A STUDY OF THE MANNICH REACTION WITH CERTAIN PHENOLS, OF THE CAUSES OF FORMATION OF COLOURED PRODUCTS AND THE PREVENTION OF THEIR OCCURENCE

Thesis submitted for the degree of Master of Philosophy

by

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ABSTRACT

Mannich bases from dimethylamine, formaldehyde and phenol, m-cresol, eugenol, p-tert-pentylphenol, p-tert-butylphenol, p-iso-propylphenol, 3,4,5-trimethylphenol, resorcinol, 3-pentadecylphenol and the component phenols of cashew nut shell liquid (CNSL) have been prepared. Mannich bases have also been prepared from methylamine, formaldehyde with phenol and with m-cresol, from diethylenetriamine, formaldehyde and phenol, m-cresol, resorcinol, 3-pentadecylphenol and the component phenols of CNSL. All the Mannich bases were examined by ^{1}H nuclear magnetic resonance, infra-red spectroscopy and by T.L.C.

The coloured products formed from autoxidation of resorcinol, orcinol and hydroxy-β-orcinol in presence of ammonia, methylamine and dimethylamine were isolated by column chromatography and preparative TLC and examined by ^{1}H NMR, I.R., U.V. and mass spectroscopy. Structures of some of the products have been proposed based on chemical and spectroscopic evidence.

A new technique for the separation of cardanol and cardol in cashew nut shell liquid by extractive distillation using bases has been devised.

ACKNOWLEDGEMENT

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Part III

RESULTS AND DISCUSSION

INTRODUCTION

1. MANNICH REACTION

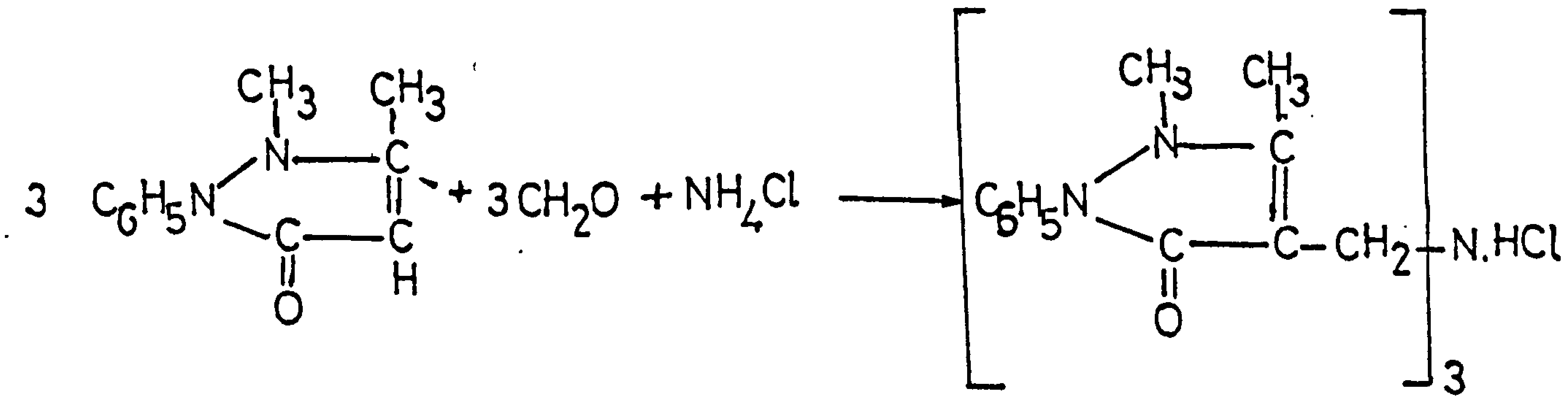
The Mannich reaction consists in the condensation of ammonia, or a primary or secondary amine with an aldehyde, usually formaldehyde, and a compound containing at least one hydrogen of pronounced reactivity. The essential feature of the reaction is the replacement of the active hydrogen atom by an aminomethyl or a subtituted aminomethyl group. The reaction may be illustrated by the following equation:

$$R_2NH + HCHO + R'H \longrightarrow R_2N\text{-}CH_2\text{-}R' + H_2O$$

The active hydrogen compound R'H is most frequently a ketone, an aldehyde, an acid, an acetylene, an ester, a phenol and recently work has been carried out with nitroalkanes[1].

The essential information on the subject of Mannich reactions has been reviewed by F.F. Blicke[2] and also in a monograph by B. Reichart[3]. Several recent reviews[4] by various workers have summarized the reaction in relation to medicinal chemistry.

The first observation of a condensation of the type now known as the Mannich reaction was made by Tollens[5,6] and later by Petrenko - Kritschenko[7] and his students but they failed to recognise the reaction as a general one. The detailed study by Mannich begun in 1917, was initiated by the observation that antipyrine salicylate, formaldehyde and ammonium chloride reacted to form a tertiary amine[8].



1a. Scope of the Mannich Reaction

Use of Ammonia

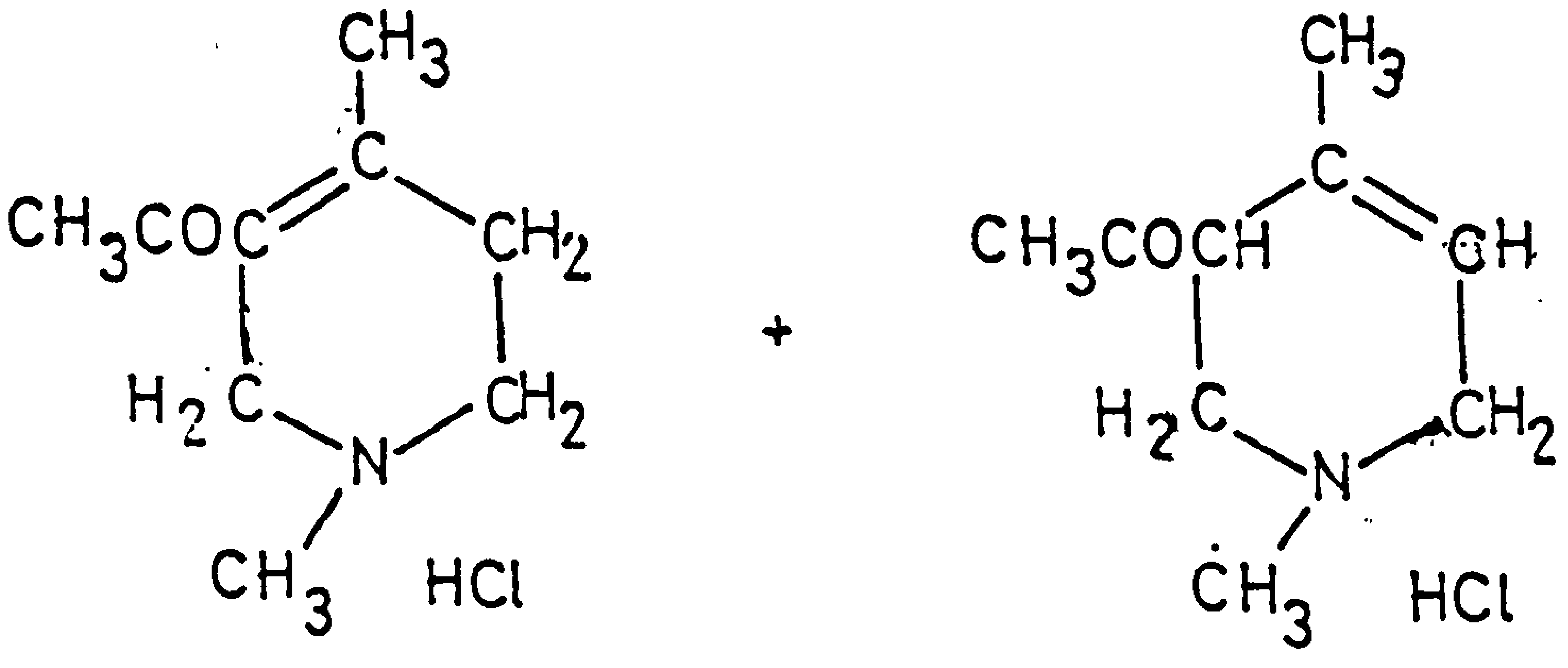
A primary amine is the first product to be expected from a Mannich reaction in which ammonia or an ammonium salt and formaldehyde react with a compound containing an active hydrogen atom. With simple compounds subsequent reaction of the primary amine so formed usually leads to the production of tertiary amines, thus for example acetophenone, formaldehyde and ammonia give tris (β- benzoylethyl)-amine[9].

Use of Primary Amine

Various primary amines[2] or their salts have been successfully used in the Mannich condensation.

When a primary amine or its salt is used in a Mannich reaction the first product is a secondary amine, but this often reacts with more of the reagents to give a tertiary amine. Frequently such products derived from two molecules of formaldehyde, two molecules of ketone and one molecule of primary amine, are unstable and readily undergo cyclisation. The compounds obtained from acetone, formaldehyde and methylamine are illustrated:-[10]

$$2\ CH_3COCH_3 + 2HCHO + CH_3NH_2.HCl \longrightarrow$$



Aliphatic ketones and primary amines as well as phenols and primary amines usually give rise to a mixture of products, as illustrated in the previous example, depending on the molar ratio of the reactants used.

Use of Secondary Amine.

A vast number of secondary amines have been successfully used including the cyclic and the aromatic amines. However, dicyclohexylamine[11] and tetrahydroquinoline[12,13] are said not to take part in the reaction.

The reactions of secondary amines with ketones, aldehydes, acids, esters and phenols are less complicated and usually give pure products in good yield.

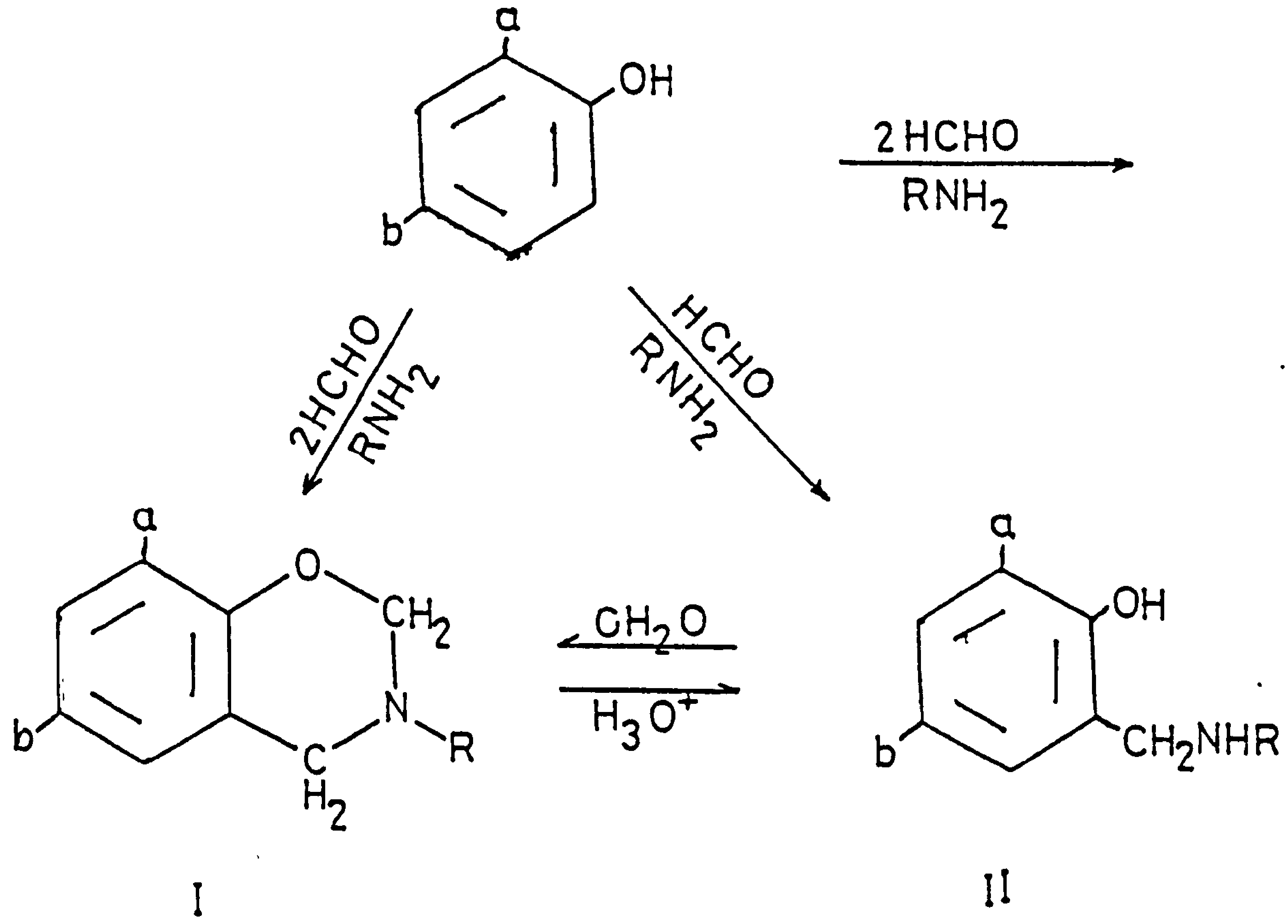
1b. Mannich Reaction with Phenols

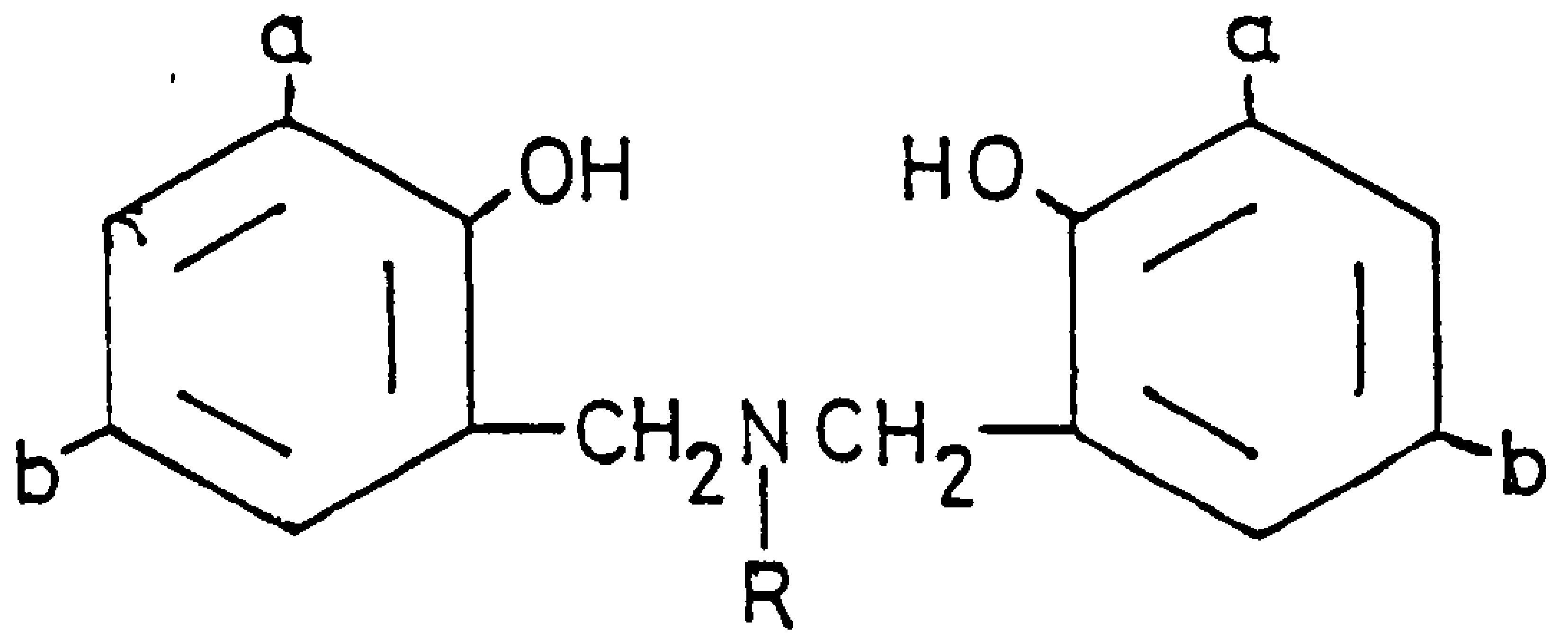
The o-and p-hydrogens in phenols are sufficiently active to enter into the Mannich reaction. Thus, products from phenol[14,15,16], 4-acetaminophenol[14], o- and p-cresols[15], m-cresol[16], 3,5-dimethylphenol[17], 2-methyl-4-ethylphenol[15], 2- and 4-methoxyphenol[18], β-naphthol[18] as well as other numerous phenols[19] with various amines have been reported. Mannich reactions with a variety of phenols bearing long chains have been carried out although the work has not been reported[20] and led to the present programme of work.

Bruson and MacMullen[16] found that an excess of formaldehyde (at least three moles) reacted with phenol and m- cresol in presence of at least three moles of strongly basic, non-aromatic secondary amines to form phenolic tri-amines. Dimethylamine, for example, gave an almost quantitative yield of 2,4,6, tris- (dimethylaminomethyl)-phenol from phenol and 2,4,6, tris- (dimethylaminomethyl)-m-cresol from m-cresol.

Before 1949 analogous studies involving primary amine rather than secondary aliphatic amine appear to have been limited to the use of 2-aminoethanol[21]. Reaction of equimolar quantities of this amine with formaldehyde and certain o- or p- substituted phenols resulted in crystalline compounds having o- or p-hydroxyethylaminomethyl groups. Other phenols such as the three cresols gave resins which could not be purified.

