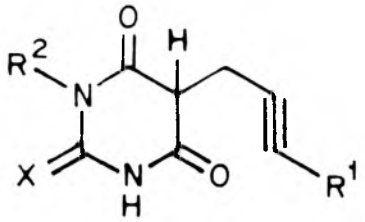


IX

Scheme 4

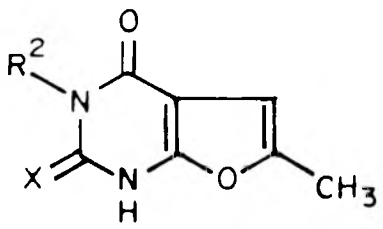


V

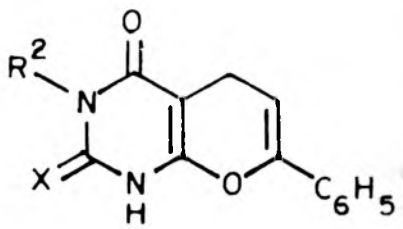


XI a – d

XI	R^1	R^2	X
a	H	H	O
b	H	CH_3	O
c	H	H	S
d	C_6H_5	H	O



XII



XIII

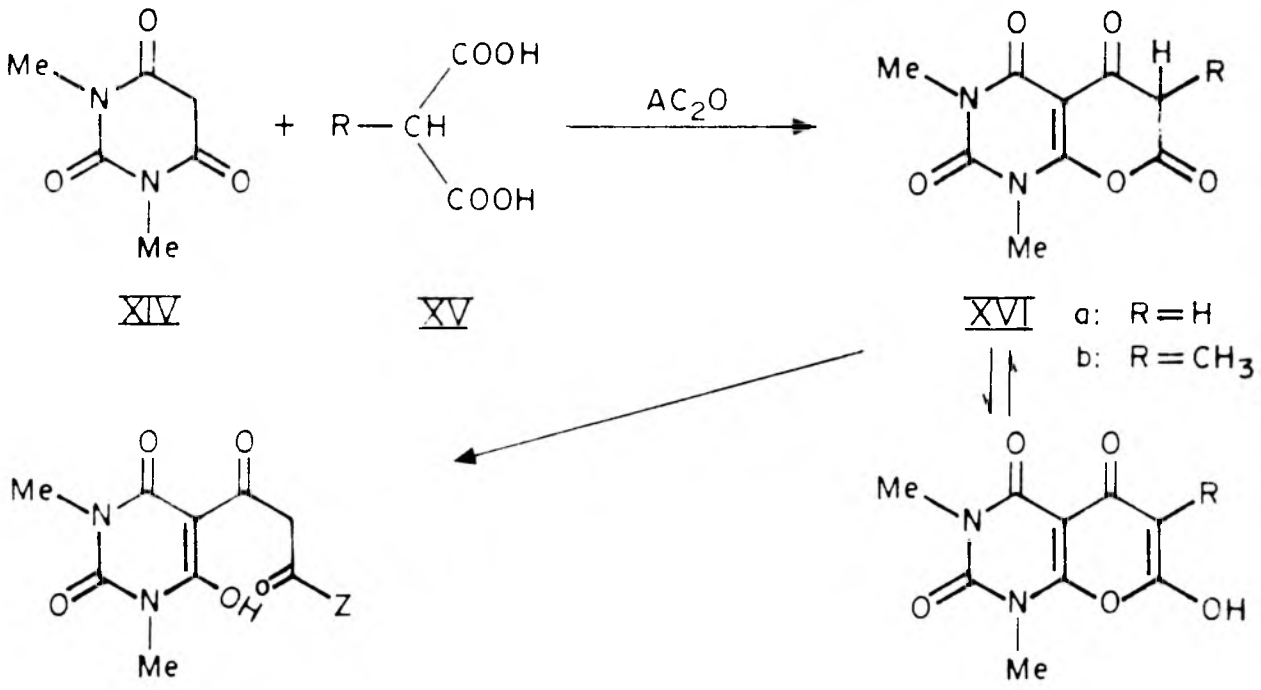
was indeed chemically reactive although both (XVIa, b) were hydrolytically stable during isolation.

The pyrano[2,3-d]pyrimidine (XVIa) reacted readily with ethanol to form ester (XVIIa) and with isopropyl alcohol to form the isopropyl ester (XVIIb). The isopropyl ester (XVIIb) was also obtained when pyrano pyrimidine (XVIa) was recrystallized from isopropyl acetate. The reaction of the pyrano[2,3-d] pyrimidine (XVIa) with aqueous ammonium hydroxide furnished an amide (XVIIc).

In attempts to obtain intramolecular N-alkylated bicyclo-compounds from 5-haloalkyl barbituric acids, only O-alkylated compounds[6] were formed. The resulting pyrano pyrimidines[6] (scheme 6) could be opened with alcohols to give the corresponding ether (XX) in the side chain of the barbituric acid. With water a side-chain alcohol (XXI) was also formed.

Pyrano[2,3-d]pyrimidines carrying substituents in 5 and 7 positions were synthesised by a general reaction of barbituric acid, aldehydes and phenylacetylene in acetic anhydride[7]. Acetaldehyde, formaldehyde and various other aromatic aldehydes having groups with negative Hammet-constant effect were found to react readily with barbituric acid and with N-alkyl or aryl barbituric acids. The pyrano[2,3-d]pyrimidines reported by the authors are given in table 1. The structure of these compounds was established by means of their analytical and spectral data. Ammonolysis of some of the derivatives gave enough evidence for dihydropyrano[2,3-d]pyrimidine ring carrying substituents at 5 and 7 positions.

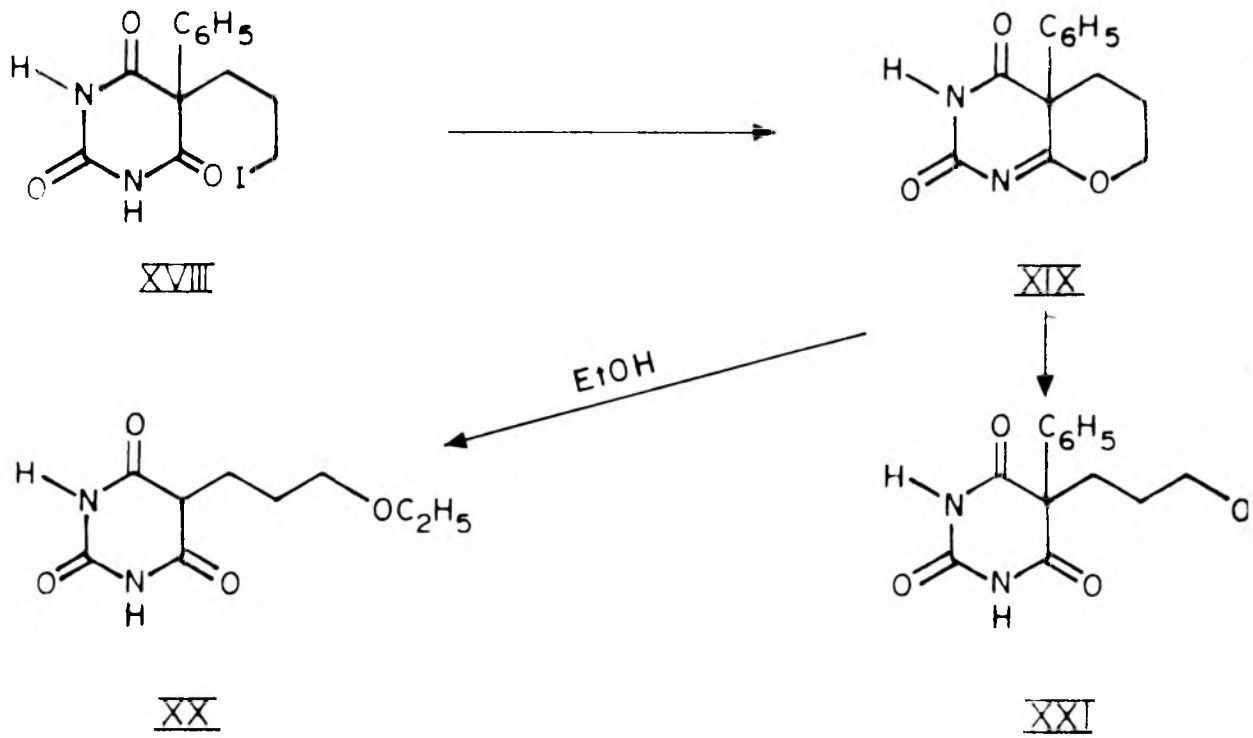
Scheme 5.



XIV XV XVI a: R=H b: R=CH3

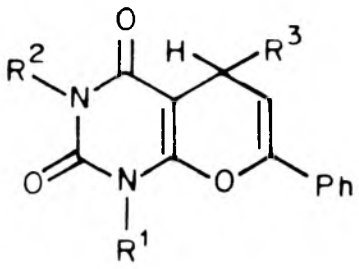
XVII a: Z OC_2H_5
b: Z $OHC-(CH_3)_2$
c: Z NH_2

Scheme 6.



XVIII XIX XX XXI

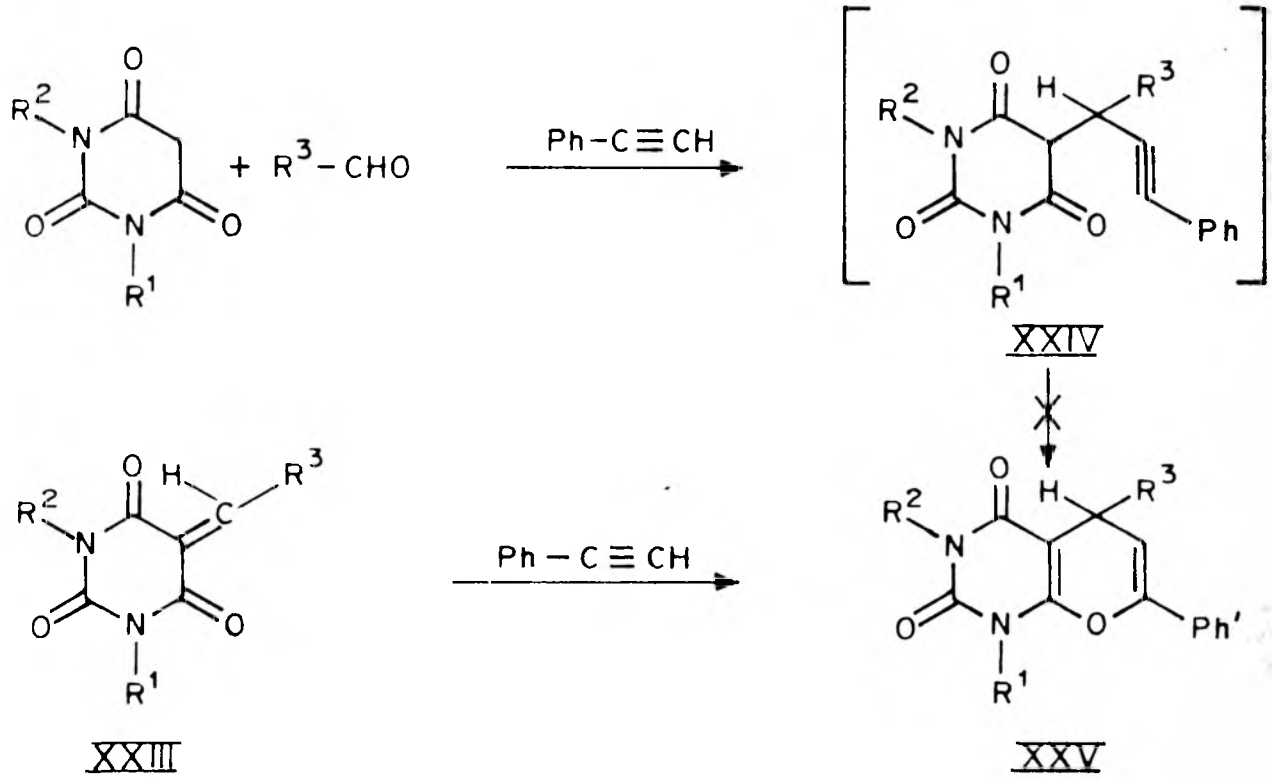
Table 1.



XXII a–p

XXII	R^1	R^2	R^3
a	H	H	H
b	H	CH_3	H
c	CH_3	CH_3	H
d	H	H	CH_3
e	H	H	C_6H_5
f	H	H	p–NO_2–C_6H_4
g	H	H	m–NO_2–C_6H_4
h	H	H	p–Cl–C_6H_4
j	H	H	m–Cl–C_6H_4
k	H	H	O–Cl–C_6H_4
l	C_6H_5	C_6H_5	H
m	H	H	P,CH_3–C(=O)–O–C_6H_4
n	H	H	m-CH_3O–C_6H_4
o	H	H	O–HO–C_6H_4
p	H	P–NO_2–C_6H_4	H
q	CH_3	P,NO_2–C_6H_4	H

Scheme 7.



XXIV

XXIII

XXV

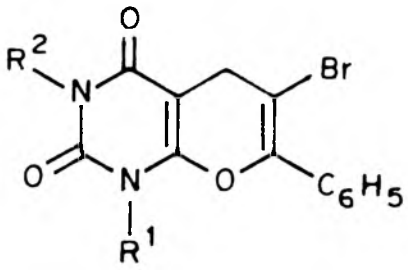
Ammonolysis of XXII-P at 200° under pressure gave 2,4-dioxo-7-phenyl-1,2,3,4-tetrahydro-pyrido[2,3-d]pyrimidine which was reported earlier.

A mechanism was proposed by the authors to explain the formation of pyrano[2,3-d]pyrimidine ring system. Obviously barbituric acid reacted first with aldehyde to form alkylidene or arylidine barbituric acid (XXIII-Scheme 7) and then 1:4-addition of phenylacetylene to α,β-unsaturated system to give the desired pyran ring system. The other mechanism, ring closure of 5-phenyl alkynylbarbituric acid (intermediate (XXIV) was ruled out experimentally by an attempt to cyclise 5-(3-phenyl propyn-(2)-yl) barbituric acid to (XXIIIa), which was unsuccessful.

The condensation of N-alkyl or aryl barbituric acid, formaldehyde and 1-bromo-2-phenylacetylene in acetic anhydride gave 6-bromo-7-phenyl-2,4-dioxo-1,2,3,4-tetrahydropyrano[2,3-d] pyrimidines (XXVIa-g). Ammonolysis of XXVIc at 200-220°C gave 6-amino-7-phenylpyrido[2,3-d]pyrimidine and 6-OH-7-phenyl pyrido[2,3-d]pyrimidine, which established the presence of a bromine at position C_6 of the pyrano[2,3-d]pyrimidine ring system.

1:4 Addition of styrene, instead of phenylacetylene, to the alkylidine or arylidine intermediate (XXIII) formed in the reaction furnished completely saturated pyrano[2,3-d] pyrimidines (Table XXVIIa-g). The NMR spectrum showed signals 5.5 - 4.75 (δ ppm) as double doublets or a multiplet. Such a low field proton was assigned to the H at C-7 position of pyrano [2,3-d]pyrimidine which is in the vicinity of oxygen atom and a phenyl ring.

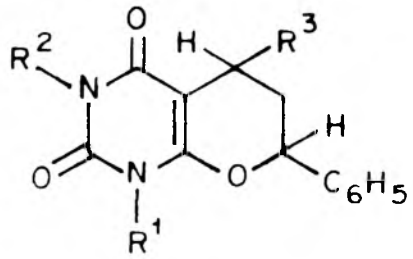
Table 2.



XXVI a-d

XXVI	R^1	R^2
a	H	H
b	H	CH_3
c	CH_3	CH_3
d	H	$P-NO_2-C_6H_4$

Table 3.



XXVII a-g

XXVII	R^1	R^2	R^3
a	H	H	H
b	CH_3	CH_3	H
c	H	H	C_2H_5
d	H	H	$P-NO_2-C_6H_4$
e	H	H	$P-Cl-C_6H_4$
f	H	H	C_6H_5
g	H	H	$m-CH_3O-C_6H_4$

DISCUSSION OF PRESENT WORK

Synthesis of Pyrano[2,3-d]pyrimidines[16]

Discussion of Present Work

Many alkyl and arylbarbiturates are used in medicine as sedatives, analgesics and as antibacterial agents. Several pyrano[2,3-d]pyrimidine derivatives have been prepared and tested for their pharmacological properties[8]. These compounds, like xanthines and purine bases, contain a basic pyrimidine 2:4-dione ring in their structures. The importance of purine bases and analogous compounds in the biological and pharmaceutical fields is well-known.

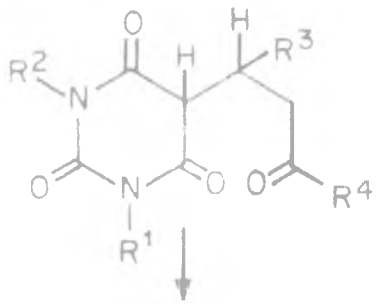
In search of new compounds in this series, a new two steps synthesis of pyrano[2,3-d]pyrimidines was carried out. Alkylations[9], nitration[10], nitrosation[11] reactions are known in the chemistry of barbituric acids. Electrophilic substitutions take place invariably at C-5 position of the pyrimidone ring system. However, there are no references in literature regarding Michael addition reactions of barbituric acid with α,β-unsaturated ketones or esters. Since such Michael adducts with a carbonyl function could be useful intermediates for the synthesis of 5,7-disubstituted pyrano[2,3-d]pyrimidines, a detailed study was undertaken for the synthesis of these adducts and their subsequent cyclisation.

An equimolar solution of 1,3-dimethylbarbituric acid (Ib, scheme 1), benzalacetophenone (IIa), and triethylamine as catalyst in refluxing methanol gave the adduct (IIIb) in

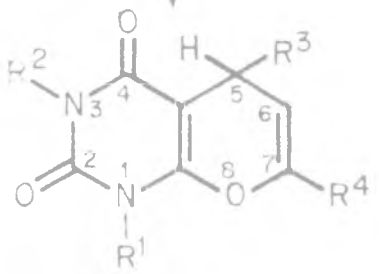
SCHEME

I – a. $R^1, R^2 = H$
b. $R^1, R^2 = CH_3$

II – a. $R^3, R^4 = C_6H_5$
b. $R^3 = C_6H_5; R^4 = CH_3$



III – a. $R^1, R^2 = H$; $R^3, R^4 = C_6H_5$
b. $R^1, R^2 = CH_3$; $R^3, R^4 = C_6H_5$
c. $R^1, R^2 = CH_3$; $R^3 = C_6H_5$, $R^4 = CH_3$



IV – a. $R^1, R^2 = H$, $R^3, R^4 = C_6H_5$
b. $R^1, R^2 = CH_3$; $R^3, R^4 = C_6H_5$
c. $R^1, R^2 = CH_3$; $R^3 = C_6H_5$; $R^4 = CH_3$

good yield. The adduct gave molecular weight 364 and its IR spectrum showed absorption at 1695-1740$^{cm^{-1}}$ corresponding to the amide and benzoylcarbonyl bands. The n.m.r. spectrum of this compound gave signals for two N-CH_3's as two singlets of three proton intensity each at 3.06. A benzilic proton at 3.56 and methylene protons adjacent to a carbonyl at 3.96 indicated a two carbon side-chain. The low field broad singlet at 4.23 is assigned to the proton at C-5 of pyrimidone ring. Since it is expected to be deshielded by carbonyls at C-4 and C-6 of the ring. The aromatic proton resonances indicated the presence of a phenyl group at 7.13 and the two ortho protons of benzoyl group at 7.86 and the two meta and one para at 7.36 region. It is clear from the above spectral data that the original 2,4,6-trioxoform structure of barbituric acid is undisturbed after the reaction and a 2-benzoyl-1-phenylethane group is substituted for a hydrogen at C-5 of pyrimidone ring. The appearance of cations at m/e 209, 105, 77 from the molecular ion in the mass spectrum of this compound correspond to 2-benzoyl-1-phenylethane, a benzoyl and phenyl radical ions respectively also confirm the structure 1,3-dimethyl-5(2-benzoyl-1-phenylethane) barbituric acid (IIIb).

The adduct (IIIb) when refluxed with P_2O_5 in glacial acetic acid solution cyclised to the expected 5,7-diphenyl-pyrano[2,3-d]pyrimidine (IVb). The structure IVb proposed for it was confirmed by its molecular weight 346 and also by its n.m.r. which showed the two adjacent hydrogens in the pyran ring at 4.65 (d, J = 5 Hz CH-) and at 5.78 (d, J = 5 Hz) olefinic -H).

Condensation of barbituric acid (Ia) with benzal-acetophenone (IIa) in the presence of one mole equivalent of triethylamine gave the adduct IIIa. Its IR spectrum showed amide NH bands at 3100-3300cm^{-1} and between 1695-1750cm^{-1} amide and aromatic carbonyl bands. The n.m.r. spectrum gave characteristic signals at 3.71 (b.m. 1H, benzylic CH), 4.00 (b.m., 2H, $-CH_2-\overset{O}{\overset{\|}{C}}-$), 4.36 (b,s,H, ring C_5-H) besides the low field aromatic protons and a two proton signal exchangeable with D_2O belonging to NH's of the pyrimidone ring. The mass spectrum gave molecular ion at M^+ 336. The fragmentation pattern was similar to that of IIIb. This adduct on treatment with P_2O_5 in glacial acetic acid gave the cyclised compound 2,4-Dioxo-5,7-diphenyl-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine (IVa) which was earlier prepared by Schulte et al.[7] from barbituric acid, benzaldehyde and phenylacetylene in acetic anhydride. The compound IVa agreed with melting point and other analyses reported by Schulte et al.

So far the synthesis of pyrano[2,3-d]pyrimidines involved barbituric acid, its N-methyl derivative and an α,β-unsaturated ketone having same R^3 and R^4 groups. If one started with α,β-unsaturated ketones carrying different R^3 and R^4 groups, compounds with a variety of substituents at C-5 and C-7 positions of pyran ring could be synthesised.

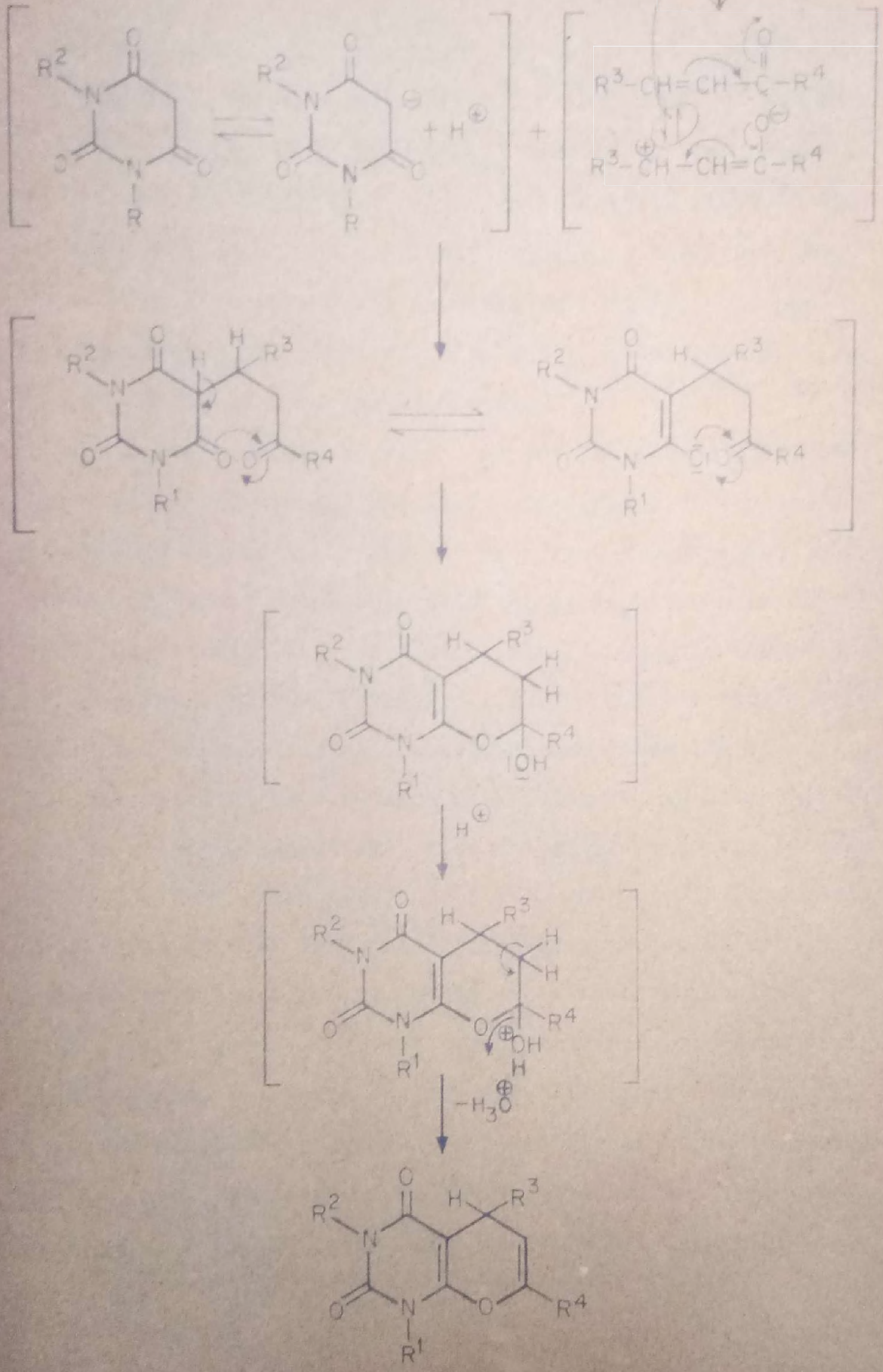
1,3-Dimethylbarbituric acid (Ib) and benzalacetone (IIb) were condensed in presence of triethylamine as catalyst in methanol solution to give the adduct (IIIc). Its IR spectrum showed

the carbonyl bands between 1695-1750 cm^{-1}. The n.m.r. of this adduct gave signals at 2.20 (s, 3H, $-\overset{O}{\overset{\|}{C}}-CH_3$), 2.90 (s, 3H, $N-CH_3$), 3.08 (s, 3H, $-NCH_3$), 3.46 (q, 1H, benzylic H), 3.80 (t, 2H, $-CH_2-\overset{O}{\overset{\|}{C}}-$), 4.05 (t, 1H, ring C-5, H), 7.06 (m.c. 5H, phenyl-H's). These spectral characteristics and the molecular weight obtained by mass spectrum M^+ 302 justify the structure (IIIc); cyclisation of the adduct (IIIc) in P_2O_5 and glacial acetic acid furnished the pyrano[2,3-d]pyrimidine (IVc). It's structure was confirmed from its n.m.r. which gave C_7-methyl signal at 1.91 and the two adjacent hydrogens in the pyran ring at 4.30 (d, 1H, J = 4 Hz, C_5-H) and 4.90 (d, 1H, J = 4 Hz, olefinic H) respectively.

It was of interest to look into the mechanistic aspects of the reactions involved in the synthesis. Barbituric acid and its N-alkyl derivatives show a two proton signal in n.m.r. at δ 3.66 which is readily exchanged with D_2O; a general characteristic feature of all carbon-acids[12]. The CH-acids are known to undergo Michael addition reactions. In the presence of a base the protons at C-5 position of pyrimidone ring could be exchanged and the anion, generated (scheme 2), forms a bond with electrophillic β-carbon of the α,β-unsaturated ketone to give the enol (scheme 2). The enol picks up a proton either from the solvent or from the protonated base present in the reaction medium. The reaction in total is a 1:4 addition of barbituric acid to the α,β-unsaturated ketone resulting in the Michael adducts. The second step, cyclisation

Be careful ! This is not tautomerism

SCHEME-2

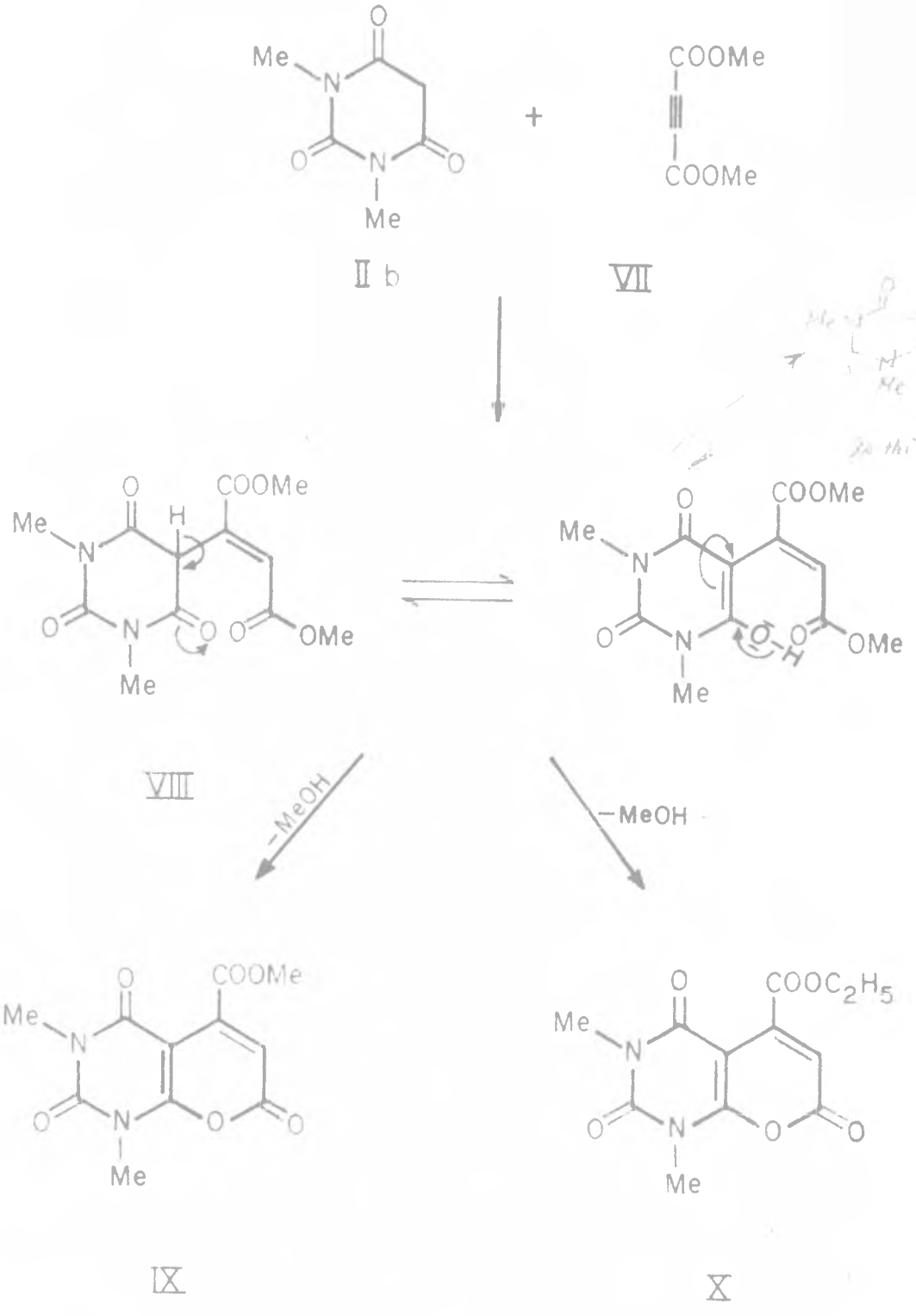


V a-c

of michael adducts in phosphorus pentoxide and glacial acetic acid medium involves a net effect of dehydration of 1:5 diketones suitably positioned in the michael adducts to form a pyran ring. Phosphours pentoxide in glacial acetic acid is known to form polyphosphoric acid or acetates. These polyacetates or acids with structure[13] are expected to form enol phosphate esters with enolisable diketones, which act as good leaving groups during cyclisation reactions.

Acetylene dicarboxylic acid and its esters have been used successfully in Michael and Diels-Alder reactions. In an attempt to extend the synthesis of pyrano[2,3-d]pyrimidines having different substituents in the pyran ring, michael addition reaction was carried out with acetylenic ester instead of an α,β-unsaturated ketone. 1,3-Dimethyl barbituric acid and dimethylacetylene dicarboxylate when condensed in presence of triethylamine in refluxing methanol gave the adduct (VIII). Its IR spectrum showed the amide and ester carbonyls between 1675-1745 cm^{-1}. The n.m.r. exhibited characteristic signals for C-5 proton at 6.21 as a broad hump which exchanged with D_2O and the vinylic proton in the side chain showed a signal at 7.16 as a singlet. However, when the n.m.r. spectrum of the same compound was taken in pyridine as solvent a broad singlet appeared at 12.51. Such a low field signal could be assigned to C-4 or C-6 enol proton of the pyrimidone. It appears from the n.m.r. data that the adduct exhibits keto-enol tautomerism;

SCHEME – 3


Me
N
O
O
O
Me
+
COOMe
COOMe
II b
VII
COOMe
Me
N
O
H
O
O
OMe
Me
VIII
COOMe
Me
N
O
O
O
H
OMe
Me
–MeOH
–MeOH
COOMe
Me
N
O
O
O
O
Me
IX
COOC2H5
Me
N
O
O
O
O
Me
X

the enolic form predominates in the spectra. The addition of various nucleophiles to acetylene dicarboxylic esters are known[14] to give products arising from both cis and trans-addition. The cis addition products resulting in maleate esters show the vinylic proton in n.m.r. spectra at a higher field (5.3). The trans-addition products exhibit the olefinic proton more deshielded at 6.6 - 7.5. Addition reaction conducted in methanol as solvent and base as catalyst promote the formation of trans-product[15]. Based on the above data and its facile cyclisation to 5-carbomethoxy-7-oxo-pyrano[2,3-d] pyrimidine (IX) by heating at 170°C the adduct was assigned the fumrate geometry. Treatment of the adduct (VIII) with BF_3-etherate also gave a cyclised pyrano[2,3-d]pyrimidine (X) with the ester group exchanged from methyl to ethyl ester, which was confirmed by n.m.r. spectrum.

Pyrano[2,3-d]pyrimidines

Experimental

All melting points are uncorrected. IR spectra were taken in nujol on Perkin-Elmer infracord model 137-B and the values are expressed in reciprocal centimeters. NMR spectra were recorded on A-60 or T-60 instrument with TMS as internal standard and chemical shifts are expressed in δ (ppm) and coupling constants J in Hz. The abreviations while mentioning chemical shifts such as b.s. = broad singlet, b.m.c. broad multiplet centre, m.c.: multiplet centre are used for convenience. Mass spectra were recorded on CEC-21-110B double focussing instrument with direct inlet system.

5-(2-Benzoyl-1-phenylethane)barbituric acid (IIIa)

To a solution of barbituric acid (Ia, 5.1 g, 0.04 mol), benzalacetophenone (IIa, 8.3 g, 0.04 mol), in methanol (100 ml), triethylamine (4.5 ml) was added and refluxed at 80-85°C for 3 hrs. The reaction mixture was cooled and neutralised with conc. HCl (30 ml), at 10°C. The resulting solution was concentrated by distillation under water suction upto one third volume. The residual liquid was diluted with 100 ml water and cooled in ice. The solid separated was filtered and recrystallised from rect. spirit. Yield 9.2 g (68.5%), m.p. 178°C.

Elemental analysis: Found: C, 68.20; H, 4.92; N, 8.70.
$C_{19}H_{16}N_2O_4$ requires C, 67.85, H, 4.80;
N, 8.33%.

IR^{nujol}_{max} 3100-3200 (NH's), 2900 (CH-stretch)
1745-1695 cm^{-1} (amide, aromatic carbonyls).

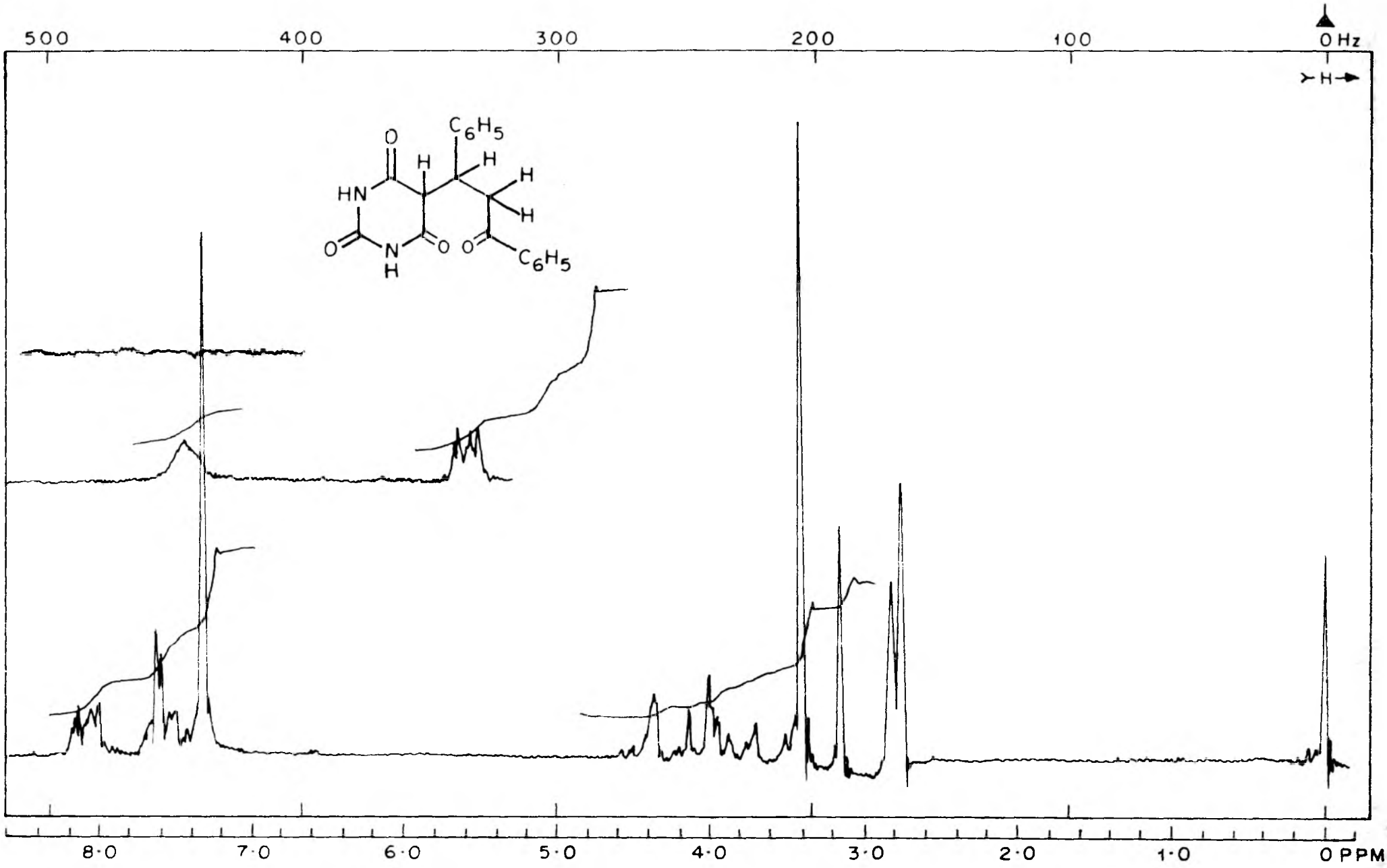
NMR (acetone): 3.71 (b.m.c. 1H, C-H), 4.00 (b.m.c.
2H, $-CH_2-\overset{O}{\overset{\|}{C}}-$), 4.36 (b.s. 1H, C_5-H),
7.33 (b.s. 5H, Arom), 7.60 (b.m.c.
3H, arom), 8.10 (b.m.c. 2H, arom), 10.03
(b.s. 2H, 2NH's exchanged with D_2O).