The Mannich reaction of phenols with primary amines was studied in greater details by Burke[22] and Burke, Smith and Weatherbee[23]. They isolated three different products depending on the molar ratio of the reactants used. A scheme showing the formation of the three products, N-alkyl-3,4-dihydro-1,3,2H-benzoxazines (I), 2-alkylaminomethylphenols (II), and N,N,-bis-(2-hydroxybenzyl)-alkylamines (III) is outlined below:-





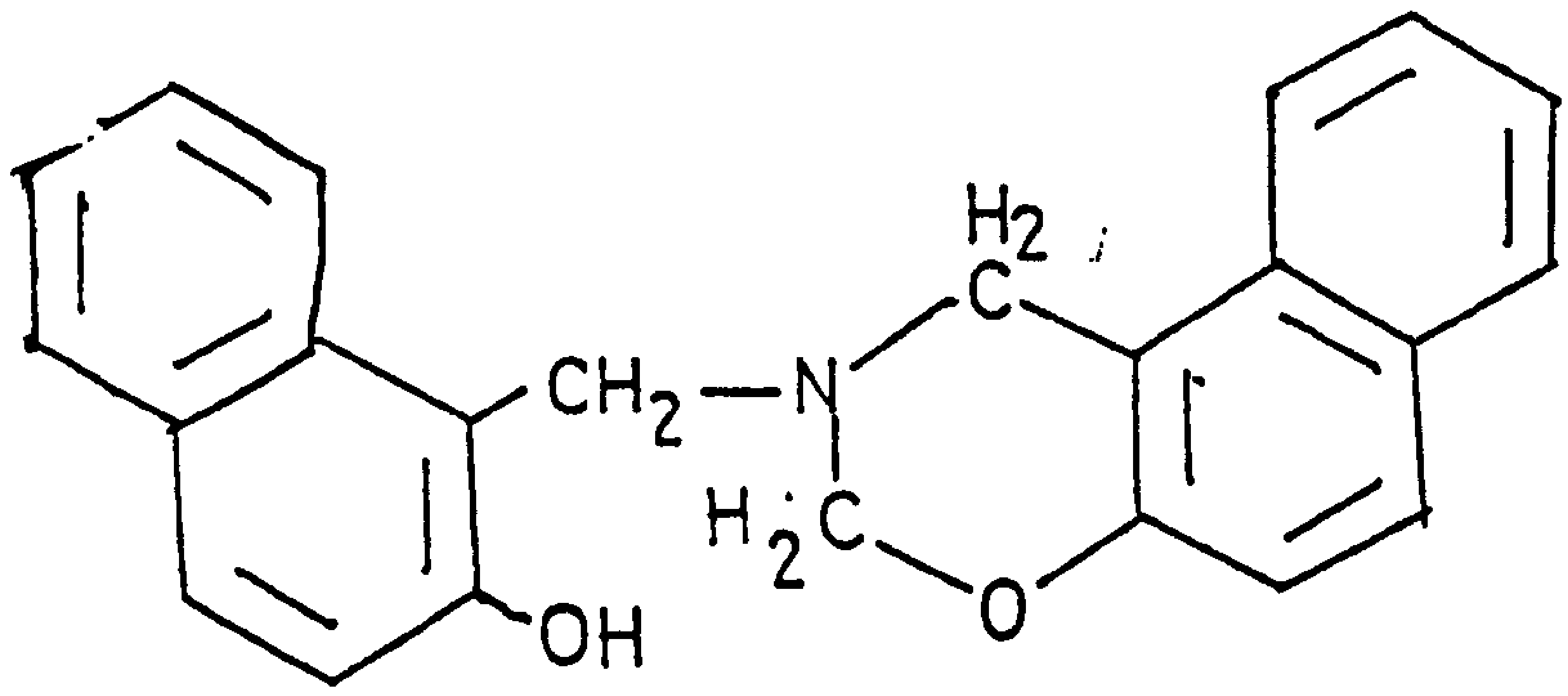
III

RNH_2 = benzyl, cyclohexyl, or methylamine

a = CH_3 , $C(CH_3)_3$, or Cl

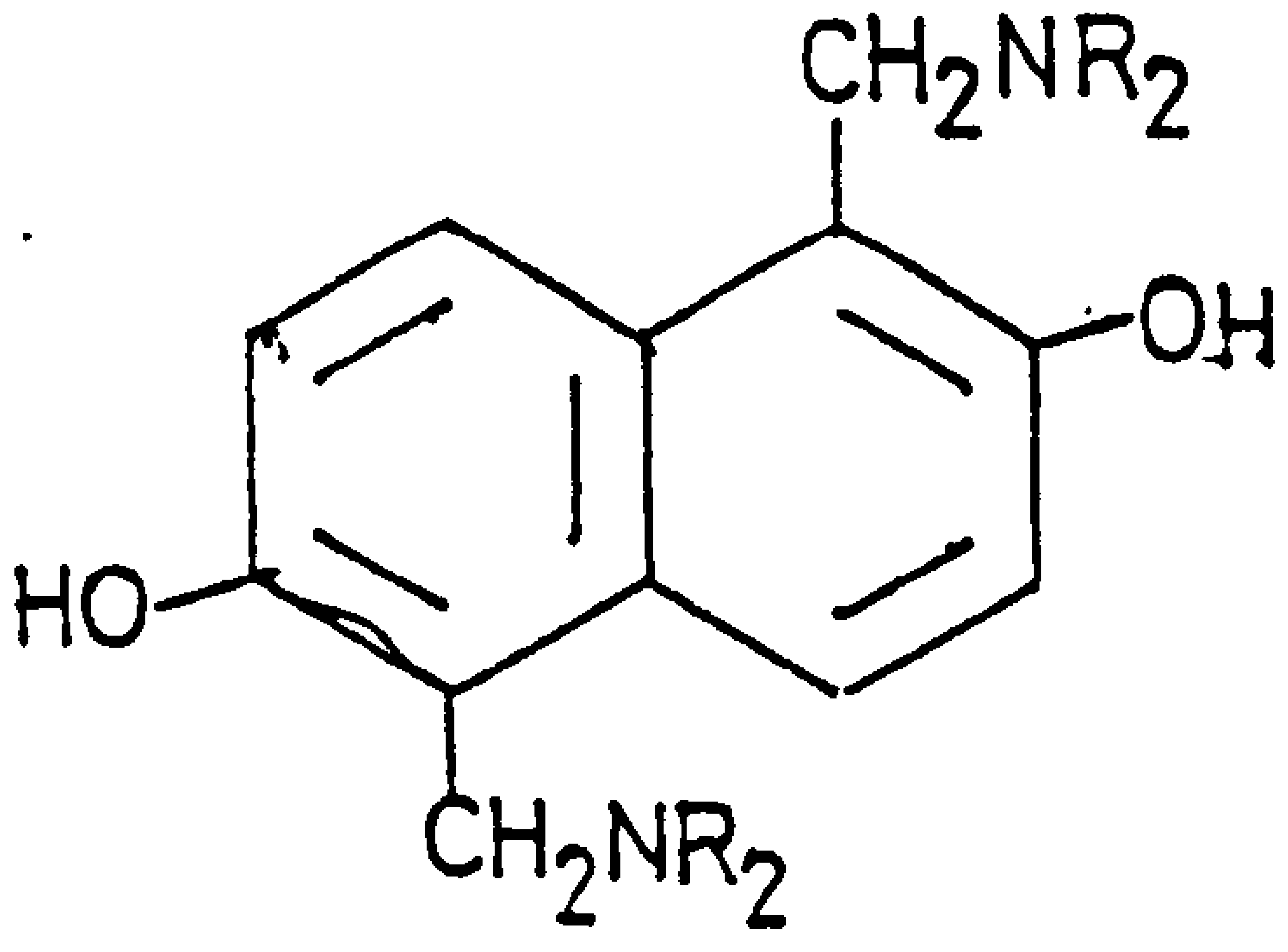
b = CH_3 or $C(CH_3)_3$

Moehrle and Gusowski[24] isolated the naphthoxazine (IV) from the reaction of 2-naphthol with hexamethylenetetramine.



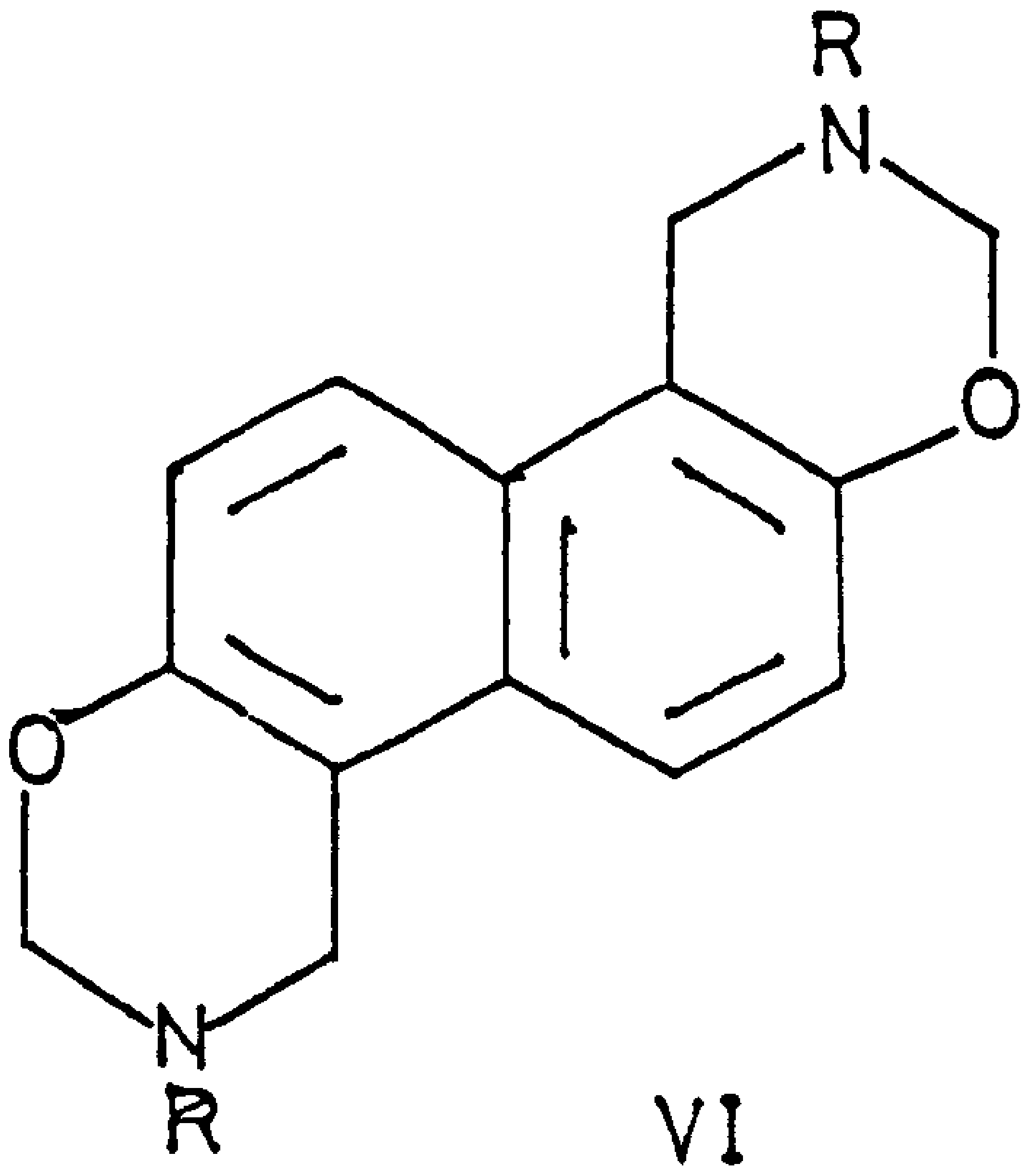
IV

Similar products (V) and (VI) have also been isolated by Kuriakose[25] from the reaction of dihydroxynaphthalene, formaldehyde and primary and secondary amines.



V

NR_2 = piperidino or morpholino



VI

R = Ph or $PhCH_2$

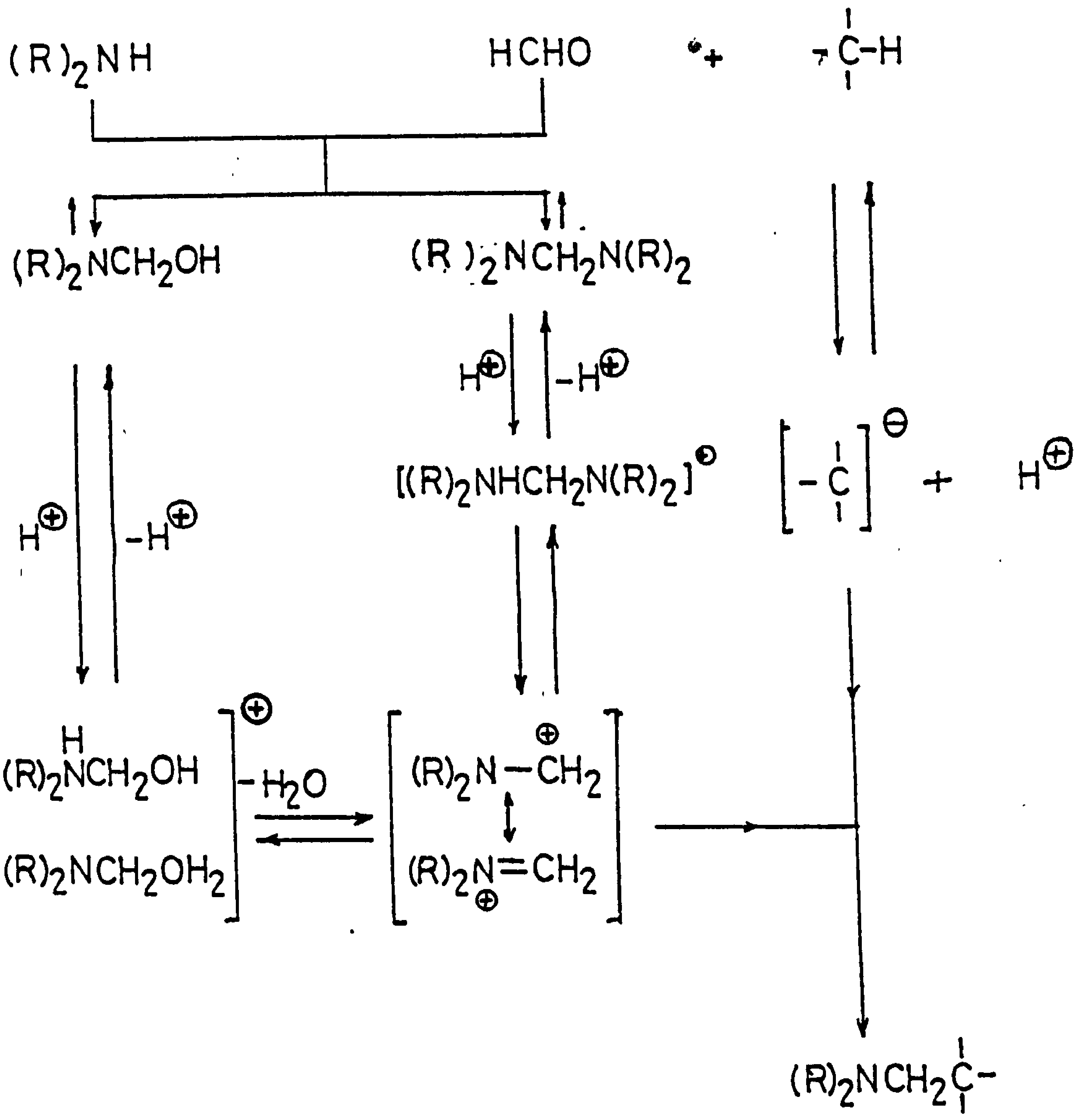
The condensation of eugenol with formaldehyde and various amines has been reported to give 2-alkylaminomethyleugenols and iminodimethylene-bis(eugenols)[26].

1c. Mechanisms of Mannich Reaction

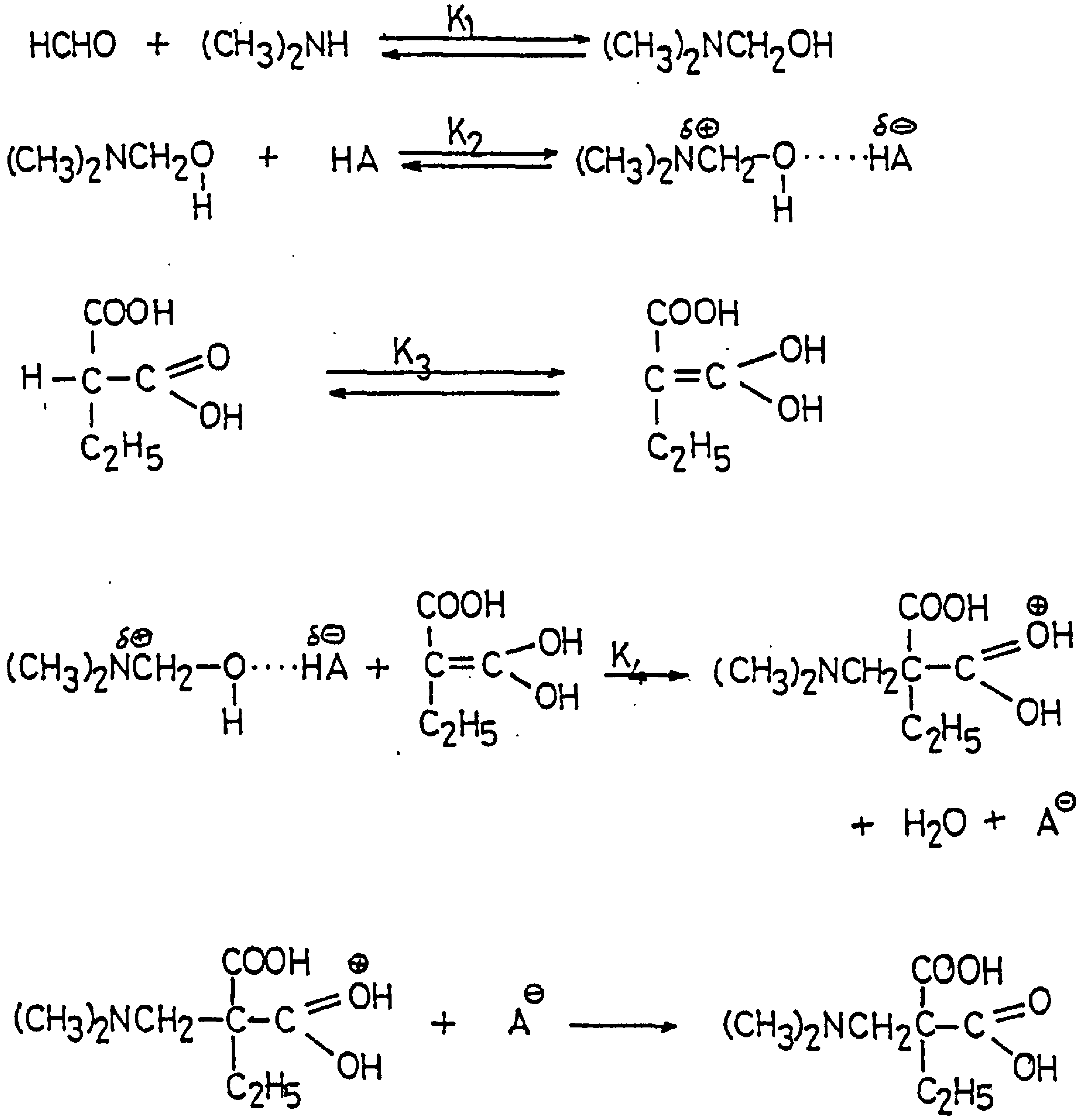
A great deal of work has been carried out on the kinetic aspects of the Mannich reaction and several workers have proposed mechanisms[27-35]. The mechanism has also been the subject of a review by Thompson[36]. Only a brief historical development will be presented here.

From their investigation of the Mannich reaction of antipyrine with dimethylamine and formaldehyde, Bodendorf and Koralewski[32] concluded that neither the condensation of the formaldehyde with the amine nor with the active hydrogen compound to yield the corresponding methylols represented the true course of the reaction

Lieberman and Wagner[33] presented an attractive mechanism involving the formation of the carbonium ion, $R_2\overset{+}{N}{=}CH_2$, from the amine and formaldehyde and also the formation of a carbanion, R^-, by the removal of a proton from the active hydrogen compound. The final, essentially irreversible step was the combination of the carbonium ion and carbanion to yield the Mannich base. Formation of the anion was promoted by the base present or by added alkali or both. The suggested reaction scheme showing the course of the Mannich reaction is outlined below:-



Alexander and Underhill[34] carried out a kinetic study on the Mannich reaction involving dimethylamine, formaldehyde and ethylmalonic acid in acidic medium. Their experiments showed third order kinetics with no primary salt effect. This was at variance with the mechanism of Lieberman and Wagner which in postulating the final rate-controlling step as the reaction between the two ions should show a primary salt effect. Alexander and Underhill's proposed reaction scheme is outlined below:-



Cummings and Shelton[30] studied the kinetics of the reaction between cyclohexanone, formaldehyde and dimethylamine under acidic and basic conditions. The base-catalysed reaction was thought to involve the reaction of a carbanion, derived from the active hydrogen compound with the "aminomethylol" by an S_N2 mechanism the reaction in acid media was said to involve the carbonium ion (derived from the aminomethylol) with the active hydrogen compound.

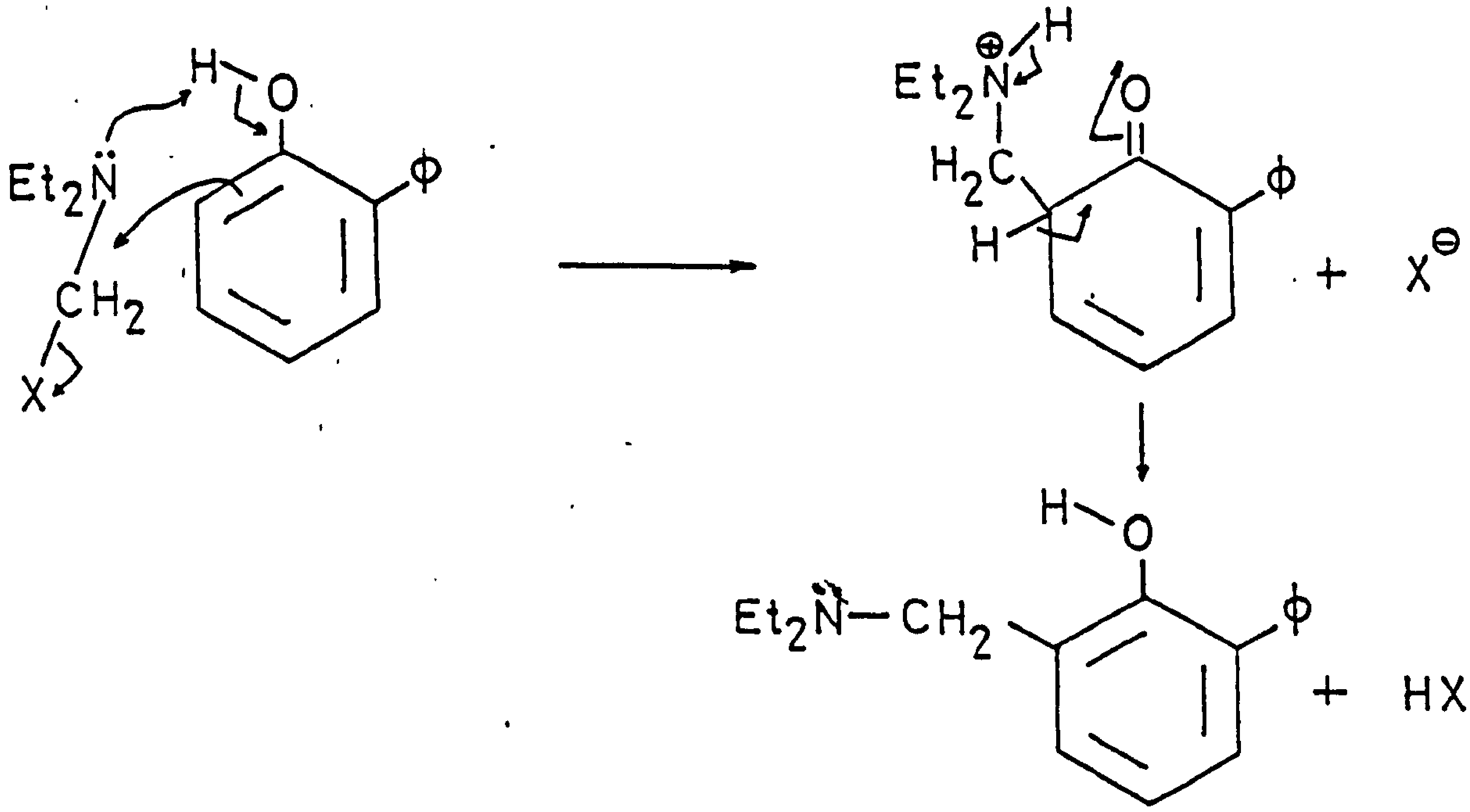
The rate in acidic medium was found to be slower than that for the reaction in basic media and also was independent of pH at low pH values.

Hellman and Opitz[29,37-41], in a series of comprehensive studies proved that N-hydroxymethylamine, N-methoxymethylamine and methylenediamine could all be formed in the course of the Mannich reaction depending upon the conditions employed. Since the highest yields were obtained when one of these materials was added to a mixture of excess aqueous acid and the acidic or labile hydrogen compound, a method which gives the highest concentration of the aminomethyl carbonium ion,[42] it was concluded that this ion was the active aminoalkylating agent.

Burckhalter and co-workers[27,35] have studied the mechanism of the Mannich reaction on phenols with emphasis on the observed preponderance of ortho- substitution.

In the mechanistic and kinetic studies carried out in basic media by Burckhalter and co-workers, the rate of condensation of formaldehyde and morpholine with 2,4-dimethylphenol was controlled by the formaldehyde if its concentration was less than half the morpholine concentration. Conversely, the morpholine concentration was critical if it was less than twice the formaldehyde concentration. These data suggested the participation of methylene-bis-(N-morpholine) as an intermediate. A pure sample of this compound gave data kinetically indistinguishable from those of the formaldehyde and morpholine mixture. Calorimetric data by Fernandez and Butler[43] also supported a methylene-bis-(amine) intermediate.

Burckhalter and co-workers suggested that ortho-substitution predominates in aminomethylation of phenols because of hydrogen bond participation. The process was visualized as in the scheme below:-



A maximum rate was observed between pH 9.6 and 10.2 which supported the concept of a methylene-bis(amine) as the most likely intermediate under basic conditions.

2. THE CASHEW NUT AND CNSL

2a. The Cashew Nut Occurrence

The cashew nut is the fruit of the tree named *Anarcardium occidentale*. The fruit occurs as a kidney shaped structure, 2-4 cm long attached to the end of a large penduncle known as the cashew apple. The nut consists of an inner ivory coloured kernal covered by a thin brown testa and enclosed by an outer brown shell. The kernels, after removal of the testa, are either consumed directly mainly as roasted andsalted nuts, or in confectionary and bakery products.

The cashew nut shell is approximately 0.3 cm thick and consists of three distinct layers, a coriaceous epicarp, spongy mesocarp and stoney endocarp. The thickest layer is the spongy mesocarp which contains a viscous reddish brown oil known as cashew nut shell liquid (CNSL). The oil is present to the extent of approximately 20%[44] of the total raw nut weight.

The cashew nut tree was originally a native of Brazil but they are now also found in Mozambique, Kenya, Tanzania and India. At present Mozambique is the largest producer of cashew nuts followed by Brazil.

2b. CNSL - Extraction

Of the 20% by weight of CNSL present in raw cashew nuts, only about 30 to 50% of the total CNSL present in the shells is extracted, depending on the method used.

CNSL was originally obtained as a by-product during isolation of the kernel by roasting the raw nut in an open pan or perforated drum. Most of the CNSL is now extracted by the "hot oil bath" process whereby raw nuts are heated in a bath of CNSL at 180 - 190^{o} whilst travelling on a conveyor belt moving at approximately 3cm/min. The shells lose some of the CNSL present which supplements that in the oil bath, whilst simultaneously becoming brittle thus facilitating shelling.[45]

The CNSL is decarboxylated during the heating process through the conversion of the major component, anacardic acid, to cardanol. The resulting decarboxylated CNSL is termed "technical CNSL".

A similar U.S. patented method, not generally used, employs molten solder as the heating vehicle.[46]

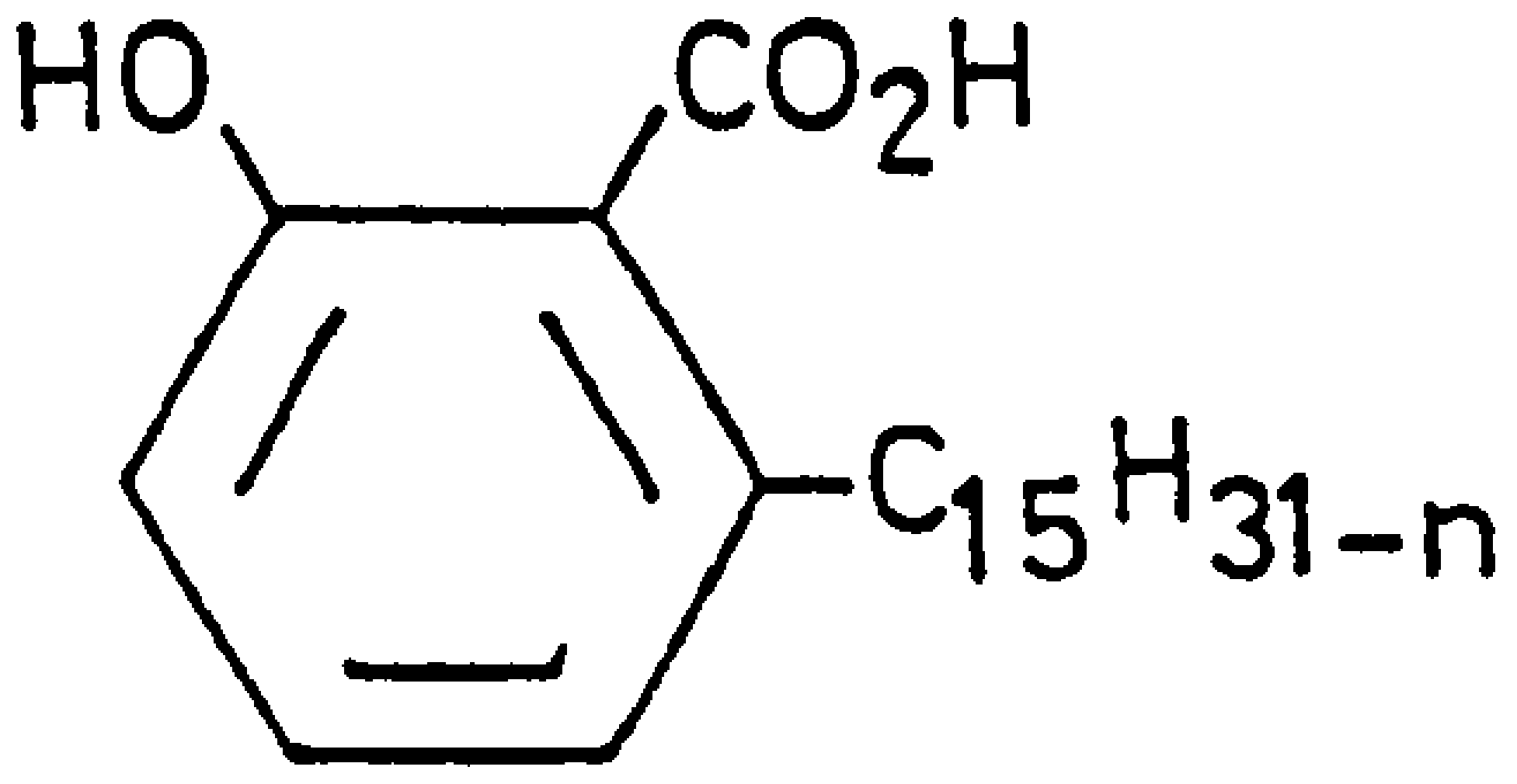
A solvent extraction process is used commercially in Brazil but elsewhere there are only two plants, both in Mozambique. The "natural" CNSL obtained by this process is considered inferior to the "technical" grade obtained by hot extraction since for most industrial purposes natural CNSL must be heated to convert anacardic acid to cardanol before it may be polymerised. A further disadvantage of the extraction of CNSL using the cold method is the higher capital outlay required than that in the hot extraction method.

90% of all CNSL produced is exported to three countries. The U.S.A. imports 50% of the total, followed by Japan and then the U.K. Other importers include Australia, South Korea, France and Italy.

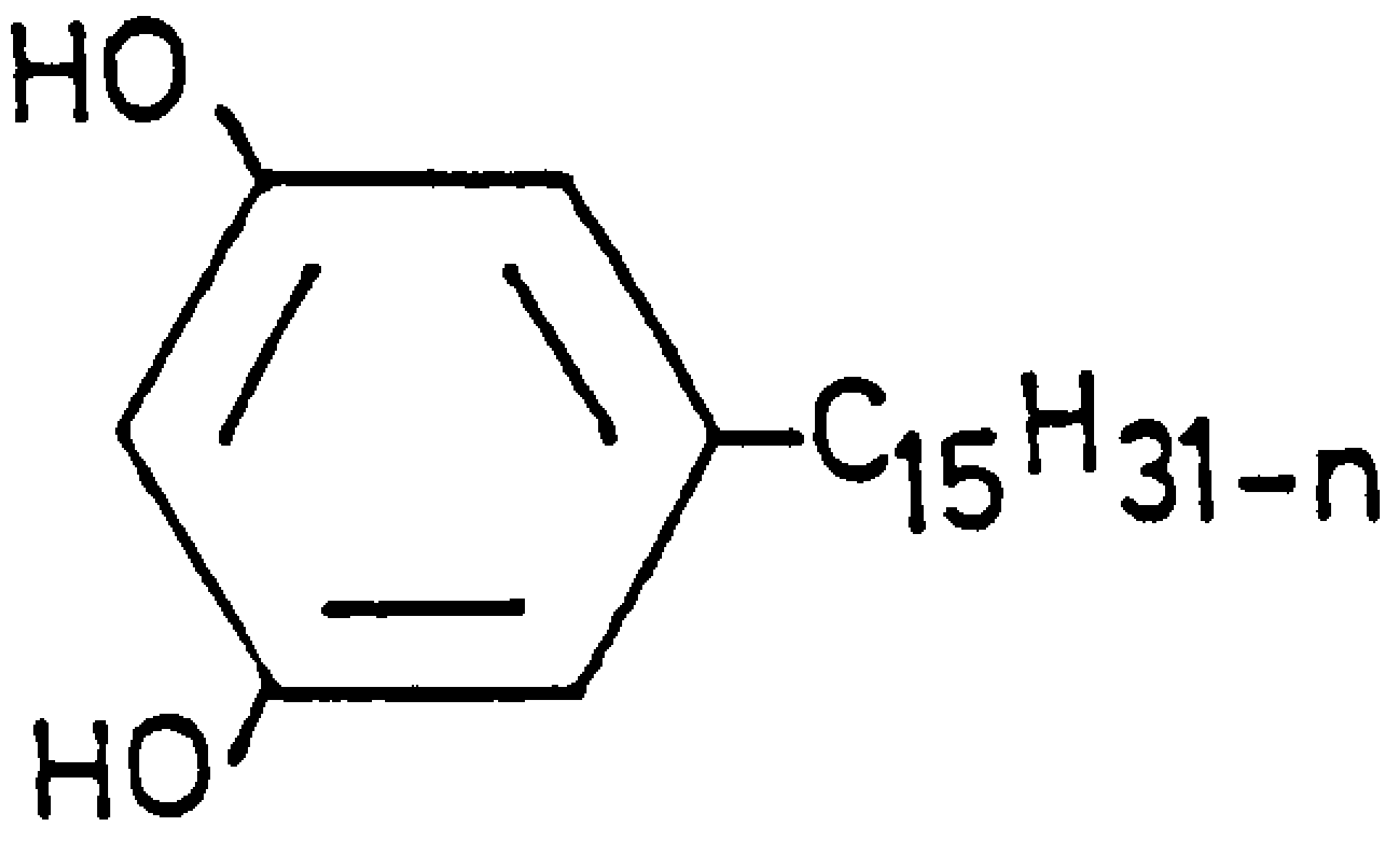
2c. Structure of the component phenols from CNSL

Natural CNSL from one source has the following composition.[47]