Mass spectrum: m/e(%): 336(66.7), 231(83), 215(79.5),
209(71), 208(100), 207(94), 196(55.6),
191(60), 189(58), 179(88), 165(87), 152(72),
145(72), 105(97), 89(68), 77(58), 51(56).

1,3-Dimethyl-5-(2-benzoyl-1-phenylethane)barbituric acid (IIIb)

A solution of 1,3-dimethyl barbituric acid (Ib, 5 g 0.032 mol), benzalacetophenone (IIb, 7 g, 0.032 mol), triethylamine (0.3 ml) and methanol (50 ml) was refluxed at 80-85° for 4 hrs. The product obtained on cooling the reaction mixture was filtered and was recrystalised from methanol. Yield 8.9 g (76%), m.p. 146-147°C.

Elemental analysis: Found: C, 69.52; H, 5.80; N, 7.83.
$C_{21}H_{20}N_2O_4$ requires C, 69.21; H, 5.53;
N, 7.69%).



N.M.R. SPECTRUM OF 5(2-BENZOYL-1-PHENYLETHANE) BARBITURIC ACID (IIIa)

IR $\overset{\text{nujol}}{\text{max}}$ 2900 (CH stretch), 1740-1695 cm^{-1}
Amide and aromatic carbonyls.

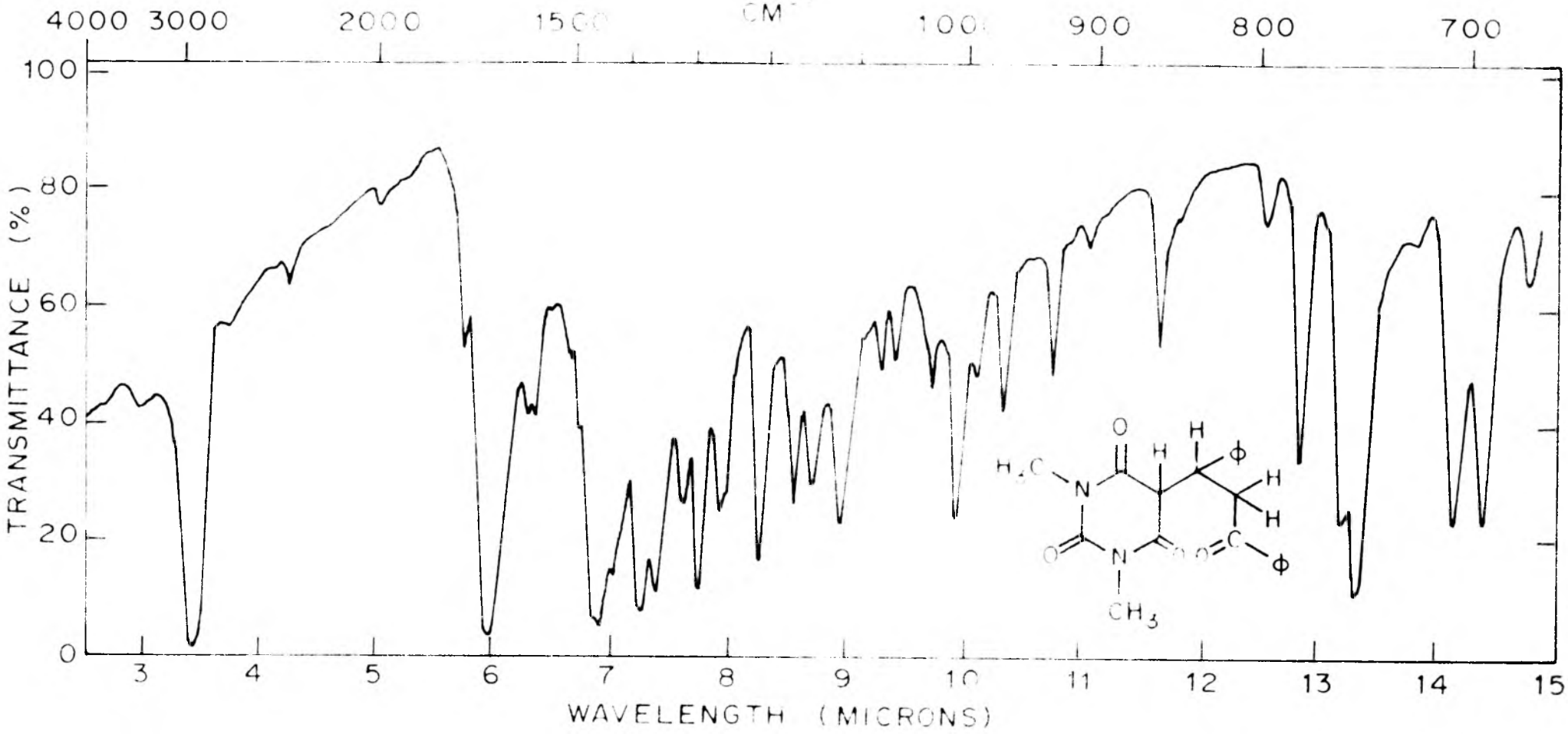
NMR($CDCl_3$) 3.06 (d, 6H, 2-NCH_3's), 3.56 (b.d.H, C-H), 3.96 (b.m.c. 2H, $-CH_2-\overset{O}{\overset{\|}{C}}$), 4.23 (b.s. 1H, $-C_5-H$), 7.13 (b.s., 5H arom-HS), 7.36 (b,d,3H, arom-H), 7.86 (b.m.c. 2H-arom-HS).

Mass spectrum: m/e(%) 364(85), 346(46), 269(17), 259(100), 245(77), 209(82), 208(93), 207(89), 179(56), 156(74), 145(47), 131(66), 115(43), 105(78), 77(59), 51(36), 43(31), 43(32), 28(25).

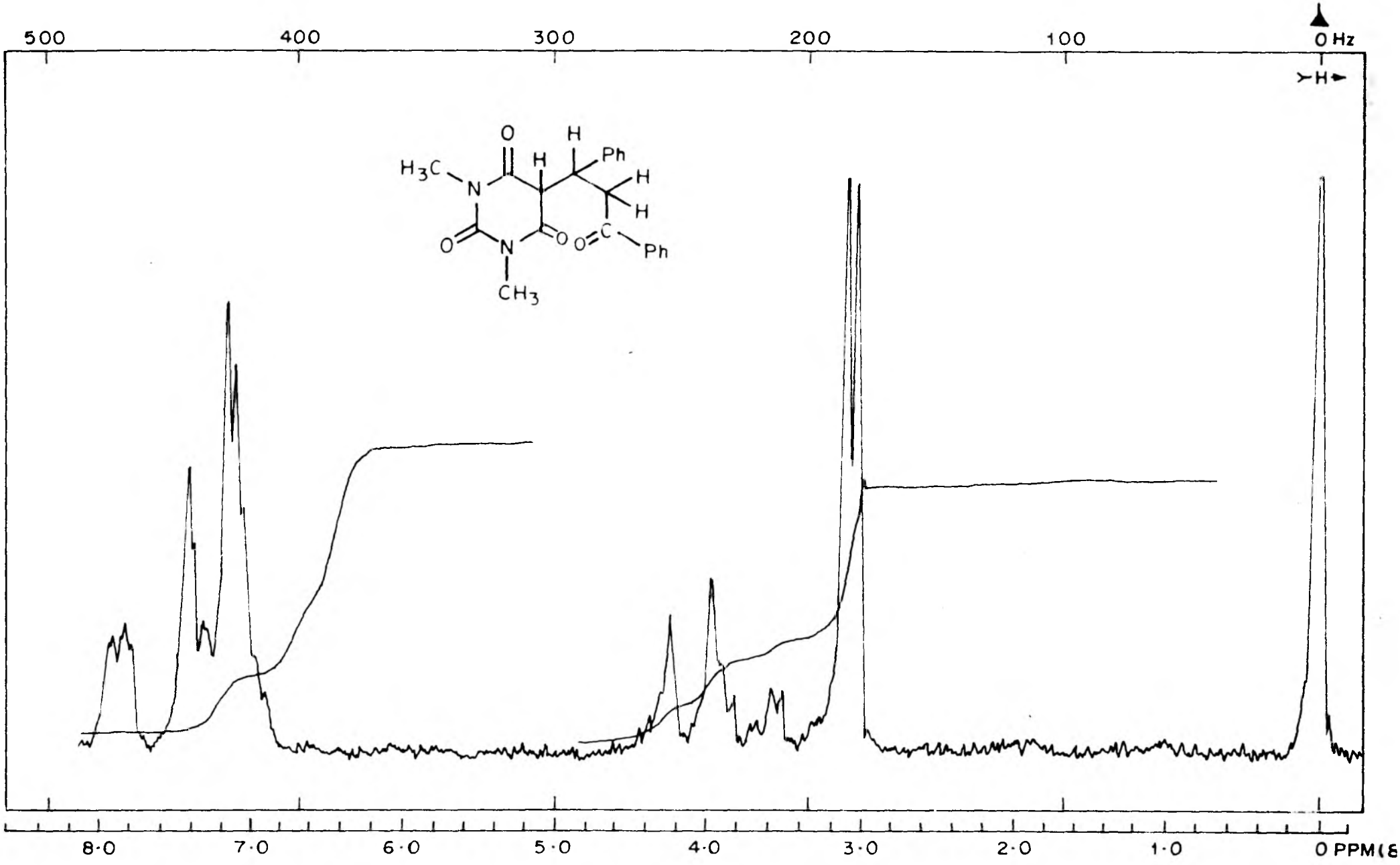
5,7-Diphenyl-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine (IVa)

The adduct (IIIa, 1.3 g, 0.007 mol) was treated with phosphorus pentoxide (1 g, 0.07 mol) in glacial acetic acid (6 ml) and the solution was refluxed over an oil bath held at 130-135° for an hour. The reaction mixture after cooling to room temperature was stirred with ice cold water. The dark brownish product obtained was filtered, washed with cold water (10 ml). Recrystallised twice with rectified spirit and with a little amount of animal charcoal to furnish colourless crystals. Yield 0.63 g (51%), m.p.275-276°C.

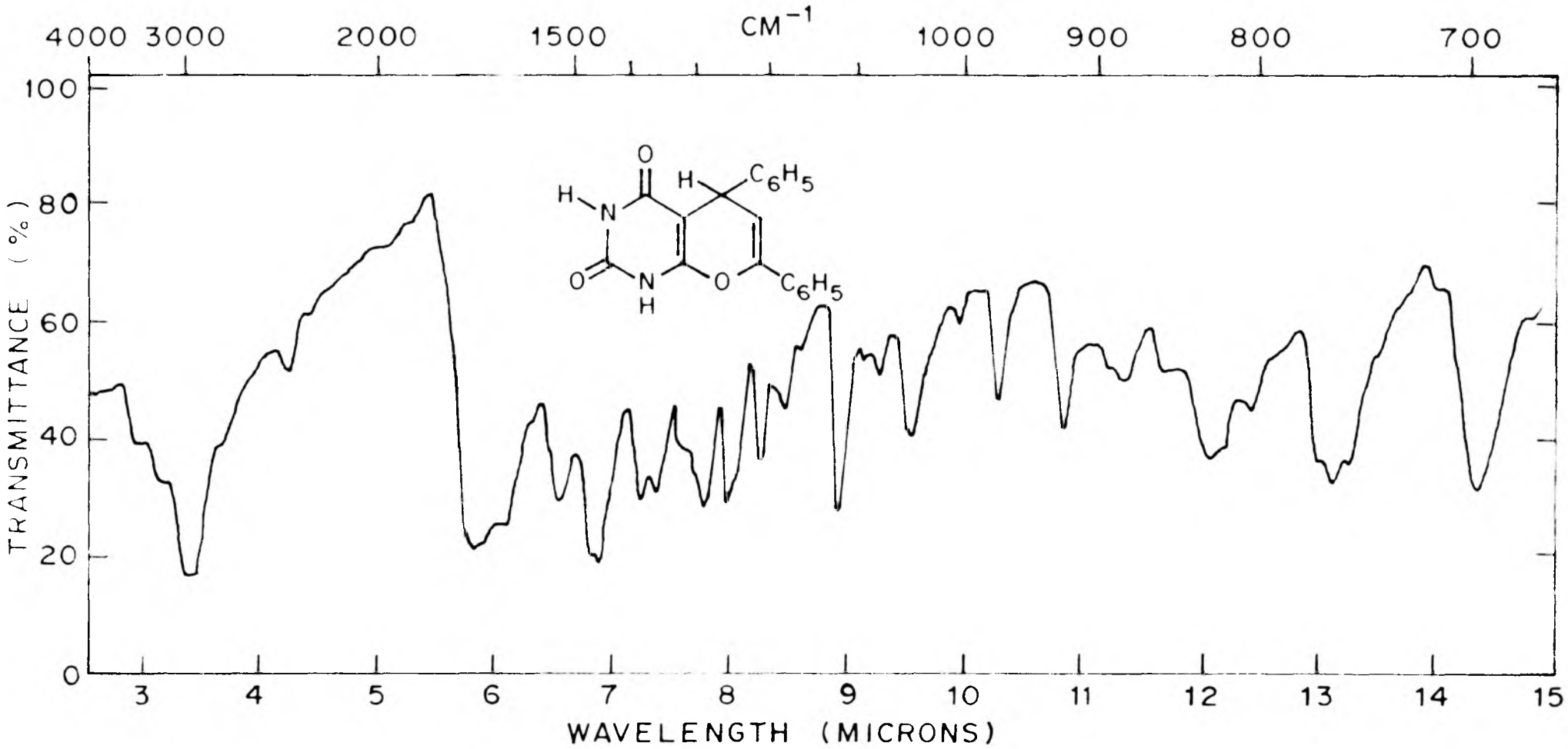
Elemental analysis: Found: C, 71.26; H, 4.22; N, 8.60; $C_{19}H_{14}N_2O_3$ requires C, 71.69; H, 4.43; N, 8.80%.



I.R. SPECTRUM OF 1,3-DIMETHYL-5 2-BENZOYL-1-PHENYLETHANE) BARBITURIC ACID (IIIb)



N.M.R. SPECTRUM OF 1,3-DIMETHYL-5-(2-BENZOYL-1-PHENYLETHANE) BARBITURIC ACID (IIIb)



I.R. SPECTRUM OF 2,4-DIOXO-5,7-DIPHENYL-1,3,4,5-TETRAHYDRO-2H-PYRANO [2,3-d]

(IVa)

IR_{max}^{nujol} 3300-3100 (NH's stretch), 1690-1750 cm^{-1} (amide and aromatic carbonyls).

Mas spectrum m/e(%) 318(100), 274(35), 258(24), 241(39), 231(57), 198(70), 191(70), 178(44), 169(33), 115(58), 105(41), 77(31), 51(12).

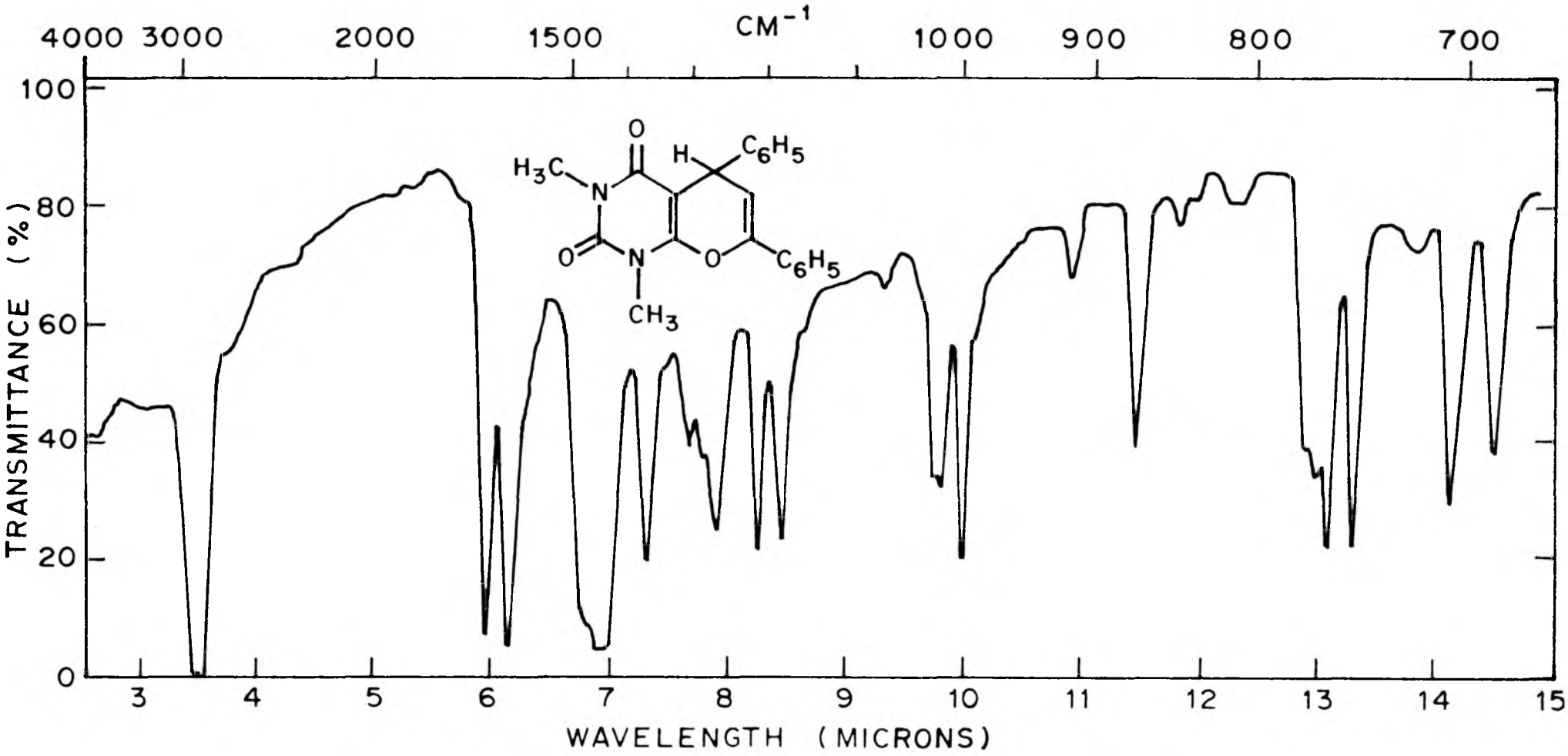
1,3-Dimethyl-5,7-diphenyl-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine (IVb)

To a solution of phosphorus pentoxide (14.2 g, 0.1 mol) in glacial acetic acid (50 ml), the adduct (IIIb) was added and the solution while stirring was refluxed at 120°C for 2 hrs. The reaction mixture after cooling was poured over crushed ice. The dark brown solid obtained was filtered and washed with dil. acetic acid (5% 20 ml). The crude product was dissolved in chloroform and filtered. To the filtrate pet.ether (60-80°) was added and the solution allowed to crystallise. The product obtained gave m.p. 276-278°C, yield 4.5 g (67.6%).

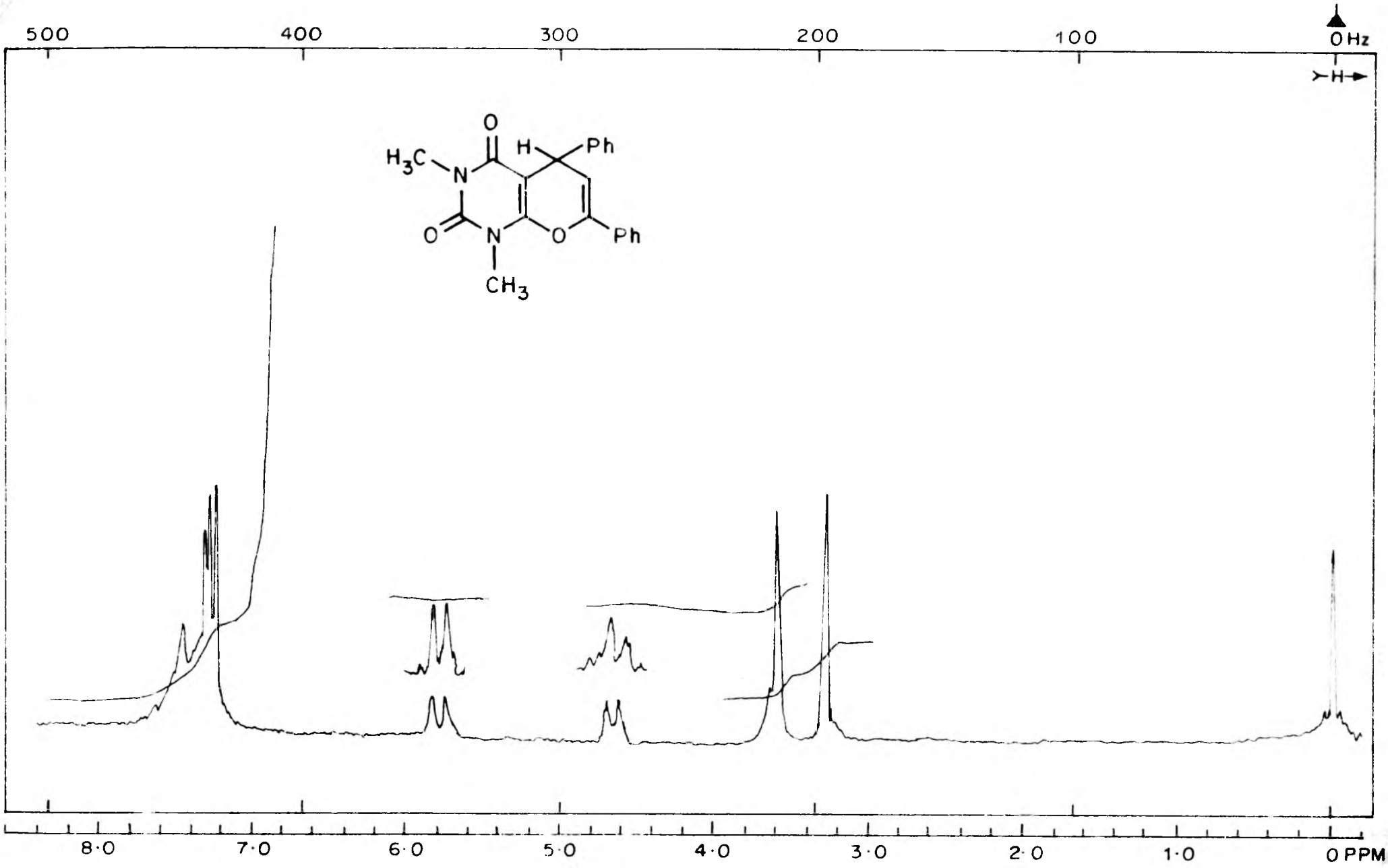
Elemental analysis: Found: C, 73.28; H, 5.53; N, 7.95; $C_{21}H_{18}N_2O_3$ requires C, 72.82; H, 5.24; N, 8.09%.

IR_{max}^{nujol} 2900 (CH stretch), 1640-1690 cm^{-1} amide carbonyl.

NMR($CDCl_3$) 3.28 (s, 3H, N-CH_3), 3.59 (s, 3H, N-CH_3) 4.65 (d, H, C_5-H, J = 5 Hz), 5.78 (d, H, C_6-H, J = 5 Hz), 7.40 (m.c. 10H, aromatic H).



I.R. SPECTRUM OF 1,3-DIMETHYL-2,4-DIOXO-5,7-DIPHENYL-1,3,4,5-TETRAHYDRO-2H-PYRANO [2,3-d] PYRIMIDINE (IVb)



N.M.R. SPECTRUM OF 1,3-DIMETHYL-2,4-DIOXO-5,7-DIPHENYL 1,3,4,5-TETRAHYDRO-2H-PYRANO [2,3-d] PYRIMIDINE (IVb)

Mass spectrum : m/e(%) 346(100), 288(14), 269(89), 260(10), 241(5), 231(18), 212(68), 202(38), 191(49), 184(23), 178(29), 169(24), 155(47), 144.5(6), 140(20), 130(15).

1,3-Dimethyl-5-(2-acetyl-1-phenylethane)barbituric acid (IIIc)

A solution of 1,3-dimethylbarbituric acid (1.56 g, 0.01 mol) benzalacetone (1.46 g 0.01 mol), triethylamine (0.2 ml) and methanol (20 ml) was refluxed at 85°C for six hours. Afterwards the methanol was distilled from the reaction mixture. The residue left was acidified with conc. hydrochloric acid (0.2 ml). The solution was diluted with water (50 ml). A thick syrupy liquid obtained was separated and treated with ether (20 ml). The ethereal solution on cooling overnight gave colourless crystals 1.6 g (52%), m.p.82°C.

Elemental analysis : Found: C, 63.80; H, 5.75; N, 9.60
$C_{16}H_{18}N_2O_4$ requires C, 63.57; H, 5.96; N, 9.27%.

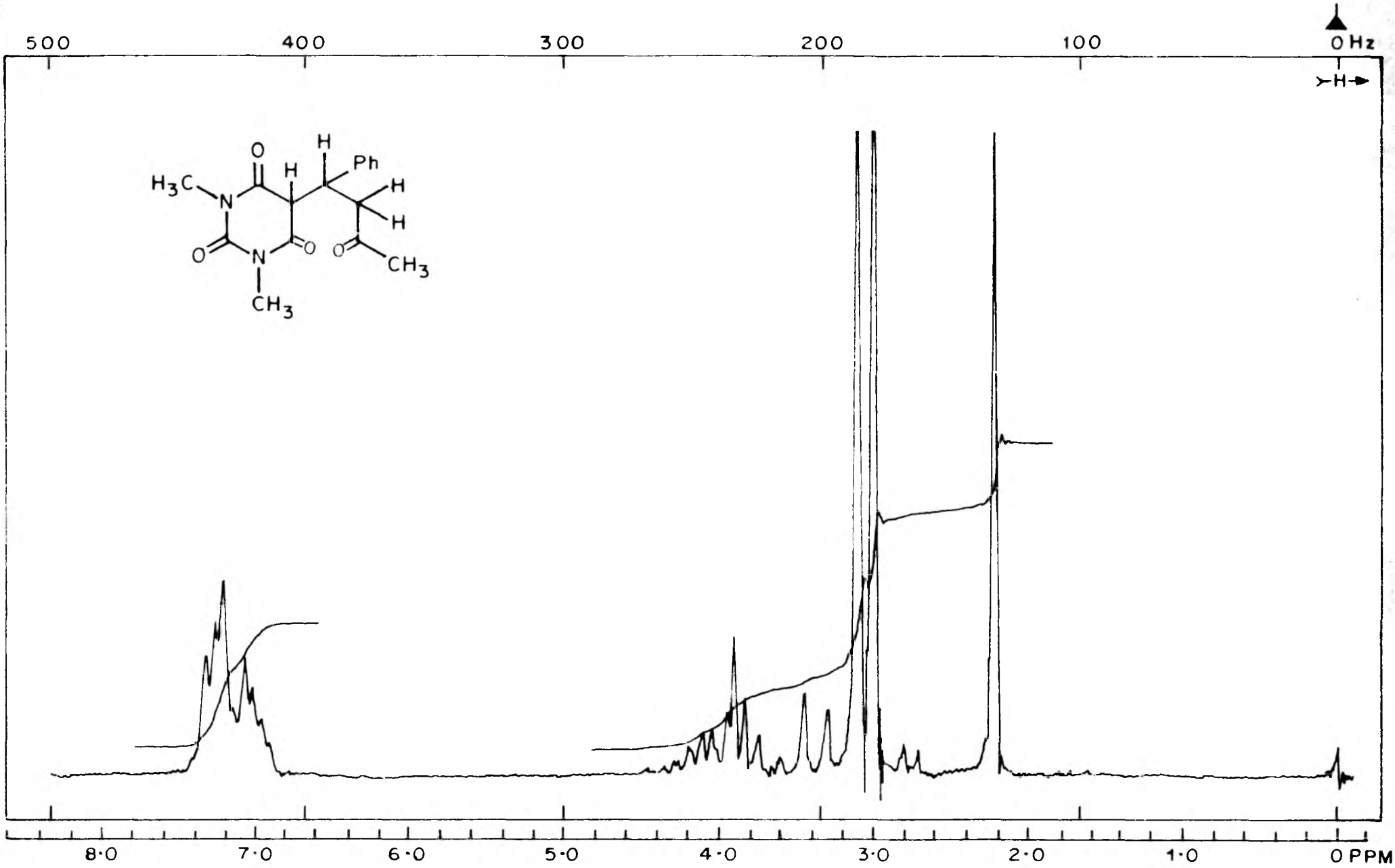
IR^{nujol}_{max} 1695-1750^{cm-1} (amide and aromatic carbonyls).

Mass spectrum: M^+ 302.

NMR ($CDCl_3$): 2.20 (s, 3H, $-\overset{O}{\overset{\|}{C}}-CH_3$), 2.90 (s, 3H, $N-CH_3$), 3.08 (s, 3H, $N-CH_3$), 3.46 (d, 1H, C-H), 3.80 (t, 2H, $-CH_2-\overset{O}{\overset{\|}{C}}$), 4.05 (t, 1H, ring C_5-H), 7.06 (m.c. 5H, aromatic H's).

1,3-Dimethyl-2,4-dioxo-5-phenyl-7-methyl 1,3,4,5-tetrahydro-2H-pyrano/2,3-d/pyrimidine (IVc)

The adduct (IIIc, 0.2 g, 0.007 mol) was added to a



N.M.R. SPECTRUM OF 1,3-DIMETHYL-5-(2-ACETYL-1-PHENYLETHANE) BARBITURIC ACID (IIIc)

solution of phosphorus pentoxide (0.2 g, 0.014 mol) in glacial acetic acid (2 ml). The solution with frequent agitation was refluxed in an oil bath held at 140°C for two hours. The reaction mixture was neutralised with sodium carbonate solution under ice cold conditions. The solution after neutralisation was extracted with chloroform solvent. It was dried over anhydrous sodium sulfate and distilled. The residue obtained was subjected to TLC analysis over silica gel plate with solvent system benzene and ethylacetate (4:1) which showed impurities. This was purified over silica gel column using benzene, benzene:ethylacetate (9:1) as eluents. The benzene;ethylacetate fractions gave pure pyrano[2,3-d]-pyrimidine. Yield 0.172 g (60%), m.p. 75°C.

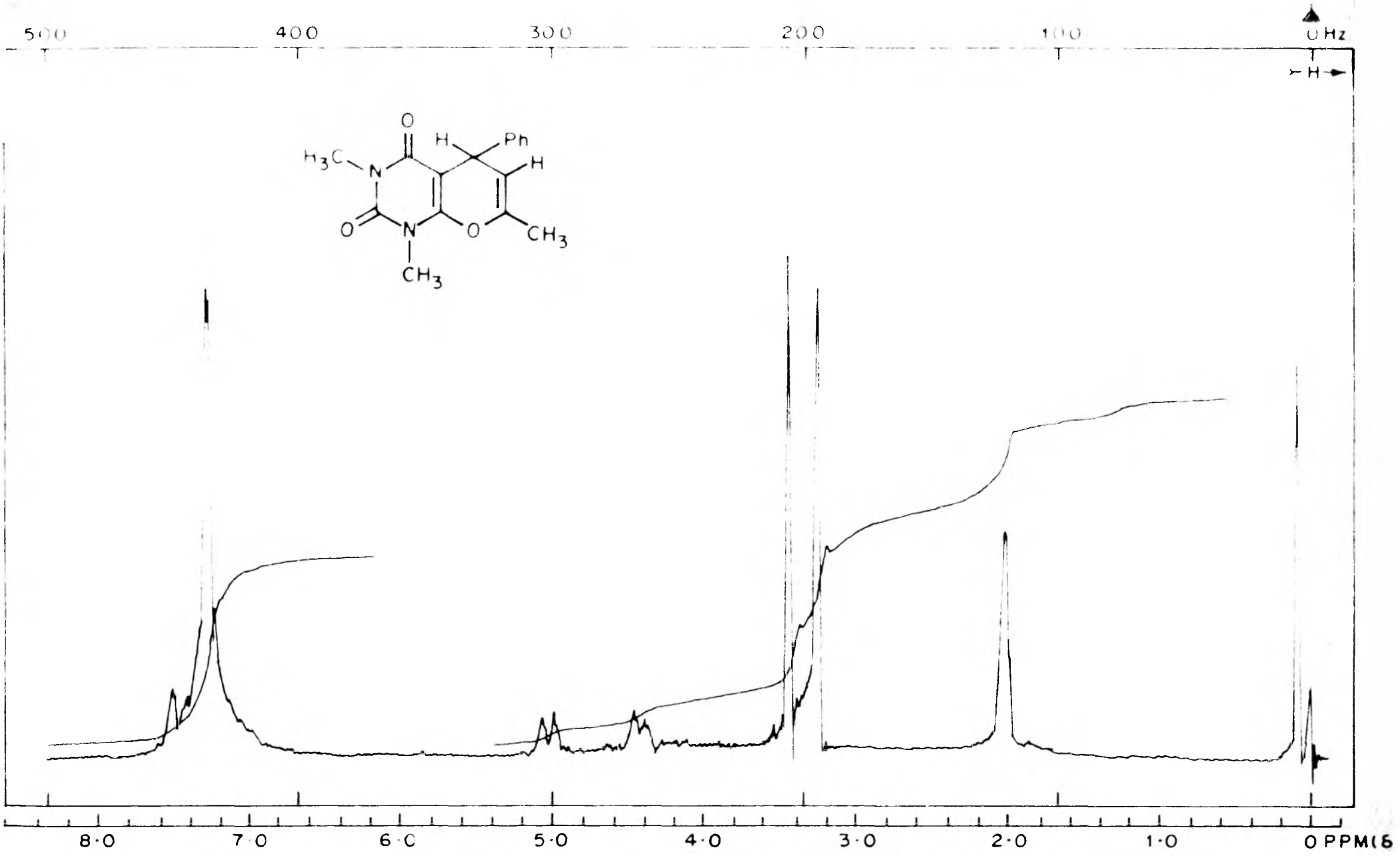
Elemental analysis: Found: C, 67.45; H, 5.80; N, 9.62;
$C_{16}H_{16}N_2O_3$ requires C, 67,61; H, 5.63;
N, 9.97%.

Mass spectrum: M^+ 284.

NMR($CDCl_3$) 1.91 (s, 3H, C_7-CH_3), 3.16 (s, 3H, -N-CH_3), 3.33 (s, 3H, N-CH_3), 4.30 (d, 1H, J = 4 Hz, C_5-H), 4.90 (d, 1H, J = 4 Hz, C_6-H), 7.13 (s, 5H, Arom H's).

1,3-Dimethyl-5-(1,2-dimethoxy carbovinyl)barbituric acid (VIII)

Dimethyl acetylene dicarboxylate (VII, 2.35 g, 0.016 mole) was added to a solution containing 1,3-dimethylbarbituric acid (IIb, 2.6 g 0.016 mole), triethylamine (0.2 ml) and methanol (50 ml). This was refluxed at 80-85°C for 3 hrs. Methanol and triethylamine were distilled off and the last traces were



N.M.R. SPECTRUM OF 1,3-DIMETHYL-2,4-DIOXO-5-PHENYL-7-METHYL-1,3,4,5-TETRAHYDRO-2H-PYRANO [2,3-d] PYRIMIDINE (IVc)

removed by water suction. The residue was dissolved in methanol (5 ml) and benzene (25 ml) by heating over steam bath and the solution cooled over night at 5°C. The crystals obtained (0.9 g unreacted barbituric acid) were filtered. The filtrate was treated with pet.ether (60-80°, 20 ml) and cooled for a day at 5° to furnish impure ester (VIII). It was recrystallised from methanol to give colourless crystals of m.p. 151-153°C, yield 1.04 g (32%).

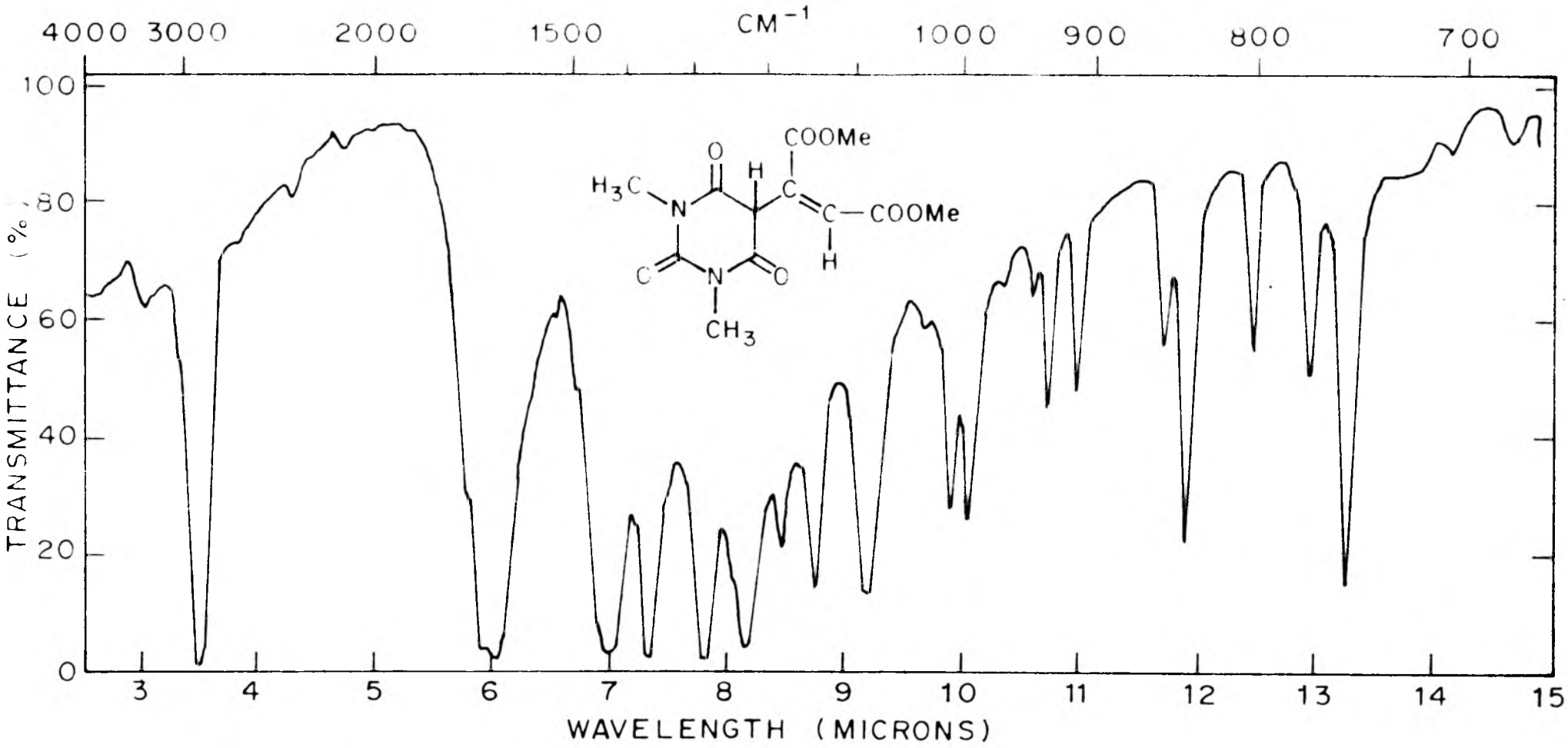
Elemental analysis: Found: C, 48.54; H, 4.79; N, 9.43, $C_{12}H_{14}N_2O_7$ requires C, 48.32; H, 4.73, N, 9.39%.