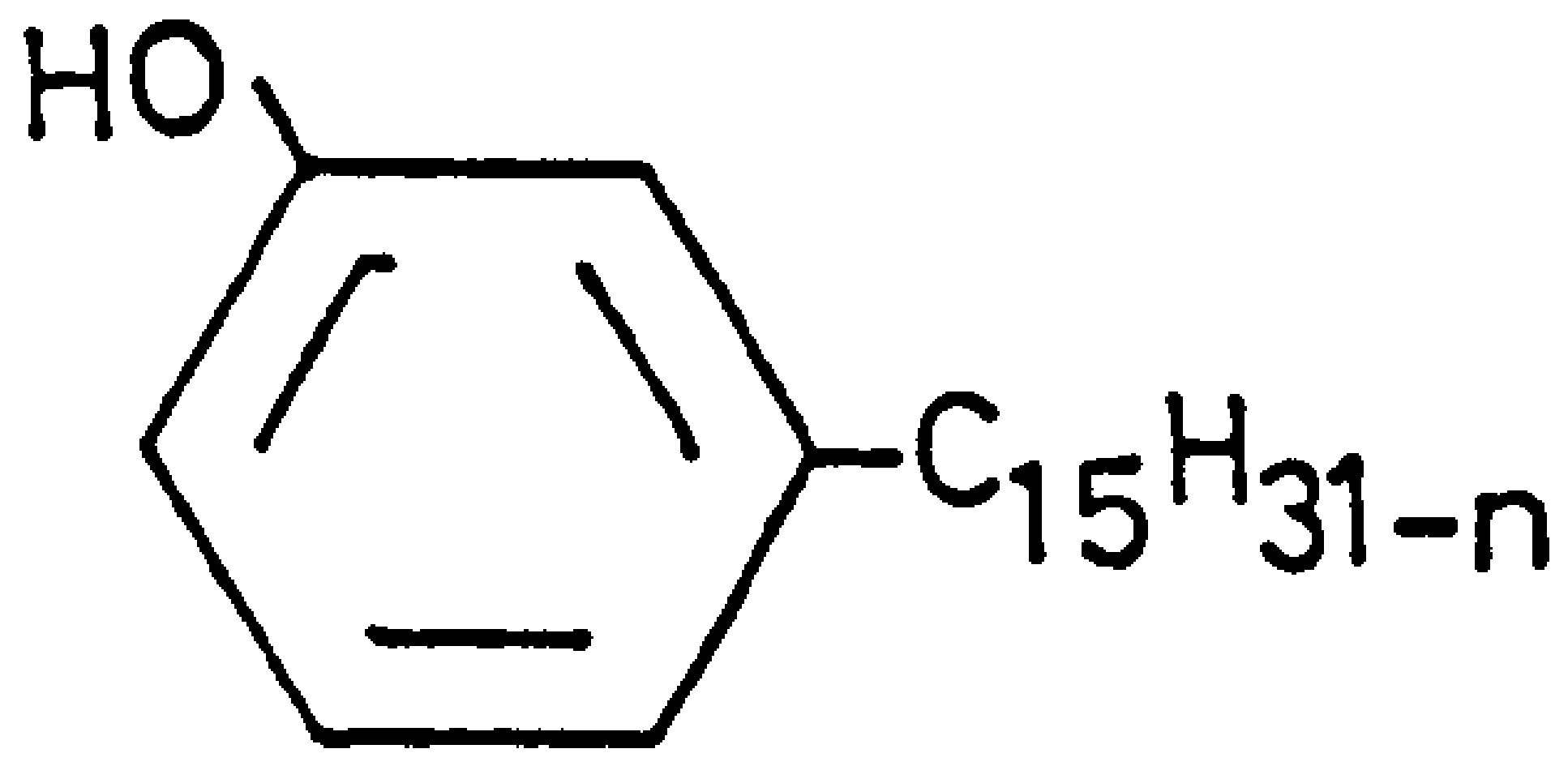
Anacardic acid - 71.7%



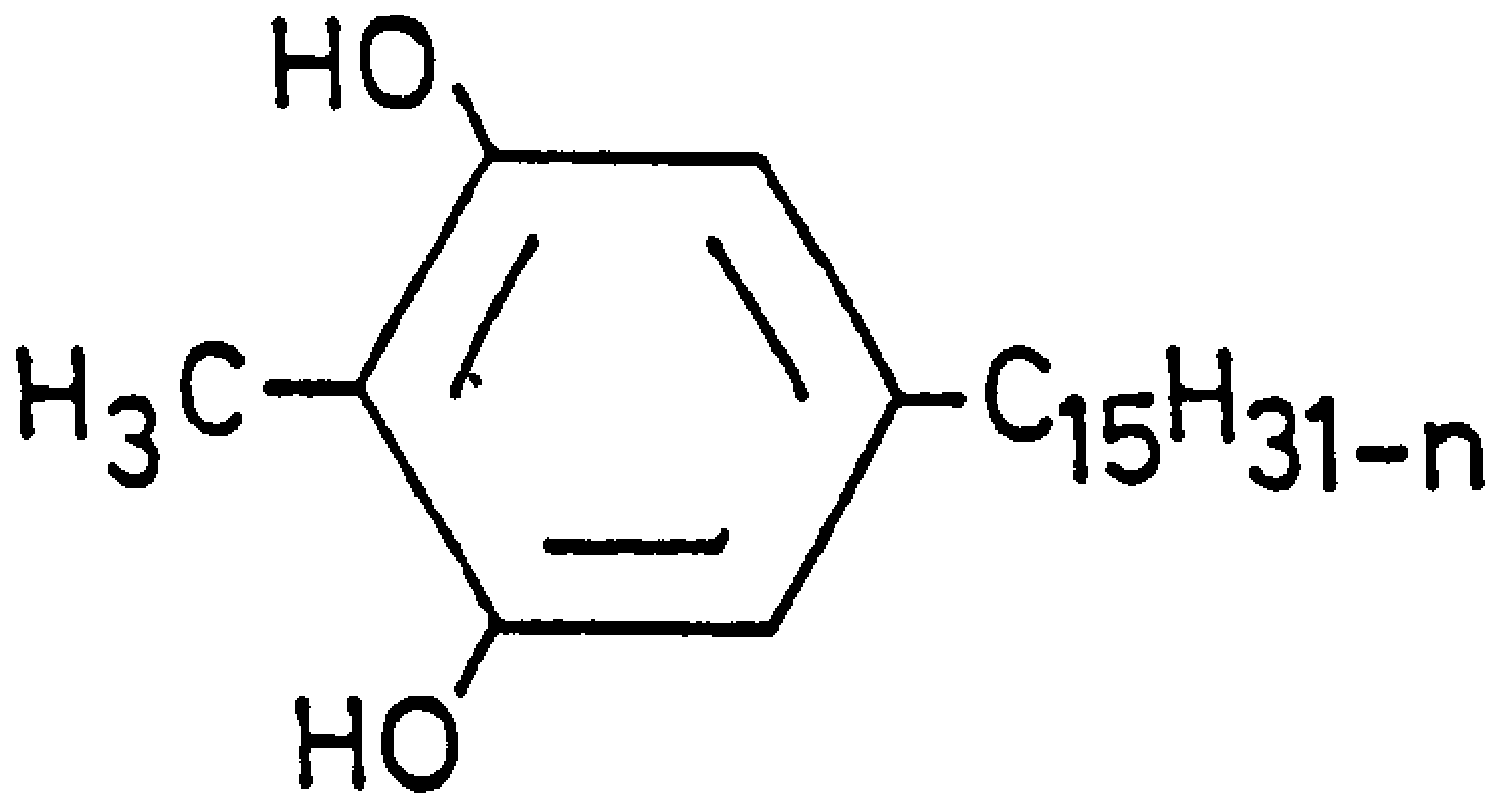
Cardol - 18.7%



Cardanol - 4.7%



2-Methyl cardol 2.7%



In all cases n=o , 2,4, and 6. Other minor components amount to approximately 2.1%.

N.B. There is a small difference in composition[48] of natural CNSL depending on its source.

In technical CNSL most of the anacardic acid has been decarboxylated to cardanol and the cardanol concentration is approximately 75% in the former.

2d. CNSL - Chemistry

The structure of the component phenols of natural and technical CNSL has been deduced after work carried out by many workers over a long time, dating back to 1847.

In 1847 Städeler[49] isolated an acidic fraction which he named anacardic acid comprising 90% of the total and the remainder which he named cardol was phenolic in character. He assigned empirical formulae and molecular weights to both "compounds" but these were much higher than the true figures for anacardic acid and cardol.

Forty years later Ruhrmann and Skinner[50] repeated Stadeler's investigation and postulated the formula $C_{22}H_{32}O_3$ for anacardic acid. This was actually the correct formula for anacardic acid diene. The same workers also correctly suggested that anacardic acid was a hydroxycarboxylic acid.

A few years later the work of Spiegel et al [51,52] on the constitution of cardol was published. They suggested that cardol was a phenol but an incorrect formula $C_{32}H_{50}O_3$ H_2O was given .

In 1931, Smit[53] came to the conclusion that anacardic acid was a homologue of salicylic acid having a C_{15} unsaturated side chain. He correctly concluded this as a result of the oxidation degradation and destructive distillation of anacardic acid and cardol before and after hydrogenation. The position of the side chain was however not established.

Ten years later Backer and Haack[54] synthesised saturated cardanol and showed it to be identical to the natural saturated product. The structure of saturated anacardic acid was also established by oxidation of the dimethyl derivative to 3-methoxyphthalic acid.

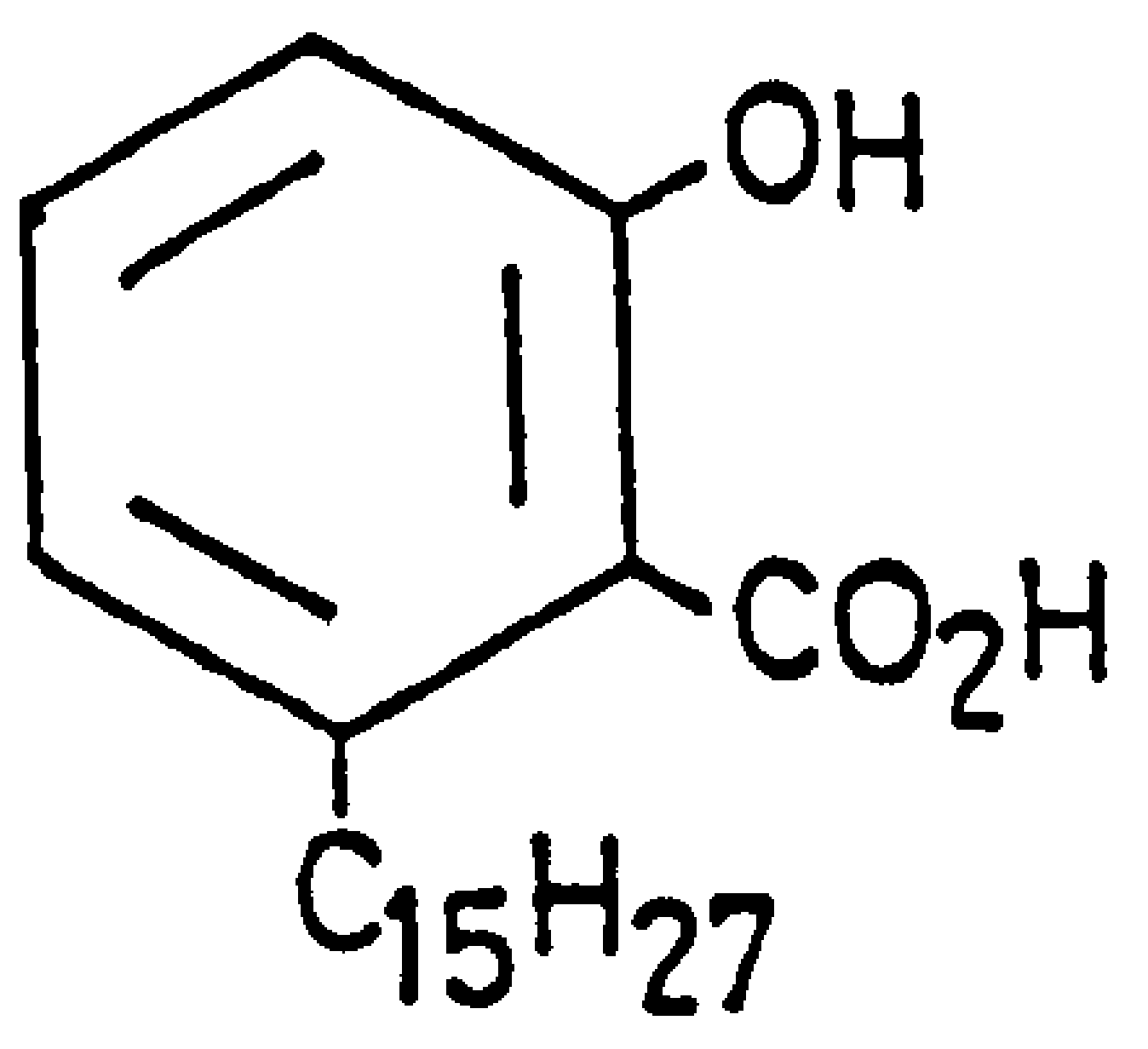
At about the same time Gokhale et al[55] published independent work in which 2- and 4- pentadecylphenols were synthesised confirming the structure of cardanol as deduced by Backer and Haack.

In 1940, Harvey and Caplan[56] isolated cardanol from technical CNSL by vacuum distillation and wrongly concluded it to be mono unsaturated compound with a C_{14} side chain.

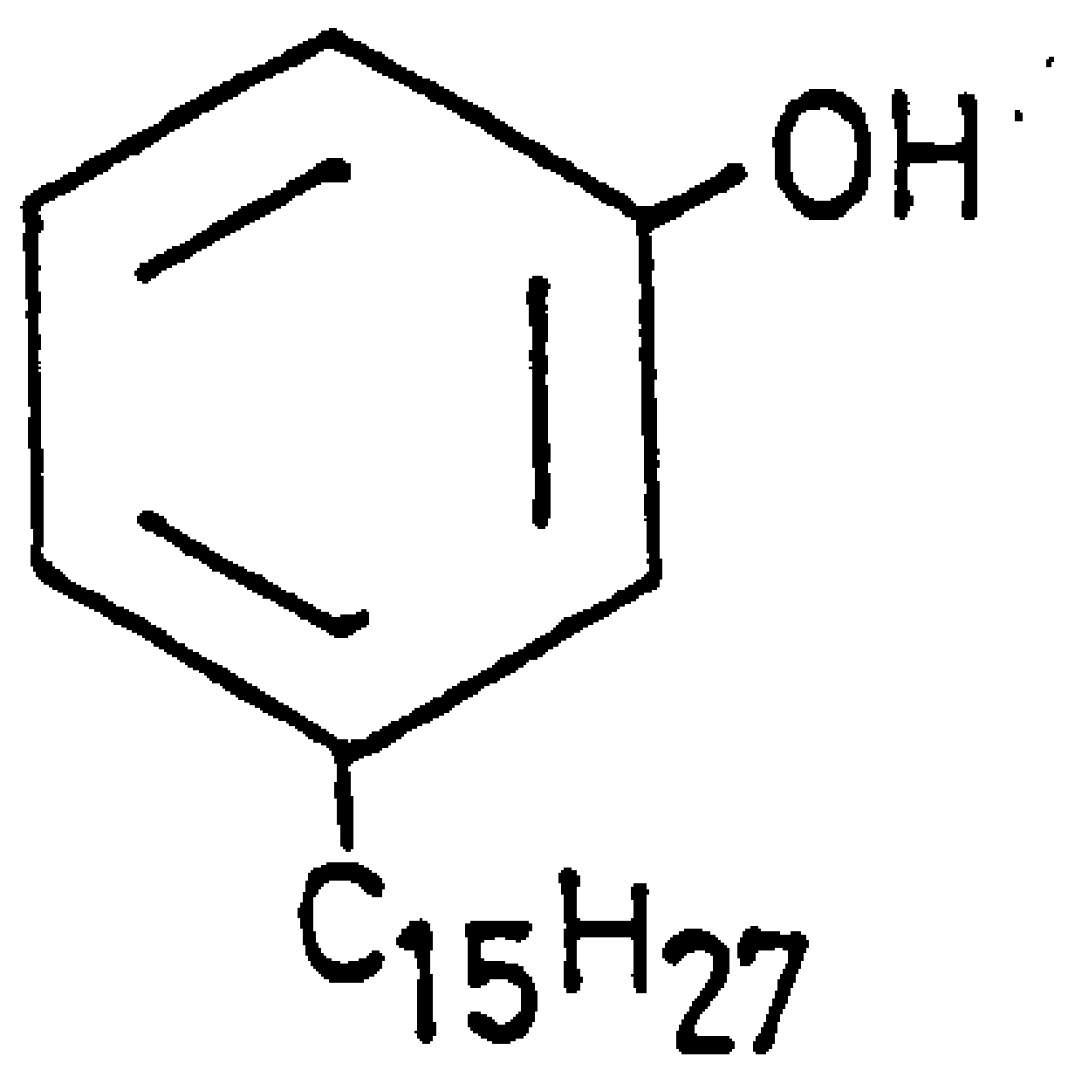
In 1945 Wasserman and Dawson[57] isolated pure cardanol from CNSL obtained by solvent extraction and decarboxylation rather than vacuum distillation. The methyl ether was then oxidised with alkaline permanganate to obtain 3-methoxybenzoic and palmitic acids, so confirming the m-position of the pentadecadienyl side chain with respect to the hydroxyl group.

They also confirmed Backer and Haack's results on the length of the side chain in cardanol and later synthesised 5-pentadecylresorcinol which was identical to saturated cardol. They further showed that the cardol whether obtained from raw or heated CNSL is the same.

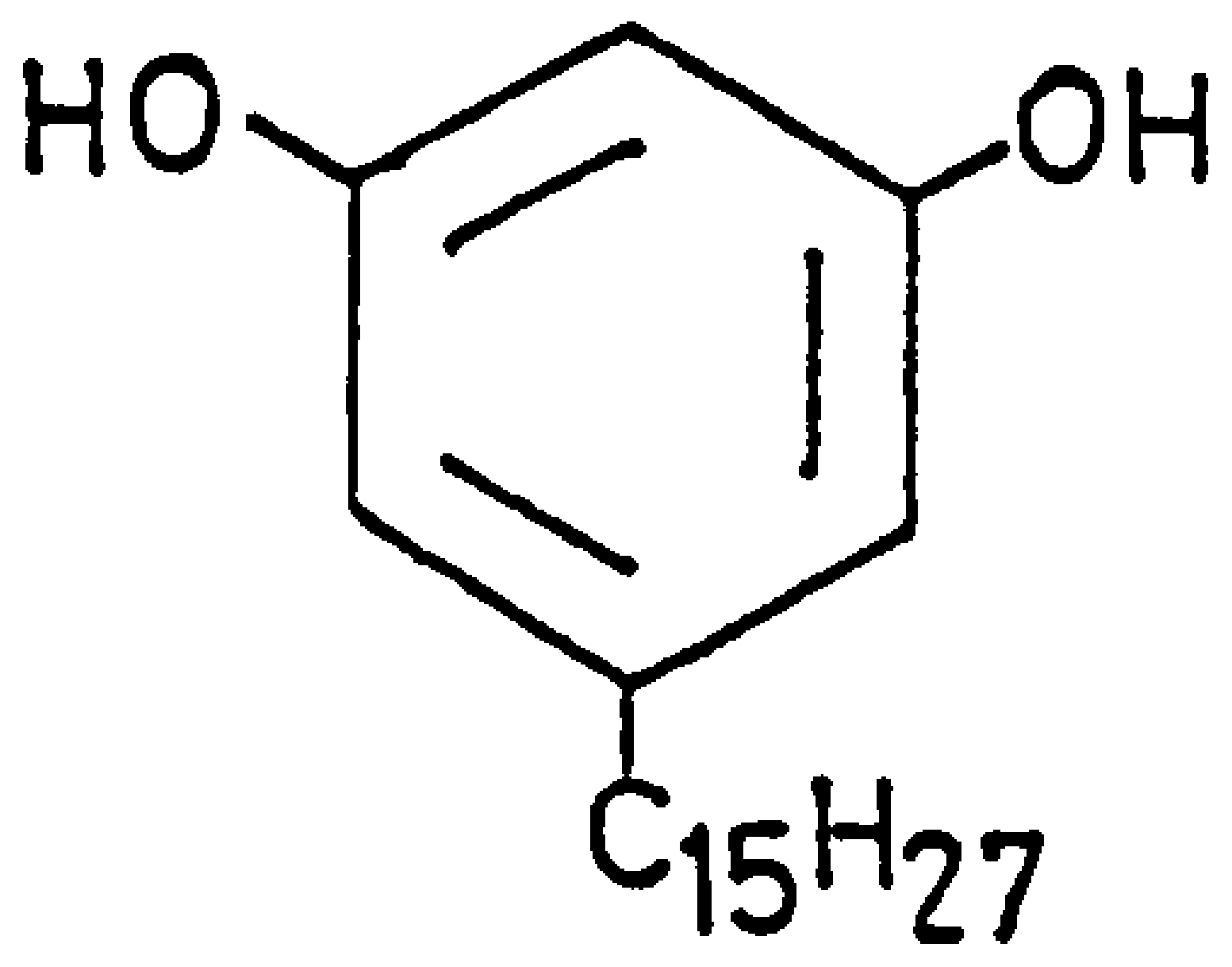
The positions of the centres of unsaturation in cardanol and cardol were not determined till later but the following structures were postulated for anacardic acid(VII), cardanol(VIII) and cardol (IX) from the available information.



(VII)



(VIII)

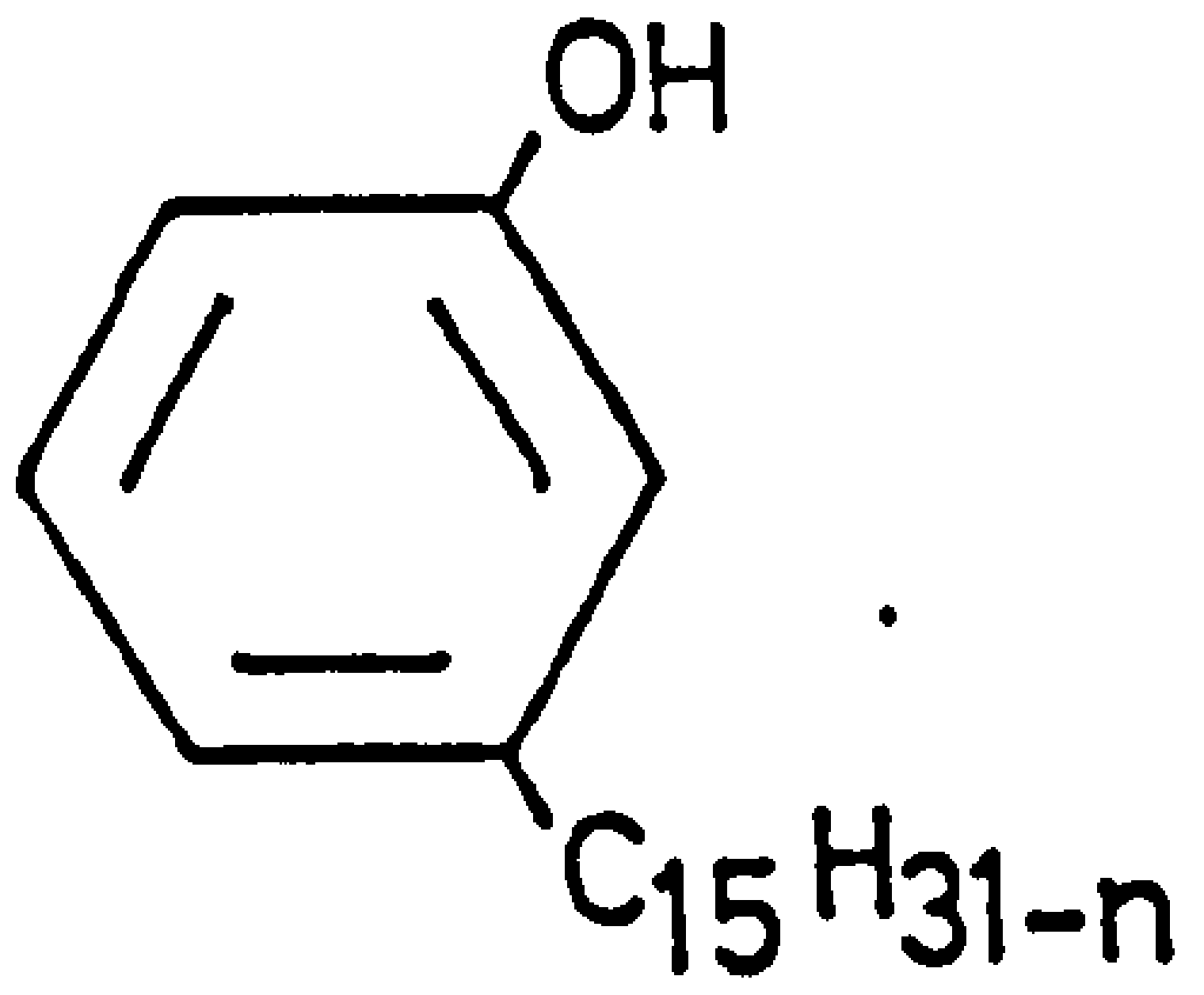


(IX)

Unsaturated components of CNSL

In 1949, Izzo and Dawson[58] published some work which demonstrated the hetro-olefinic nature of anacardic acid. They showed that it consisted of a mono - and di-olefine and, they speculated, probably a higher olefin .

In 1953 Symes and Dawson[59] described work which demonstrated the presence of a saturated component, a mono-, a di- and a tri-olefinic component in cardanol. They showed this by careful chromatographic and degradation studies on cardanol methyl ether which enabled them to give the following structures for the four constituents of cardanol.



saturated cardanol	n=o
cardanol mono-ene	n=2
cardanol di-ene	n=4
cardanol tri-ene	n=6

Positions of double bonds are 8' ; 8' and 11', 8', 11' and 14' in the monoene, diene, and triene.

Structure Elucidation by Physical Methods

By use of a multi-development thin layer chromatographic procedure Tyman el al[60,61,62,63,64] have separated, characterised and quantitatively determined all the major coponents of CNSL.

The usual characterisation techniques were used for the eluted bands from preparative TLC, including U.V.,N.M.R. and I.R. spectroscopy.

More recent work has been carried out with an initial TLC separation followed by mass spectrometry.[65] Each of the constituents of the component phenol, the saturated and the three unsaturated materials volatilise virtually to the same degree in the mass spectrometer and so give peaks due to their parent ions in proportion to their relative concentrations in the mixture. The four parent ion peaks differ by 2 m/e units for each constituent and so each constituent can be determined by measurement of the peak height of the respective parent ion.

GLC analysis of CNSL[64] has also proved feasible and useful for determination of the phenols. By use of a relatively non-polar stationary phase such as SE30 or SE52 all the major phenolic components have been separated and determined. Use of a more polar stationary phase such as polyethylene glycol adipate (PEGA) has also proved useful, although only if the phenols are first hydrogenated and then converted to methyl, or silyl ethers.

Later experiments with GC/MS have shown that a total analysis can be obtained without prior separation of component phenols.

Thus, by use of a combination of all the preceding methods, CNSL has been conclusively analysed both qualtitatively and quantitatively and its composition is no longer in doubt.

2e. Uses of CNSL

CNSL can be subjected to a variety of treatments including polymerisation, treatment with aldehydes, etherification and hydrogenation to give a wide range of products, which are of considerable importance in many industries. Brake linings, clutch facings, cements, oilstops and insulating varnishes represent some of the major ones.

Over 90% of the exports are processed into CNSL resins for use as friction dust in brake linings.[66,67,68] The CNSL is polymerised with or without added synthetic phenolic monomers by heating in the presence of an acid. The resulting polymer is comminuted and added to an asbestos filler. Alternatively the polymerisation may be carried out in the presence of the other friction lining components which act as binders. This particular application makes use of the thermoplastic properties of cashew resins because the dusts soften and do not cross link further or undergo chemical change at the friction surface and the CNSL based lining show absence of 'fade'. This property is maintained up to approximately 400°F above which synthetic phenolic resins have superior properties and for this reason the latter are preferred in disc brake pads when such temperatures are often encountered.

The reaction between cashew polymers and formaldehyde to form a rubbery gel is utilized in the preparation of cashew cements.[66,67,68] The rubbery gel formed takes several days to harden but the hardening time can be accelerated by the application of heat. The hardened material has excellent adhesion properties for the bonding of brickwork, steel and carbon blocks, and is resistant to both acidic and alkaline conditions.

Resins produced by the co-condensation polymerisation of phenol, formaldehyde and CNSL have excellent electrical properties, strong chemical resistance and high strength. These materials are used as laminating and impregnating resins.

A range of polymers derived from CNSL is used in surface coatings. Certain of these specially refined polymers are used as insulating varnishes, in which the CNSL polymer is usually co-polymerised with an etherified urea/formaldehyde resin. CNSL coatings have only very limited decorative value because of their characteristic brown colour, however work is being carried out to obtain less coloured surface coating resins and progress has been made in this area. The work described in this dissertation has contributed to this.

The demand for CNSL for use as a friction modifier may possibly decline by perhaps 20% by 1980,[69] due to economic factors, the increased use of disc brakes and the use of new synthetic materials with superior properties.

The demand for CNSL may further drop due to the recent rapid rise in price following the drop in output by East African sources probably because of the political situation.

3. PROPOSED SCHEME OF WORK

The proposed scheme which led to the present work has been concerned with three aspects:

(i) A study of the Mannich reaction with certain amines and readily available long chain phenols, in particular those occuring in CNSL.

(ii) Attempts to identify coloured by-products formed in the reaction.

(iii) Experimentation to find ways of eliminating or lessening the formation of such products in the Mannich reaction.

(i) Mannich Reaction

Mannich reactions have been carried out with several different phenols to establish the best general conditions and the relationship between structural factors and colour development in the reaction.

All reactions were, from the commencement, routinely monitored by TLC to examine the rates of formation of products. All the products or reaction mixtures were examined by ^{1}H NMR and IR spectroscopy.

(ii) Nature of Coloured Products in the Mannich Reaction

To define the conditions for formation of coloured materials, the reaction conditions of the Mannich reaction were simplified. It was possible that all the reactants were involved or only two. Accordingly, mixtures of phenol/formaldehyde, formaldehyde/amine, and amine/phenol were examined.

Experiments were directed to the isolation of coloured materials from resorcinol/dimethylamine, resorcinol/ammonia, resorcinol/diethylenetriamine and various other resorcinol/amine mixtures. These were then examined by UV, IR, ^{1}H and ^{13}C NMR, mass spectroscopy, elemental analysis and by their chemical reactions.

(iii) Prevention of Colour Development in the Mannich reaction

After finding the conditions causing colouration of Mannich bases, several preventative modifications were tried. These included (i) the acceleration of the Mannich reaction using an electrophilic type reagent, (iii) the use of an inert atmosphere and of a chemical antioxident, (iii) acetylation of the Mannich base, and lastly (iv) the removal of the cardol fraction of the CNSL by distillation. This last method led to an industrially viable process.

PART TWO

EXPERIMENTAL

1a - Laboratory Techniques

Thin layer Chromatography (TLC)

Analytical thin layer chromatography was performed using plates (microscope slides)coated in the laboratory (approximately 0.25 mm thickness) with "Kieselgel G nach stahl (Merck) Type 60". Preparative TLC plates (20 x 20 cm) were similarly prepared in the laboratory to give a silica gel layer of approximately 1mm. thickness. Spots/bands were visualised by spraying with rhodamine 6G (0.1% solution in I.M.S.) and irradiating with ultra violet light (250 nm) or simply irradiating with ultra violet light in the case of fluorescent spots.

A variety of solvents were used in developing the TLC plates and these are represented by letters in the experimental denoting the following solvents.

E - Chloroform: Ethyl acetate (95:5)
F - Chloroform: Ethyl acetate (80:20)
G - Chloroform: Ethyl acetate (93:7)
H - Pet. Ether (60-80°): Diethyl ether (95:5)

Gas Liquid Chromatography (GLC)

GLC was conducted using a Pye-Unicam Gas Chromatograph (GCD) fitted with flame ionisation detector, and a programmed digital integrator (Infotronics CRS 201). Conditions and results of each analysis are given under individual compound where applicable.

Column Chromatography

Column chromatography was carried out on "Kieselgel G nach Stahl (Merck) Type 60" (mesh 70-230) in a glass column equipped at the lower end with a sintered disc (of zero porosity) to support the column packing and a tap to control the flow of solvents.

The progress of separation was monitored by TLC on the collected fractions.

Proportions of adsorbent and solvents used are given under individual compound where applicable.

Mass Spectroscopy

Mass spectroscopy was carried out on an MS 902 (Brunel) and an MS 50, (by courtesy of Physico and Chemical Measurement Unit, PCMU) at Harwell.

Elemental Analysis

The C, H and N analysis was carried out by courtesy of Mr. G. Crouch at School of Pharmacy, University of London.

Nuclear Magnetic Resonance (NMR) Spectroscopy

^1H Nuclear magnetic resonance (^1H NMR) spectra were recorded at 60 mHz using a Varian T60 NMR Spectrometer (Brunel) and on a Varian FT-80A by courtesy of Dr. C. Turner of Varian Associates with tetramethylsilane as internal standard. Abbreviations used in spectroscopic interpretation for NMR are:-

s - singlet

bs - broad singlet
t - triplet
q - quartet
h - heptet
m - multiplet

^{13}C NMR spectra were recorded on a Varian CFT-20.

Infra-red Spectroscopy

Infra-red (IR) spectra were recorded on a Perkin-Elmer 700 and SP2000 Infra-red spectrometer

Ultra-Violet Spectroscopy

Ultra-violet (UV) spectra were recorded on a Pye-Unicam SP 800.

Melting points were determined using a Gallenkamp melting point apparatus.

Boiling points are uncorrected.

Hydrogenation

These were carried out in a Parr hydrogenator at low pressure.

Materials

Distilled and raw cashew nut shell liquid were supplied by 3M Research and were used without further purification. The materials were believed to be of Brazilian origin.

Diethylenetriamine (DETA) as supplied by Kodak was 99% pure and was further purified by vacuum distillation.

Purity of other amines was checked by GC and they were used without further purification.

Abbreviations

The following abbreviations have been used:

Industrial methylated spirit	(IMS)
Cashew nut shell liquid	(CNSL)
Diethylenetriamine	(DETA)

2. MANNICH REACTIONS

2a. General procedures

Method A. Aqueous solution of formaldehyde (35-40%) was added drop wise during a 15-30 min. period to a stirred mixture of the required phenol and 25% aqueous dimethylamine (or other appropriate amine) maintained at 10-15°C. The mixture was stirred for 1hr at 25°C and then for 2 hrs on a steam bath. The hot solution was treated with 160 g of sodium chloride per mole of phenol employed. The oily layer was separated, dissolved in ether, the solution dried over anhydrous sodium sulphate and the solvent evaporated.

Method B

This procedure was the same as A except for the following variations. Methanol was used as a solvent and the addition of sodium chloride was omitted. The reactants were refluxed using an oil bath and stirred with a magnetic stirrer. After the heating period was completed, the mixture was concentrated in vacuo. The oily product was washed with water and extracted with ether, the extract dried and the ether evaporated. The product was examined by TLC and purified by crystallisation or if it was a mixture, then the components were separated by preparative TLC or column chromatography.

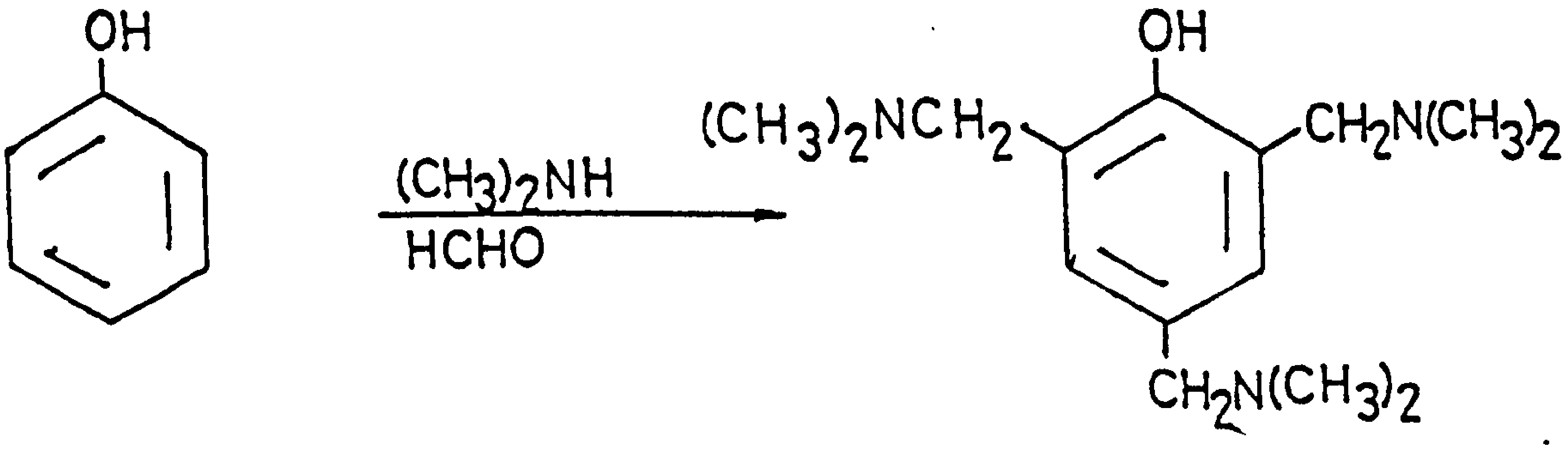
Method C

This procedure was the same as A except for the following variations. Addition of sodium chloride was omitted and the reaction mixture was washed with water, extracted with ether and the ether layer separated, dried and evaporated.

The molecular amounts of reactants employed in method A to C and analytical results obtained for each compound are given under the titled compound. If any variation in the conditions from the general method was used then this has been mentioned under the relevant compound.

2b. 2,4,6-Tri-(dimethylaminomethyl)-phenol

Reactants :	Phenol 9.4g	(0.1m)
	25% aq. dimethylamine 72.0g	(0.4m)
	35-40% aq. formaldehyde 28.4g	(0.35m)

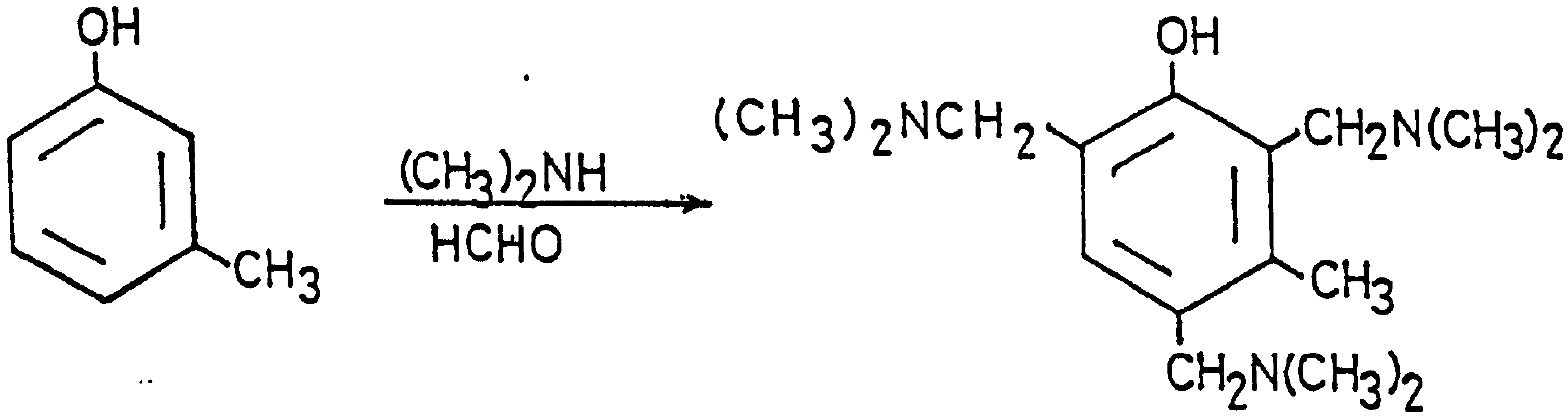


Experimental method A

The titled compound (pale yellow-brown oil) was obtained in 80% yield; $\nu_{max.}$ (neat) 2960, 2800, 1615, 1360, 1300, 1260 cm^{-1}; $\delta(CDCl_3)$ 2.20 (6H, s, $N-(CH_3)_2$), 2.25 (12H, s, $(N-(CH_3)_2)_2$), 3.27 (2H, s, $N-CH_2-Ph$), 3.50 (4H, s, $(N-CH_2-Ph)_2$), 6.98 (2H, s, ArH) and 7.76 (1H, s, PhOH, exchangeable).