IR^{nujol}_{max} : 2800-2900 cm^{-1} (CH stretch)
1690-1745 cm^{-1} (amide and ester carbonyls)

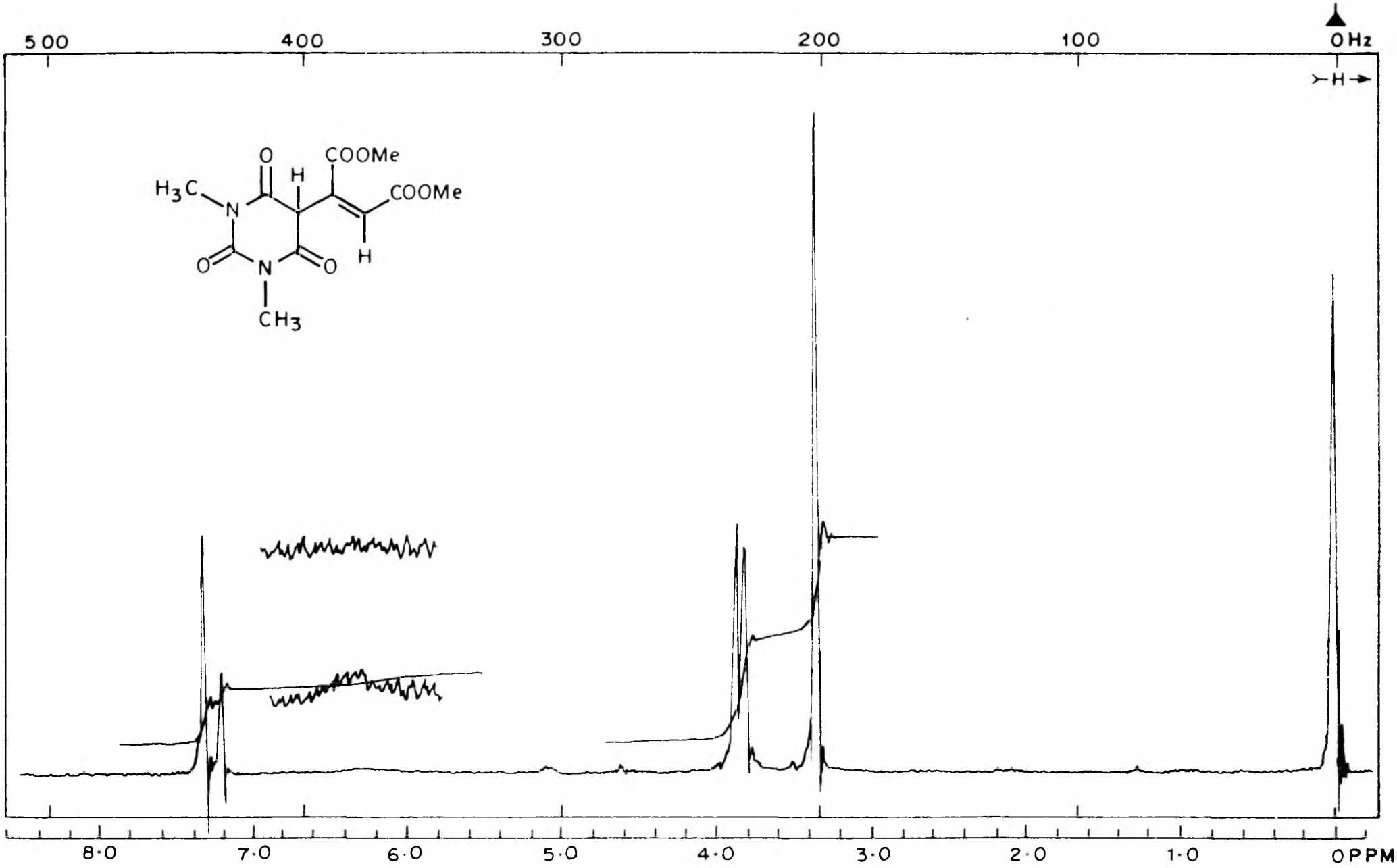
NMR($CDCl_3$) : 3.33 (s, 6H, 2 x N-CH_3), 3.80 (s, 3H, -COOCH_3), 3.85 (s, 3H, -COOCH_3), 6.21 (b.m.c. 1H, C_5-H exchanged with D_2O). 7.16 (s, 1H, vinylic-H).

NMR (pyridine) : 3.33 (s, 6H, 2 x N-CH_3), 3.56 (s, 3H,-COOCH_3) 4.01 (s, 3H, -COOCH_3), 12.51 (b.s., 1H = C-OH exchanged with D_2O).

Mass spectrum: m/e(%): 298(78), 281(4), 267(93), 266(100), 240(99), 239(98), 235(10), 207(98), 181(92), 173(90), 156(78), 154(72), 141(55), 125(60), 103(18), 93(34), 82(18), 69(23), 66(29), 59(32), 39(18), 29(17).



I.R. SPECTRUM OF 1,3-DIMETHYL-5-(1,2-DIMETHOXY CARBOBINYL) BARBITURIC ACID (VIII)



N.M.R. SPECTRUM OF 1,3-DIMETHYL-5(1,2-DIMETHOXY CARBORINYL) BARBITURIC ACID (VIII)

5-Carbomethoxy-1,3-dimethyl-1,3,4,7-tetrahydro-2,4,7-trioxo-2H-pyrano[2,3-d]pyrimidine (IX)

The adduct (VIII) (0.28 g) was heated in a test tube at 170°C for one hr. The crude compound obtained showed on TLC (silica gel + 20% $CaSO_4$, benzene:ethylacetate 3:1) two major spots corresponding to unreacted adduct and cyclised product (IX) (R_f 0.65). The crude product was chromatographed over silica gel column and eluted with benzene, chloroform and methanol. Chloroform elutions gave pure ester (IX), m.p.98-100°C. Yield 0.12 g (50%).

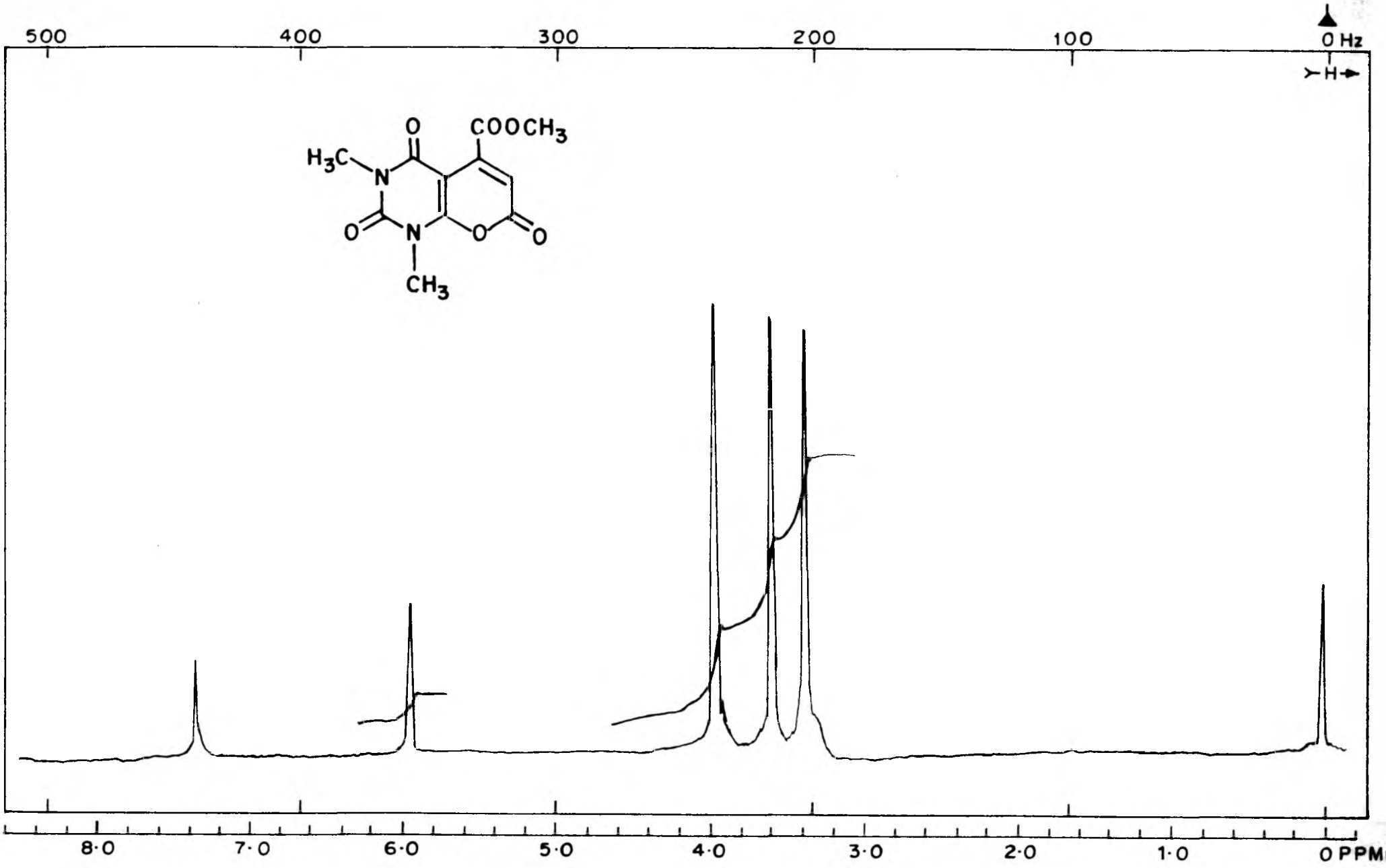
Elemental analysis: Found: C, 49.85; H, 3.50; N, 10.36

$C_{11}H_{10}N_2O_6$ requires C, 49.63; H, 3.79; N, 10.52%.

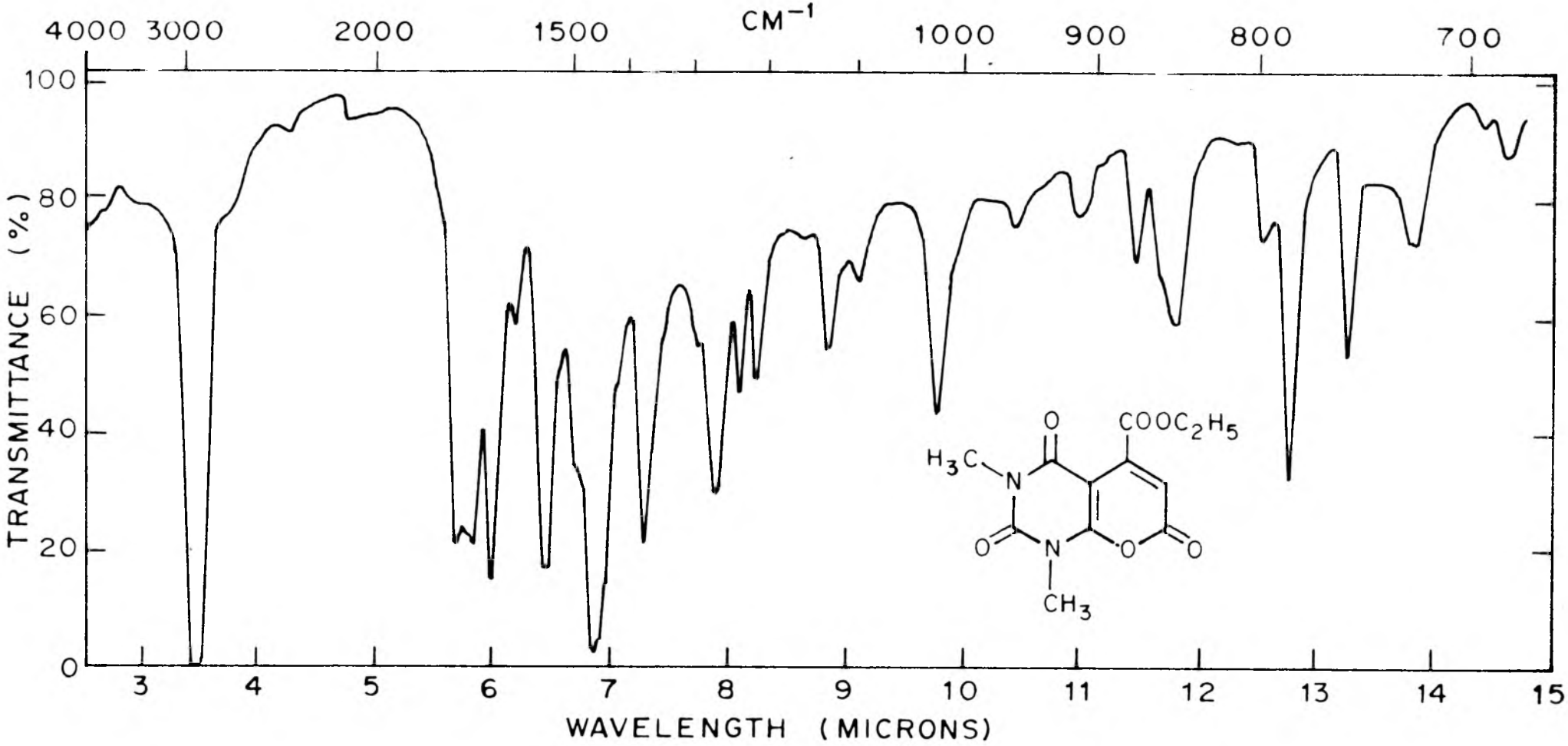
NMR($CDCl_3$) δ 3.35 (s, 3H, N-CH_3), 3.41 (s, 3H, N-CH_3), 3.95 (s, 3H, -COOCH_3), 5.93 (s, 1H, C_6-H).

5-Carbethoxy-1,3-dimethyl-1,3,4,7-tetrahydro-2,4,7-trioxo 2H-pyrano[2,3-d]pyrimidine (X)

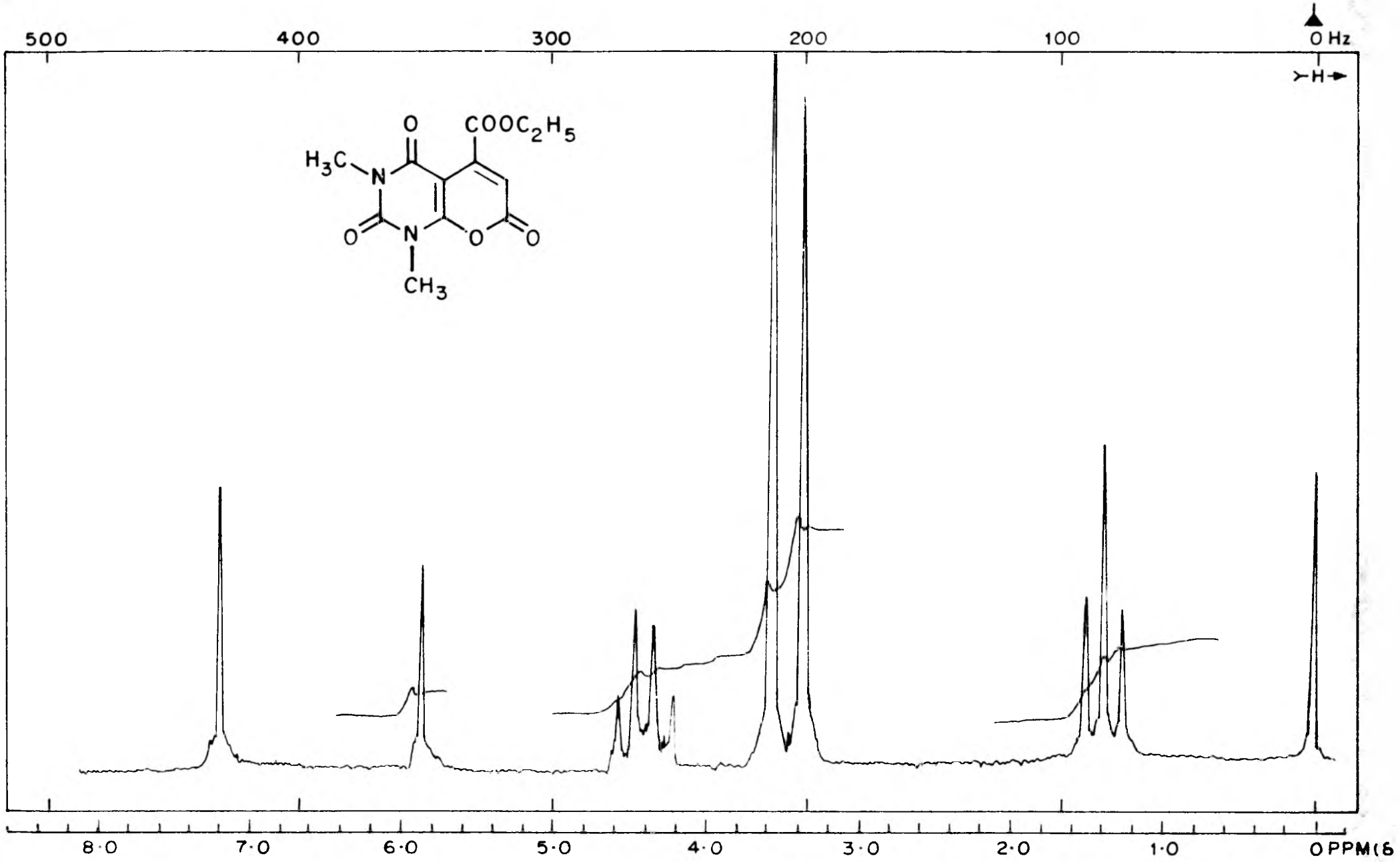
The adduct (VIII, 0.23 g) was added to a solution of BF_3-etherate (3 ml) and the solution was refluxed at 120-130°C for 3 hrs. The cooled reaction mixture was poured into ice-cold water (10 ml) and the solid that separated was filtered. The TLC showed a spot (under the conditions used in the experiment for IX) having same R_f value as methyl ester. It was purified further using the same experimental conditions as reported for methyle ester (IX), m.p.162°C. Yield 0.08 g (37%).



N.M.R. SPECTRUM OF 5-CARBOMETHOXY-1,3-DIMETHYL-1,3,4,7-TETRAHYDRO-2,4,7-TRIOXO-2H-PYRANO [2,3-d] PYRIMIDINE (IX)



I.R. SPECTRUM OF 5-CARBETHOXY-1,3-DIMETHYL-1,3,4,7-TRIOXO-2H-PYRANO [2,3-d] PYRIMIDINE (X)



N.M.R. SPECTRUM OF 5-CARBETHOXY-1,3-DIMETHYL-1,3,4,7-TETRAHYDRO-2,4,7-TRIOXO-2H-PYRANO [2,3-d] PYRIMIDINE (X)

Elemental analysis: Found: C, 51.25; H, 4.69; N, 9.68.
$C_{13}H_{12}N_2O_6$ requires C, 51.43; H, 4.32;
N, 9.99%).

NMR($CDCl_3$): 1.36 (t, 3H, J = 6 Hz ester CH_3), 3.32 (s, 3H, N-CH_3), 3.55 (s, 3H, N-CH_3), 4.38 (q, 2H, J = 6 Hz, ester CH_2), 5.88 (s, 1H, C_6-H).

Mass spectrum : m/e(%): 280(100), 266(6), 252(58), 235(75), 224(18), 208(64), 195(73), 180(74), 167(58), 151(43), 138(19), 123(58), 106(43), 93(59), 65(48), 58(31), 44(17), 28(35).

SUMMARY

S U M M A R Y

Addition of barbituric acid and its 1,3-dimethyl-derivative to benzalacetophenone, benzalacetone and dimethylacetylene dicarboxylate in the presence of base catalysts furnished Michael adducts. These adducts on cyclization with phosphorus pentoxide in glacial acetic acid gave 5,7-disubstituted-2H-pyrano[2,3-d]pyrimidine-2,4-diones (Va-c). Analytical and spectral data are presented in support of the assignment of the structures.

REFERENCES

REFERENCES

1. M.J. Kamlet, J.Am.Chem.Soc. 77, 4896 (1955).

2. V.A. Konikova and V.V. Perkaline, J.Appl.Chem. of USSR 32, 1211 (1959).

3. K.E. Schulte, J. Reisch, A. Mock and K.H. Kander, Archiv. der. Pharmazie, 296, 235 (1963).

4. H.C. Scarborough, J.org.Chem. 29, 219 (1964).

5. H. Schulte, Ber., 87, 820 (1954).

6. Edward E. Smissan, Robert A. Robinson and Alice Jean Boyer Matuszak, J.org.Chem., 35 (11), 3823 (1970).

7. K.E. Schulte, Volker Von Weissenborn and George L. Tittle, Chem.Ber., 103, 1250-1261 (1970).

8. Senda, Shigeo, Fujima, Hajime, Izumi & Hiroshi, Chem.Abstr., 70 (1969), 78001r.

9. Gesellschaft fur Chemische Industrie in Basel, Ger.Pat. 268, 158, Frdl, 11, 933 (1912-1914).

10. Hartmann and Sheppard, org.synth.Coll.Vol. II (1943), 440.

    Gabriel, Ber. 26, 2551 (1893).

    Traube, Ber. 26, 2551 (1893).

11. A. Bayer, Ann. (1854), 130, 140.

12. Brown and Eberley, J.Am.Chem.Soc., 62, 113 (1940).

13. Frank D. Popp and William E. McEven, Chem.Rev., 58, 322-326 (1958).

14. Gudi, M.N. & George, M.V., Indian J.Chem., 7 (1969), 971; 10 (1972), 881, Acheson, R.M. Foxton, M.W. & Hands, A.R., J.Chem.Soc.(C) (1968), 387.

15. Dolfini, J.E., J.Org.Chem. (1965), 30, 1298.

16. NCL Communication No.1814
    Synthesis of Heterocycles: Part II. Pyrano[2,3-d]pyrimidines, A. Subba Rao and R.B. Mitra, Ind.J.Chem., 12(10), 1028(1974).

CHAPTER III
SYNTHESIS OF
THIOPYRANO[2,3-d]PYRIMIDINE-2:4-DIONES

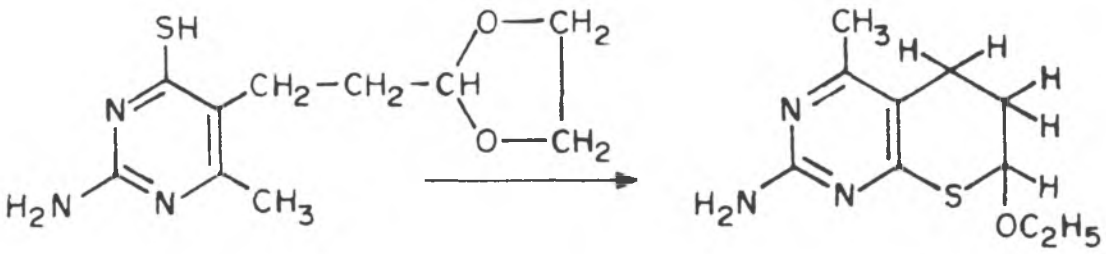
LITERATURE ON EARLIER SYNTHESES

Literature on earlier syntheses

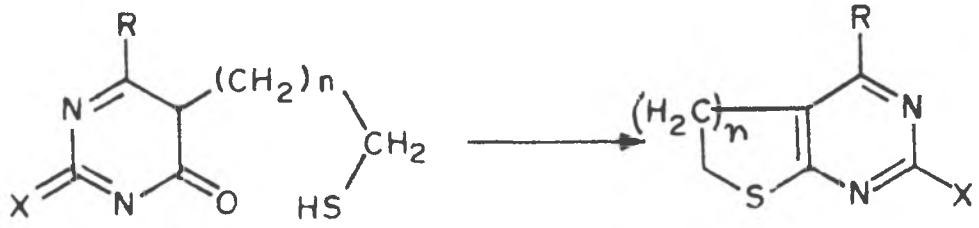
In a synthesis of mercaptoanalogs of tetrahydrofolic acid[1] B.R. Baker et al. have reported 2-amino-5[2-(1,3-dioxalan-2-yl)ethyl]-6-methyl-4-pyrimidinethiol (1) which on refluxing with absolute ethanol and concentrated sulphuric acid (95%) was converted to 2-amino-5,6-dihydro-7-ethoxy-4-methyl-7H-thiopyrano[2,3-d]pyrimidine (II).

Heinrich Warnhoff and Friedhelem Korte[2] have cyclized 5(2-mercaptoethyl) and 5(3-mercapto propyl)-6-hydroxy pyrimidines in polyphosphoric acid to give 5,6-dihydro-thiopheno[2,3-d]pyrimidine (III) and 5,7-dihydro-5H-thiopyrano [2,3-d]pyrimidines (Iva-i).

Cycloaddition[3] of diketene to 6-mercapto-1,3-dimethyl-uracil gave 7-methyl-5-oxo-thiopyrano[2,3-d]pyrimidine-2:4-dione (V).

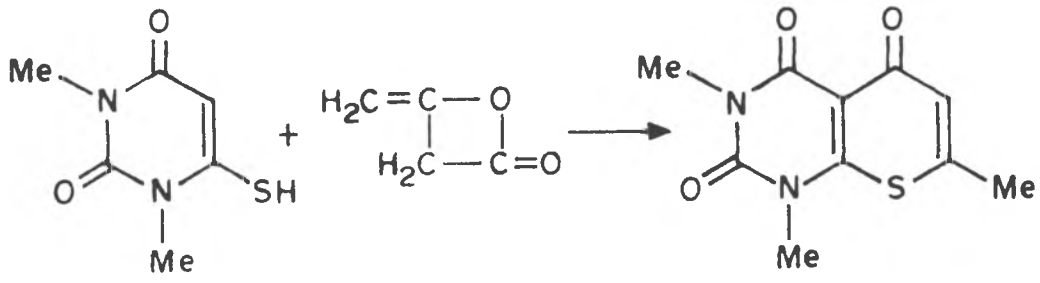


I II



III a-i IV a-i

III,IV	R	X	n
a	H	NH_2	1
b	CH_3	OH	2
c	CH_3	SH	2
d	CH_3	SH	2
e	CH_3	NH_2	1
f	CH_3	NH_2	2
g	NH_2	OH	2
h	NH_2	SH	2
i	C_6H_5	NH_2	2



V

DISCUSSION OF PRESENT WORK

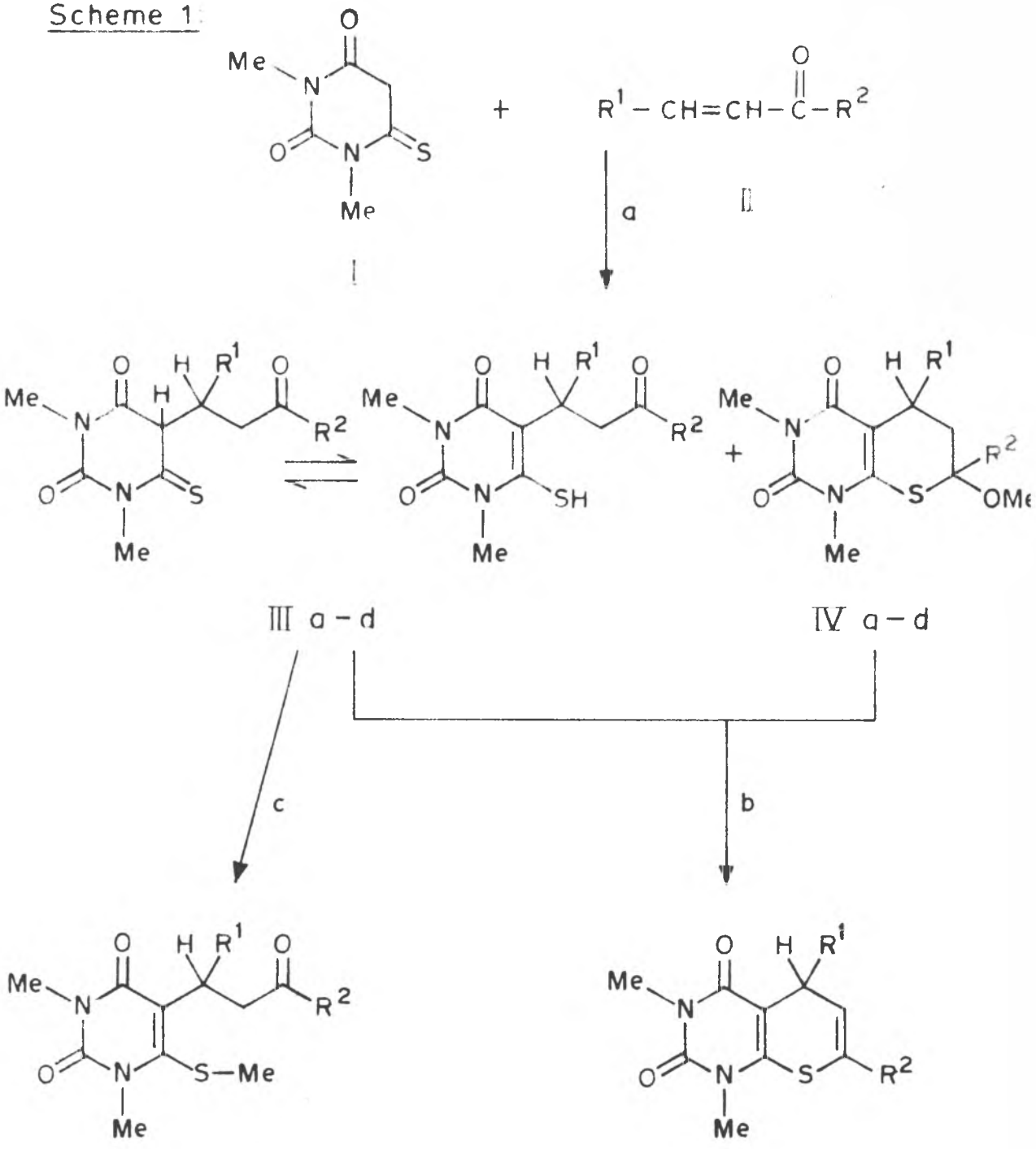
DISCUSSION OF PRESENT WORK

Only a few literature references have so far appeared on the synthesis of thiopyrano[2,3-d]pyrimidine derivatives. Warnhoff and Korte[2] have cyclized 5(3-mercaptopropyl)6-hydroxy pyrimidines in polyphosphoric acid to give 5H-thiopyrano-[2,3-d]pyrimidines. B.R. Baker et al.[1] have reported the synthesis of 7-ethoxy-5H-thiopyrano[2,3-d]pyrimidine derivative by the cyclodehydration of 2-amino-5[2-(1,3-dioxolan-2-yl)ethyl]-6-methyl-4-pyrimidinethiol in conc. H_2SO_4 and ethanol. Cyclo-addition[3] of diketene and 1,3-dimethyl-6-mercaptouracil gave a 7-methyl-5-oxo-1,3-dimethyl-2H-thiopyrano[2,3-d]pyrimidine-2,4-dione.

With a view to synthesize and evaluate the biological and pharmacological activity of the title compounds, our earlier 2H-pyrano[2,3-d]pyrimidine synthesis[4] has been extended to these new compounds. Michael addition reaction of 1,3-dimethyl-6-mercaptouracil (1) and α-β-unsaturated ketones (Scheme 1, IIa-d) in the presence of triethylamine or piperidine in refluxing methanol resulted in the isolation of two sets of products (IIIa-d) and (IVa-d). Elemental analysis and molecular weights of IIIa-d indicated that they are formed out of 1:1 molar condensation of the uracil (1) and the α-enones (IIa-d) respectively. Some common spectral features were noticed in the IR and NMR spectra of these compounds. The IR spectra of the adducts (IIIa-d) showed

THIOPYRANO [2,3-d] PYRIMIDINES

Scheme 1



a MeOH, C_5H_9N, or Et_3N, Reflux

b P_2O_5 + g·HAC, reflux

c MeI, Et_2O, K_2CO_3

II – VI,	R^1	R^2
a	Ph	Ph
b	Ph	CH_3
c	CH_3	Ph
d	H	CH_3

the presence of hydroxy or thiol group at 3550-3450 cm^{-1} region. In the n.m.r. spectra the absence of resonances in the olefinic region (5-6 ppm) indicated C-alkylation rather than S-alkylation. The four singlets of intensity six protons in the region δ 3.20 - 3.60 were assigned to N-methyls of keto-enol forms. The methylene protons adjacent to carbonyl appeared at δ 1.80 - 2.60 ppm as a multiplet with 4 and 7 Hz as coupling constant. The methine protons of the side chain, situated in an asymmetric environment appeared as a multiplet in the region δ 3.00 - 4.00 ppm with J 4 and 7 Hz. The protons attached to side chain carbon carrying phenyl ring (IIIa,b) and the uracil ring C_5-proton appeared as broad doublets at down field δ 4.30 - 4.60 with coupling constant 6 Hz.

Methylation of the adducts (IIIa-d) with methyliodide in ether followed by potassium carbonate furnished the 6-~~mercaptomethyl~~methylthioketones (VIa-d). In the n.m.r. of these compounds besides other resonance signals, the S-methyls[5] appeared as singlets at δ 2.40 - 2.50 region. This and the mass spectral molecular weights confirmed the structures assigned to them. On refluxing the adducts (IIIa-d) in P_2O_5 and glacial acetic acid, thiopyrano[2,3-d]pyrimidines (Va-d) were obtained. The n.m.r. spectra of the cyclized products (Va-c) showed characteristic two doublets[6] with the same J value corresponding to C_5-methine and C_6-olefinic protons. Besides this an unequivocal synthesis of Va by another method

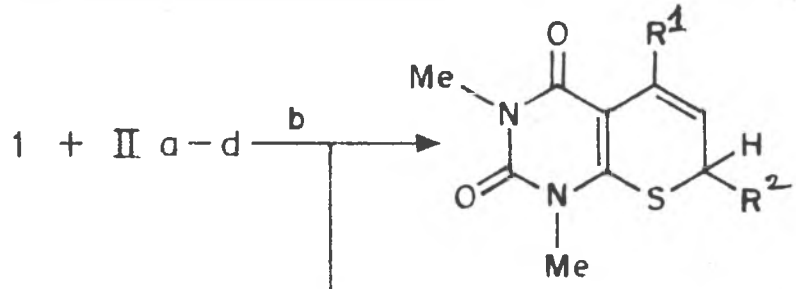
which follows confirmed the structures as 5,7-substituted-2H-thiopyrano[2,3-d]pyrimidine-2,4-diones (Va-c). The cyclised thiopyrano[2,3-d]pyrimidine (Vd, R' = H, R^2 = CH_3) showed characteristic peaks in its n.m.r. besides the resonances of N-methyls; a singlet of three protons for the C_7-methyl group appeared at δ 2.11. The methylene protons at C_5-position appeared as a multiplet at δ 3.31 with J 2 and 6 Hz. A triplet of one proton at δ 5.30 J:2 and 6 Hz was assigned to the olefinic proton at C_6-position. The mass spectral molecular weight and the n.m.r. confirmed the structure (Vd).

The other set of compounds (IVa-d) isolated in the michael addition step gave mass spectral molecular weights fourteen units more than the corresponding adducts (IIIa-d). In their IR no-OH or -SH was shown. The n.m.r. spectra exhibited besides other resonances a singlet of three protons at δ 3.20 - 3.45 ppm region which could be assigned to protons of a methoxy group. On refluxing with a strong acid (P_2O_5 + HAc) they were converted to a 2H and 3H thiopyrano[2,3-d]pyrimidines (Va-d) in good yields, IIIa-d and Va-d when refluxed individually with base catalysts in methanol only the former set gave IVa-d and the latter were unchanged. Based on this and their facile conversion to Va-d, 7-methoxy-thiopyrano[2,3-d]pyrimidine structures (IVa-d) were assigned.