<u>2,4,6-Tri-(dimethylaminomethyl)-m-cresol</u>

Reactants :	m-Cresol	10.8 g	(0.1m)
	25% aq. dimethylamine	72g	(0.4m)
	35-40% aq. formaldehyde	28.4g	(0.35m)



Experimental Method A - In this case the mixture was heated for 90 mins. The oily product solidified on standing for three days and was recrystallised from benzene.

The titled compound was obtained in 76% yield, m.p. 54-57°C (lit.[16], b.p. 200° at 0.5 mm); $\nu_{max.}$ (neat) 2950, 2860, 2820, 2760, 1620, 1595, 1460 cm^{-1}; δ (CCl_4) 2.10 (6H, m, $N-(CH_3)_2$), 2.20 (12H, m, $(N-(CH_3)_2)_2$), 3.25 (3H, s, $ArCH_3$), 3.43 (2H, s, $ArCH_2$), 3.50 (4H, s, $(ArCH_2)_2$), 6.80 (1H, s, ArH), 10.03 (1H, s, PhOH, exchangeable).

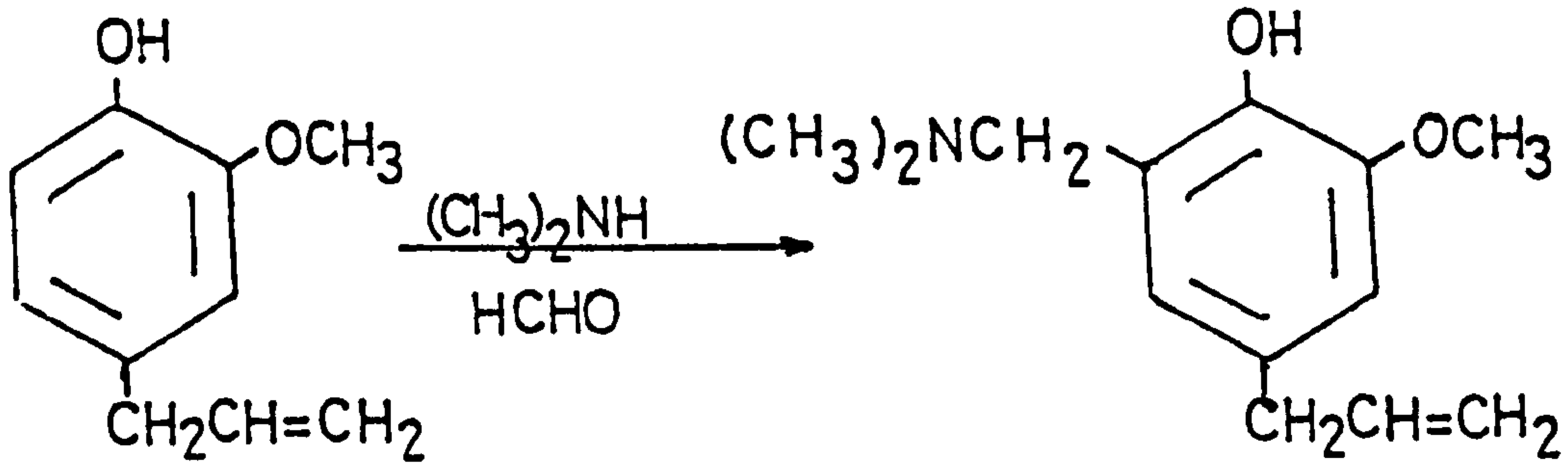
Found: C, 68.89; H, 10.37; N, 14.63; Required for $C_{16}H_{19}N_3O$:C, 68.81;

3.45, 3.50 (4H,2s, NCH_2PH)

H, 10.39; N, 15.05%.

6-Dimethylaminomethyl-2-methoxy-4-allylphenol

Reactants:	2-methoxy-4-allylphenol	2.73 g	(0.017m)
	25% aq. dimethylamine	12.2 g	(0.068m)
	35-40% aq. formaldehyde	4.86 g	(0.060m)

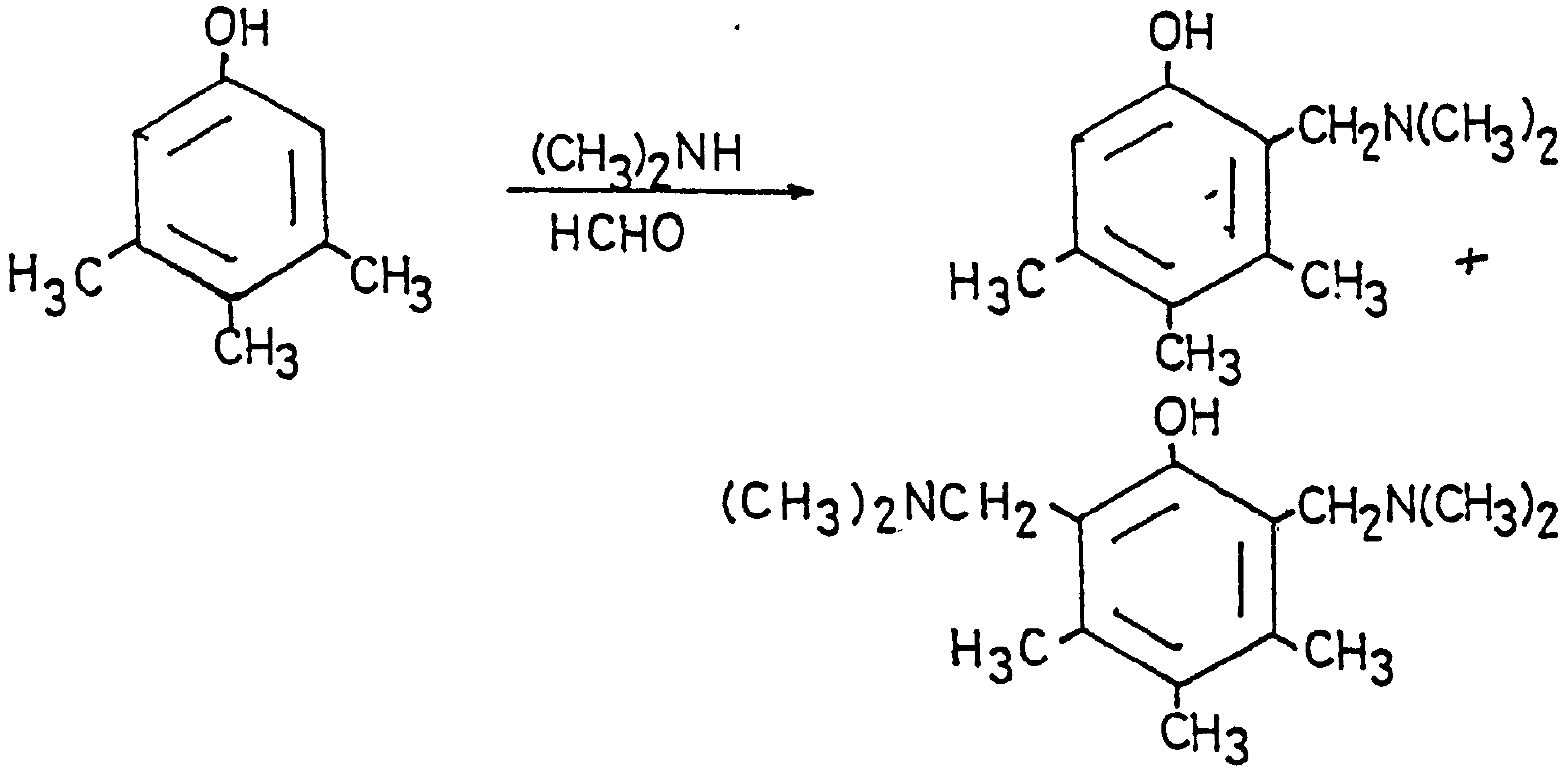


Experimental method C- Heating time 150 mins. at 70°C

The product (yellow-organge oil) was obtained in 87% yield; $\nu_{max.}$ (neat) 3000, 2960, 2850, 2800, 1820, 1680, 1635, 1600, 1490, 1460 cm^{-1}; δ (CCl$_4$) 2.28 (6H, s, N-(CH$_3$)$_2$), 3.20 (2H, d, J4Hz, ArCH$_2$C =), 3.50 (2H, s, -N-CH$_2$Ar), 3.70 (3H, s, OCH$_3$), 4.97 (2H, m, C=CH$_2$), 5.80 (1H, m, -CH =), 6.30-6.50 (2H, m, Ar), 9.38 (1H, s, Ph-OH, exchangeable).

2-Dimethylaminomethyl-3,4,5- trimethylphenol and 2,6-bis (dimethylaminomethyl)-3,4,5-trimethylphenol.

Reactants:	3,4,5,trimethylphenol	2.72 g	(0.02m)
	25% aq. dimethylamine	9.0 g	(0.05m)
	35-40% aq. formaldehyde	4.0 g	(0.05m)



Experimental method B - Reaction mixture was refluxed for 6hrs. The oily product on examination by T.L.C. showed two spots. The product solidified on standing for a week and was purified by preparative T.L.C. using solvent F.

The monosubstituted product (R_f 0.45) was obtained in 35% yield m.p. 71-72°C; $\nu_{max.}$ (KBr) 2850, 1560, 1580, 1440, 1390, 1360, 1320, 1280, 1220 cm^{-1}; δ (CCl_4) 2.17 (9H, m, $ArCH_3$), 2.37 (6H, s, $-N(CH_3)_2$), 3.67 (2H, s, $ArCH_2N$), 6.50 (1H, s, aromatic), 10.1 (1H, s, PhOH, exchangeable).

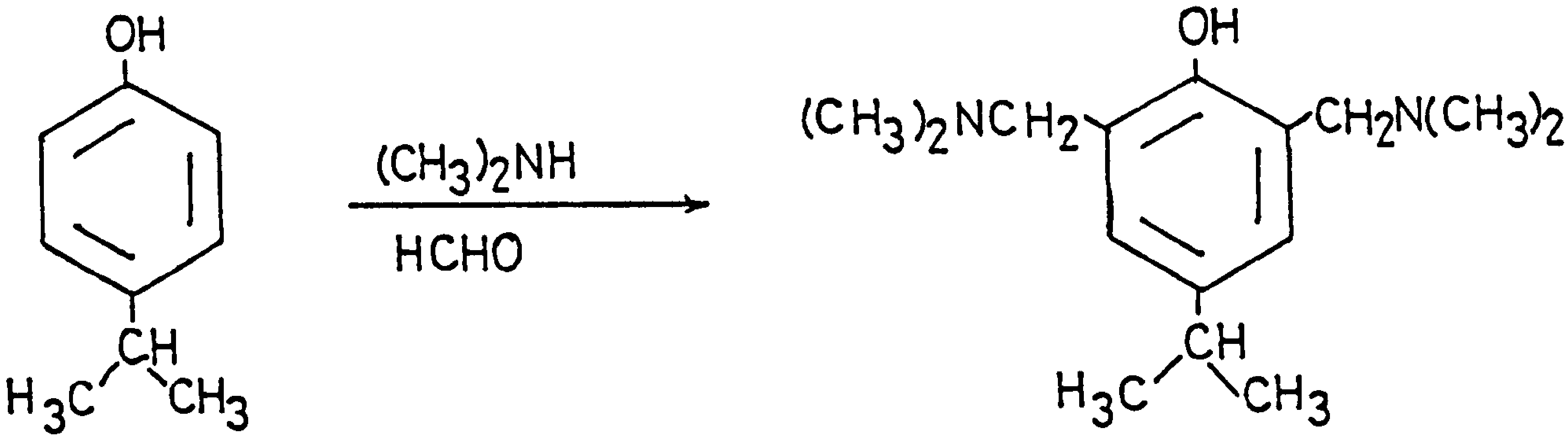
Found: C, 72.65; H, 9.70; N, 6.50; Required for $C_{12}H_{19}NO$; C, 74.61; H, 9.85; N, 7.25%.

The disubstituted product (base line band) was obtained in 25% yield, m.p. 55-56.5°C, $\nu_{max.}$ (KBr) 2950, 2850, 2760, 1720, 1600, 1570, 1450, 1350, 1305, 1285, 118 cm^{-1}, δ (CCl_4) 2.23 (9H, bs, $ArCH_3$), 2.28 (12H, s, $(-N(CH_3)_2)_2$), 3.57 (4H, s, $ArCH_2$-N), 10.18 (1H, s, phOH, exchangeable).

Found: C,70.54, H,10.27, N,10.19; Required for $C_{15}H_{26}N_2O$, C,72.00, H,10.40, N,11.20%

2,6-Bis (dimethylaminomethyl)-p-isopropylphenol

Reactants:			
	p - isopropylphenol	2.72 g	(0.02m)
	25% aq. dimethylamine	10.8 g	(0.06m)
	35-40% aq. formaldehyde	4.8 g	(0.06m)



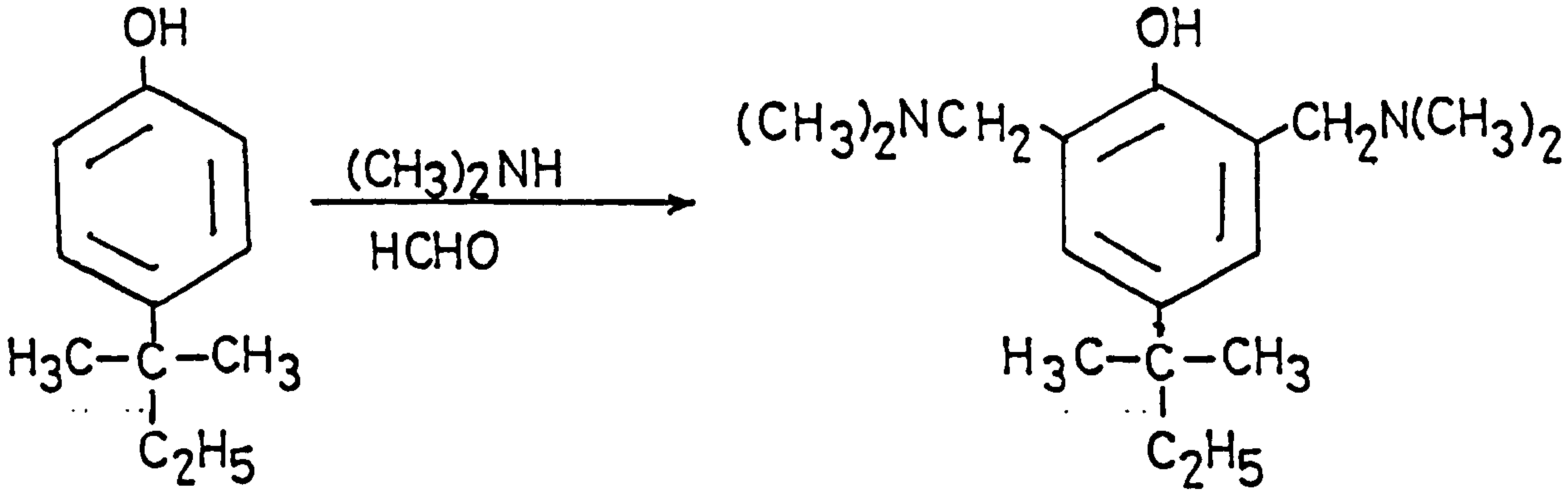
Experimental method B - Reaction mixture was refluxed for 6 hrs.

The pale yellow oily product was obtained in 90% yield, $\nu_{max.}$ (film) 2950, 2860, 2820, 2760, 1610, 1460, 1390, 1350, 1170, 1020, 840 cm^{-1}; $\delta(CCl_4)$ 1.23 (6H, d, J6Hz, $-CMe_2$), 2.30 (12H, s, $(-N(CH_3)_2)_2$), 2.75 (1H, h, J6Hz, ArCH), 3.52 (4H, s, $ArCH_2N$), 6.97 (2H, s, ArH) and 9.28 (1H, s, PhOH, exchangeable).

Found: C, 72.66; H, 10.95; N, 11.17; Required for $C_{15}H_{26}N_2O$; C, 72.00, H, 10.40; N, 11.20%.

2,6.-Bis (dimethylaminomethyl)-p-tert-pentylphenol

Reactants:			
	p-tert-pentylphenol	3.28g	(0.02m)
	25% aq. dimethylamine	10.8 g	(0.06m)
	35-40% aq. formaldehyde	4.6 g	(0.06m)

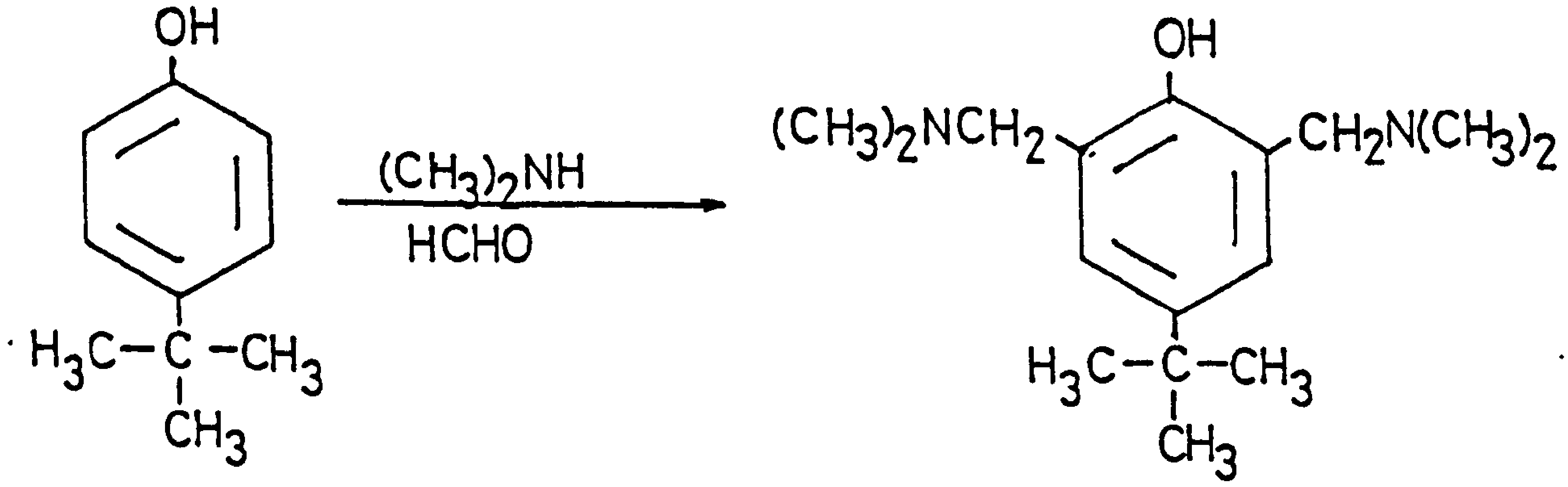


Experimental method B - Reaction mixture was refluxed for 6hrs.