Although the cyclization of 1,5-mercapto-ketones (IIIa-d) in P_2O_5-glacial acetic acid proceded quite satisfactorily, the yields in the preparation of IIIa-d itself

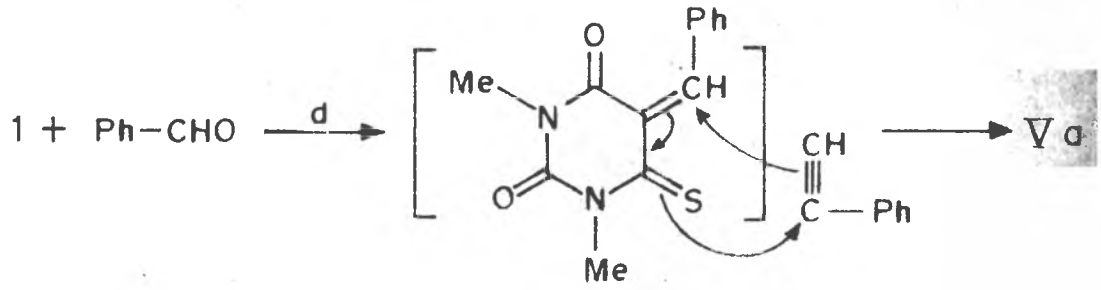
were not encouraging due to known reasons. In order to achieve better yields of the title compounds, condensation of 1,3-dimethyl-6-mercaptouracil (1) and α-enones (IIIa-d) involving addition and cyclization in one step has been carried out. Since Michael additions[7] in acid media are known, this reaction was also expected to give the same products (Va-d) that were mentioned earlier. In practice reaction of (I) and (IIb,c,d) gave the same products (Vb,c,d) but benzal-acetophenone (IIa) condensation with (I) under these conditions gave a different compound. It showed the same molecular weight as Va but differed in m.p. n.m.r. and R.F. value on t.l.c. The n.m.r. showed besides signals for N-methyls and aromatic protons, two doublets at δ 5.10 and 5.20 region with J value 6 Hz. Since these low field signals could be assigned to a methine and an olefinic proton of the thiopyran ring, this compound (VIIa) and (Va) differing in chemical shifts and J values apparently are double bond isomers. A simple unambiguous synthesis (Scheme III) from I, benzaldehyde and phenylacetylene in analogy to an earlier reported synthesis of 2H-pyrano[2,3-d]pyrimidine[8] furnished Va as a confirmation of its divinyl sulfide structure. The u.v. absorption maxima of Va were observed at higher wave length 262 (4.38), 308 (3.83) when compared to the isomer (VIIa) 255 (3.83), 340 (3.02). This is in agreement with earlier reported values[9] that compounds with divinyl sulfide structure absorb at higher wave lengths than the simple vinyl sulfides. Consistent with

Scheme 2:

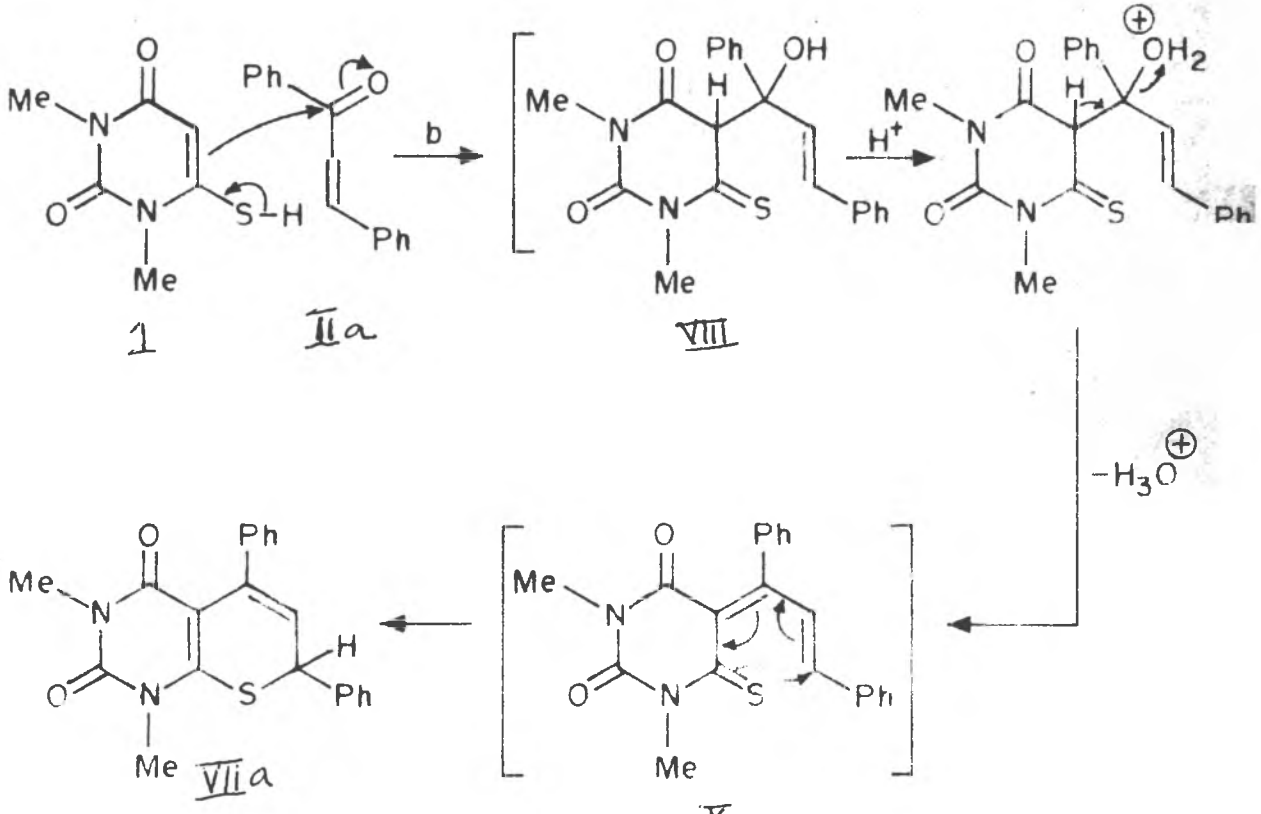


V b-d VII a $R^1 = R^2 = Ph$.

Scheme 3:



Scheme 4:



b = P_2O_5, gHAc, Reflux

d = Ac_2O, Reflux

the above data this ~~x~~ isomer was given a vinylsulfide structure (VIIa).

The formation of VIIa from I and IIa in one step reaction is apparently not proceeding through the intermediate Va isomerisation of double bond to C_5-C_6 position, since VIIa is not detected after cyclization of michael adduct (IIIa) in P_2O_5 + glacial acetic acid. Initial addition of thio-enolate anion of (I) to α-enones (IIa-d) and subsequent cyclization followed by dehydration leading to VIIa also appears to be not possible, under these conditions, as this reaction would have been general to other α-enones (IIa-d) in furnishing isomeric thiopyrano[2,3-d]pyrimidines. Since a michael adduct intermediate is ruled out in the formation of VIIa under these conditions, an aldol condensation product of I and IIa appears most probable intermediate. Knoevenagel reaction of 1,3-dimethyl barbituric acid with simple and unsaturated aldehydes both in acidic[8] and basic media[10] to give C_5-alkenylated product is known. One can expect ~~a~~ a similar reaction from 6-mercaptouracil and an α-β-unsaturated carbonyl compound. Benzalacetophenone undergoes both 1:4-addition (orbital controlled) and 1:2 addition (charge controlled) with charge localised anions[11] depending on reaction conditions. Consistent with the above information the following mechanism (Scheme ~~IV~~ 4) that is most probably operating is suggested.

In a highly acidic polar medium a 1:2 addition of 6-mercaptouracil (1) to carbonyl of benzalacetophenone gives an α-enol (Scheme ~~IV~~ 4 VIII) in the first step. Protonation of the enol (VIII) and subsequent dehydration results in an α-S-dienothione (X). This by a cyclic rearrangement furnishes the 2H-thiopyrano[2,3-d]pyrimidine 2,4-dione (VIIa).

EXPERIMENTAL

E X P E R I M E N T A L

All melting points are uncorrected. NMR spectra were recorded on T.60 instrument with TMS as internal standard. Chemical shifts were expressed in δ ppm and the J values in HZ. IR spectra were recorded on Perkin-Elmer model 137-B or on 221 instruments. UV spectra were taken on Perkin-Elmer UV spectrophotometer-350. Mass spectra were taken on CEC-21-110B double focussing instrument with direct inlet system. Mass spectral data are reported as percentages of the base peak which was assigned a value 100.

General procedure for the preparation of adducts (IIIa-d) and 7-methoxy-3H-thiopyrano[2,3-d]pyrimidine 2,4-diones (IVa-d)

A solution of 1,3-dimethyl-6-mercaptouracil (1,5 x 10^{-3} mol) and the α,β-unsaturated ketone (IIa-d, 5 x 10^{-3} mol) with a base* catalyst such as triethylamine or piperidine (0.1 - 0.2 ml) in methanol (20 ml) was refluxed at 80° on a steam bath for 4 hrs. Afterwards methanol was distilled off from the reaction mixture under water suction at 50-60°C. A TLC of the crude reaction mixture was performed over silica gel plate (contg. 0.5% of plaster of paris, solvent system benzene:ethylacetate 4:1. Spots were developed in iodine chamber) showed two spots corresponding to 7-methoxy-derivatives (IVa-d) with R.F. values 0.50 - 0.60 and the adducts (IIIa-d) with 0.20 - 0.30. The crude product were

chromatographed over silicagel column (35 x 2 cm) using benzene, benzene;ethyl acetate (9:1) eluted 7-methoxy derivatives and benzene:ethylacetate (4:1, 3:2) elutions gave the adducts in pure condition.

1,3-Dimethyl-5(2-benzoyl-1-phenylethyl)-6-mercaptouracil (IIIa)

M.P. 158°. Yield 0.6 g (31.5%).

Elemental analysis: Found: C, 66.22; H, 5.48; N, 7.52; S, 8.72

$C_{21}H_{20}N_2O_3S$ requires C, 66.31; H, 5.26; N, 7.36; S, 8.42%.

Mol. wt. by M.S. : 380.

IR in CCl_4: 3520 cm^{-1} (SH-stretch shifts on deuteration to 2640 cm^{-1}), 1690, 1645 cm^{-1} (Amide and benzoyl carbonyls).

NMR ($CDCl_3$): 2.56 (m.c. 2H, J = 4 Hz, CH_2-C(=O)-),

3.01 (t or q, J = Hz, benzylic H)

3.23, 3.36 (2S, 3H, N-CH_3's of keto and enol forms)

3.46, 3.51 (2S, 3H, N-CH_3's of keto-enol forms)

4.30 (b.s., 1H, C_5-H or benzylic H of enol forms)

4.46 (b.s., 1H, C_5-H, or benzylic H of enol forms)

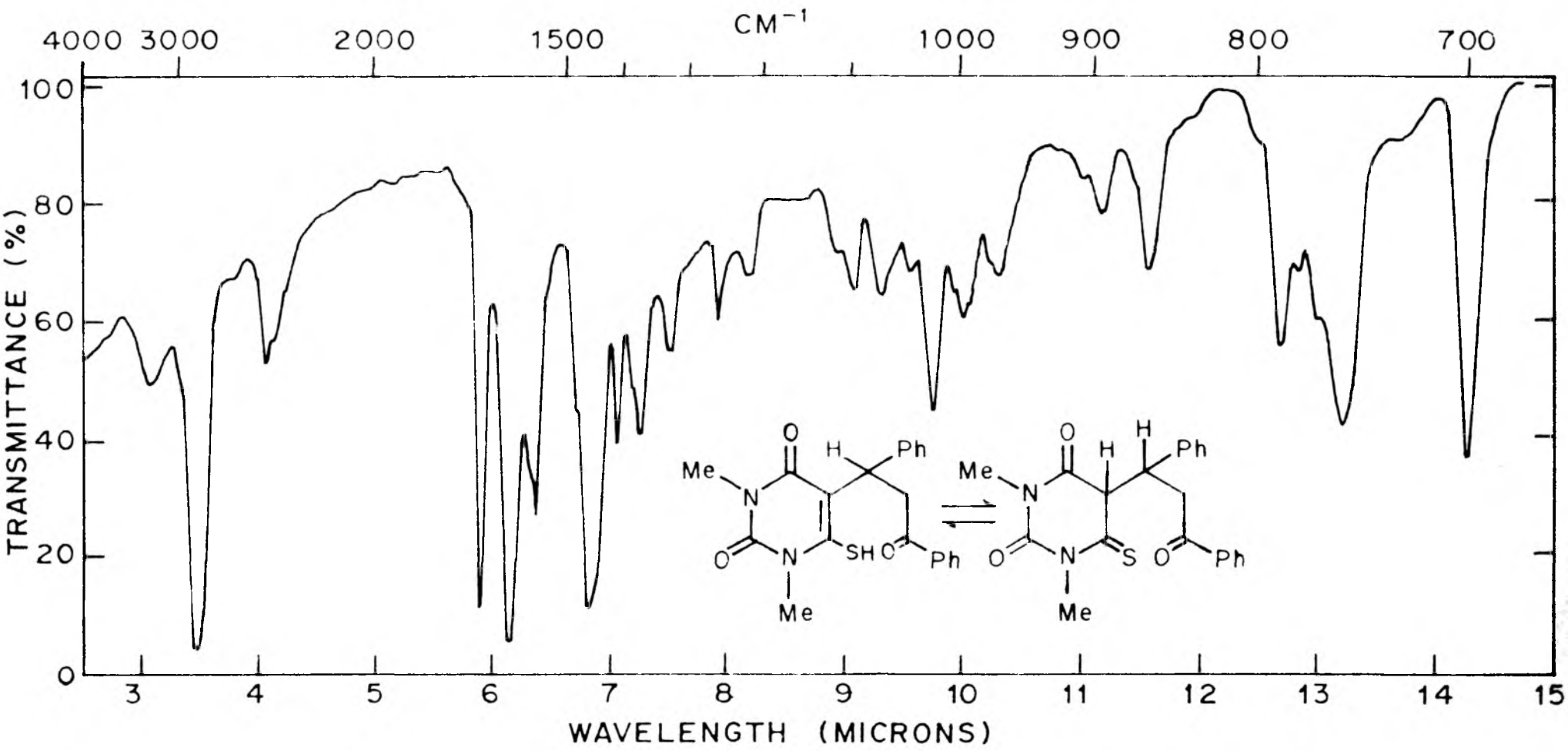
7.23 (S, 5H, Arom), 7.50 (m.c. 3H, Arom) 8.00 (S, 2H, Aromatic).

1,3-Dimethyl-5-(2-acetyl-1-phenylethyl)-6-mercaptouracil (IIIb)

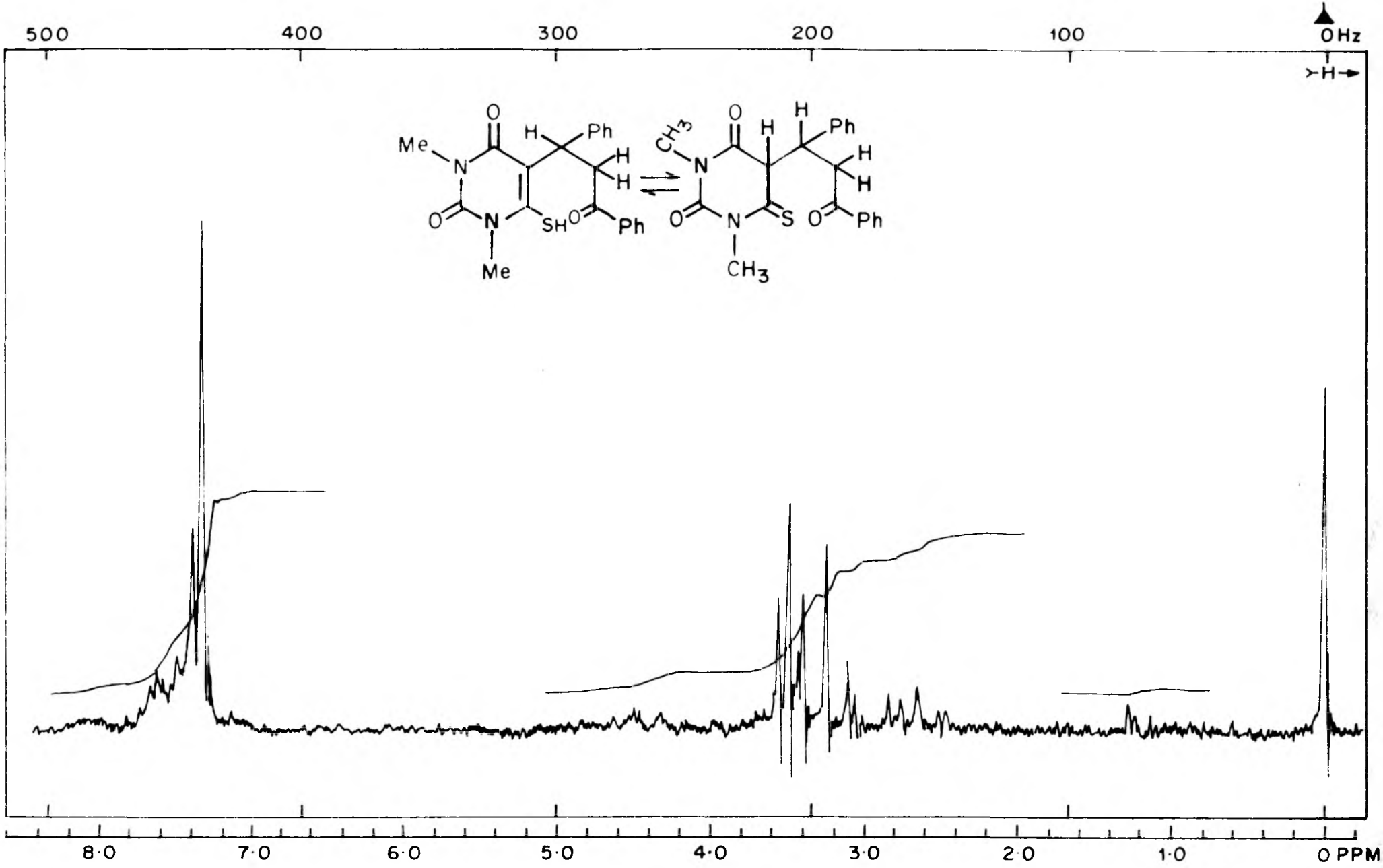
M.P. 176-178°, yield 0.55 (34.6%).

Elemental analysis: Found C, 58.92; H, 5.76; N, 8.94%, S, 10.88%

$C_{16}H_{18}N_2O_3S$ requires C, 60.39; H, 5.66; N, 8.80; S, 10.07%. 58.92 1.47


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
Me
N
O
H
Ph
SH
S
Me

IR OF III a


500
400
300
200
100
0 Hz
Me
N
O
H
Ph
H
H
SH
O
Ph
Me
CH3
S
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM (δ

N.M.R. OF III a

Molecular wt. by M.S. : 318

IR in nujol: 3550 (SH-stretch), 1715-1640 cm^{-1} (amide and acetyl carbonyls).

NMR($CDCl_3$): 1.70 (S, 3H, $-\overset{O}{\overset{\|}{C}}-CH_3$), 2.40 (m.c., 2H's, $-CH_2-\overset{O}{\overset{\|}{C}}$), 3.23, 3.35 (2S, 3H, $N-CH_3$'s keto-enol forms), 3.46, 3.51 (2s, 3H, $N-CH_3$'s keto-enol forms), 4.30 (m.c. 1H, benzylic H or C_5H), 4.66 (m.c. 1H, benzylic H or C_5-H) 7.23 (b.s., 5H, aromatic H).

1,3-Dimethyl-5(2-benzoyl-1-methyl-ethyl)-6-mercapto uracil (IIIc)

M.P. 166-7°. Yield 0.4 (25%).

Elemental analysis: Found C, 59.30; H, 5.72; N, 9.25, S, 10.42

$C_{16}H_{18}N_2O_3S$ requires C, 60.39; H, 5.55; N, 8.80; S, 10.07%.

IR in nujol: 3550 (SH stretch), 1695-1640 cm^{-1} (amide and aromatic carbonyls).

Molecular wt.: 318.

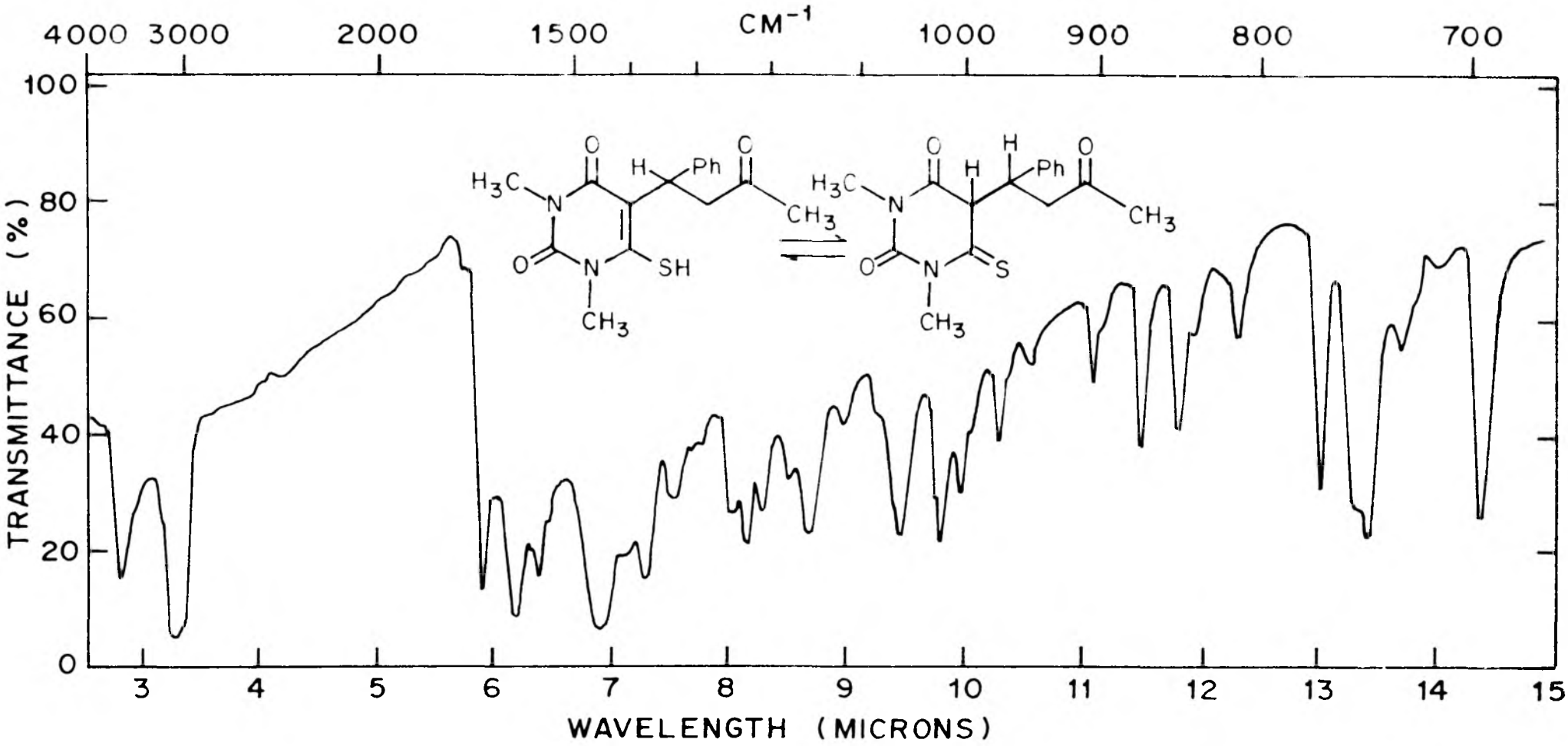
1,3-Dimethyl-5(2-acetyl-ethane) 6-mercaptouracil (IIId)

M.P. 128-30°C. Yield 0.3 (31%).

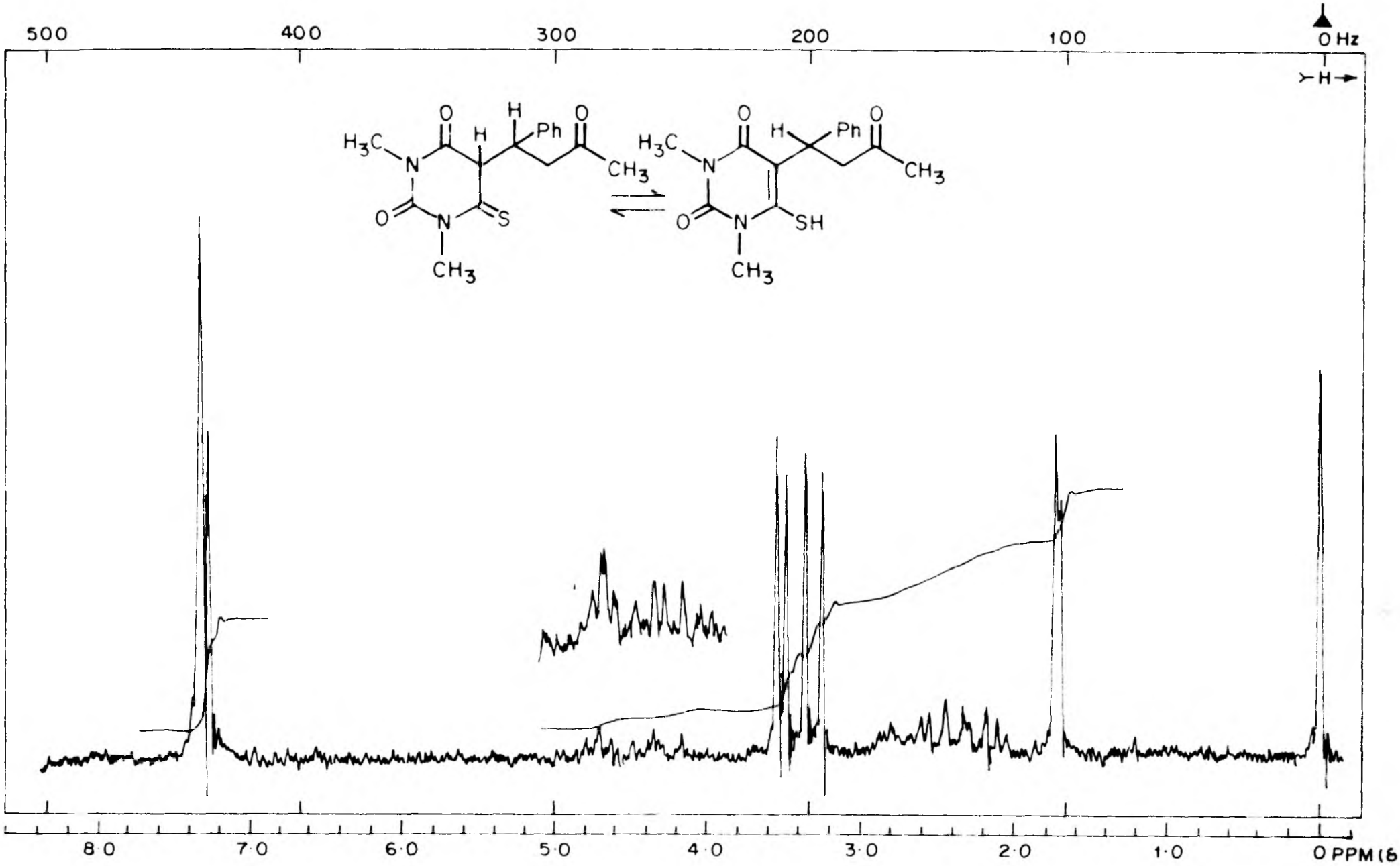
Elemental analysis: Found C, 49.82; H, 5.95; N, 11.42; S, 13.50

$C_{10}H_{14}N_2O_3S$ requires C, 49.55; H, 5.78; N, 11.56; S, 13.22%.

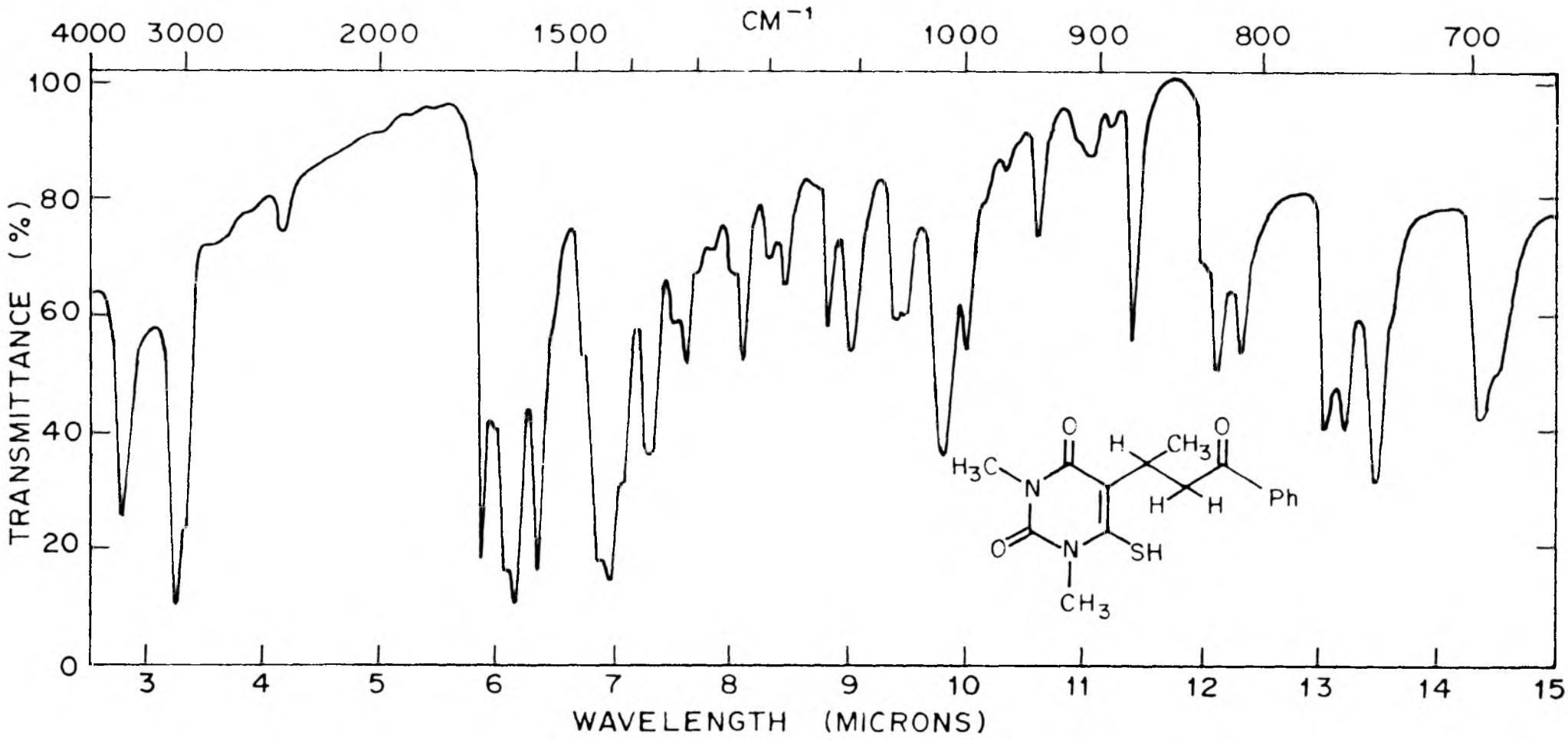
Molecular weight by MS: 242.0.


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
H3C
N
O
H
Ph
CH3
SH
S

IR OF III b


500
400
300
200
100
0 Hz
H
O
H
Ph
O
H3C
N
CH3
O
N
S
CH3
O
H
Ph
O
H3C
N
CH3
O
N
SH
CH3
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM (δ

N.M.R. OF III b


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
O
H
CH3
O
H3C
N
H
H
Ph
O
N
SH
CH3

IR OF III c

NMR($CDCl_3$): 1.8 (S, 3H, $-\overset{O}{\overset{\|}{C}}-CH_3$), 2.16 (m.c. 2H, CH_2) 2.73 (m.c., 2H, $-CH_2-\overset{O}{\overset{\|}{C}}-CH_3$), 3.43 (s, 3H-N-$CH_3$), 3.56 (s, 3H, -N-$CH_3$), 4.60 (t, 1H, J = 7 cps C_5-H).

1,3-Dimethyl,2:4-dioxo-5,7-diphenyl-7-methoxy-3H-thiopyrano [2,3-d]pyrimidine (IVa)

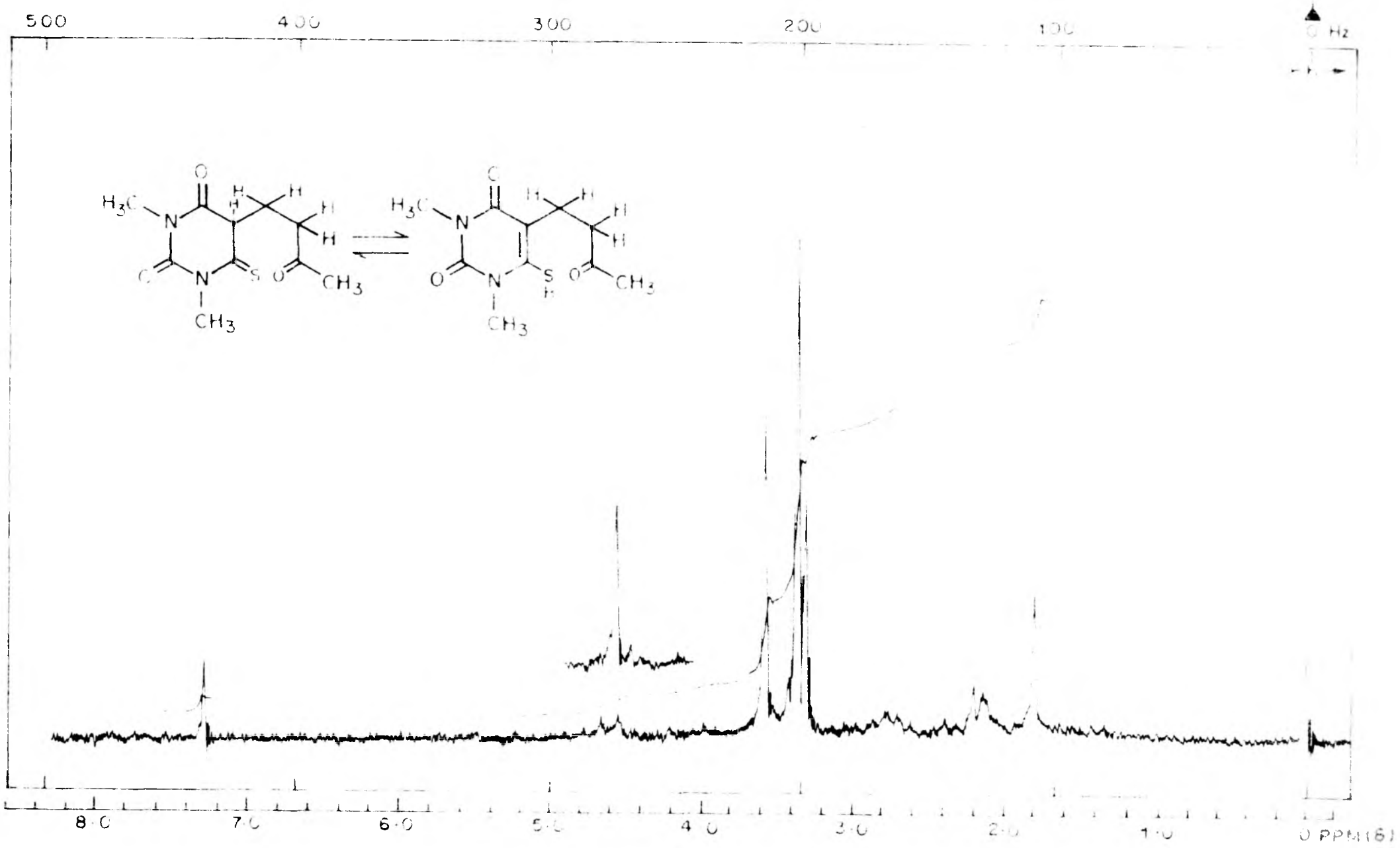
M.P. 126-127°. Yield 0.21 g (21%).

Elemental analysis: Found C, 67.15; H, 5.62; N, 7.36; S, 8.40; $C_{22}H_{22}N_2O_3S$ requires C, 67.01; H, 5.58; N, 7.09; S, 8.12%.

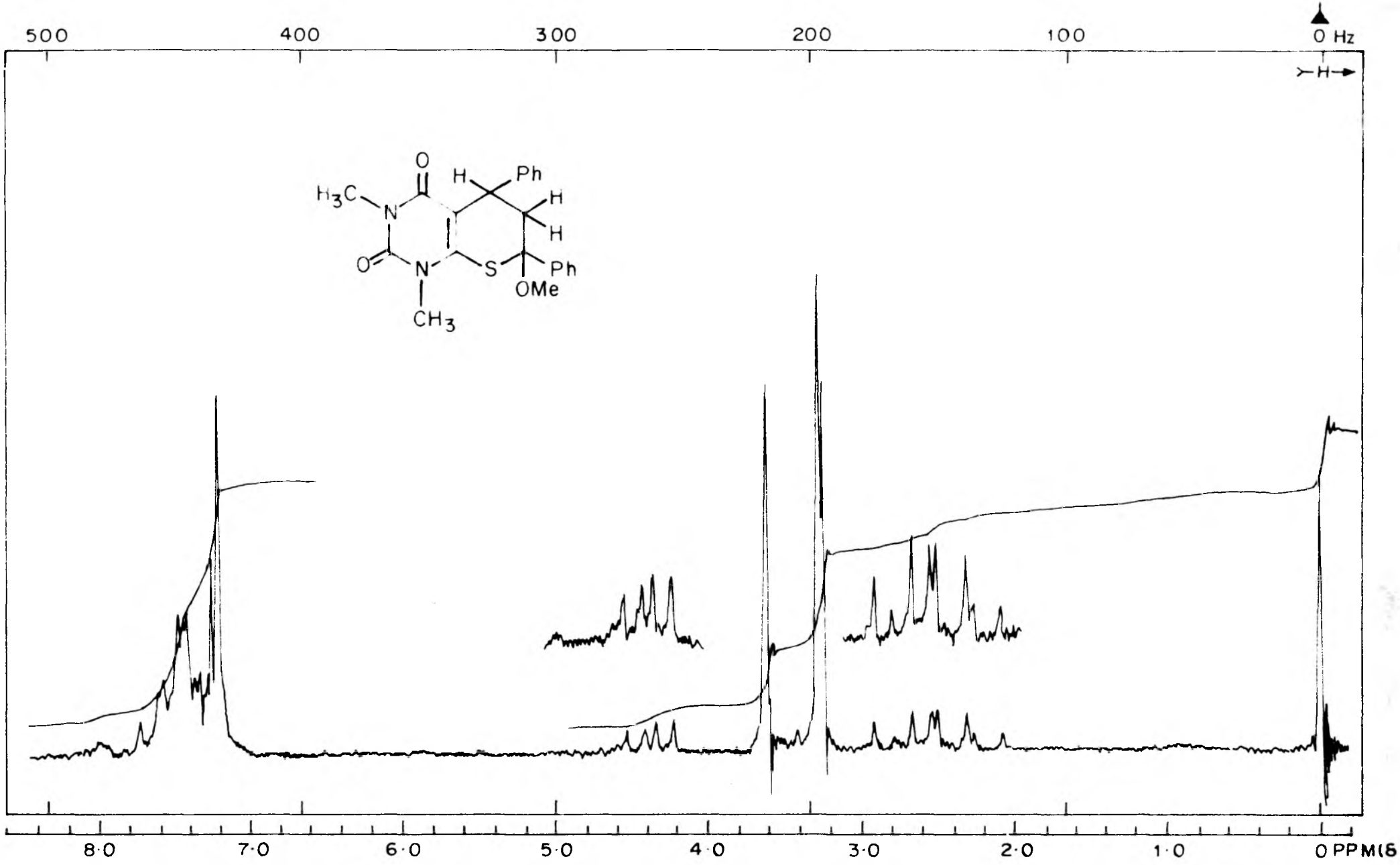
IR (Nujol): 3050-2900 cm^{-1} (CH-stretch)
1645-1700 cm^{-1} (amide carbonyl)

NMR($CDCl_3$): 2.60 (m.c. 2H, J, 7 and 12 Hz C_6-H's), 3.26 (d, 6H, N-CH_3 and OCH_3) 3.61 (s, 3H, N-CH_3), 4.38 (q, 1H J = 7 cps, C_5-H), 7.20 (s, 5H Aromatic), 7.46 (m.c. 5H, aromatic).

Mass spectrum: m/e(%) 396(4), 395(15), 394 (59), 381(15), 380(42), 379(88.5), 274(11), 273(26), 272(100), 261(19.5), 260(23.7), 251(65), 258(83), 224(1.5), 223(9), 222(30), 203(8, 202(16), 201(48.6), 133(57), 132(57), 120(57), 105(68), 104(45), 103(53), 102(51), 93(10), 92(25), 78(39), 77(38), 76(22.6), 75(30), 74(36), 69(24), 60(3), 59 (6.5), 58(26), 52(21.6), 51(27), 50(21.6), 45(17), 44(8), 43(19.5), 42(20).



N.M.R. OF III d


500
400
300
200
100
0 Hz
H
O
H
Ph
H3C
N
H
H
O
N
S
Ph
OMe
CH3
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM(δ)

N.M.R. OF IV a

1,3-Dimethyl-2:4-dioxo-5-phenyl-7-methyl-7-methoxy-3H-thiopyrano[2,3-d]pyrimidine (IVb)

M.P. 176°C. Yield 0.2 g (12%).

Elemental analysis: Found: C, 61.52; H, 6.18; N, 8.60; S, 9.92. $C_{17}H_{20}N_2O_3S$ requires C, 61.45; H, 6.03; N, 8.43; S, 9.64%.

IR (nujol) 2900 cm^{-1} (CH stretch), 1695, 1645 cm^{-1} (amide carbonyls).

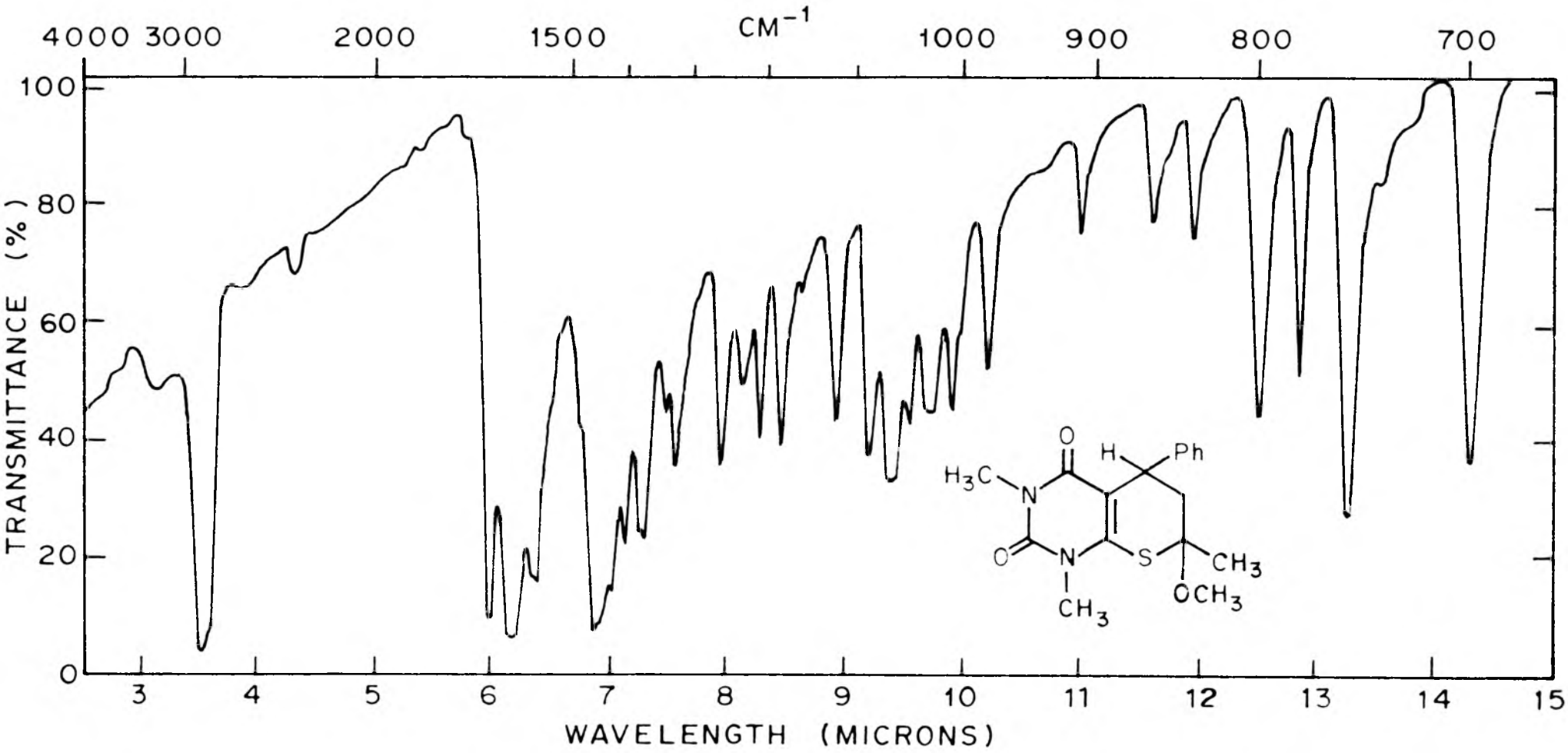
NMR($CDCl_3$): 1.28 (s, 3H, C_7-CH_3), 2.33 (m.c., 2H, J 7 and 11 Hz, C_6-CH's), 3.20 (s, 3H, OCH_3 or N-CH_3 ~~or N-CH_3~~), 3.33 (s, 3H, NCH_3 or OCH_3) 3.50 (s, 3H, NCH_3 or OCH_3), 4.20 (q, 1H, J = 7 Hz - C_5-H) 7.20 (s, 5H, aromatic).

Mass spectrum: m/e(%), 335 (29.4), 334 (57.6), 333 (66.5), 332 (83.20), 319 (62.72), 318 (74.2), 317(100), 302(28), 301(52), 300(58), 299(70.4) 285(56.3), 276(55), 275(74), 274(61.4), 273(81), 261(62), 260(75), 259(95), 202(59), 198(58), 161(74), 145(58), 142(58), 77(38), 57(50), 43(43.5), 42(41), 41(37), 28(38).

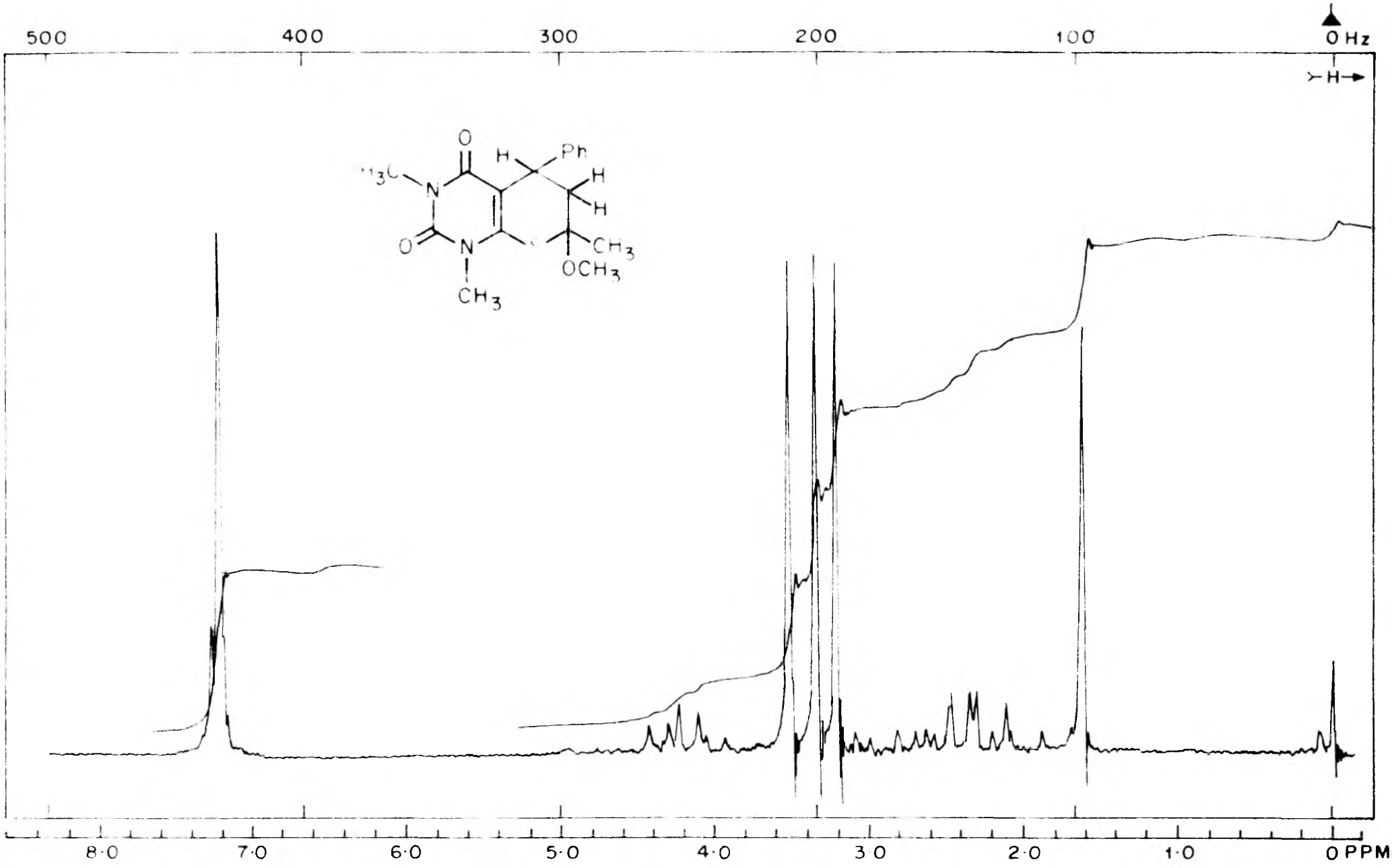
1,3-Dimethyl-2:4-dioxo-5-methyl-7-methoxy-7-phenyl-3H-Thiopyrano[2,3-d]pyrimidine (IVc)

Viscous solid: Yield 0.5 g (30%).

The purification should be repeated!


4000 3000
2000
1500
CM⁻¹
1000
900
800
700
100
80
60
40
20
0
TRANSMITTANCE (%)
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
O
H
Ph
H3C
N
O
N
S
CH3
OCH3
CH3

IR OF Ⅳ b


500
400
300
200
100
0 Hz
H
O
H
Ph
H
H
H_3C
N
O
N
CH_3
CH_3
OCH_3
CH_3
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM(δ

N.M.R. OF IV b

Elemental analysis: Found: C, 61.28; H, 6.15; N, 8.36; S, 9.82. $C_{17}H_{20}N_2O_3S$ requires C, 61.45. H, 6.03; N, 8.43; S, 9.64%.

Molecular weight by M.S. : 332

NMR($CDCl_3$): 1.30 (d, 3H, J = 7 cps CH_3 at C_5), 2.33 (m.c. 2H, C_6H's), 3.00 (tϕ or m.c. 1H, C_5-H), 3.16 (s, 3H, OCH_3 or N-CH_3) 3.30 (s, 3H, N-CH_3 or OCH_3) 3.53 (s, 3H, N-CH_3 or OCH_3) 7.36 (m.c. 3H, aromatic) 7.80 (m.c. 2H aromatic).

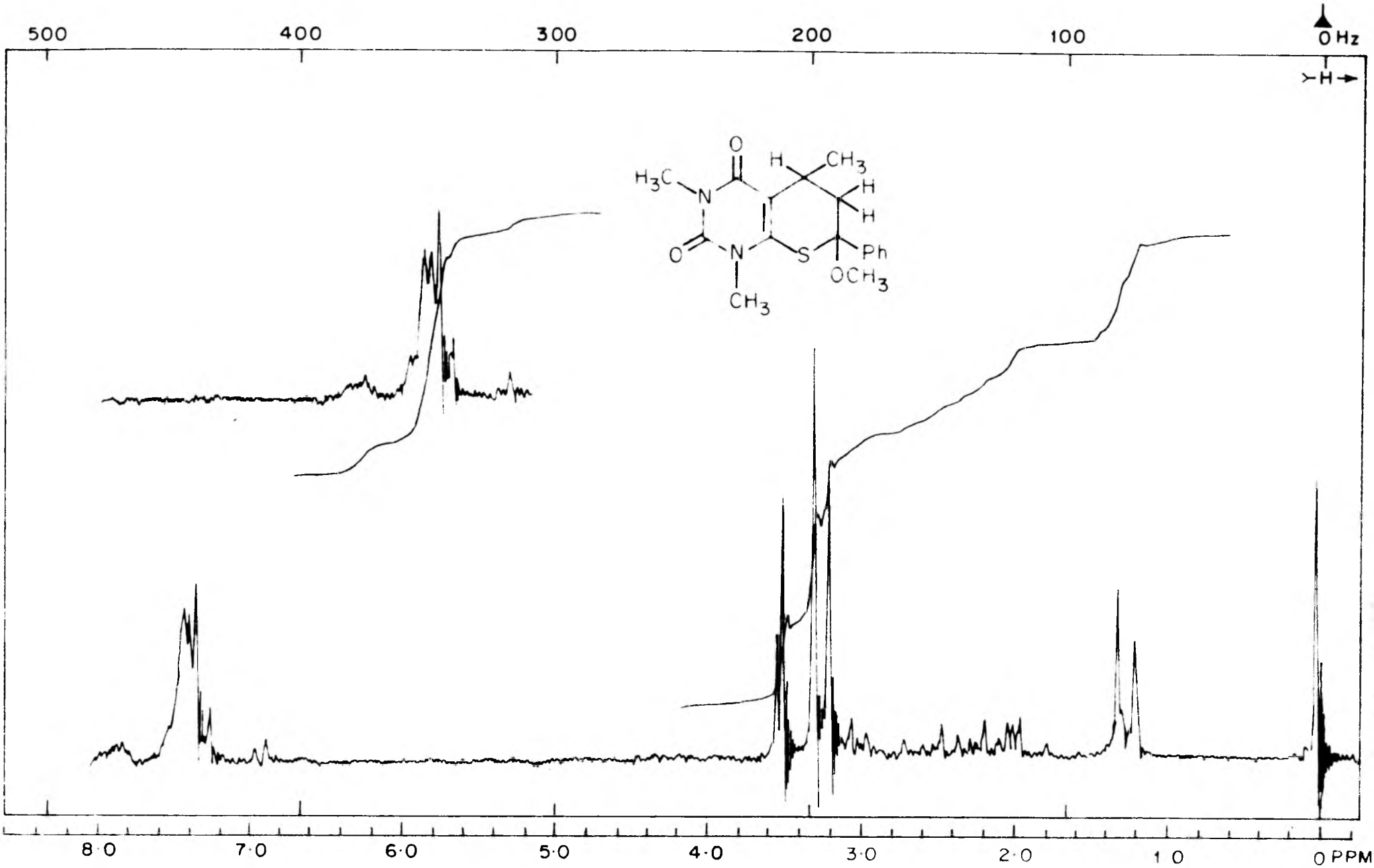
1,3-Dimethyl-2:4-dioxo-7-methoxy-7-methyl 1,2,3,4,5,6-hexahydro-4 H-Thiopyrano[2,3-d]pyrimidine (IVd)

Yield 0.06 g (24%) M.P. 145°.

Elemental analysis: Found: C, 51.82; H, 6.30; N, 11.25: S, 12.68; $C_{11}H_{16}N_2O_3S$ requires C, 51.57; H, 6.25; N, 10.94%.

Molecular wt. 256.

NMR($CDCl_3$): 1.30 (s, 3H, C_7-CH_3) 2.35 (m.c. 2H, C_6-H's) 2.73 (m.c. 2H, C_5-H's) 3.30 (s, 3H, N-CH_3 or OCH_3) 3.43 (s, 3H, N-CH_3 or OCH_3) 3.56 (s, 3H, N-CH_3 or OCH_3).


500
400
300
200
100
0 Hz
H
O
H
CH3
H3C
N
H
H
O
N
S
Ph
OCH3
CH3
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM (δ

N.M.R. OF IV c

General procedure II for the preparation of 6-mercapto-methyl uracils (VIa-c)

A solution of the appropriate adduct (IIIa-c, 3 x 10^{-4} mol) and methyl iodide (6 x 10^{-4} mol) in diethyl ether (10 ml) was stirred at 0-5°C for 2 hrs. The reaction mixture was later treated with potassium carbonate solution (5% 10 ml) and was left stirred for one more hour. The ether solution was separated, and washed with water, dried over anhy. sodium sulfate and was concentrated to about 5 ml. This solution was chromatographed over a silicagel column (20 x 1.5 cm) and eluted with benzene, and benzene:ethyl acetate (9:1). The later eluted fractions gave pure S-methyl adducts (VIIa-c).

1,3-Dimethyl-5(2-benzoyl-1-phenylethyl)-6-mercapto-methyl uracil (VIa)

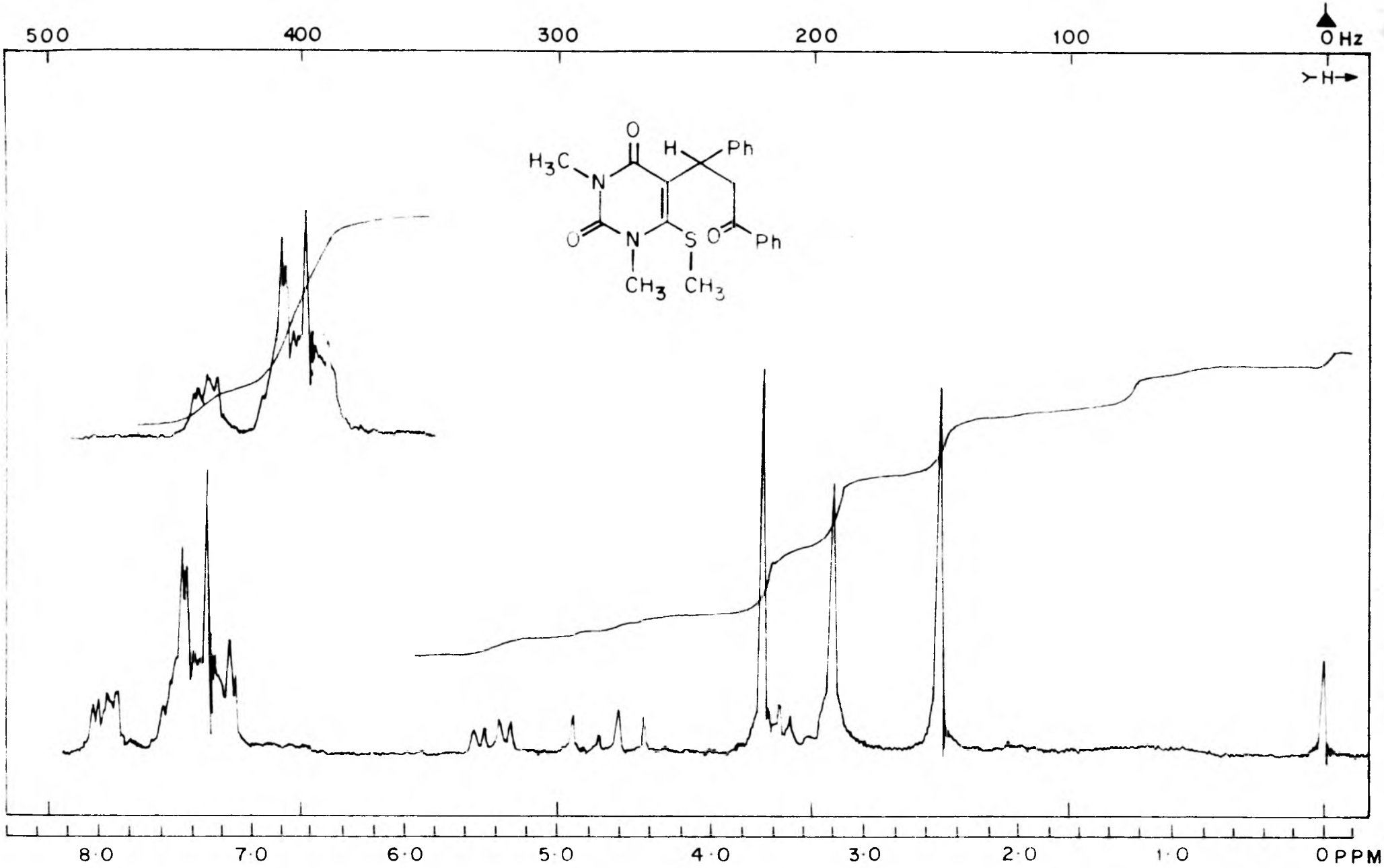
M.P. 85°. Yield: 0.995 g (72%).

Elemental analysis: Found: C, 67.23; H, 5.65; N, 7.26; S, 8.50. $C_{22}H_{22}N_2O_3S$ requires C, 67.01; H, 5.58; N, 7.09; S, 8.12%.

Molecular weight by M.S.: 394

NMR(CCl_4) 2.50 (s, 3H, S-CH_3), 3.16 (s, 3H, N-CH_3), 3.48 (d, 2H, J = 4 cps -CH_2-C(=O)- Ph), 3.63 (s, 3H, N-CH_3), 4.66* (2d, 1H, J = 10 cps benzylic -H) 5.38*(q 2d, 1H, J = 4 cps, benzylic H), 7.27 (m.c., 8H's, Aromatic) 7.90 (m.c., 2H's, aromatic)

*Separate resonances of protons in asymmetric environment.


500
400
300
200
100
0 Hz
H
O
H
Ph
H_3C
N
O
N
S
O
Ph
CH_3
CH_3
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM(δ

N.M.R. OF VI a

1,3-Dimethyl-5(2 -acetyl-1phenylethane)-6-mercaptomethyl) uracil (VIb)

M.P. 118°. Yield 0.065 g (68%).

Elemental analysis: Found C, 61.39; H, 6.21; N, 8.75; S, 9.50; $C_{17}H_{20}N_2O_3S$ requires C, 61.45 H, 6.03; N, 8.43; S, 9.64%.

NMR(CCl_4) : 2.03 (s, 3H, $-\overset{O}{\overset{\|}{C}}-CH_3$), 2.41 (s, 3H, $S-CH_3$), 2.70 - 3.00 (2d, 1H J = 5 Hz, $CH_2-\overset{O}{\overset{\|}{C}}-Ph$), 3.80 - 4.11 (2d, 14, J = 10 Hz, $CH_2-\overset{O}{\overset{\|}{C}}-Ph$) 5.05 = 5.30 (2 d, 1H, J = 5 Hz benzylic H's) 7.25 (m.c. 5H, Aromatic H's).

Molecular wt. 332.

1,3-D imethyl-5(2-benzoyl-1-methyl-ethane 6-methyl-mercaptouracil (VIc)

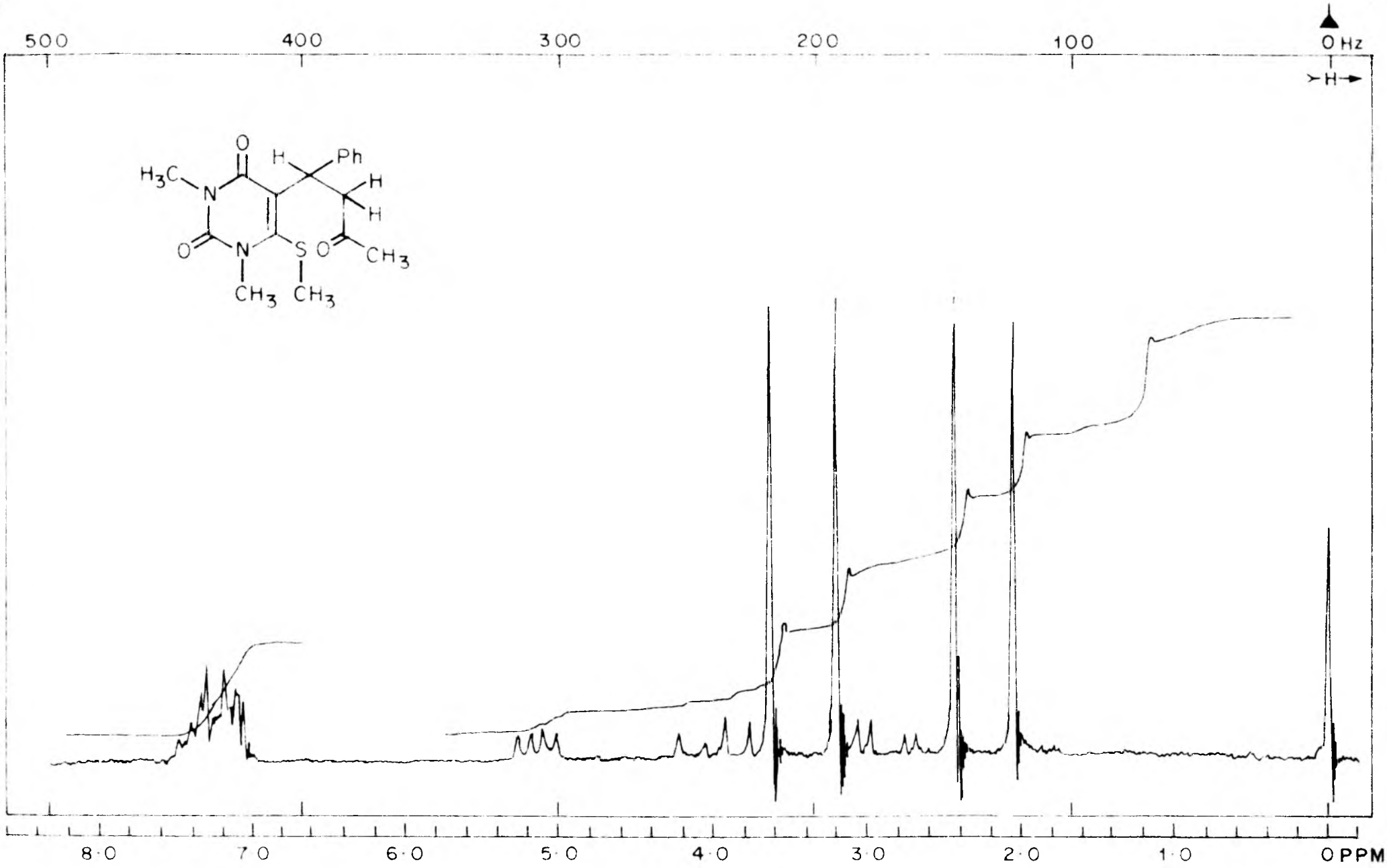
Yield: 0.066 g (64%) M.P. 152°.

Elemental analysis: Found: C, 61.54; H, 6.28; N, 8.70; S, 9.30%. $C_{17}H_{12}N_2O_3S$ requires C, 61.45; H, 6.03; N, 8.43; S, 9.64%.

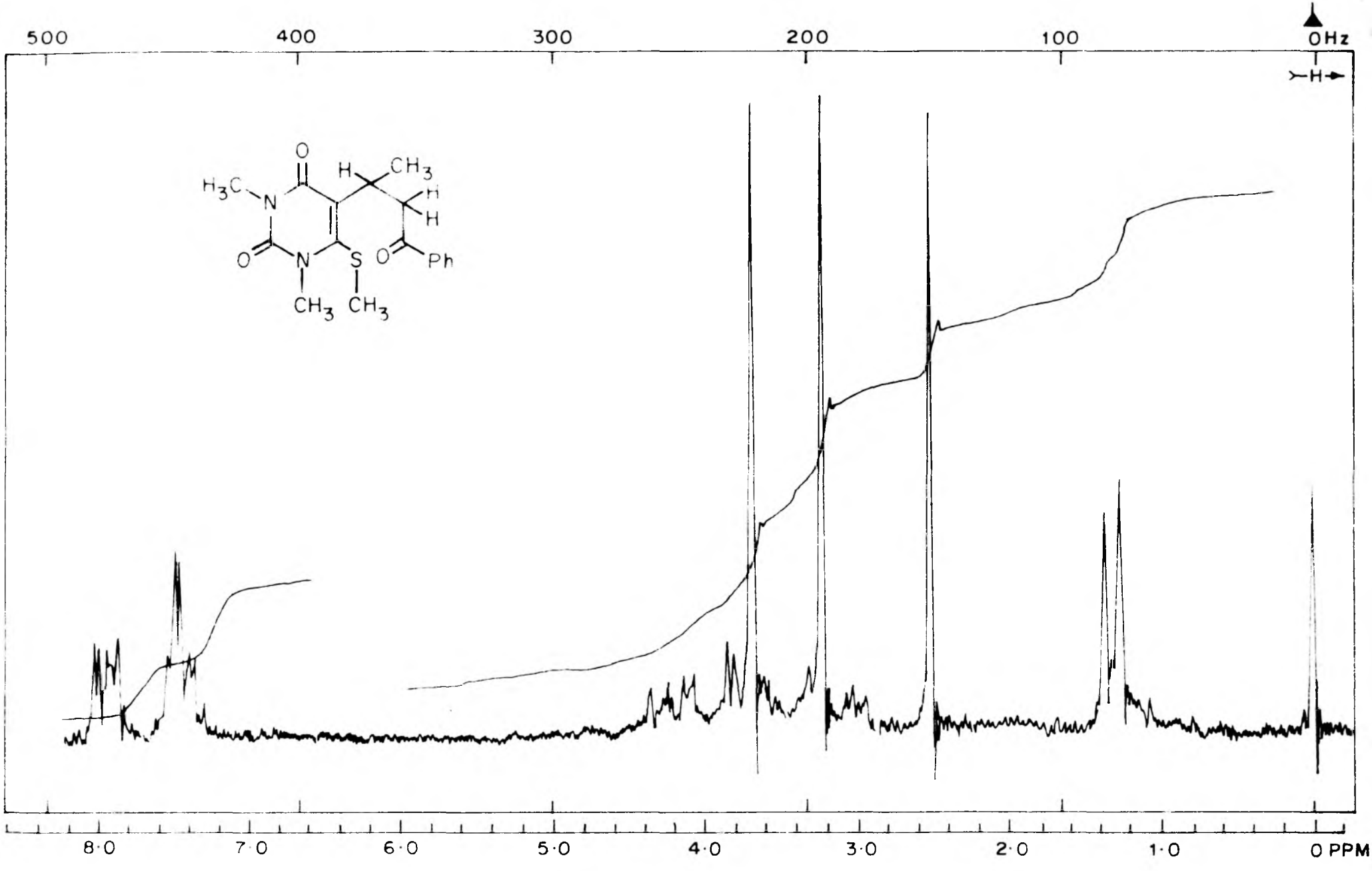
Molecular wt. by MS: 332.

NMR (CCl_4): 1.35 (d, 3H, J = 6 Hz, $C_6\ CH_3$), 2.51 (s, 3H, $S-CH_3$), *2.98 or 3.30 (m.c. $CH_2-\overset{O}{\overset{\|}{C}}-Ph$ or $-CH-CH_3$), *3.75 or 4.20 (m.c. $-CH_2-\overset{O}{\overset{\|}{C}}-Ph$ or $CH-CH_3$) 7.41 (m.c. 3H, Arom H) 7.90 (m.c. 2H, Arom H).

*Asymmetric carbon protons with different chemical shifts.


500
400
300
200
100
0 Hz
H
O
H
Ph
H3C
N
H
O
N
S
O
CH3
CH3
CH3
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM (δ

N.M.R. OF VI t



N.M.R. OF VI c

General procedure III preparation of 2H or 3H-thiopyrano-[2,3-d]pyrimidine 2:4-diones (Va-d, VIIa)

To a solution of (a) adducts (IIIa-d; 0.25 x 10^{-3} mol), or (b) 7-methoxy-3H-thiopyrano[2,3-d]pyrimidine (IVa-d, 0.25 x 10^{-3} mol) or (c) I and IIa-d (1 x 10^{-3} mol) in glacial acetic acid (5 ml), phosphorus pentoxide (with a,b, 0.35 x 10^{-3} mol, with c, 1.5 x 10^{-3} mol) was added at room temperature. The solution was refluxed over an oil bath held at 130°C for 3 hrs. Afterwards the reaction mixture was cooled to room temperature and poured over crushed ice and stirred. The solution with any suspended solid was neutralized with sodium carbonate solution (5%, 50-100 ml). The solution was extracted with chloroform (25-50 ml each), twice washed with water, dried over anny. Na_2SO_4 and was distilled to recover the solvent. A t.l.c. of the residue left after distillation was performed over silica gel plate (conditions same as in procedure 1). The thiopyrano compounds developed into dark brown spots at R.F. values 0.5 - 0.7. Purification:- Va, b,c were recrystallised from ether. Vd was chromatographed as in procedure I on a smaller scale. VIIa was recrystallised from rect. spirit.

1,3-dimethyl-2:4-dioxo-5,7-diphenyl-1,2,3,4,5-pentahydro-2H-Thiopyrano [2,3-d]pyrimidine (Va)

Yield: 0.14 (75%)[a] M.P. 127°

0.30 g (56%)[b]

Elemental analysis: Found: C, 69.26; H, 4.92; N, 7.58; S, 8.72; $C_{21}H_{18}N_2O_2S$ requires C, 69.61; H, 4.97; N, 7.73; S, 8.41%.

IR(nujol): 1695-1645 cm^{-1} (amide carbonyl).

NMR($CDCl_3$): 3.33 (s, 3H, N-CH_3), 3.56 (s, 3H, N-CH_3) 5.20 (d, 1H, J = 7 Hz C_5H), 6.38 (d, 1H, J = 7 Hz, C_6H), 7.41 (m.c. 10H, Arom H).

UV λ^{max}_{EtOH} (ε) : 262 (4.38), 308 (3.83).

Mass spectrum: m/e(%), 362(100), 329(15), 305(18), 285(86), 271(38), 229(64), 228(64), 223(15), 215(12), 202(30), 191(22), 187(46), 153(14), 152.5(14), 147(12), 145(10), 121(36), 116(39)., 102(26), 89(21), 77(32), 67(20), 51(22).

1,3-Dimethyl-2:4-dioxo-5,7-diphenyl-1,2,3,4,7-pentahydro-2H-thiopyrano/2,3-d/pyrimidine (VIIa)

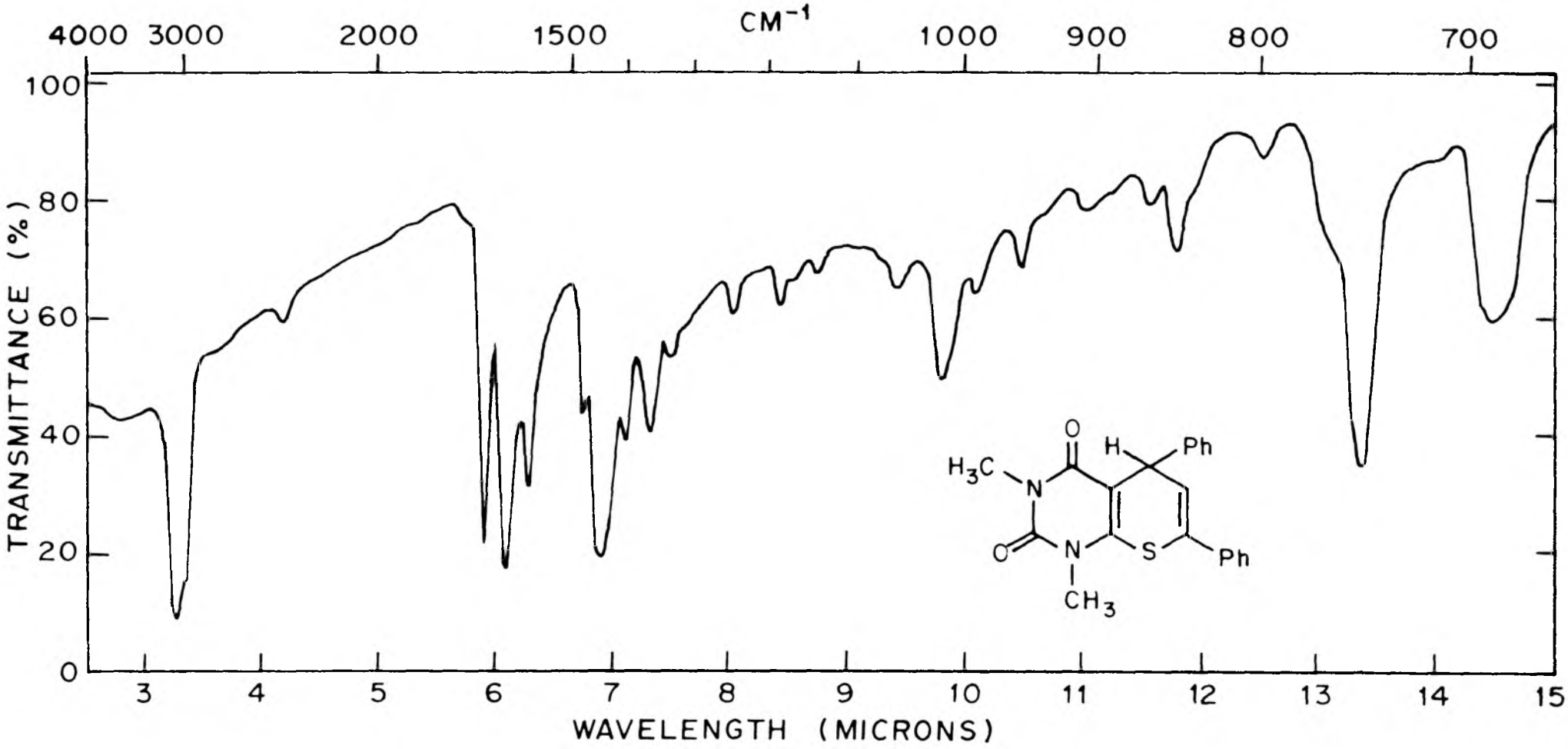
Yield: 0.56 g (52%) M.P. 201°C.

Elemental analysis: Found: C, 69.54; H, 4.83; N, 7.85; S, 8.65. $C_{21}H_{18}N_2O_2S$ requires C, 69.61, H, 4.97; N, 7.73; S, 8.41%.