The pale yellow oily product was obtained in 86% yield, $\nu_{max.}$ (neat). 2950, 2820, 2760, 1610, 1460, 1360, 1260, 1180, 1020, 840cm^{-1}; δ (CCl_4) 0.68 (3H, t, J8Hz, Ar-C-C-CH_3), 1.27 (6H, s, Ar-C-$(Me)_2$), 1.67 (2H, q , J8Hz, Ar-C-CH_2), 2.30 (12H, s, $(-NMe_2)_2$), 3.53 (4H, s, $ArCH_2N$), 7.03 (2H, s, ArH), 9.70 (1H, s, PhOH, exchangeable). Found: C74.95, H11.25, N9.87, Required for $C_{17}H_{30}N_2O$, C73.38, H10.79, N10.07%

<u>2,6-Bis (dimethylaminomethyl)-p-tert-butylphenol</u>

Reactants:	p-tert-butylphenol	3.0g	(0.02m)
	25% aq. dimethylamine	4.0 g	(0.05m)
	35-40%-aq. formaldehyde	9.0 g	(0.05m)

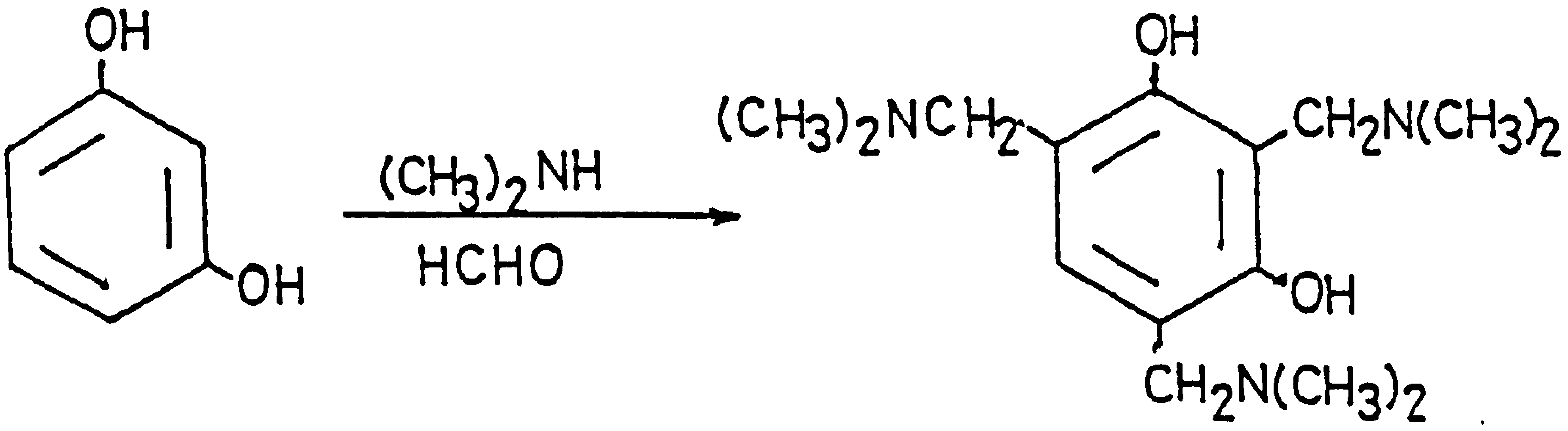


Experimental method B - Reaction mixture was refluxed for 6 hrs.

The product was obtained in 83% yield, m.p. 40-42°C, $\nu_{max.}$ (film) 2950, 2820, 2760, 1610, 1460, 1360, 1260, 1040, 1020, 840 cm^{-1}; δ (CCl_4) 1.33 (9H, s, $ArCMe_3$), 2.37 (12H, s, $(-N-Me_2)_2$) 3.63 (4H,s, $ArCH_2N$), 7.17 (2H, s, ArH), 11.07 (1H, s, PhOH, exchangeable). Found: C,72.10, H,10.33, N,1074; Required for $C_{16}H_{28}N_2$), C,72.73, H,10.61, N,10.61%.

<u>Condensation of resorcinol with dimethylamine and formaldehyde</u>

Reactants:	Resorcinol	2.8 g	(0.025M)
	25% aq. dimethylamine	18 g	(0.1m)
	35-40% aq. formaldehyde	7.0g	(0.0875m)

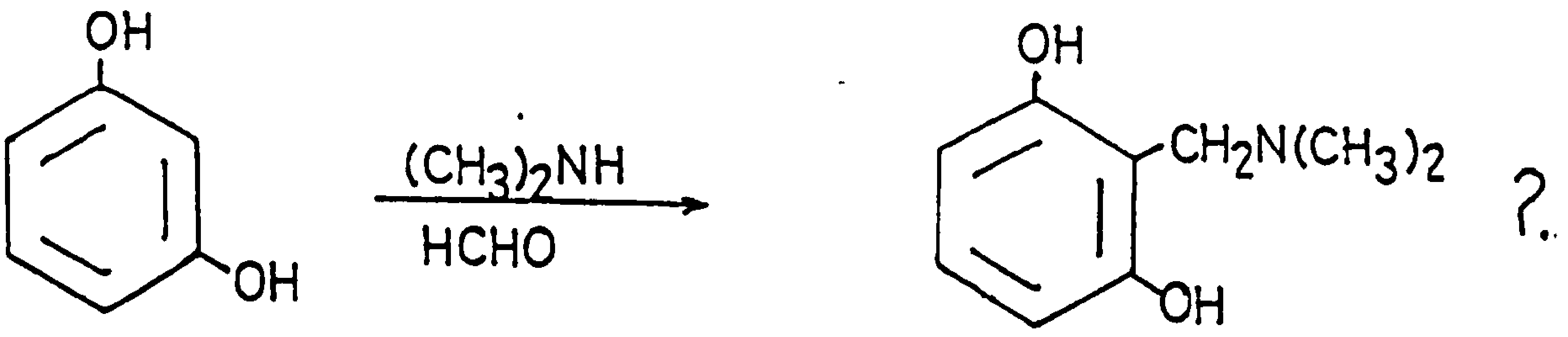


Experimental method C - The reaction mixture was heated for 2½ hrs at 80°C. On adding chloroform to the dark red reaction mixture a solid separated which was filtered and dried.

The dark red product was obtained in 22% yield, m.p. > 300°; $\nu_{max.}$ (KBr). broad peak between 3400-2700, 1640, 1480 cm^{-1}; δ (DMSO) 2.60 (m, $-N(CH_3)_2$), 3.62 (m, $Ar-CH_2-N$), 4.95 (broad s, exchangeable). Found: C 59.04, H 6.39, N 5.66; Required for $C_{15}H_{27}N_3O_2$, C64.06, H9.61, N 14.95%.

<u>Condensation of resorcinol with dimethylamine and formaldehyde</u>

Reactants:			
	Resorcinol	1.1 g	(0.01m)
	25% aq. dimethylamine	1.8 g	(0.01m)
	35-40% aq. formaldehyde	0.81 g	(0.01m)



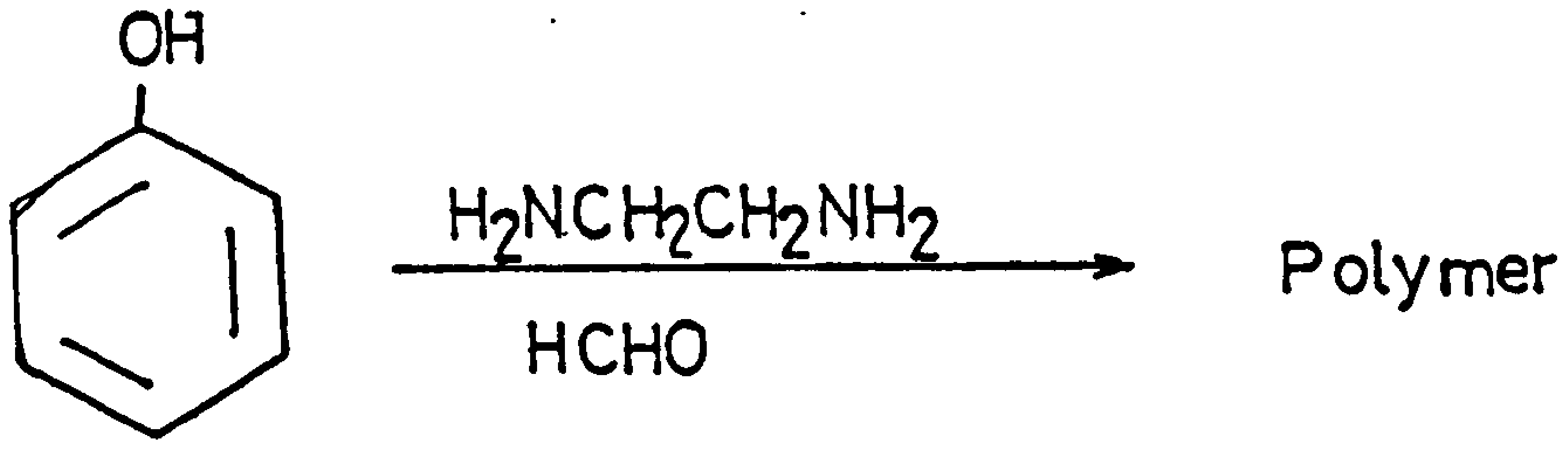
Experimental method B- The reaction mixture was heated for 3hrs at 40° and then concentrated in vacuo.

The red solid isolated was insoluble in water and methanol and had no clear melting point up to 300°.

<u>Condensation of phenol with ethylenediamine and formaldehyde</u>

Reactants:			
	Phenol	4.7 g	(0.05m)
	Ethenediamine	12 g	(0.2m)

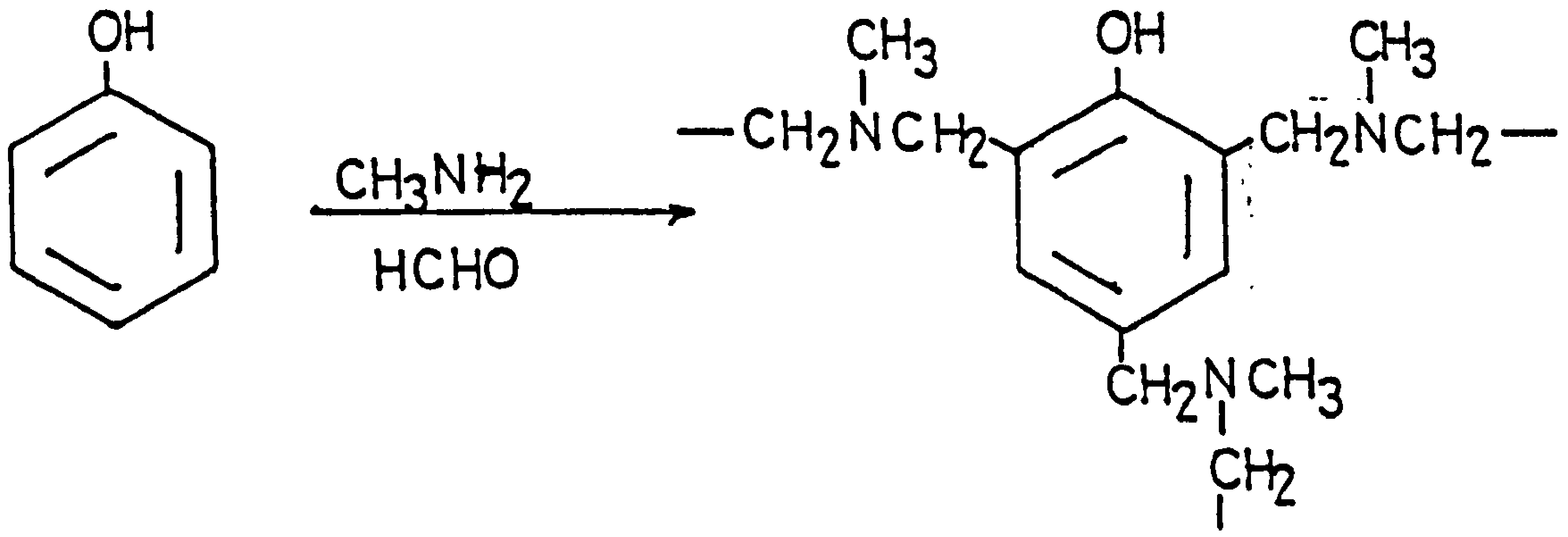
35-40% aq. formaldehyde 14.18 g (0.175m)



Experimental method C - A yellow rubbery polymer separated on cooling of the reaction mixture.

Condensation of phenol with methylamine and formaldehyde

Reactants:	Phenol	4.7 g	(0.05m)
	30% aq. methylamine	20.46	(0.2m)
	35-40% aq. formaldehyde	14.18	(0.175m)



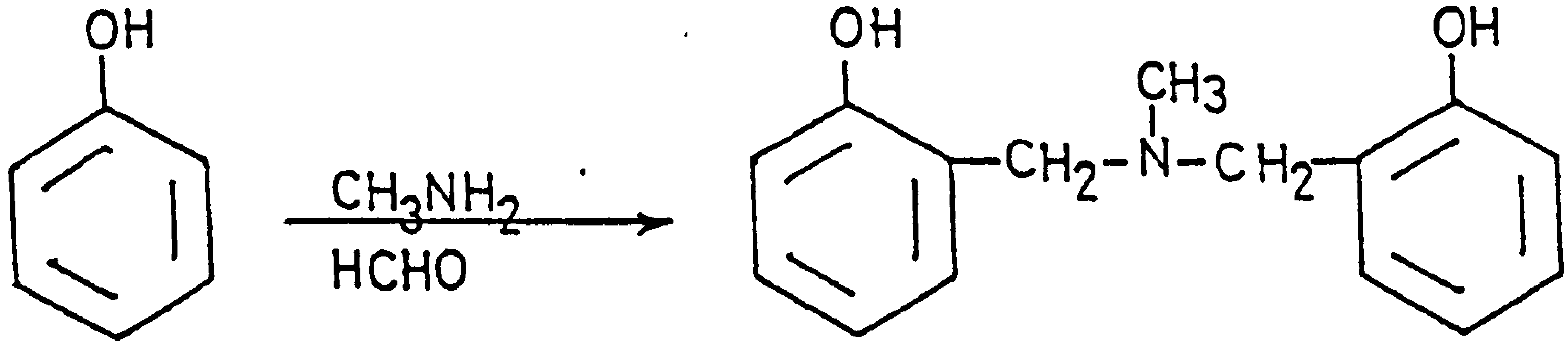
Experimental method C - A white solid separated from the reaction mixture on refluxing for 2hrs.

The product softened at 70° but did not melt; $\nu_{max.}$ (KBr)

2950, 2800, 1600, 1460, 1350, 1260, 1020, and 890 ; δ (CCl_4) 2.0-2.5 (m), 3.10 (s), 3.2-4.0 (m), 6.8 (m, ArH and PhOH).
Found: C 67.926, H 7.67, N 10.31%.

Reactants:

Phenol	3.11 g	(0.033m)
25-30% aq. methylamine	4.1 g	(0.033m)
35-40% aq. formaldehyde	2.7 g	(0.033m)



+ other products

Experimental method C - The reaction mixture was not heated at all but stirred at room temperature for 24 hrs.

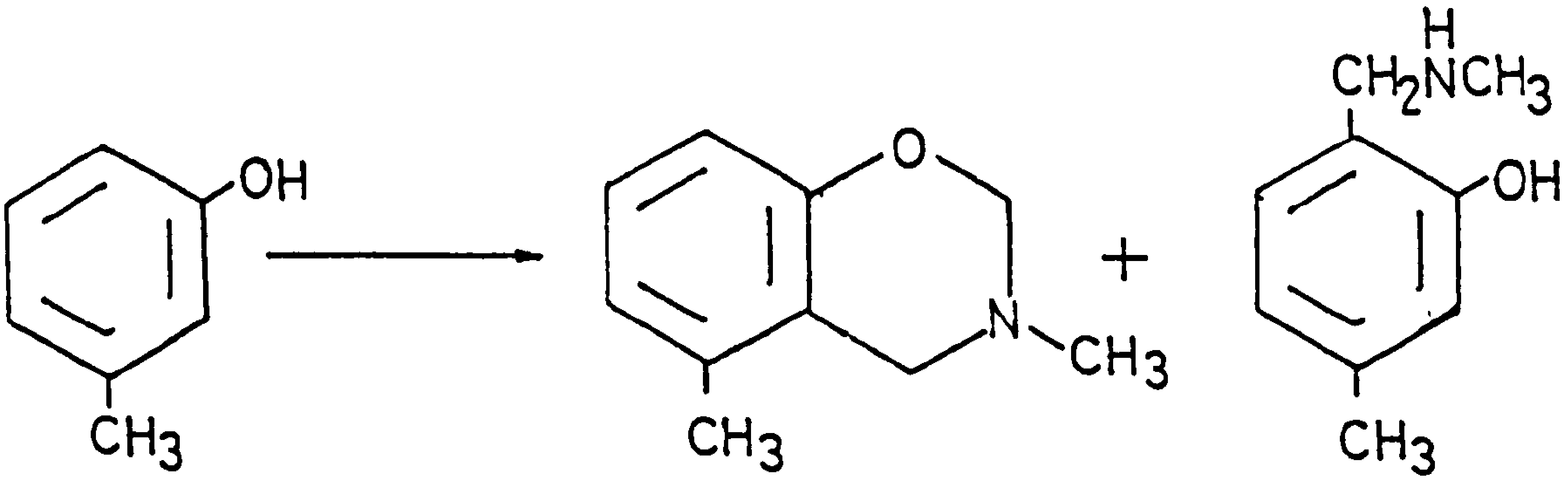
The syrupy reaction mixture showed three components on examination by TLC. The mixture was separated by preparative TLC using solvent E.