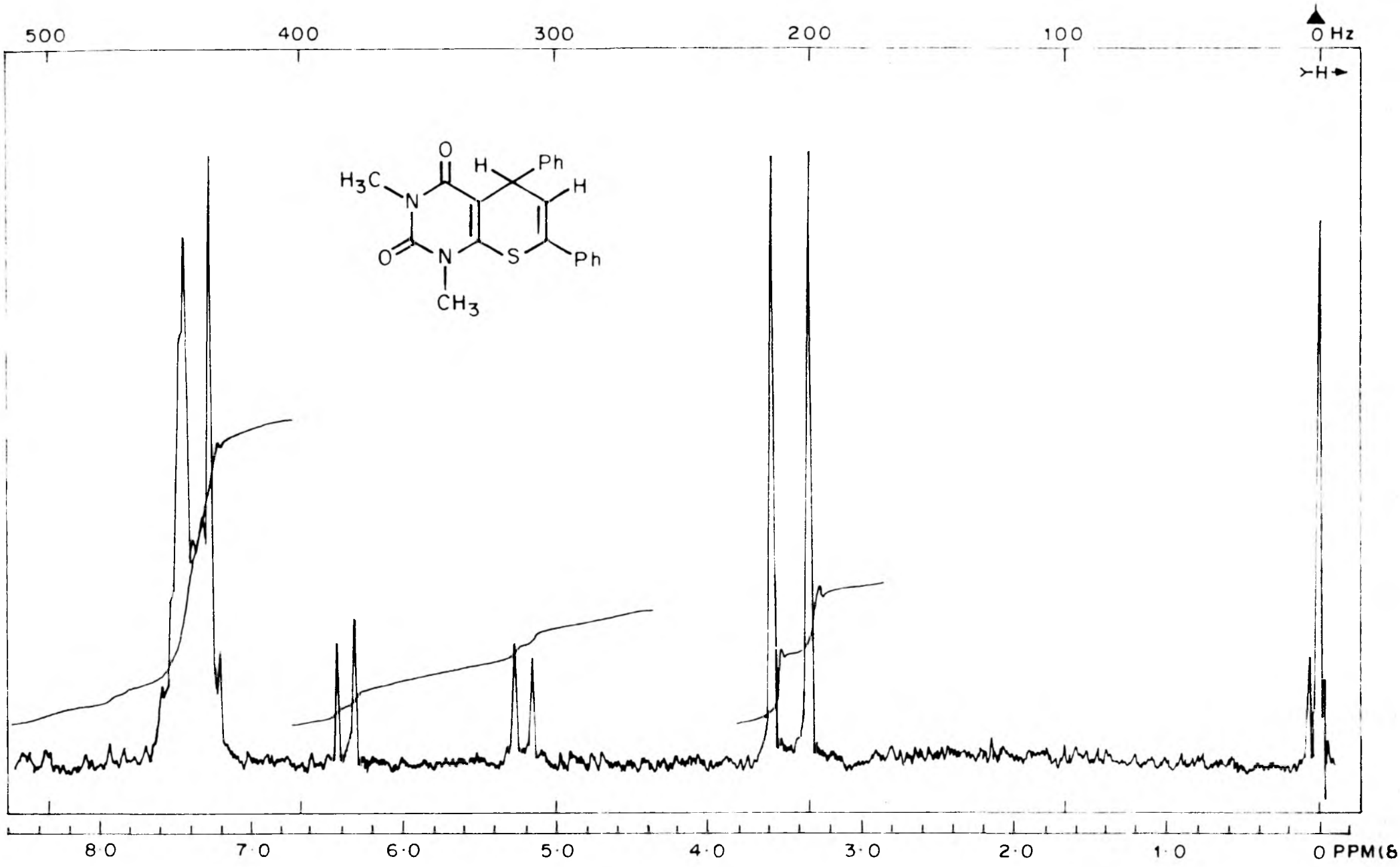
IR(nujol): 1695-1645 cm^{-1} (Amide carbonyl).

UV λ^{max}_{EtOH} (ε): 255(3.83), 340 (3.02).

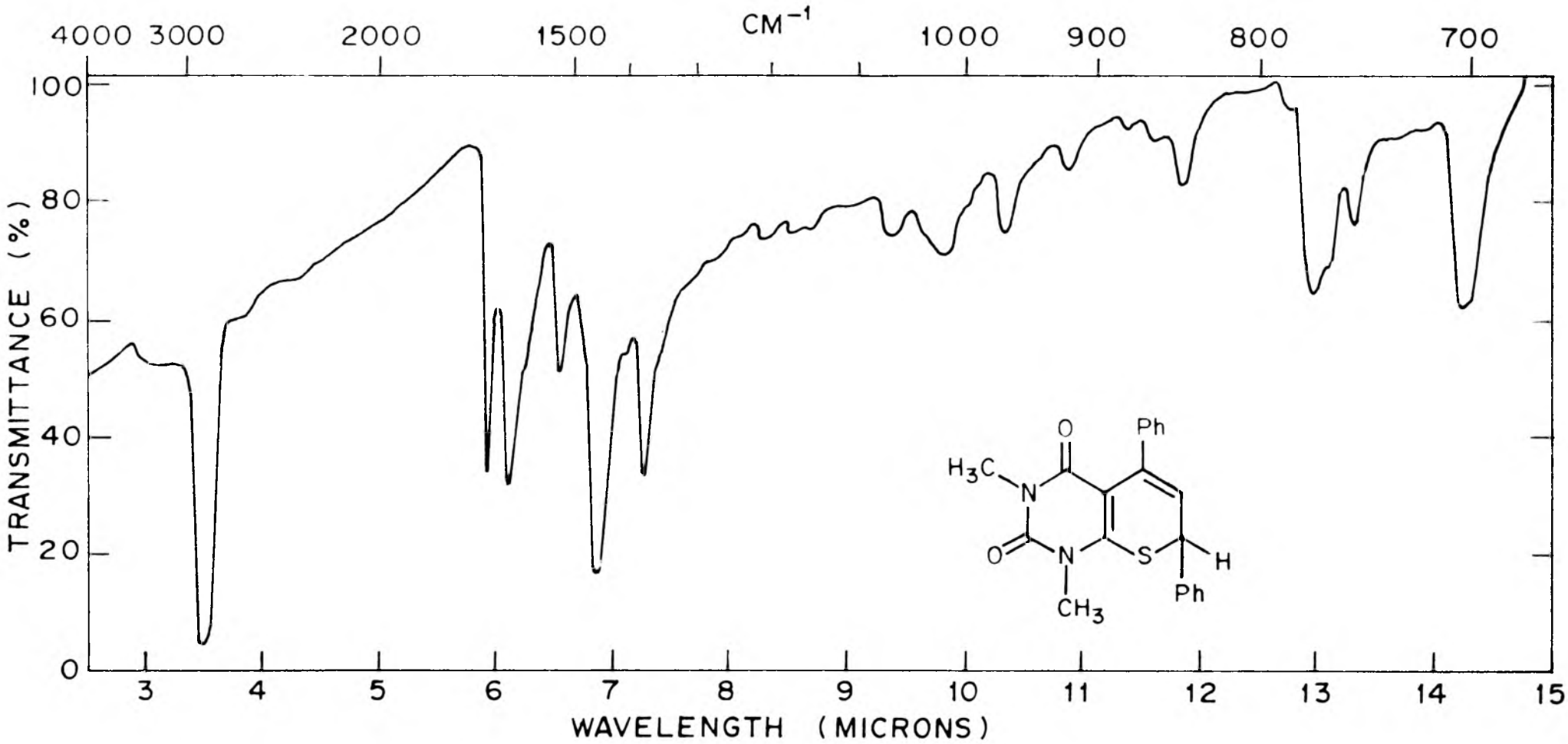
NMR($CDCl_3$): 3.26 (s, 3H, N-CH_3), 3.56 (s, 3H, N-CH_3), 5.10 (d, 1H, J = 6 Hz, C_7H), 5.80 (d, 1H, J = 6 Hz, C_7H), 5.80 (d, 1H, J = 6 Hz, C_6H), 7.33 (m.c., 10H, Arom H').


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
O
H
Ph
H3C
N
N
S
Ph
O
CH3

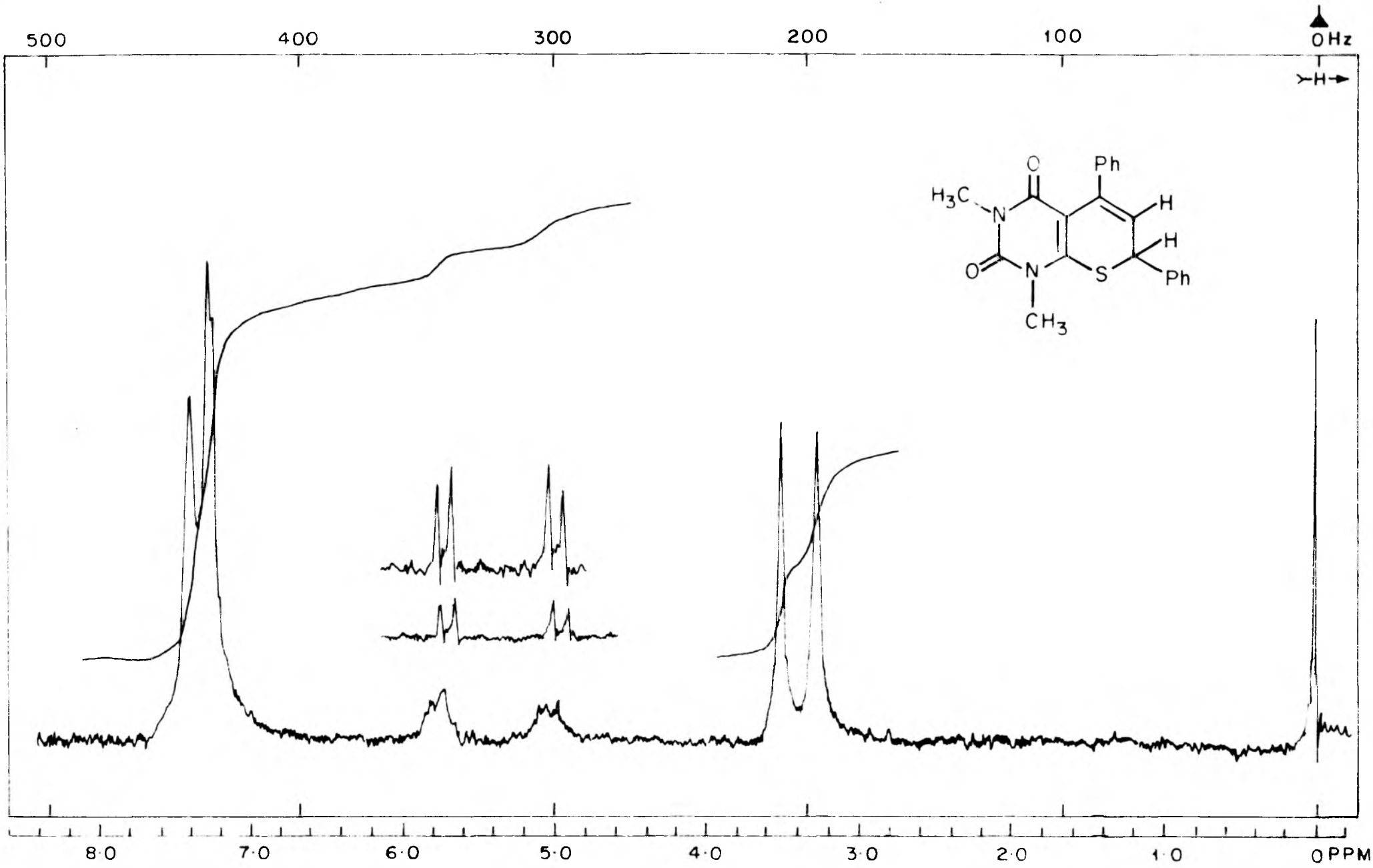
IR OF V a


500
400
300
200
100
0 Hz
>H<
O
H
Ph
H3C
N
H
O
N
S
Ph
CH3
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM(δ

N.M.R. OF V a


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
O
Ph
H3C
N
O
N
S
H
Ph
CH3

IR OF VII a


500
400
300
200
100
0 Hz
→H←
O
Ph
H3C
N
H
H
O
N
S
Ph
CH3
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM (δ)

N. M. R. OF VII a

Mass spectrum: m/e (%) 362(100), 329(3), 305(8), 285(66), 261(8), 259(16), 228(27), 215(8), 209(10), 202(10), 121(14), 115(19), 105(32), 77(37), 75(13), 69(10), 57(11), 55(12), 51(12), 28(29)

1,3-Dimethyl-2:4-dioxo-5-phenyl-7-methyl 1,2,3,4-tetrahydro-2H-thiopyrano[2,3-d]pyrimidine (Vb)

Yield 0.58 g (63%)[b], M.P. 138-139°
0.18 g (59%)[a], 0.1 g (68%).

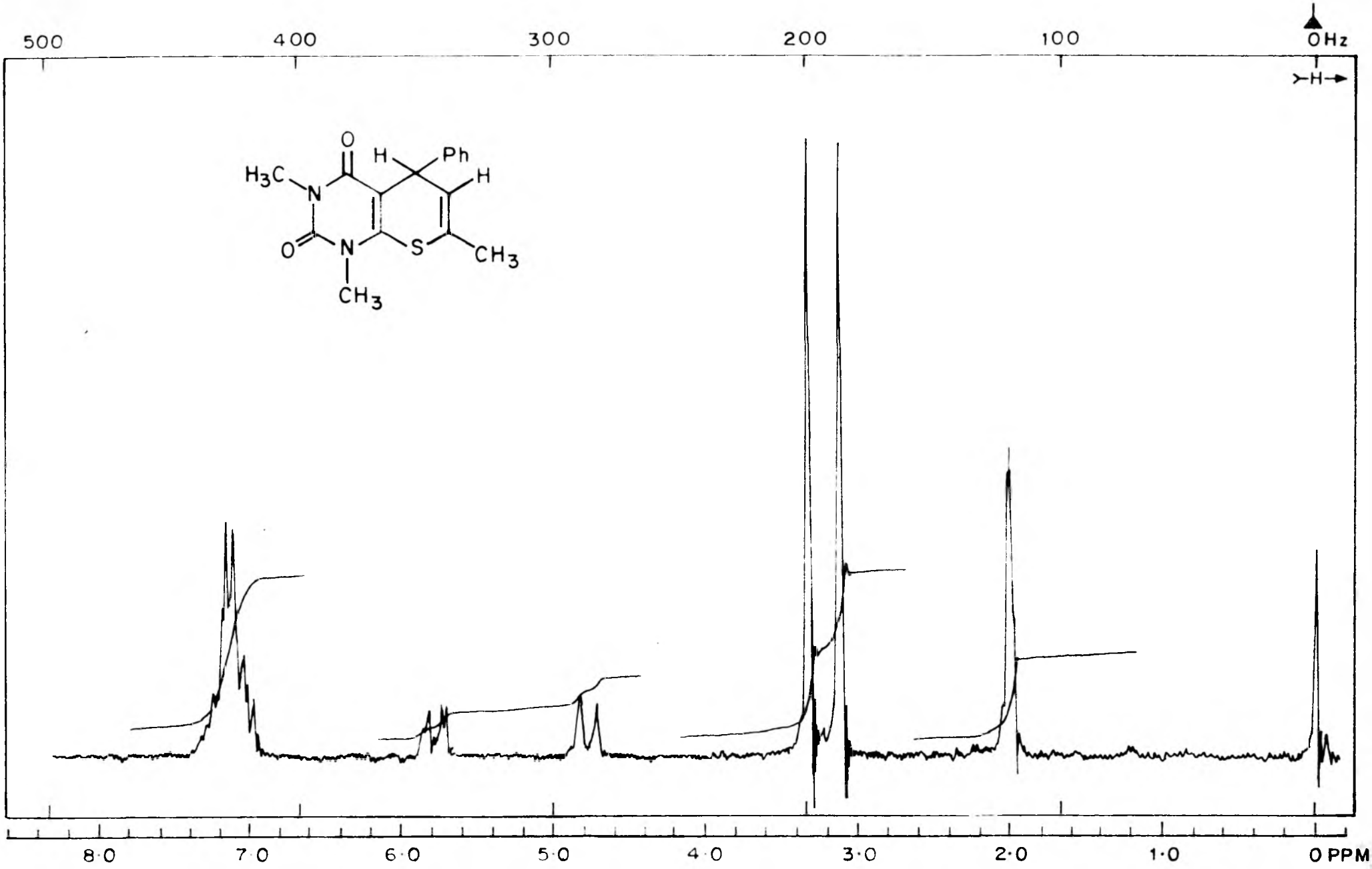
Elemental analysis: Found: C, 64.25; H, 5.48; N, 9.65. S, 10.22. $C_{16}H_{16}N_2O_2S$ requires C, 64.00; H, 5.33; N, 9.33; S, 10.66%.

NMR(CCl_4): 2.00 (s, 3H, C_7-CH_3), 3.10 (s, 3H, N-CH_3), 3.31 (s, 3H, N-CH_3), 4.75 (d, 1H, J = 7 Hz, C_5-H), 5.76 (d, 1H, J = 7 Hz C_6-H), 7.10 (m.c., 5H, Arom H).

Mass spectrum: m/e(%) 300(100), 285(80), 267(33), 242(71), 228(59), 225(74), 224(78), 223(97), 222(50), 213(76), 210(66), 167(66), 166(78), 141(51), 138(54), 129(54), 128(68), 127(57), 125(61), 123(58), 122(61), 115(59), 102(51), 77(48), 59(71),45(68), 43(54).

1,3-Dimethyl-2:4-dioxo-5-methyl-7-phenyl 1,2,3,4-tetrahydro-2H-thiopyrano[2,3-d]pyrimidine (Vc)

Yield 0.64 (71%)[c] M.P. 135°
0.16 (52%)[a]
0.11 (75%)[b]


500
400
300
200
100
0Hz
H
O
H
Ph
H
H3C
N
O
N
S
CH3
CH3
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM(δ

N.M.R. OF V b

Elemental analysis: Found C, 64.15; H, 5.25; N, 9.54; S, 10.91
$C_{16}H_{16}N_2O_2S$ requires C, 64.00; H, 5.33;
N, 9.33; S, 10.66%.

M.S. Molecular Wt.: 300

NMR($CDCl_3$): 1.36 (d, 3H, J = 7 Hz, C_5-CH_3), 3.28 (s, 3H, N-CH_3), 3.58 (s, 3H, N-CH_3), 3.93 (t or m.c. 1H, J = 6 Hz, -C_5-H), 5.58 (d, J = 6 Hz, C_6-H), 7.23 (b,s, 5H, Arom H)

1,3-Dimethyl-2:4-dioxo,7-methyl-1,2,3,4-tetrahydro-3H,thiopyrano[2,3-d]pyrimidine (Vd)

Yield 0.27 g (40%)[c] viscous solid
0.15 g (45%)[a]
0.11 g (65%)[b]

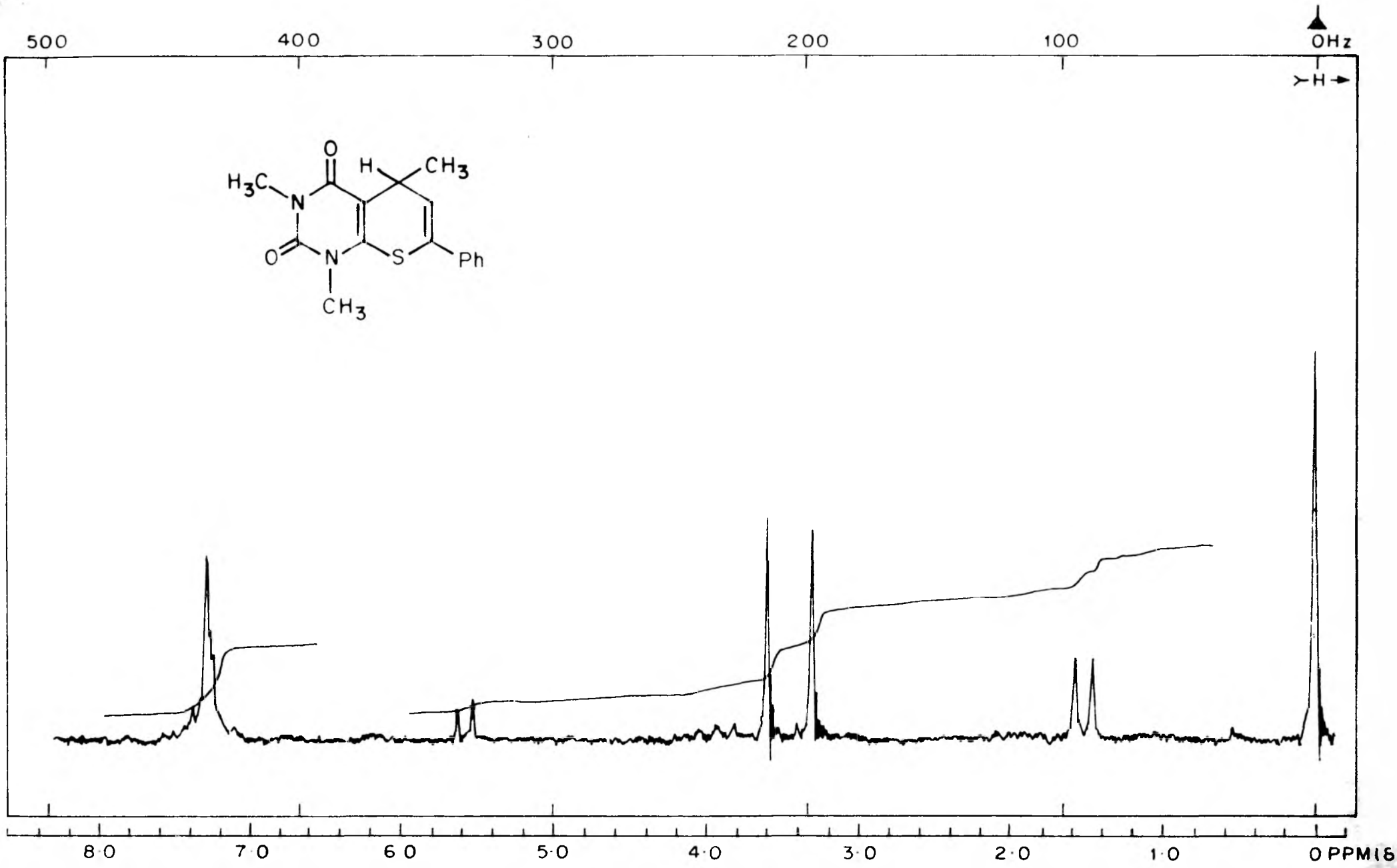
Elemental analysis: Found: C, 53.65; H, 5.81; N, 12.92;
S, 13.62. $C_{10}H_{12}N_2O_2S$ requires C, 53.53;
H, 5.35; N, 12.50; S, 14.29%.

Molecular wt. by M.S.: 224.

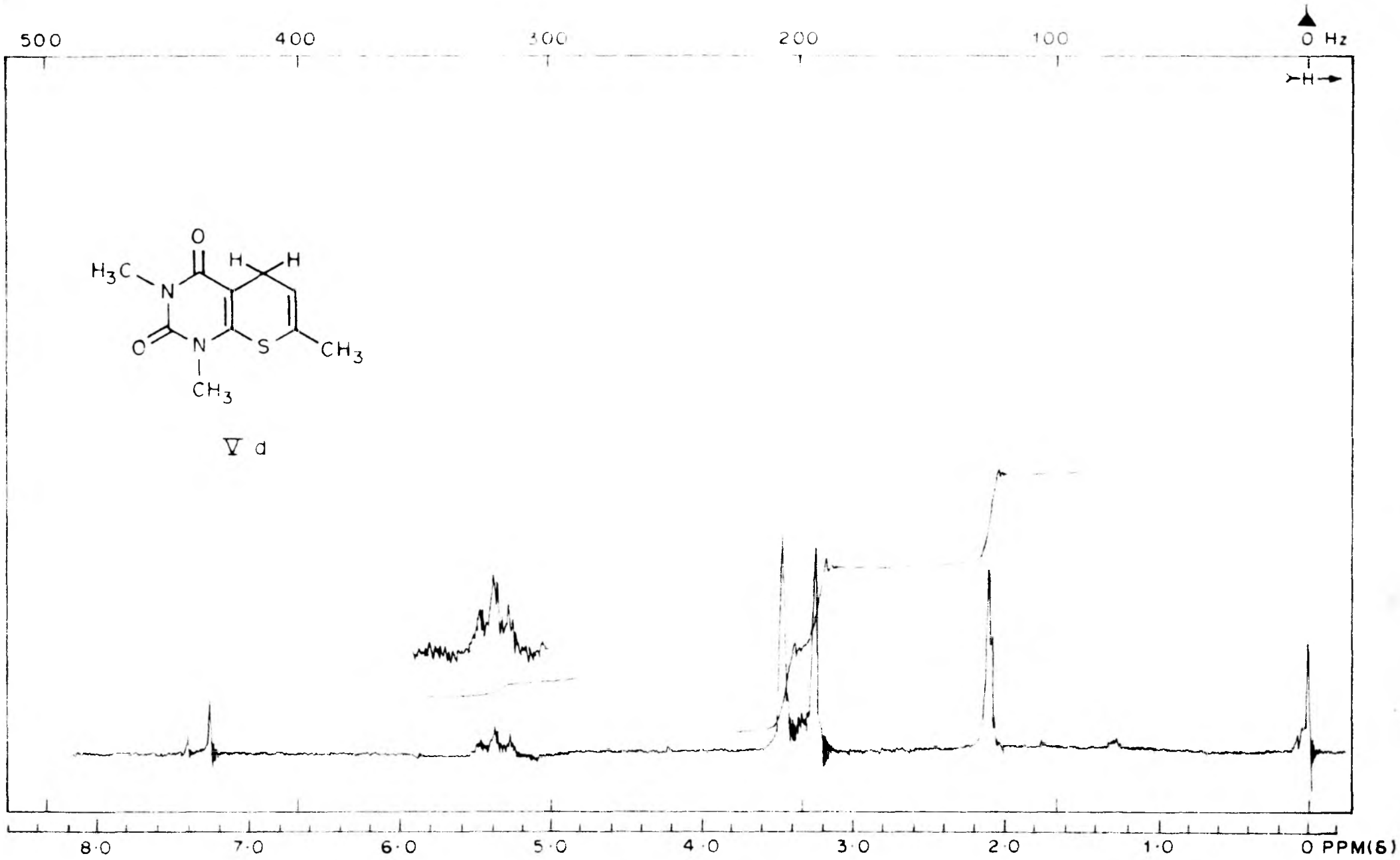
NMR (CCl_4): 2.11 (b.s., 3H, C_7-CH_3), 3.23 (s, 3H, N-CH_3), 3.31 (m.c. 2H, J = 2 and 6 Hz, C_5H') 3.43 (s, 3H, N-CH_3), 5.30 (t, 1H, J = 2 and 6 Hz, C_6-H)

Synthesis of 1,3-dimethyl-2:4-dioxo-5,7-diphenyl-1,3,4,5-tetrahydro-2H-thiopyrano[2,3-d]pyrimidine (Va)

A solution of 1 (2.5×10^{-3} mol), benzaldehyde (2.8×10^{-3} mol) and phenylacetylene (3.4×10^{-3} mol) in acetic anhydride (12 ml) was refluxed over an oil bath held at


500
400
300
200
100
0Hz
H
O
H
CH3
H3C
N
O
N
S
Ph
CH3
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPMIδ

N.M.R. OF Vc


500
400
300
200
100
0 Hz
H
O
H
H
H_3C
N
O
N
S
CH_3
CH_3
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM(δ)

∇ d

N. M. R. OF ∇ d

135-140° for one hour. Acetic anhydride was distilled from the reaction mixture under reduced pressure at 30 mm and 60-70° bath temperature. The crude reaction product was spotted over a silica gel t.l.c. plate along with Va and VIIa and the plate was developed in benzene;ethylacetate (4:1) solution. The spots developed in iodine chamber showed the presence of only Va in the reaction mixture among others (VIIa ~~xx~~ compound was not present). The crude product was purified by preparative chromatography over silica gel using the same solvent M.P. 128°, yield 0.24 g (26%). Identical in n.m.r. mol. wt. with Va.

General procedure IV. Preparation of 7-methoxy-thiopyrano-[2,3-d]pyrimidines (IVa-d)

A solution of the adducts (IIIa-d, 0.25 x 10^{-3} mole) in methanol (5 ml) and piperidine (0.1 ml) was refluxed for 4 hrs. at 80°. Methanol was distilled under water suction (40 mm) from the reaction mixture. The product was purified by chromatography over silicagel column as described in the ~~proe~~edure II. The products obtained were identical in their m.p., n.m.r. and molecular weights with IVa-d. Yield (%): IVa, 0.021 g (22); IVb, 0.023 g (28), IVc, 0.012 g, (15%), IVd 0.015 (24).

S U M M A R Y

S U M M A R Y

A new synthesis of 5,7-disubstituted 2H-thiopyrano-[2,3-d]pyrimidine-2:4-diones involves the base catalysed michael addition of 1,3-dimethyl-6-mercaptouracil (1) to α-β-unsaturated ketones (II) and subsequent cyclization of the mono-adducts so formed. Acid catalysed addition and cyclization of (I) and (II) in one step reaction also furnished the same thiopyrano compounds in better yields. However, the one step condensation of (I) and benzal-acetophenone (IIa) gave a double bond isomer (VIIa).

REFERENCES

REFERENCES

1. B.R. Baker, C.E. Morȳel and Beng-thong-Ho; J.Med.Chem., 6(6), 658-64 (1963).
2. Heinrich Warnhoff and Friedhelm Korte, Chem.Ber. 99, 972-78 (1966).
3. Haruo Ogura, Masakazu Sakaguchi, Chem.Lett. (8), 657-8 (1972) (Eng.), c.f. C.A. 77,114344k.
4. A. Subbarao, and R.B. Mitra, Ind.J.Chem., 12, 1028-1030(1974).
5. R.T. Hobgood, J.R., G.S. Reddy and J.H. Goldstein, J.Phy.Chem. 67, 110 (1963).
6. R.R. Schmidt, and M. Dimmler, Chem.Ber. 108, 8 (1975).
7. Josette Carretto, S. SiB et M. Simalty, Bull De.La.Soc.Chim. France (6) 2312-13 (1972).
8. K.E. Schulte, Volket Von Weissenborn and George Tittle, Chem.Ber. 103, 1250 (1970).
9. a) C.E. Scot and C.C. Price, J.Am.Chem.Soc., 81, 2672 (1959).
   b) K.K. Georgieff and A. Dupre, Can.J.Chem. 37, 1104 (1959).
   c) C.C. Price and J. Zomlefer, J.Am.Chem.Soc., 72, 14 (1950).
10. Conard and Reinbach, Chem.Ber. 34, 1339 (1901).
11. G. Kyriakakou, M.C. Rouk-Schmitt and J. Seydem-Penne, Tetrahedron, 31(6), 1883 (1975).

CHAPTER IV

REACTION OF 1,3-DIMETHYL-6-MERCAPTOURACIL AND DIMETHYLACETYLENEDICARBOXYLATE

INTRODUCTION

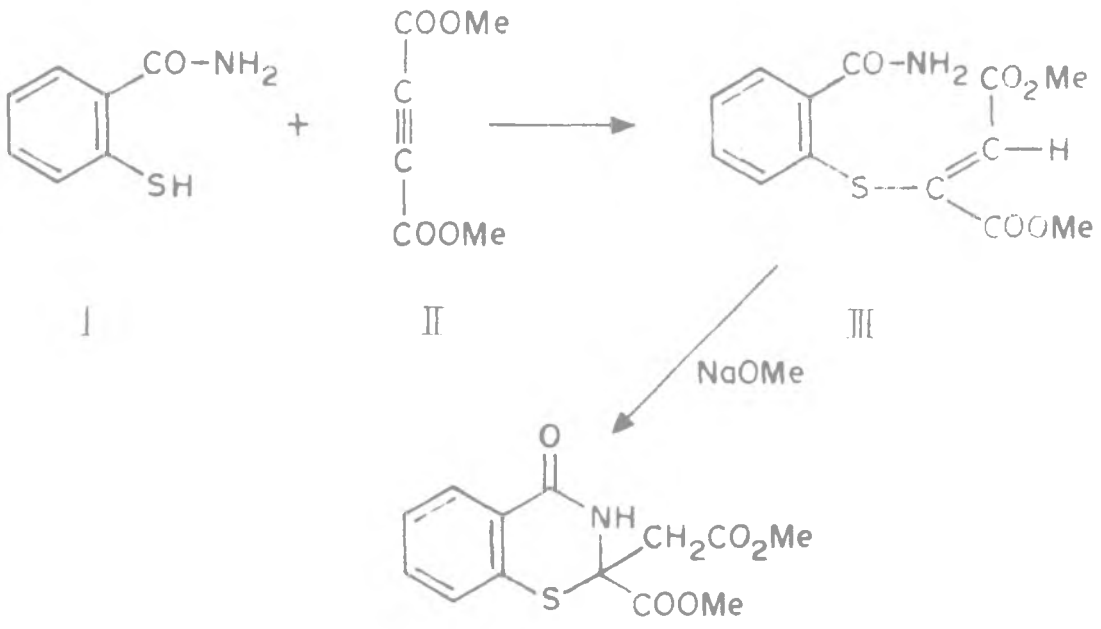
INTRODUCTION

Michael additions of thiophenols, thiophenolate and 2-nitrothiophenolates to activated triple bonds have been reported to yield the respective vinylthioethers[1,2,3].

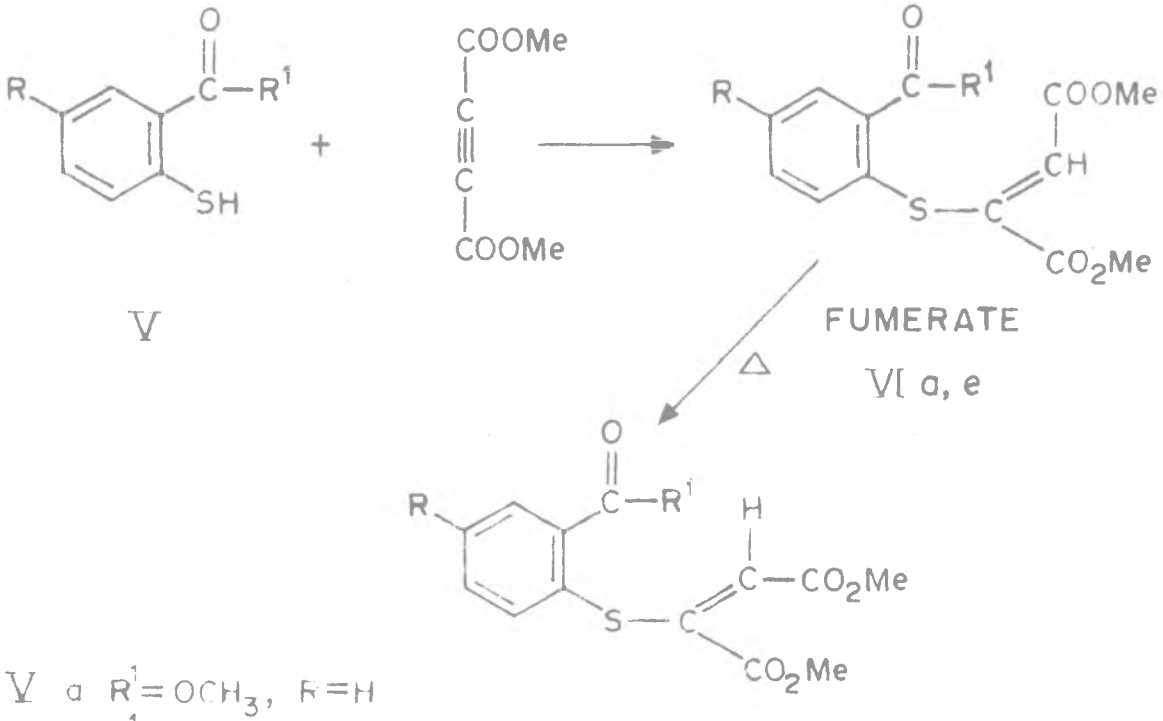
Heindal and Fish et al.[4] have investigated in detail the addition of o-mercaptobenzamides and methyl thiosalicylate to acetylene dicarboxylic ester. The o-mercaptobenzamide (1) underwent a spontaneous and mildly exothermic reaction with acetylene dicarboxylic ester which resulted in formation of the adduct (III). Absence of SH absorption in the IR and n.m.r. spectra of the product and the retention of amide NH_2 bands clearly defined the adduct as an S-substituted species.

The n.m.r. spectrum of the S-adduct (III) allowed the structural assignment of fumerate geometry to the diester portions. This adduct required a catalytic quantity of sodium methoxide to effect ring closure and the resulting product was 2-carbomethoxy-methyl-2-carbomethoxy-1,3-benzothiazin-4-one (IV). The given structure was based on its n.m.r. spectrum.

Preparation of adducts at temperatures from ambient to the boiling point of methanol furnished the thiol adducts with exclusively trans (fumerate) geometry. The n.m.r. spectra demonstrated the presence of only one vinyl and three methyl ester resonances.



I II III IV

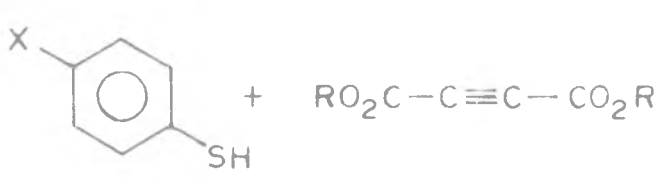


V a $R^1 = OCH_3$, R=H
b $R^1 = OCH_3$, R=Cl
c $R^1 = OCH_3$, R=Br
d $R^1 = OH$, R=H
e. $R^1 = NH_2$, R=H

The parent methyl salicylate adduct (Va) was vacuum distilled without decomposition. The distilled material gave evidence of a thermal isomerisation of the olefinic linkage; a new peak in the vinyl region (6.05 ppm) and two new methyl ester resonances for the pendant butanedioate portion (3.68 ppm). It was possible to heat the initially trans adduct 0.5 hr at 190° and to produce 35% isomerization to cis (maleate). Further conversion to 45% cis (maleate). Further conversion to 45% cis adduct was obtained after 0.5 hr at 210°.

Dolfini's[15] method for relating chemical shifts of the vinyl protons in the isomeric amine-acetylene dicarboxylate adducts to the stereochemistry of the system can be applied to the thiol adducts. The initially produced isomer (VIa) displayed vinyl resonance at 6.80 and the ester methyls at 3.46 and 3.80 ppm characteristic of fumerate geometry. This more highly deshielded vinyl proton experiences the greater diamagnetic anisotropy of the two flanking ester carbonyls. Likewise, the esters themselves are in slightly different electronic environments and hence are less equivalent than those of the maleate which appear under the same peak at 3.68 ppm.

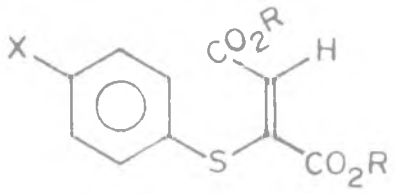
As an extension of interest in thiolactam addition to triple bonds Undheim and Lie[6] have reinvestigated the reaction between thiophenols and acetylene dicarboxylic acid and its methyl ester. In ethyl acetate the methyl ester of acetylene-dicarboxylic acid would add thiophenol and its methyl (VIIa-c) and chloro(VIIc)



VII a – d

a) X = H c) X = Cl

b) X = CH_3 d) X = NO_2



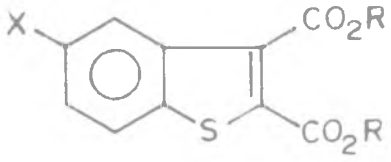
a) X = H, R = CH_3

b) X = R = CH_3

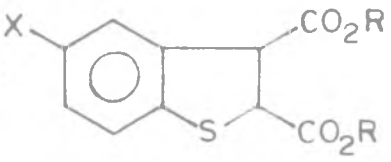
c) X = Cl, R = CH_3

d) X = NO_2, R = CH_3

VIII a – d



IX a – d



X e,f

a) X = R = H

b) X = H, R = CH_3

c) X = CH_3, R = H

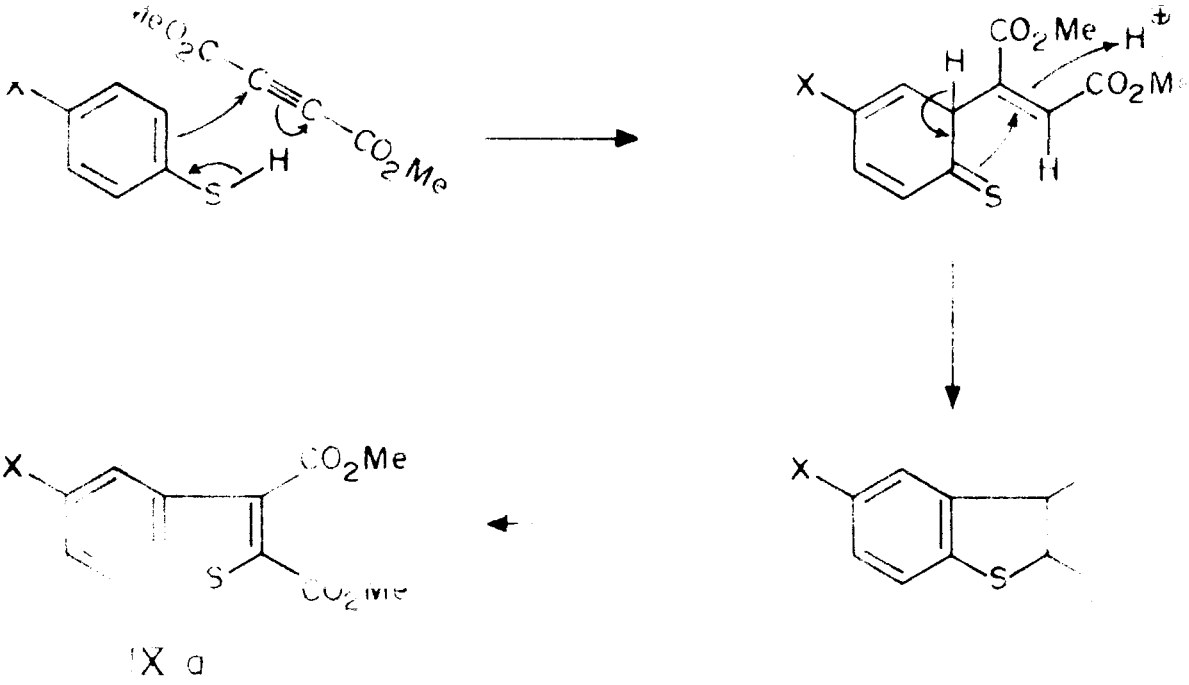
d) X = R = CH_3

e) X = Cl, R = H

f) X = Cl, R = CH_3

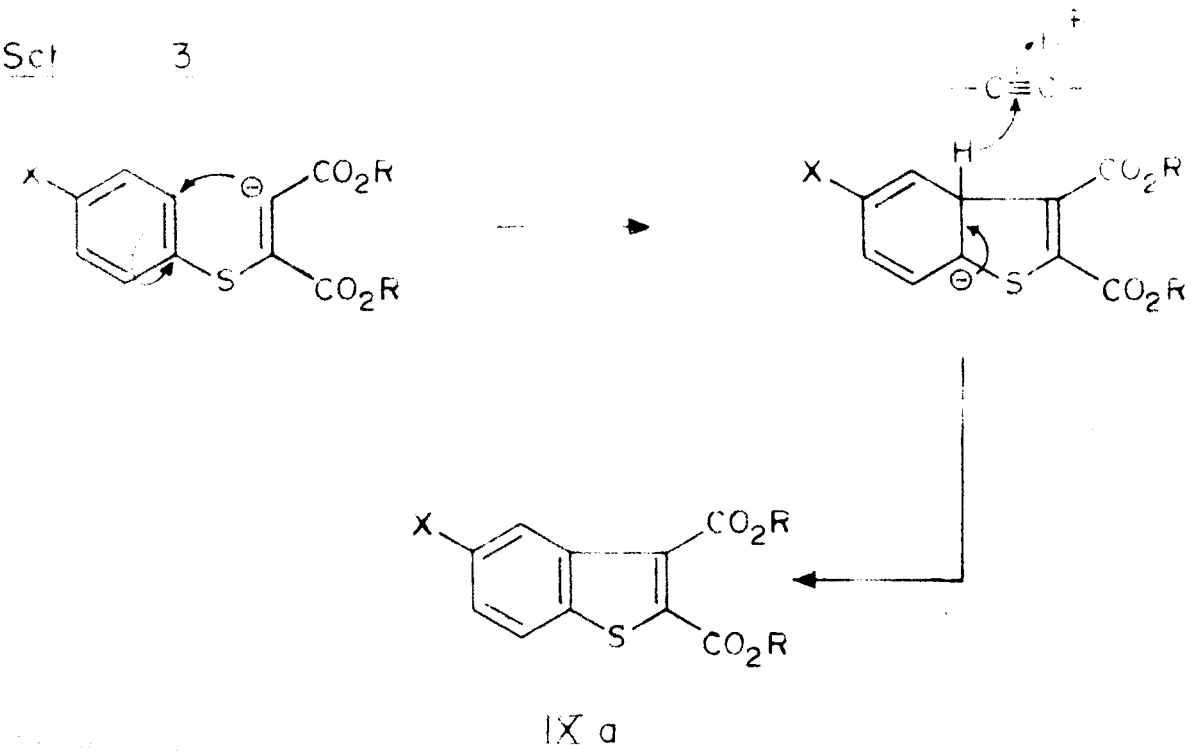
derivatives but not the nitro derivative (VIId). Acetylene-dicarboxylic acid reacted similarly. The reaction gave the cleanest product when run in the cold for several days. The product was identified as a benzo[b]thiophene (IXa-c) as discussed below. In methanol however no reaction took place in the cold. On reflux p-chloro and p-nitrothiophenol gave the vinyl thioethers (VIIIc,d), while thiophenol and its p-methyl homologue yielded a mixture of the vinyl thioether (VIIIa-c) and the ~~tri~~bicyclic product (IXa-c).

The structure of the latter was evident from the n.m.r. spectra which showed only aromatic protons and UV maxima in ethanol at about 290 nm, 245 nm and 230 nm. In the n.m.r. spectum of III ($CDCl_3$) the vinyl proton appeared as a sharp singlet at 6.5 ppm which suggested that only one stereo-isomer was present. If the usual trans addition is assumed, the carboxy groups in the vinyl thioether have the trans-configuration. The initial addition step was thought to be ionic. The direct formation of the benzo[b]thiophene could possibly take place via the vinyl thioethers (VIIIa-d) involving rapid dehydrogenation of an intermediate, 1,2-dihydrobenzo[b]thiophene (X). But investigation into crude reaction mixture did not furnish any evidence to support the above mechanism. Attempts failed to cryclise (VIIIa) by heating in ethyl acetate or methanol with and without the presence of methyl acetylene dicarboxylate which was thought to be the hydride ion abstractor. Vinyl thioethers

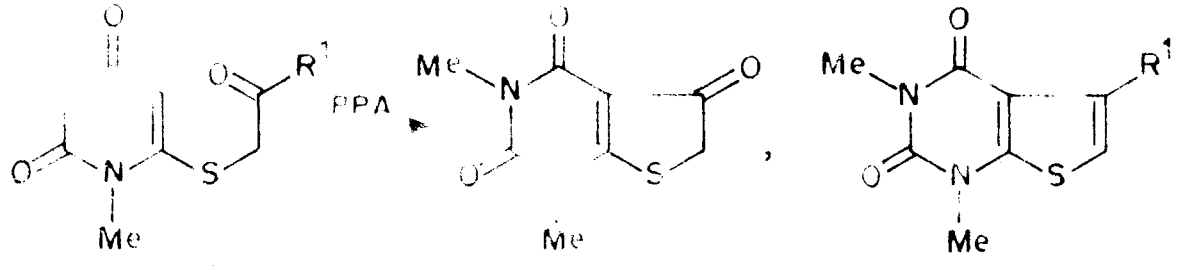


IX a

Scl 3



IX a



XI XII XIII

$R^1 = OEt$, CH_3, C_6H_5, C_6H_5Br (p)

were excluded as an intermediate in the reaction. The dihydro derivative (X) which was prepared from Na-amalgam reduction of IXa could not be converted to the benzo [b] thiophene in the presence of acetylene dicarboxylate ester. Involvement of an intermediate carbanion type structure (Scheme 3) was suggested as a possible mechanistic route leading to the bicyclic product (IXa).

Such an anion with suggested reaction path (Scheme 3), according to this mechanism both the rate of addition and hydride abstraction are dependent on the electron releasing properties of the para substituent. Thus the nitrothiophenol did not react in ethyl acetate and when forced in methanol gave the vinyl ether. On the other hand both thiophenol and its P-methyl analogue in methanol yielded both products (VIII, IXa-c). These results could be interpreted to mean that hydride abstraction is the rate determining step in the overall reaction.

1,3-Dimethyl-6-mercaptouracil was reacted with α-halogenocarbonyl compounds to yield 2,4-(6-substituted acylthio)pyrimidinediones[7] (XI) as intermediates. In this case, substitution reaction occured at C-6 mercaptohydrogen. The intermediate pyrimidylsulfide (R' = OEt) was treated with polyphosphoric acid and cyclised to the ketone (XII). Similar treatment of these intermediates (XI) caused the cyclisation to 1,3-dimethyl-2,4-thieno[2,3-d]pyrimidinediones (XIII).

Warnhoff and Korte[8] have cyclised 5(2-mercatoethyl) 6-hydroxy pyrimidines in polyphosphoric acid to give a 5,6-dihydrothiopheno[2,3-d]pyrimidines.

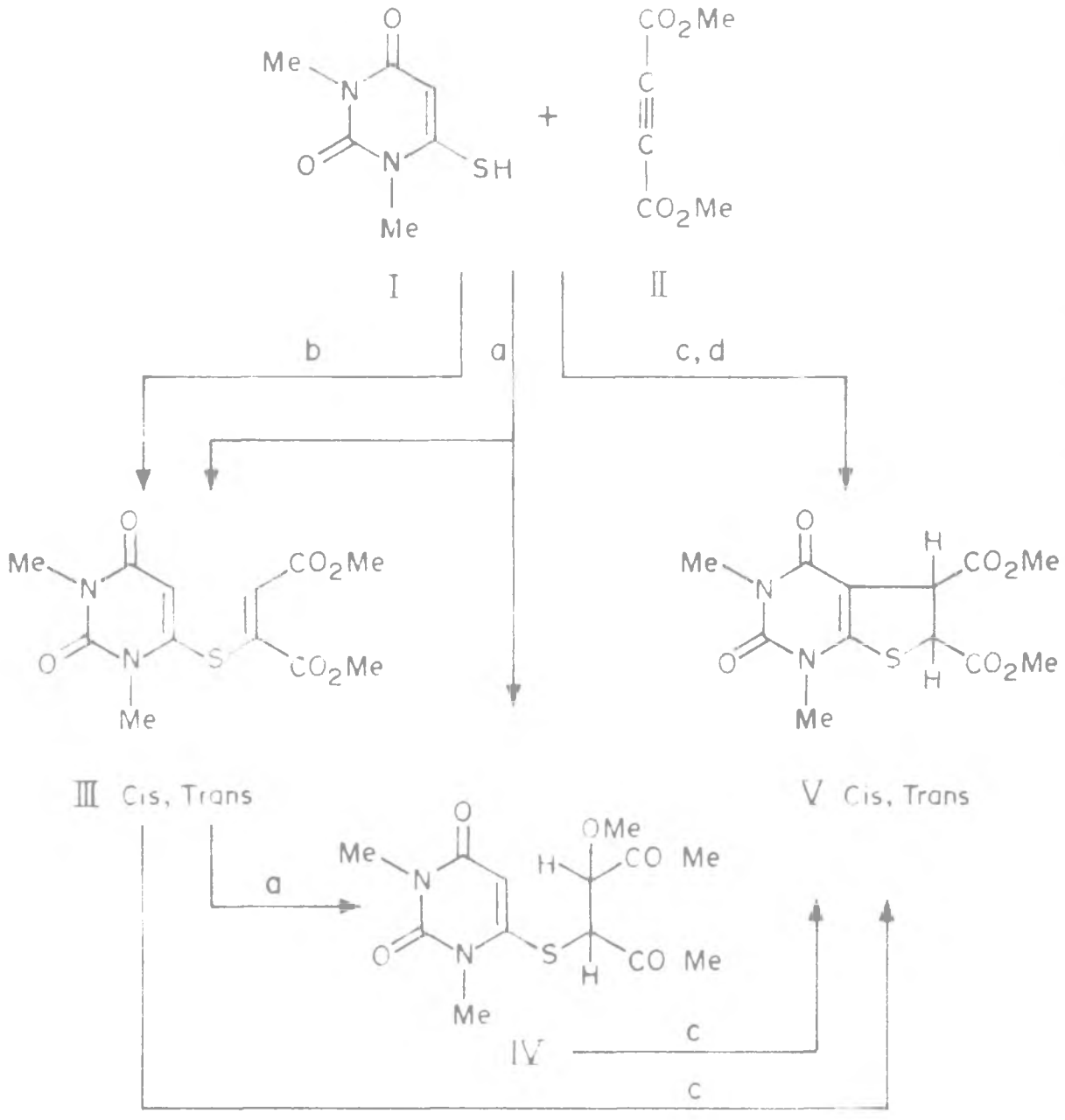
Discussion of present work

Acetylenedicarboxylic acid and its ester have been successfully utilised in many a carbocylic and heterocyclic ring syntheses. Various compounds having carbanion[9,10] and nucleophilic centres such as amino[11], hydroxy[12] and thiol[4] groups were added across the triple bond of the acid or ester resulting in adducts with cis (maleate) and trans (fumerate) geometry. These adducts in turn were versatile intermediates in building up carbocyclic or heterocyclic rings of various sizes under suitable reaction conditions.

Synthesis of two classes of fused heterocyclic ring systems by involving dimethylacetylenedicarboxylate has already been mentioned in Chapters I and II. Attempts to synthesize a 5-oxo- or 7-oxo-thiopyrano[2,3-d]pyrimidine from 6-mercaptouracil (I) and dimethylacetylene dicarboxylate (II) were unsuccessful. In the first instance condensation reaction of (I) and (II) in refluxing methanol both in the presence and absence of base catalysts was studied. Condensation reaction in methanol furnished a mixture of two compounds which was separated by column chromatography over silica gel to give pure III and IV. Compound III gave mass spectral molecular weight 314 and molecular formula $C_{12}H_{14}N_2O_6S$. The IR spectrum of III showed at 1690 cm^{-1} the amide carbonyls and at 1715-1735 cm^{-1} the ester carbonyls.

REACTION OF 1,3-DIMETHYL-6-MERCAPTOURACIL AND DIMETHYLACETYLENEDICARBOXYLATE

Scheme I



a) MeOH, Reflux

b) C_6H_6, Reflux

c) MeOH, C_5H_9N, Reflux

d) C_6H_6, C_5H_9N or Et_3N, Reflux

Proton magnetic resonance studies of both the crude reaction mixtures and of purified compounds (III) and (IV) were helpful in deciding the cis, trans isomeric structures of III. This method has been adopted by many previous workers in the structural elucidation of cis/trans adducts derived from acetylene dicarboxylic ester additions. Heindel et al.[4] have studied thiophenol additions to dimethylacetylene dicarboxylic ester and obtained a pure S-adduct which showed the dicarbomethoxyvinyl proton at δ 6.80 in its n.m.r. spectrum. This trans S-adduct was isomerized thermally to the cis isomer the n.m.r. of which showed the cis-olefinic proton upfield at δ 6.05. George et al.[12] have also observed similar results and explained that the vinyl proton in the fumerates (trans) which has an ester carbonyl group on the same side appeared deshielded compared to the proton of the maleates (cis) in which the ester carbonyls both on one side and away from the olefinic proton. The n.m.r. spectrum of the crude reaction mixture clearly showed the presence of cis and trans adducts. The pure adduct III was assigned the trans geometry based on the dicarbomethoxy vinyl proton resonance position in the n.m.r. at δ 6.91 or 6.60 in $CDCl_3$ or CCl_4 solvents respectively. In the cis-S-adduct the dicarbomethoxy vinyl proton appeared at 6.30 and 5.96 as singlets in $CDCl_3$ and CCl_4 respectively. From the n.m.r. peak integration ratios about 40% of trans and 10% of cis-isomer could be present in the reaction mixture. After

chromatographic purification process only pure trans S-adduct was obtained as shown by its n.m.r. The cis product present in the reaction mixture was isomerised to the trans during the purification step. The trans S-adduct upon heating at 140-150° was isomerised to the cis-form in about 40% yield.

In the following Table NMR chemical shifts of various groups of protons presents in cis and trans adducts is given. The spectra were recorded in $CDCl_3$ and CCl_4 solvents. The trans isomer III showed besides expected solvent shifts,

Table 1 NMR Chemical shifts of cis and trans III in CCl_4 and $CDCl_3$

S.No.	Groups	Trans		Cis		Solvent shifts (comparative shifts cis to trans)	
		CCl_4	$CDCl_3$	CCl_4	$CDCl_3$	CCl_4	$CDCl_3$
1.	N-CH_3	3.13(S)	3.15(S)	3.13(S)	3.15(S)	-	-
2.	N-CH_3	3.46(S)	3.58(S)	3.41(S)	3.55(S)	0.05	0.03
3.	$COOCH_3S$	3.70(S)	3.80(d)	3.63(S)	3.75(S)	0.07	0.05
4.	C_5-H(ring)	5.46(S)	5.73(S)	5.70(S)	6.00(S)	*0.24	*0.27
5.	Vinyl H	6.60(S)	6.91(S)	5.96(S)	6.30(S)	0.64	0.61

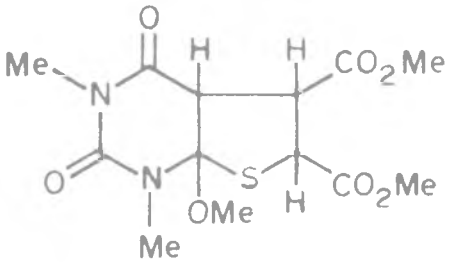
*cis-isomer appears downfield.

S = singlet, d = doublet values in δ ppm

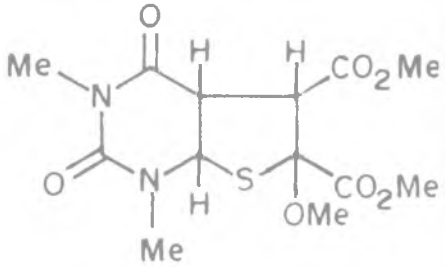
resonances of $N\text{-}CH_3$, $COOCH_3$ and vinyl protons at dhownfield positions when compared to the cis isomer in the same solvent. The C_5-ring olefinic proton in the cis-isomer appeared deshielded more than the corresponding proton of the trans isomer. This could be due to shielding or deshielding effect caused by dicarbomethoxy group over the proton in one of the isomers.

The other compound IV isolated in the same reaction gave molecular formula $C_{13}H_{18}N_2O_7S$ and mass spectral molecular weight 346. In the mass spectrum of this compound there were losses of methoxy (m/e 315) and a proton (m/e 314) directly from the molecular ion M^+ 346. The IR of IV showed the amide carbonyl at 1700 cm^{-1} and the ester carbonyls at 1735-55 cm^{-1}. The UV spectrum gave absorptions at 220 (4.12), 285 (4.08) which indicated conjugated chromophoric system in its structure and hence the assignment of cyclic structures IVa or IVb was ruled out. Although the UV data supported the structures IVc and IVd, they were in total disagreement with the n.m.r. spectrum that was obtained for this compound. In IVc the methylene protons would have shown up as a quartet at δ 3-4 region with a large geminal coupling constant about 14-20 Hz. The olefinic proton also would resonate downfield at δ 6-7 ppm region. If IVd was to be the structure of this adduct the methylene protons would appear as a clear singlet of two protons. Therefore based on the UV and n.m.r. spectra

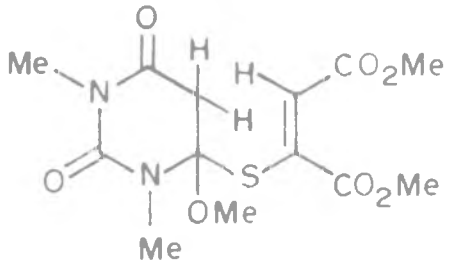
Scheme 2:



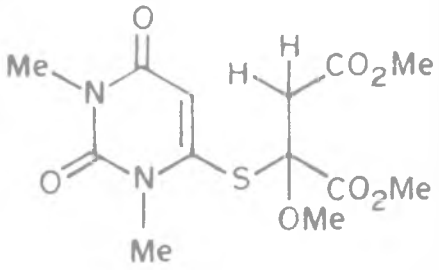
IV a



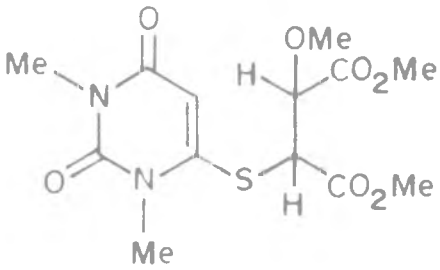
IV b



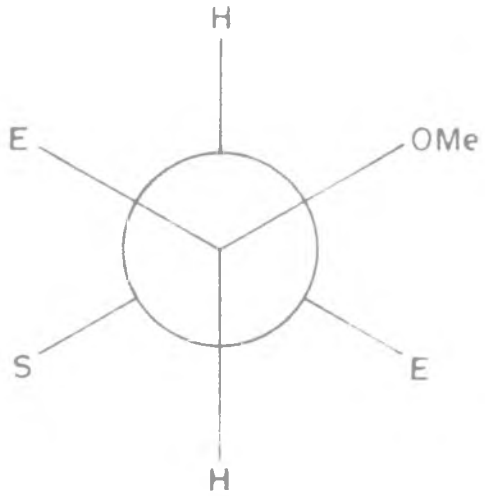
IV c



IV d

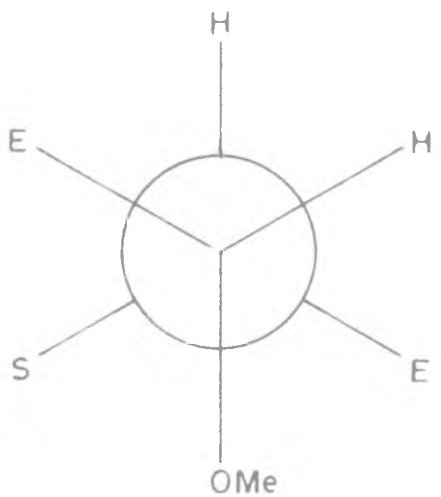


IV e



IV e_2 Erythro

(meso)



IV e_1 Threo

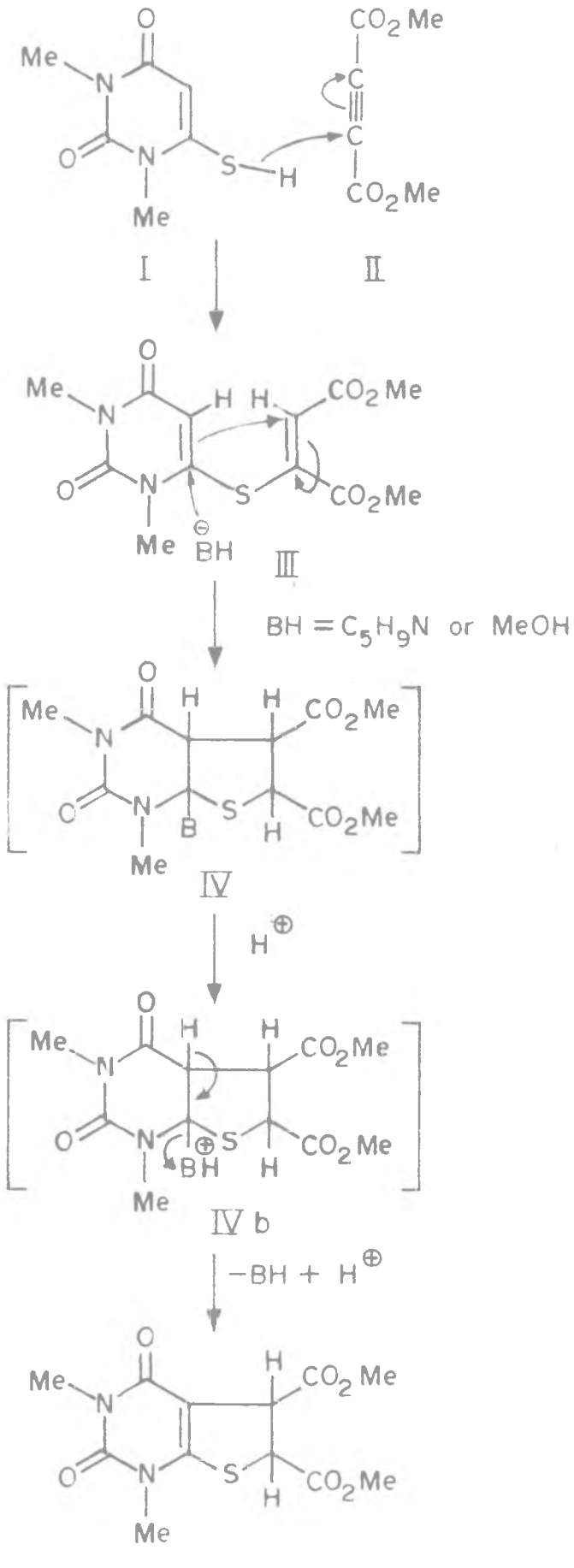
a succinate structure IVc was given to this product. A trans addition of methanol to the fumarate or maleate adduct (III) would give rise to stereoisomeric mixture of compounds (erythro and threo) IVe_1 and IVe_2 respectively. In fact this was so as was evident from its n.m.r. spectrum in which separate resonances for methine and olefinic protons of the isomeric forms were observed with different chemical shifts and coupling constants. In the n.m.r. spectrum besides the resonances of N-methyls, ester methyls and methoxymethyls which are upfield two quartets appeared between δ 4.18 - 4.33 region with J, 6 Hz and 1.5 Hz with a total integrated ratio of two protons. These were assigned to the methine protons of the corresponding isomers (IVe_1 or IVe_2). The olefinic protons of the isomers appeared at δ 5.61 as two singlets. Refluxing IV in methanol with piperidine furnished 5,6-dihydrothiopheno [2,3-d] pyrimidine dicarboxylate V in 96% yield. Compound IV is also formed when pure S-adduct (III) is refluxed in methanol.

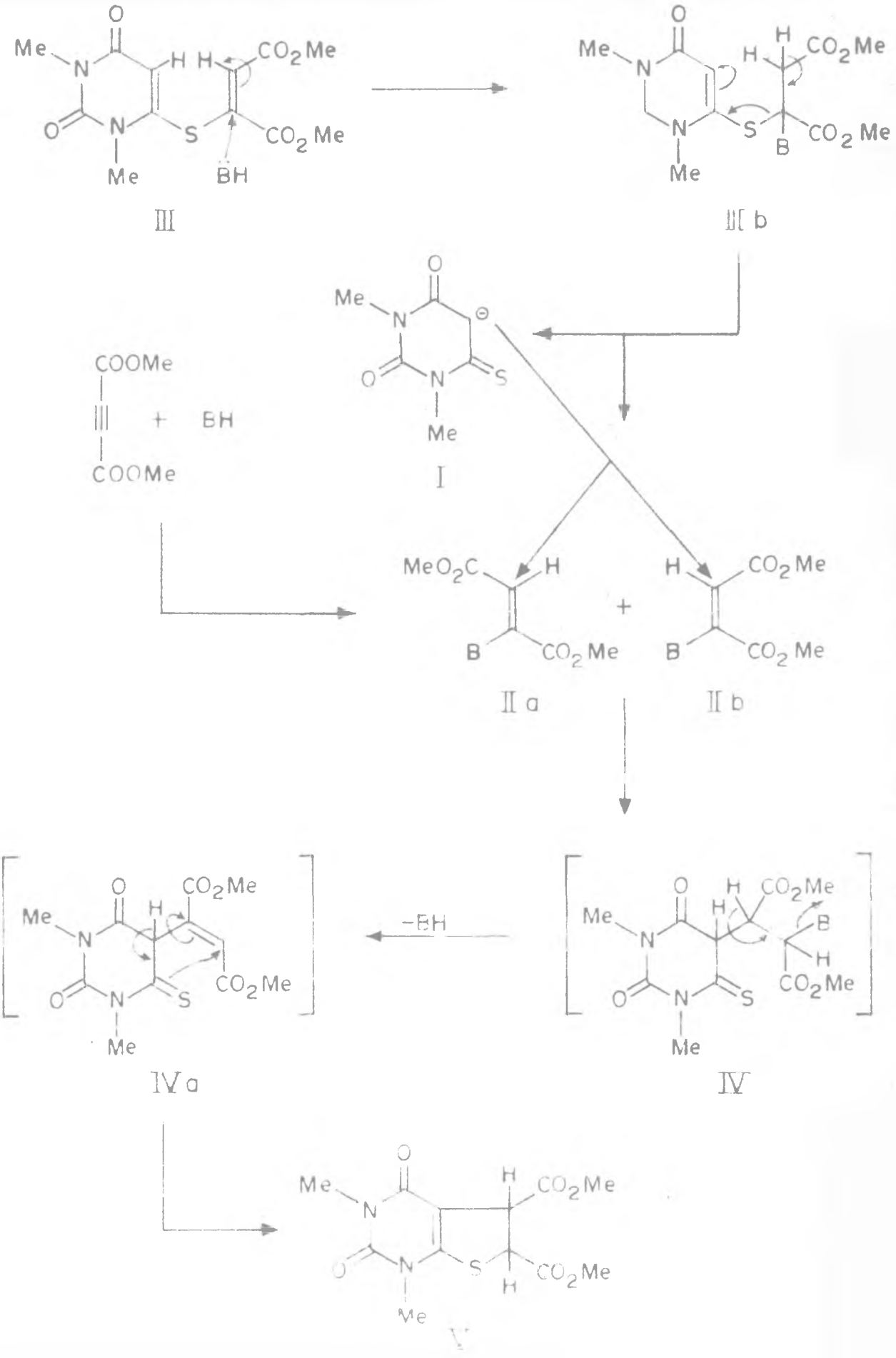
Addition of 6-mercapto-uracil (1) to dimethylacetylene dicarboxylate (II) in refluxing benzene without a base gave only cis and trans adducts (III). About 60% cis-isomer and 40% of trans isomer III could be present in the reaction mixture as shown by the n.m.r. peak integration ratios. Cyclised product V is not formed under these conditions. The trans S-adduct III in presence of piperidine and refluxing methanol gave V in good yield. When I and II were refluxed

in benzene in presence of piperidine or triethylamine and the reaction mixture acidified with conc. hydrochloric acid, a mixture of cis and trans 5,6-dihydrothiopheno[2,3-d] pyrimidinedicarboxylates (V) were obtained in 90% yield. Experiments with piperidine furnished 60% trans and 30% cis-isomer whereas triethylamine just reversed the above ratio to 60% cis and 33% transisomer. NMR spectra showed for both cis and trans isomers the same chemical shift for N-methyls and ester methyl protons. A pair of doublets situated at δ 4.31 and δ 5.01 with one J value 9 Hz were assigned to C_5 and C_6 protons of the cis-isomer. Another pair of close doublets situated at 4.45 and 4.63 with similar J value 4 Hz were assigned to trans portons of the same compound V. K. Undheim and R. Lie[6] have reported a similar n.m.r. spectrum for trans 2,3-dihydro-benzo[b]thiophene dicarboxylate which showed a quartet at δ 4.83 - 5.00 with J = 8 Hz. The above data and the molecular weight 314 confirmed the structure V proposed.

The formation of S-adduct (III) from I and II is a known thioenolate addition[4,6] to acetylenic triple bond giving predominantly transisomer in methanol and cis-isomer in benzene. As the dihydro-thiopheno[2,3-d]pyrimidine (V) is formed in presence of a base from I and II or III or IV, the participation of base appears specific not only as a proton abstractor but also in bringing about cyclisation as well by either of the mechanisms shown in schemes 3 and 4.

Scheme 5:




Me
N
O
H
H
CO2Me
S
CO2Me
BH
III
IIIb
COOMe
+
BH
COOMe
I
MeO2C
B
CO2Me
IIa
IIb
-BH
IVa
IV
V

A covalent bond is formed (Scheme 3) between the uracil C_5-position and C_2-position of dicarbomethoxy vinyl double bond with the help of nucleophilic push as depicted in III. This results in cyclisation involving a 1:4 type addition of the base or methanol to give a trihydrothiopheno[2,3-d] pyrimidine intermediate IV. Subsequent elimination of the base from the adduct IV furnishes the dihydro-compound V. Another plausible mechanism involves nucleophilic addition of base to the triple bond of the acetylenic ester in the initial stages of the reaction (scheme 4). Such additions of piperidine[13,14,15] triethylamine[16] and methanol both in protic and aprotic, polar and nonpolar solvents to the triple bond of acetylenic ester are known to give adducts with maleate or fumerate geometry. These adducts IIa and IIb could conceivably undergo michael additions with I to furnish the intermediate succinates (IV). Alternatively the S-adduct (III) could also add a molecule of base initially to give IIIa[b]-species which by way of elimination furnishes I, IIa or IIb needed for michael addition. The michael adduct (IV) by eliminating base results in dicarbomethoxy vinyl thiouracil (IVa). The thioenolate of this adds across the double bond to furnish the cyclised product (V).

EXPERIMENTAL

E X P E R I M E N T A L

All melting points are uncorrected. NMR spectra were recorded on T.60 instrument with TMS as internal standard. Chemical shifts were expressed in δ ppm and the J values in HZ. IR spectra were recorded on Perkin-Elmer model 137-B or on 221 instruments. UV spectra were taken on Perkin-Elmer UV spectrophotometer-350. Mass spectra were taken on CEC-21-110B double focussing instrument with direct inlet system. Mass spectral data are reported as percentages of the base peak which was assigned a value 100.

1,3-Dimethyl-6-mercapto(1,2,dimethoxy carbovinyl)uracil (III) and 1,3-Dimethyl-6-mercapto-(1,2-dicarbomethoxy-2-methoxy ethyl) uracil IV

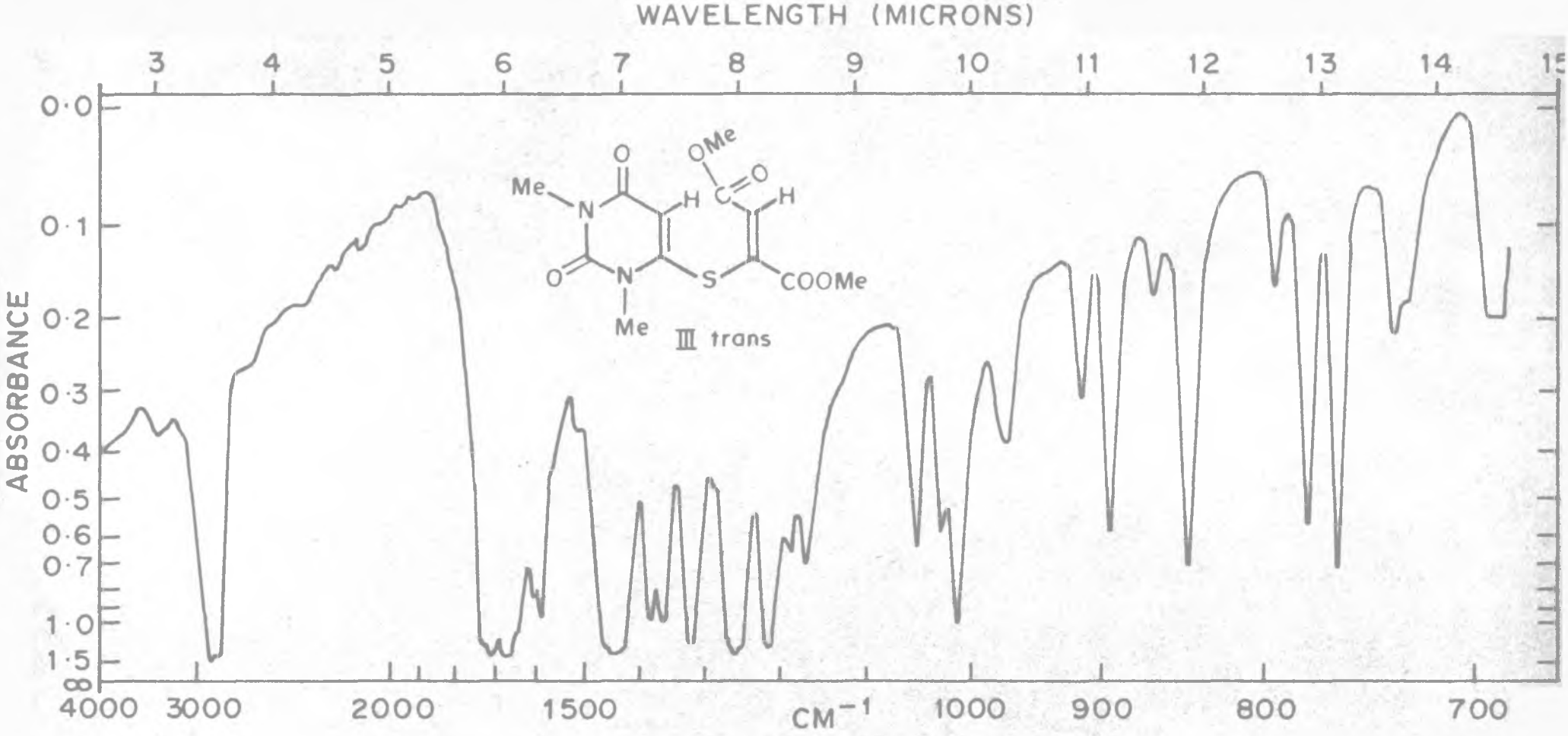
A solution of 1,3-dimethyl-6-mercaptouracil (0.9 g, 0.052 mole), dimethylacetylenedicarboxylate (0.75 g, 0.052 mole and methanol (15 ml) was refluxed over steam bath for 4 hrs. Afterwards methanol and unreacted acetylenedicarboxylate were removed. The crude product was subjected to n.m.r. analysis. Later it was chromatographed over silica gel column using benzene, benzene:ethylacetate (4:1). Benzene eluted the III followed by IV in the polar solvent mixture. Adduct III: yield 0.6 g (36.5%). M.P. 114-115°C, crystallized from CCl_4.

Elemental analysis: Found C; 45.65; H, 4.55; N, 9.23; $C_{12}H_{14}N_2O_6S$ requires C, 45.81; H, 4.46; N, 8.91%.

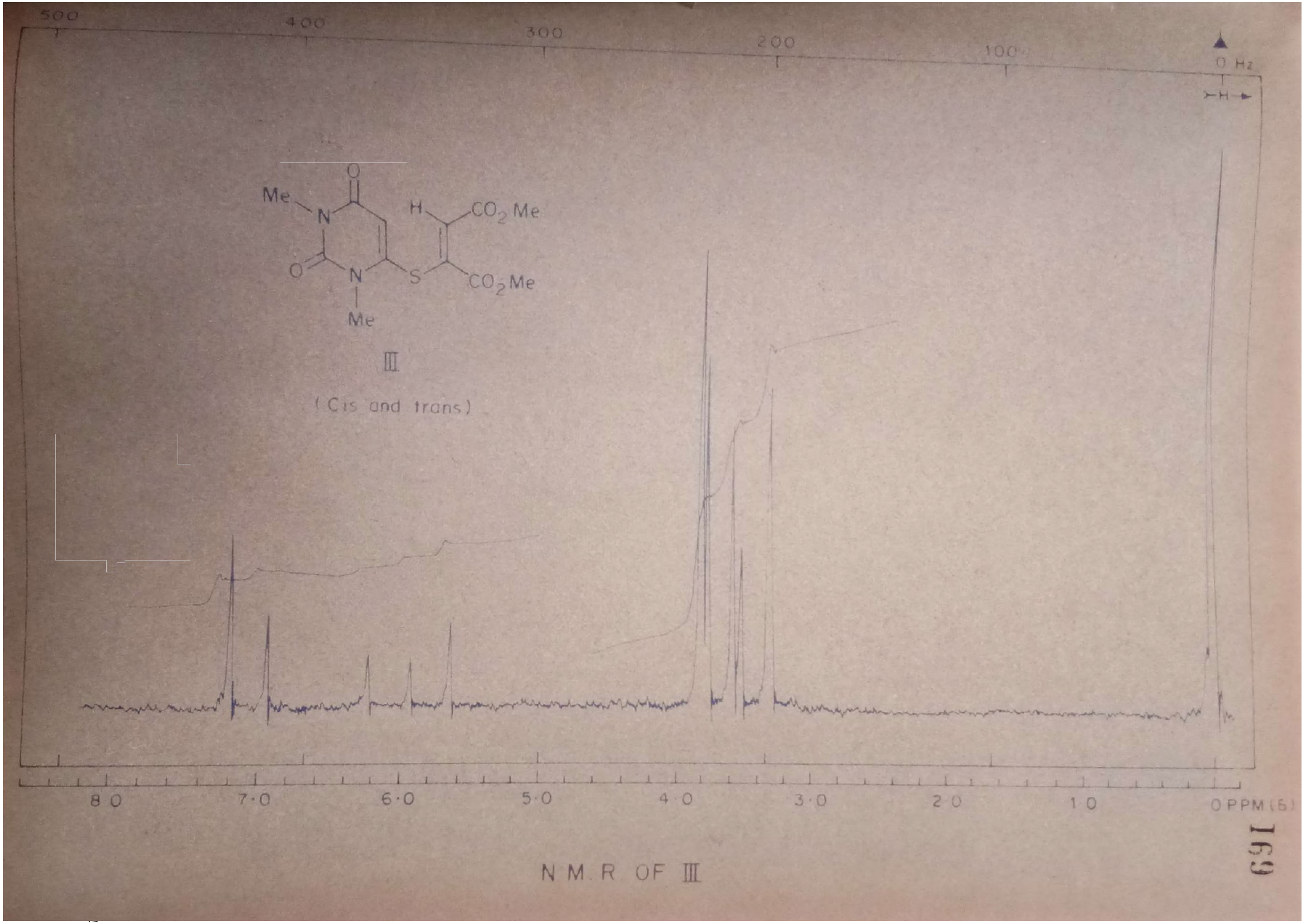
NMR($CDCl_3$) 3.30 (S, 3H, N-CH_3), 3.58 (s, 3H, N-CH_3), 3.80 (d, 6H, 2 x $COOCH_3$), 5.70 (s, 1H, C_5H) 6.91 (s, 1H >C=CH-$COOCH_3$).

IR($CHCl_3$) : 1690^{cm-1} (amide carbonyls), 1715-1735^{cm-1} (ester carbonyls).

Mass spectrum : m/e(%); 314(9), 283(2), 255(31), 251(2), 223(25), 211(7), 198(38), 170(47), 166(3), 139(2), 85(17), 82(100), 59(13), 58(3), 57(6), 54(9), 53(10), 45(6), 42(12), 28(24).


WAVELENGTH (MICRONS)
3
4
5
6
7
8
9
10
11
12
13
14
ABSORBANCE
0·0
0·1
0·2
0·3
0·4
0·5
0·6
0·7
1·0
1·5
4000
3000
2000
1500
CM⁻¹
1000
900
800
700
Me
N
O
OMe
C=O
H
H
S
COOMe
Me
III trans

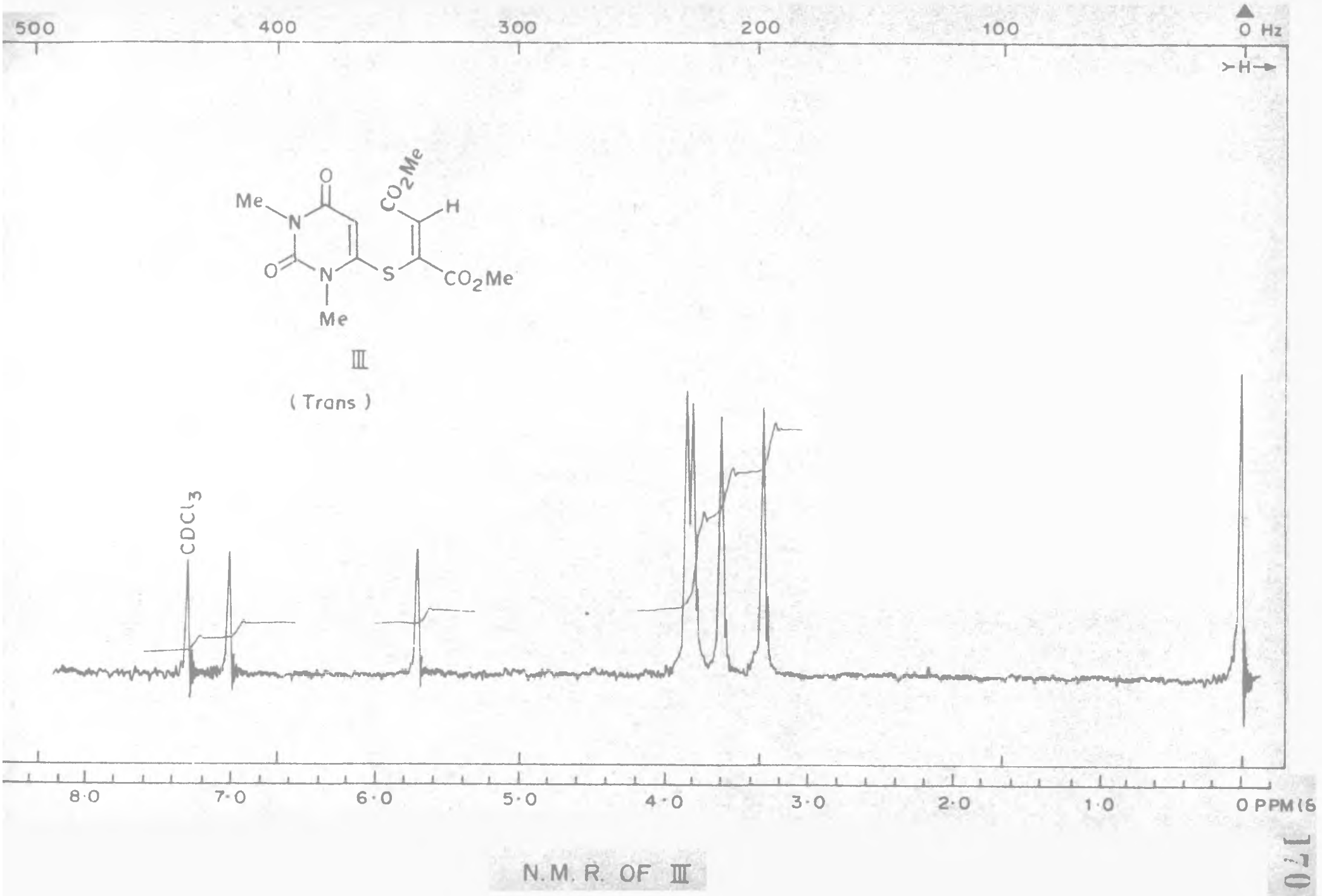
I. R. OF III



Ⅲ

(Cis and trans)

N.M.R OF Ⅲ



III

(Trans)

N.M.R. OF III

Methoxy derivative (IV): yield 0.42 (40%) m.p. 93-94°
crystallised from methanol

Elemental analysis: Found: C, 45.13; H, 5.26; N, 8.20.
$C_{13}H_{18}N_2O_7S$ requires C, 45.08;
H, 5.20; H, 8.09%.

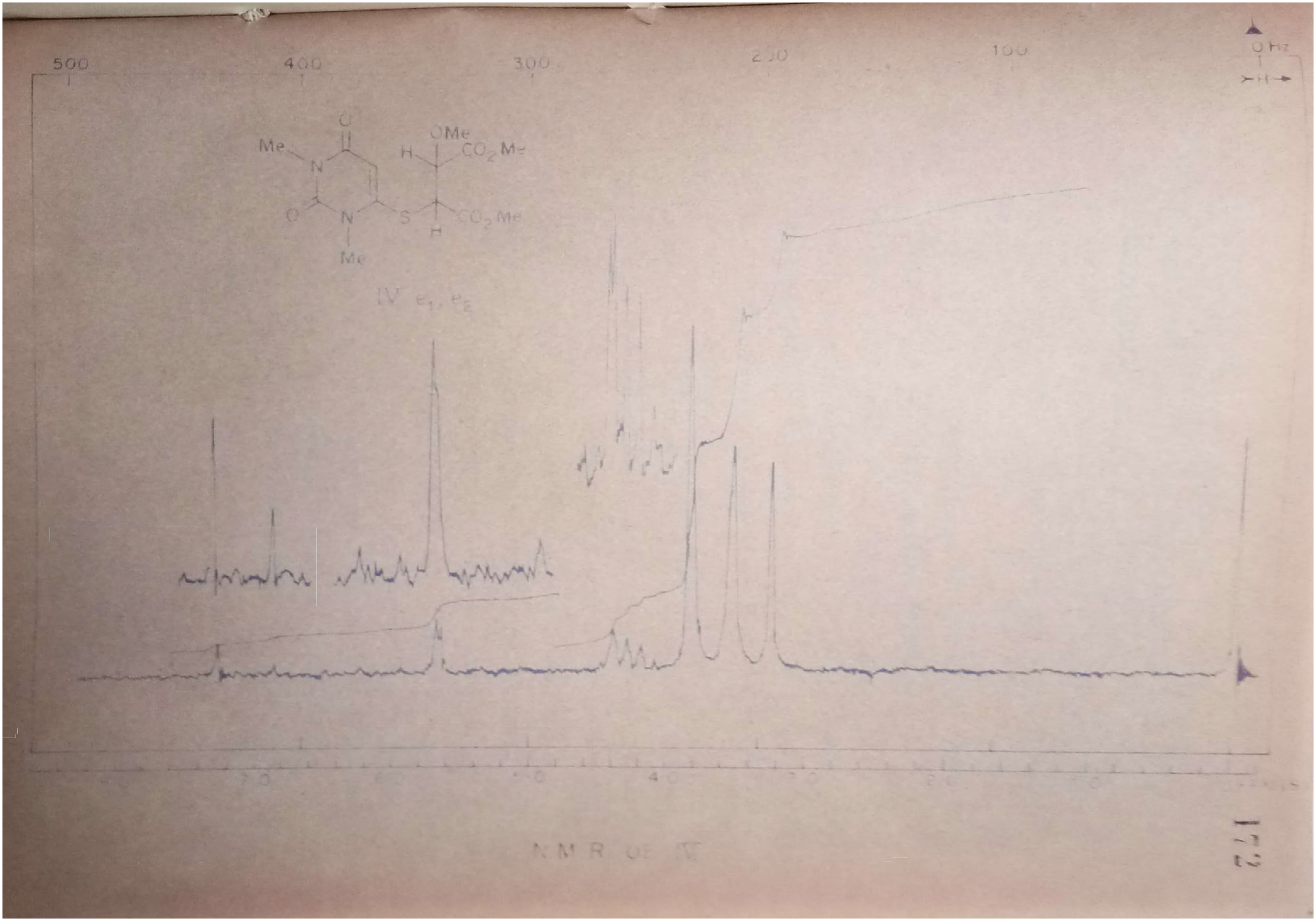
IR : 1700 (Amide carbonyls), 1735-1765 cm^{-1}
(ester carbonyls).

NMR(CCl_4): 3.20 (s, 3H, N-CH_3), 3.46
(s, 6H, N-CH_3, OCH_3), 3.76
(s, 6H, 2x COOCH_3), 4.20
(q, 2H, J = 6 Hz methine H's)
5.61 (s, 1H, C_5-ring H).

Thermal isomerisation of trans-s-adduct (III)

The trans- S-adduct (III, 0.060 g) was heated at 140-150°C under N_2 atmosphere for one hour. The product was analysed by n.m.r. which gave 40% conversion of trans into cis-adduct.

NMR(CCl_4): 315 (s, 6H, 2 x NCH_3 trans, cis)
3.40 (s, 3H, N-CH_3 cis)
3.46 (s, 3H, N-CH_3 trans)
3.63 (s, 3H, COOCH_3 cis or trans)
3.70 (s, 9H, 3 x $COOCH_3$ cis or trans)
5.46 (s, H, C_5-H trans), 5.70 (s, 1H,
C_6H of cis), 5.96 (s, 1H, vinyl H of
cis), 6.60 (s, 1H, vinyl H trans).



NMR OF IV

3. 1,3-Dimethyl-2,4-dioxo-trans-5,6-dicarbomethoxy 5,6-dihydrothiopheno/2,3-d/pyrimidine (V)

a) A solution of trans-S-adduct (III, 0.41 g, 0.013 mole), piperidine (0.1 ml) in methanol (8 ml) was refluxed at 80°C.

b) A solution of 2-methoxy succinate (IV, 02 g, 0.0058 mol) in methanol (5 ml) and piperidine (0.050 ml) was refluxed for 5 hrs.

c) A solution of 6-mercapto uracil (I, 0.45 g, 0.026 mole), dimethylacetylene dicarboxylate (II, 0.38 g, 0.026 mole) in methanol (8 ml) and piperidine (0.1 ml) was refluxed at 80° for 3 hrs.

Solvent was distilled after a,b,c procedures from the reaction under reduced pressure 50 mm and at 35-40° temperature. The residue was diluted with water (10 ml), acidified with conc. HCl (0.2 ml). The solution was extracted with chloroform (20 ml), washed the organic layer with cold water, dried over anhy. Na_2SO_4, filtered and chloroform was distilled. The residue after distillation was subjected to n.m.r. analysis. Later it was purified by column chromatography over alumina (neutral) using benzene and benzene:ethylacetate (9:1) solvents. Benzene elutions gave trans (V) isomer m.p. 124-125°. Yields (a) 0.29 g (70%), (b) 0.180 g (96%) (c) 0.42 g (53%) and trans-S-adduct (III) 0.120 g (15%).

Elemental analysis: Found C: 45.48; H, 4.32; N, 8.75;
$C_{12}H_{14}N_2O_6S$ requires C, 45.81; H, 4.46
N, 8.91%.

Mass spectrum: M^+ 314.

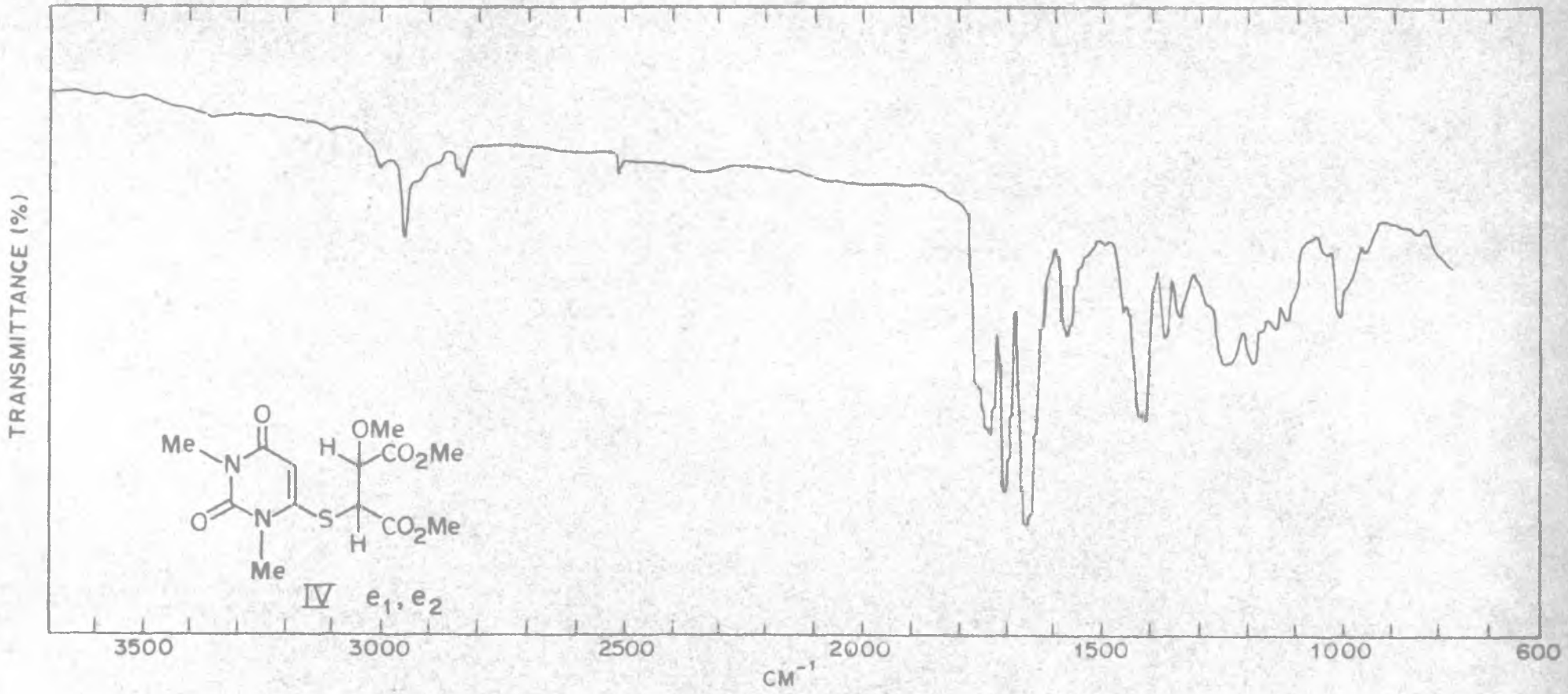
IR($CHCl_3$): $1690^{cm^{-1}}$ (amide carbonyls)
1725, $1755^{cm^{-1}}$ (ester carbonyls)

NMR(CCl_4): 3.15 (s, 3H, N-CH_3), 3.33 (s, 3H, N-CH_3)
3.70 (d, 6H, 2 x $COOCH_3$), *4.45
(d, H, J = 4 Hz, C_5-H trans)
*4.63 (d, H, J = 4 Hz, C_6-H trans)

*In $CDCl_3$ spectrum these two signals merge into a broad singlet of two protons at 4.71.

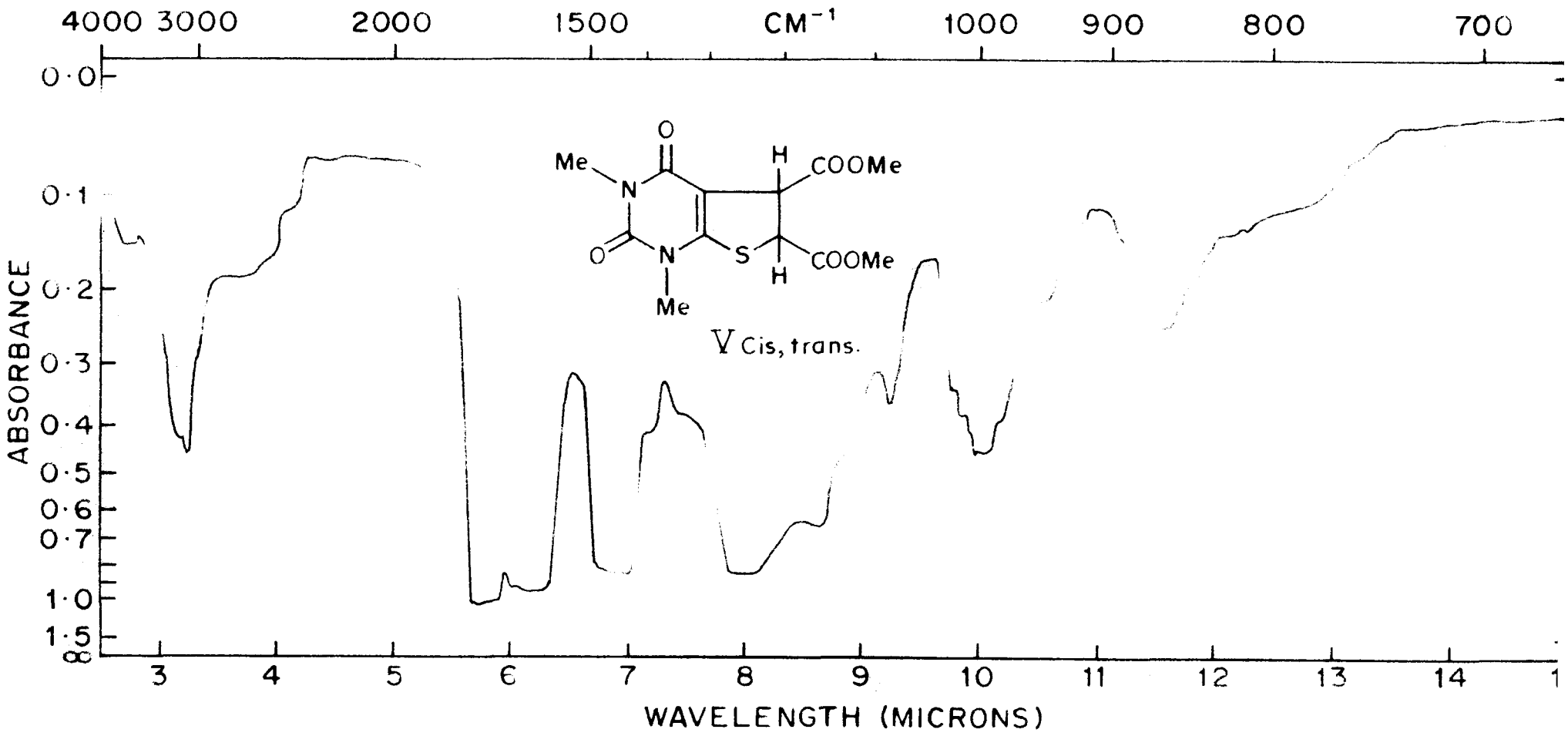
4. When benzene was used as a solvent with piperidine as base in experiments (c), a mixture of cis and trans products (V) were obtained in a total yield 90% (60% trans and 30% cis). About 10% of trans S-adduct was also observed in the n.m.r. of the crude product. In an other experiment (c) where triethylamine as a base gave cis (60%) and trans (33%) in a total yield of 80% of (V).

NMR(CCl_4) cis-trans (V) 3.13 (s, 6H, 2 x N-CH_3), 3.35
(s, 6H, 2 x NCH_3), 3.70 (3 x S, 12H, 4 x $COOCH_3$)
4.31 (d, 1H, J = 9 Hz, C_5 cis H), 4.54 (q or 2 x d,
2H, J = 4 Hz C_5, C_6-H's trans), 5.01 (d, H, J = 9 Hz,
C_6-cis H).

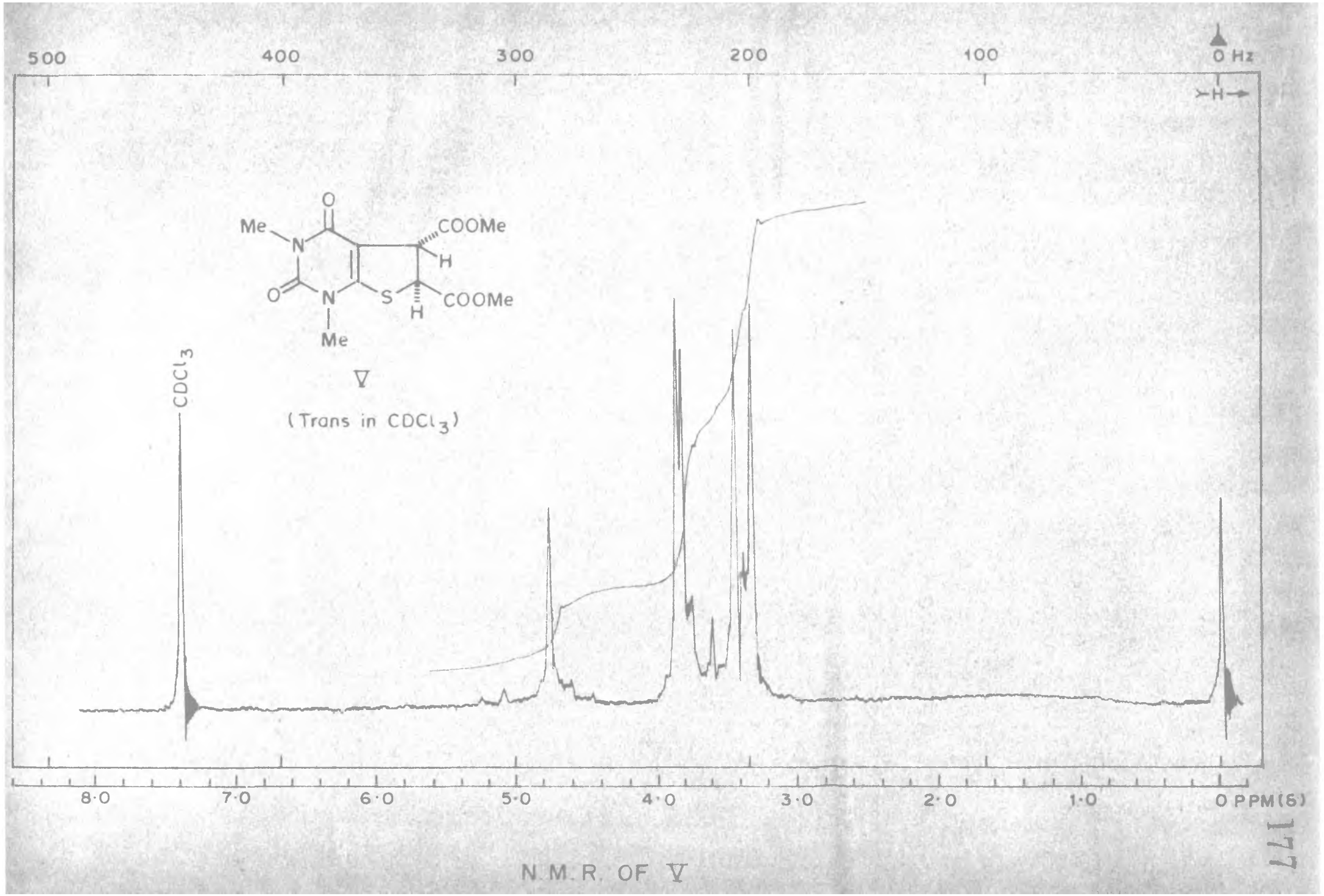


IV e_1, e_2

I.R. OF IV e_1, e_2


4000 3000
2000
1500
CM⁻¹
1000
900
800
700
0·0
0·1
0·2
0·3
0·4
0·5
0·6
0·7
1·0
1·5
ABSORBANCE
3
4
5
6
7
8
9
10
11
12
13
14
WAVELENGTH (MICRONS)
Me
N
O
H
COOMe
S
COOMe
Me
V Cis, trans.

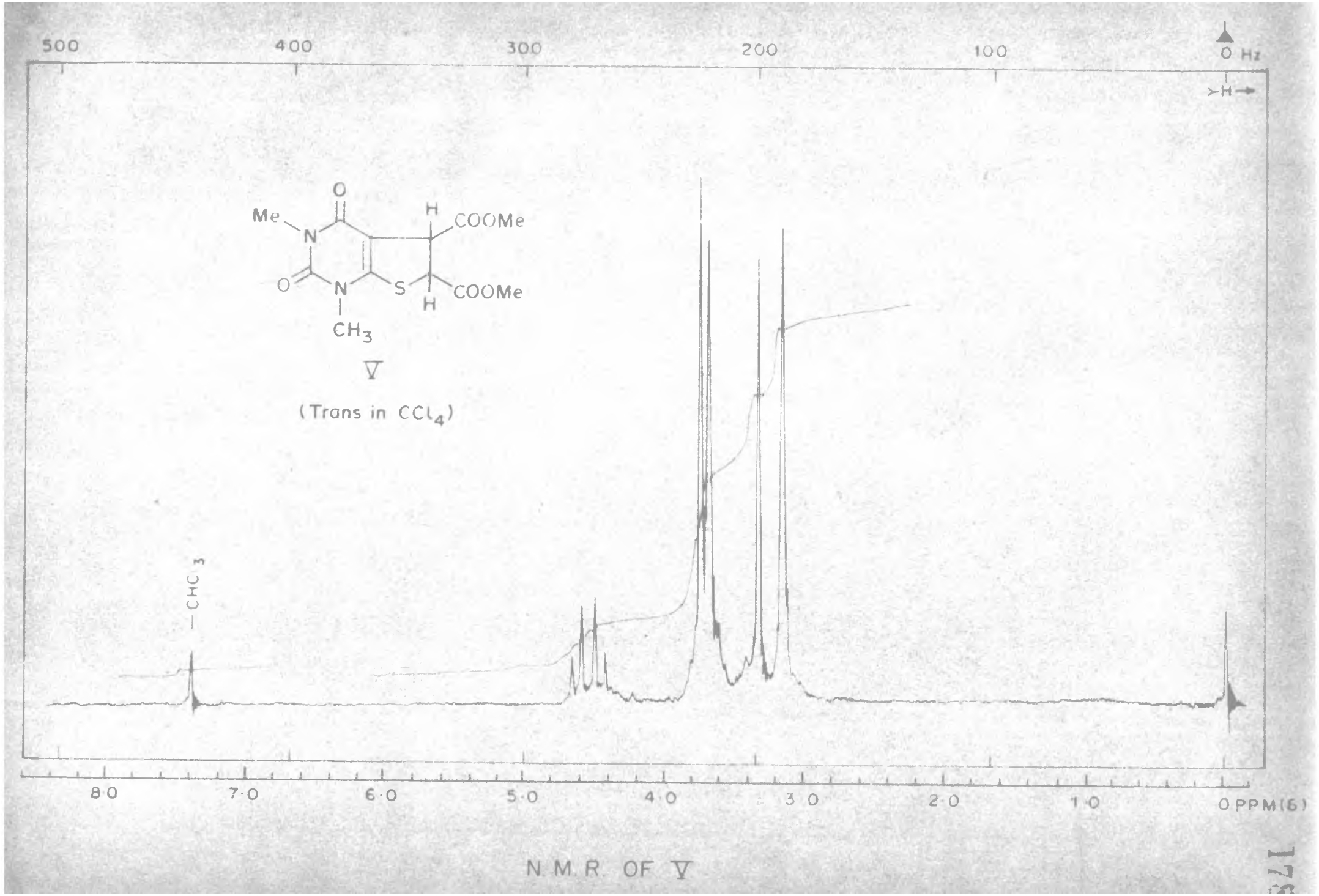
I.R. OF V



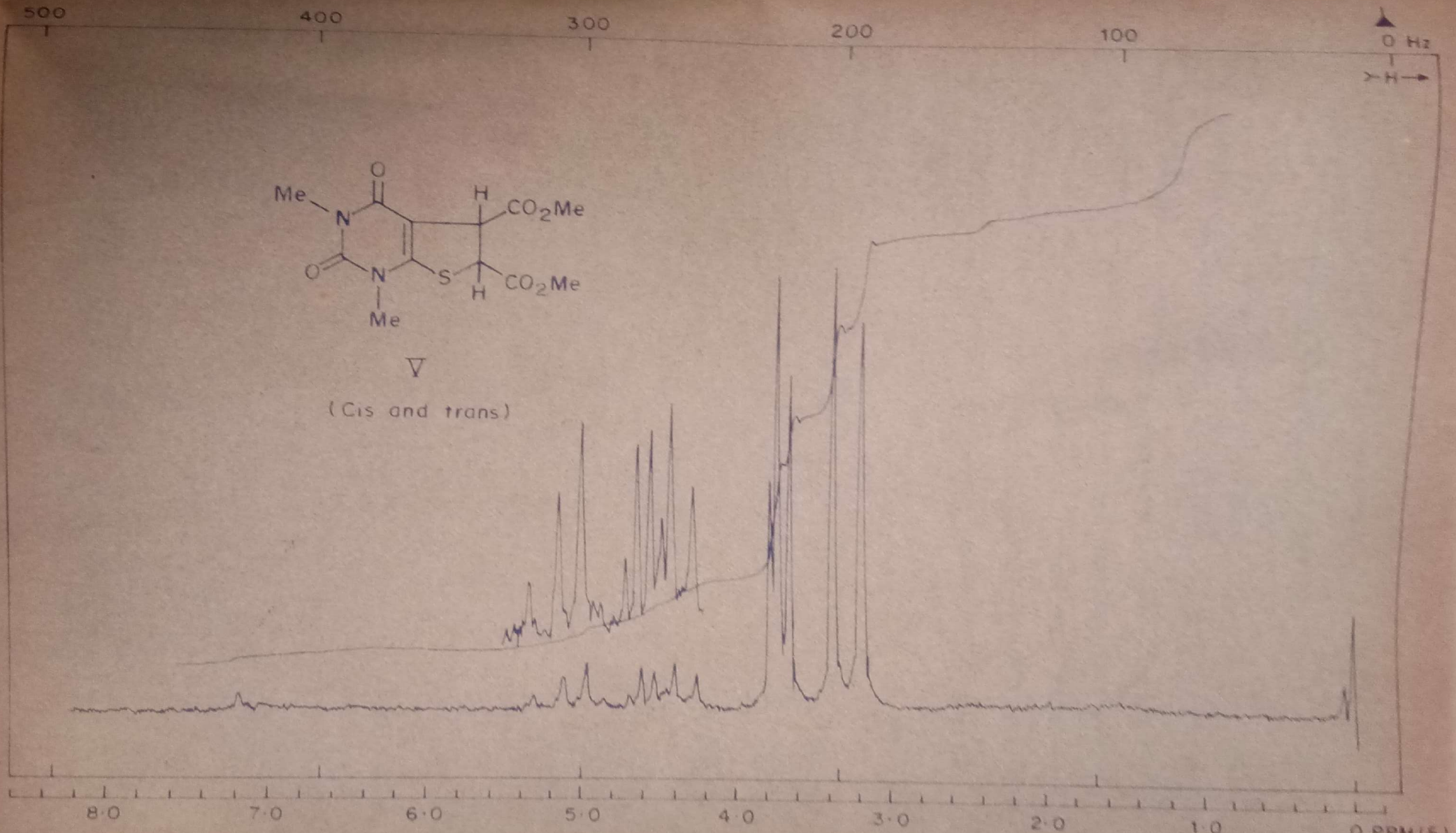
V

(Trans in $CDCl_3$)

N.M.R. OF V


500
400
300
200
100
0 Hz
≻H→
Me
N
O
O
N
S
H
COOMe
H
COOMe
CH3
(Trans in CCl4)
CHC 3
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM(δ)

N.M.R. OF V



V

(Cis and trans)

NMR OF V

5. Preparation of IV from S-adduct (III)

A solution of trans S-adduct (III, 0.160 g, 5 x 10^{-4} mol) in methanol (5 ml) was refluxed at 80° for three hours. Methanol was evaporated under reduced pressure at 40-50° temperature. The crude reaction mixture after n.m.r. analysis showed the presence of IV and III. This was chromatographed over silica gel column as described in the procedure (1) to give IV 0.069 g (40%) and III 0.085 g (49.1%).

S U M M A R Y

SUMMARY

Addition of 1,3-dimethyl-6-~~mercapto~~ thio uracil (I) to dimethylacetylene dicarboxylate (II) in methanol or benzene gave cis and trans 5-adducts (III). In presence of piperidine or triethylamine I and II furnished a bicyclic ring system 5,6-dihydro-thiopheno[2,3-d]pyrimidine dicarboxylate (V). As the cyclization of cis or trans 5-adducts (III) or its methanol addition product (IV) in the presence of piperidine gave (V) in good yields, involving these adducts two possible mechanistic routes have been proposed.

R E F E R E N C E S

REFERENCES

1. F. Montanari, Tetrahedron Letters 4, 8 (1960).

2. S.M. Kalbag, M.L. Nair, P. Rajgopalan and C.N. Talaty, Tetrahedron, 23 (1964).

3. S. Ruheman and H.E. Stapleton, J.Chem.Soc. 77, 1179 (1900).

4. D. Ned Heindel, Velmer, B. Fish, F. Ryan and Aurther, R. Lepley, J.org.Chem., 32(9) 2678 (1967).

5. J.E. Dolfini, J.Org.Chem. 30, 1298 (1965).

6. K. Undheim and R. Lie, Act.Chem.Sca 27, 595 (1973).

7. Haruo Ogura, Masakazu, Sakaguchi and Karuyoshi Takeda, Chem.Pharm.Bull., 20(2), 404-408 (1972).

8. Heinrich Warnhoff and Friedhelm Korte, Chem.Ber., 99, 872-78 (1966).

9. A. Subba Rao and R.B. Mitra, Indian J.Chem., 12(10), 1028-1030 (1974).

10. Haruo Ogura and Masakaz, Sakaguchi, Chem.Pharm.Bull., Tokyo, 21(9), 2017 (1973).

11. J.B. Hendrickson, R. Rees and J.F. Templeton, J.A.C.S. 86, 107 (1964).

12. M.N. Gudi and M.V. George, Indian J.Chem., 9, 971 (1969).

13. E. Winterfeldt and H. Preuss Angew.chem. 77(15), 679(1965).

14. E. Winterfeldt and H. Preuss, Chem.Ber. 99(2) 450-8 (1966).

15. Klaus, Herbig, Rolf Husigen and Helmut Huber, Chem.Ber. 99(8) 2546-55 (1966).

16. Robert J. Alaimo and Donald, G. Farum, Can.J.Chem. 43(3), 700-1 (1965).

A C K N O W L E D G E M E N T S

I wish to express my deep sense of gratitude to Dr. R.B. Mitra, Deputy Director, National Chemical Laboratory, Poona-8 for his valuable guidance and constant encouragement through out this investigation.

I take this opportunity to thank all my friends and colleagues for their wholehearted co-operation at all times.

Assistance from the Microanalytical, NMR, IR and M.S. group of people is gratefully acknowledged.

Finally, I am grateful to the Director, National Chemical Laboratory for allowing me to submit this work for my Ph.D. degree.

A. Subbarao

(A. Subbarao)

National Chemical Laboratory
Poona-411008

December 1978.