The oily product (Rf 0.24) was obtained in 15% yield, δ (CCl_4) 2.20 (3H, m, - N-CH_3), 3.67 (4H, m, ($ArCH_2N)_2$), 6.83 (8H, m, ArH), 8.93 (2H, s, PhOH exchangeable).

Condensation of m-cresol with methylamine and formaldehyde

Reactants:

m-cresol	5.4 g	(0.05m)
25-30% aq. methylamine	5.42g	(0.05m)
35-40% aq. formaldehyde	8.10g	(0.10m)



Experimental method B - The reaction mixture was refluxed for 40 min. TLC showed evidence of the present of three components from which two compounds were isolated by preparative TLC (solvent,E.)

The component showing the same R_f value (0.72) as m-cresol was obtained in 17% yield, m.p. 66-69°C; δ ($CDCl_3$) 2.33 (3H, s, NCH_3), 2.63 (3H, s, $ArCH_3$), 3.97 (2H, m, $ArCH_2N$), 4.83 (2H, m, $ArOCH_2$), 6.70 7.0 (3H, m, ArH).

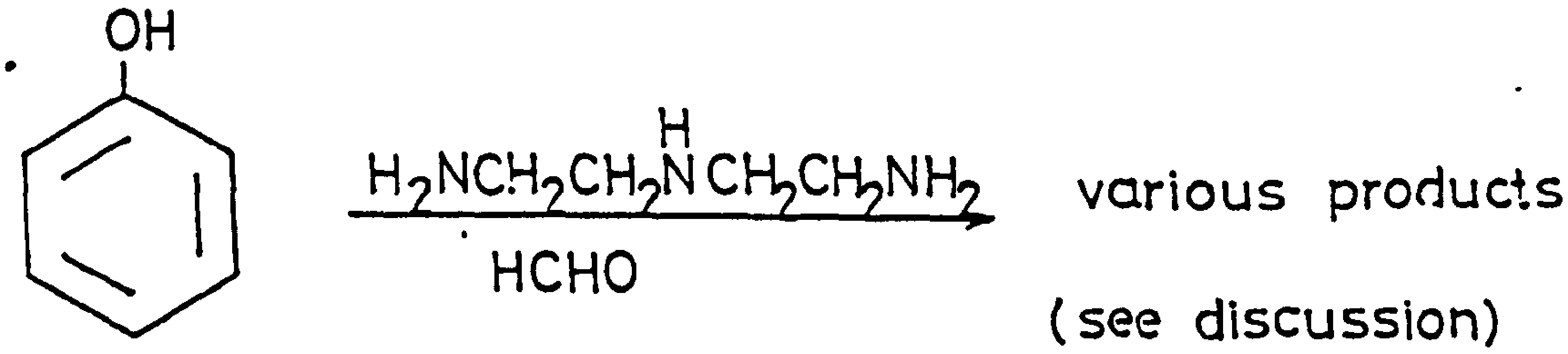
Found: C 69.49, H 7.77, N 7.55; Required for $C_{10}H_{13}NO$, C 73.62, H 7.98 and N 8.59%.

The second component (base line spot), a colourless oil, was obtained in 39% yield and gave δ ($CDCl_3$) values at 2.33 (S,N-CH_3), 3.60 (S,ArCH_3), 3.80 (s, ArCH_2N), 6.67-7.15 (m, aromatic), 8.90 (s, PhOH, -NH exchangeable).

Condensation of phenol with diethylenetriamine and formaldehyde

Reactants:

Phenol	4.70 g	(0.05m)
Diethylenetriamine	6.18 g	(0.06m)
35-40% aq. formaldehyde	4.86 g	(0.06m)



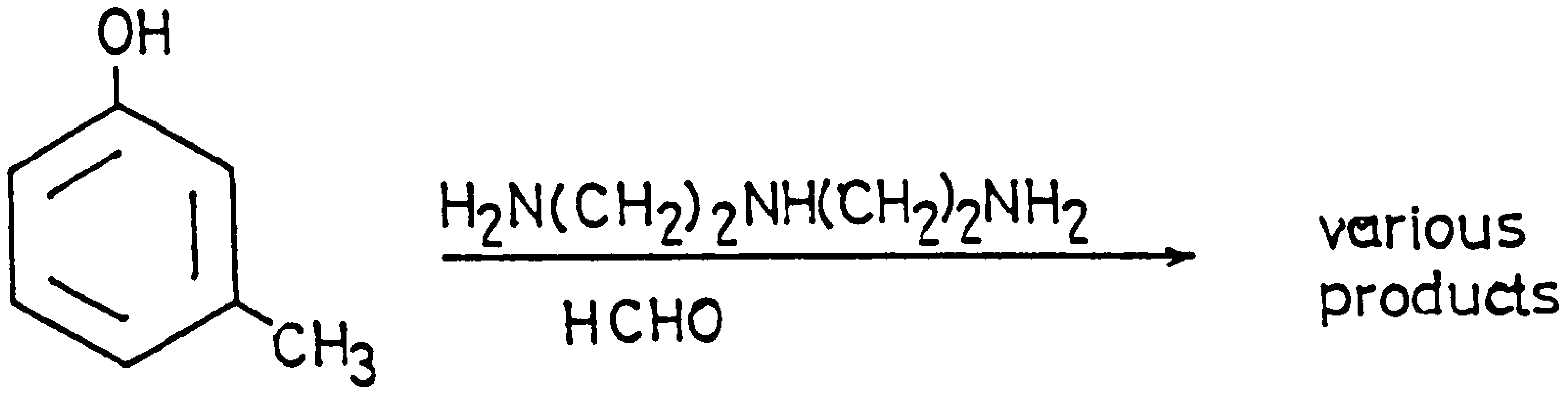
Experimental method C - The reaction mixture obtained on heating for 3hrs 80° was extracted with chloroform. An amber oil was obtained on evaporation of the solvent.

The product gave δ (CCl_4) values at 2.45-2.93 (m, N-$(CH_2)_2$-N), 3.40 (m, ArCH_2N), 4.47 (s, PhOH, -NH,-NH_2, exchangeable), 6.60 - 7.16 (m, ArH). $\nu_{max.}$ (neat) broad peak between 3600-2800, 1650, 1580 and 1460 cm^{-1}.

Condensation of m-cresol with diethylenetriamine and formaldehyde

Reactants:

m-cresol	5.4 g	(0.05m)
diethylenetriamine	6.18 g	(0.06m)
35-40% aq. formaldehyde	2.25	(0.05m)



Experimental method C - The reaction mixture was heated for 2hrs at 80°C.

The orange oily product (7.5 g) gave δ (CCl_4) at 2.18 (s, $ArCH_3$), 2.42-2.80 (bs, N-$(CH_2)_2$-N), 3.2-3.8 (m, $ArCH_2N$), 5.1 (bs, PhOH, -NH, -NH_2, exchangeable), 6.30-7.05 (m, ArH); $\nu_{max.}$ (Neat) broad peak from 3500-2800, 1650, 1580 and 1460 cm^{-1}.

Condensation of Resorcinol with diethylenetriamine and formaldehyde

Reactants:

Resorcinol	2.75 g	(0.025 m)
diethylenetriamine	7.73 g	(0.075 m)
35-40% aq. formaldehyde	6.08 g	(0.075 m)

Experimental method B - A pink solid separated out on heating the reaction mixture for 2hrs under reflux.

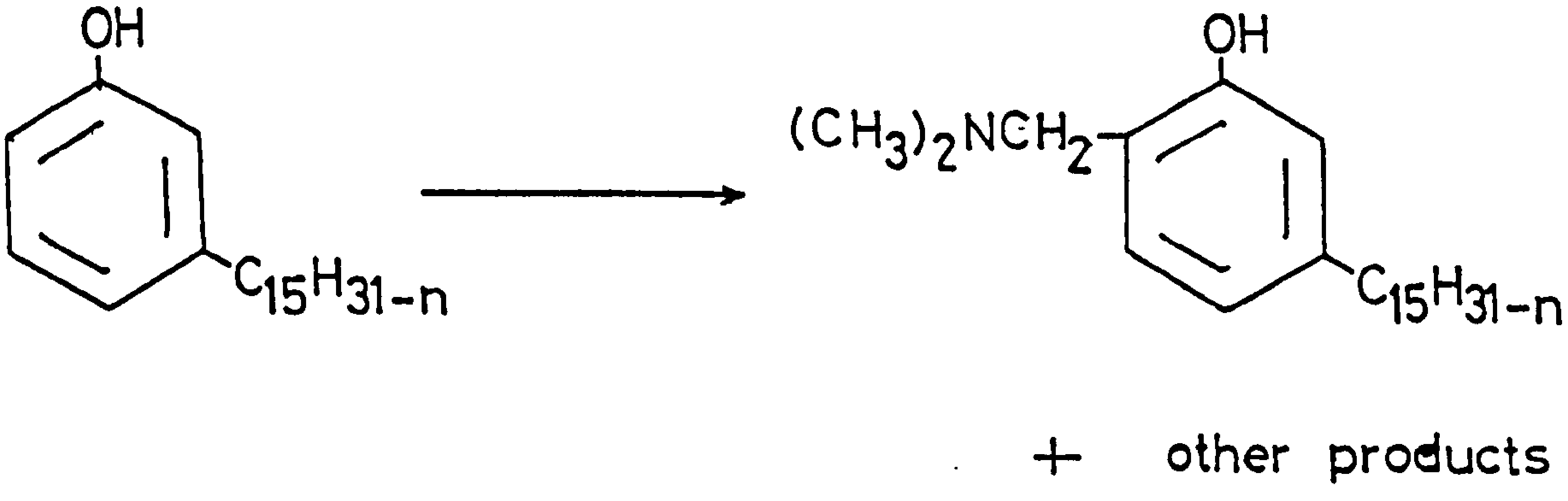
The product (3g) had melting point above 300°, δ (DMSO) at 2.50 (m, $N-(CH_2)_2-N$), 3.62 (broad m, $ArCH_2$), 6.0 (broad m, ArH, PhOH, -NH, $-NH_2$, partially exchangeable).

Found: C57.90, H 6.46, N 11.19%.

Condensation of distilled cashew nut shell liquid (CNSL) with dimethylamine and formaldehyde

Reactants:

dist. CNSL	30 g	(0.1m)
25% aq. dimethylamine	64 g	(0.35 m)
35% aq. formaldehyde	24.3	(0.3m)



Experimental method A - With the omission of addition of sodium chloride.

The product purified on a silica gel G (mesh 70-230) column with solvent E as eluant showed δ values (CCl_4) at 0.7-1.1 (m, $-CH_3$,

CH_3Ar), 1.33 (broad s, - $(CH_2)_n$-), 2.33 (s, - $N(CH_3)_2$), 2.4-3.0 (m, -C = C-CH_2), 3.57 (2H, s, $ArCH_2N$), 5.10- 5.60 (m, -CH = CH-), 6.4-6.85 (3H, m, ArH), 9.50 (1H, s, ArOH); $\nu_{max.}$ (Neat) 2950, 2870, 1630, 1630, 1585, 1510 cm^{-1}.

N.B. Average molecular weight of CNSL was taken as 300.

Condensation of technical CNSL with dimethylamine and formaldehyde

Reactants:

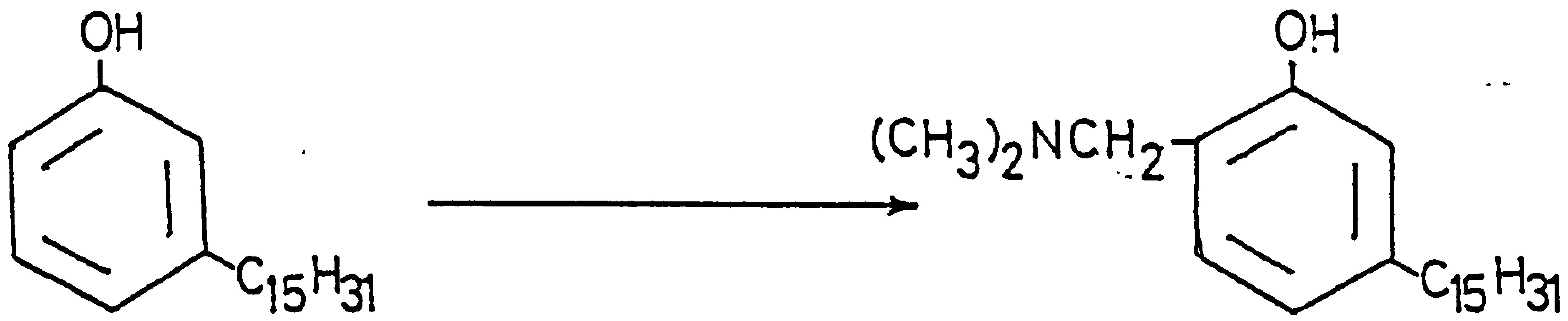
technical CNSL	30 g	(0.1m)
25% aq. dimethylamine	72 g	(0.4m)
35-40% aq. formaldehyde	28.4 g	(0.35m)

Experimental method A - An attempted purification of the crude product (34.2 g, dark brown oil). by vacuum distillation led to formation of a polymer. The ^1H NMR spectrum of the crude product was identical to that of the product from dist. CNSL.

Condensation of saturated cardanol with dimethylamine and formaldehyde

Reactants:

Sat. cardanol	3 g	(0.01m)
25% aq. dimethylamine	5.4 g	(0.03m)
35-40% aq. formaldehyde	2.43 g	(0.03m)



Experimental method B - The reaction mixture was heated for 150 mins under reflux - The solid was recrystallised from pet. ether 40-60°.

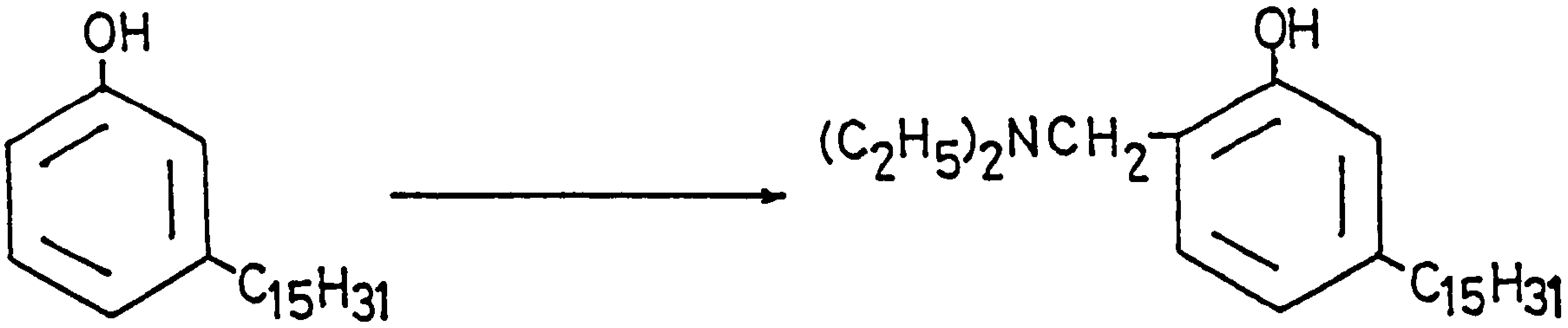
The product 6-dimethylaminomethyl-3-pentadecylphenol, was obtained in 94% yield, m.p. 44-47° (lit.[70] 47°), $\nu_{max.}$ (KBr) 2850, 1620, 1580, 1510, 1460, 1380 and 1360 cm^{-1}, δ (CCl_4) 0.90 (s, $-C-CH_3$), 1.27 (m,-$(CH_2)_n$-), 2.30 (s, $N(CH_3)_2$), 2.20 (m, $ArCH_2-C$), 3.53 (s, $ArCH_2N$), 6.24 (m, ArH), 9.60 (s, PhOH, exchangeable).

Found: C79.73, H 12.27, N 3.96; Calculated for $C_{24}H_{43}NO$, C 79.78, H 11.91, N.3.88%.

<u>Condensation of saturated cardanol with diethylamine and formaldehyde</u>

Reactants:

Sat. cardanol	0.3 g	(0.001m)
diethylamine	0.15g	(0.002m)
35-40% aq. formaldehyde	0.16g	(0.002m)



Experimental method B - The reaction mixture was refluxed for 5 hrs. The product was isolated by preparative TLC of the reaction mixture using solvent G as eluant.

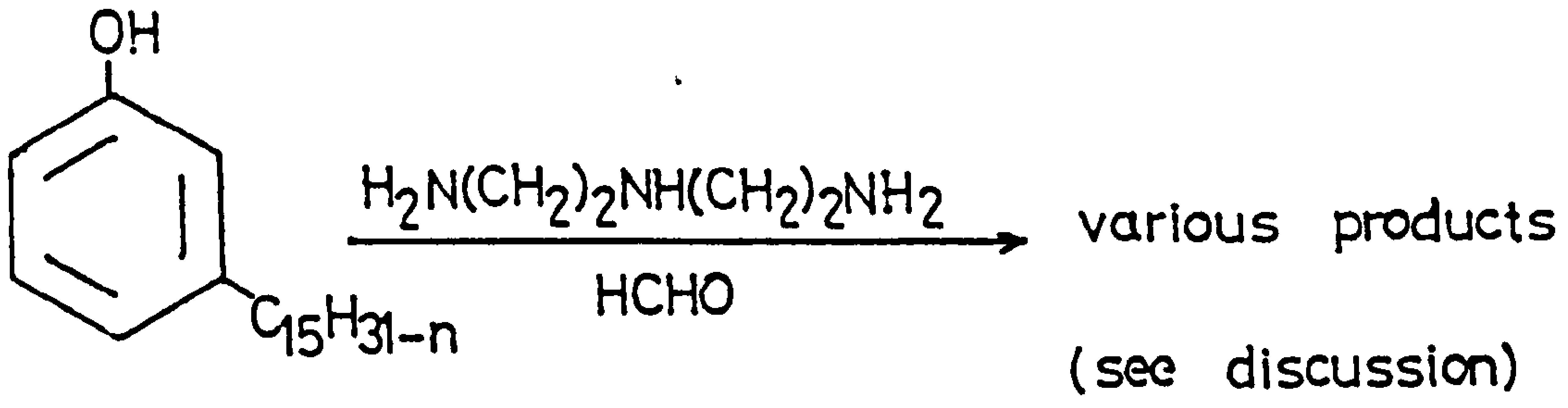
The product, 6-diethylaminomethyl-3-pentadecylphenol, was obtained in 29% yield, m.p. 15°, $\nu_{max.}$ (film) 2920, 2850, 1620, 1580, 1470 and 1380 cm^{-1}; δ (CCl_4) 1.03 (t, $^-CH_3$), 1.17 (t, $NCCH_3$), 2.63 (m, $N-CH_2$ - Me, $ArCH_2C$), 1.33 (m, $-(CH_2)_n-$), 3.80 (s, $ArCH_2N$), 6.63-7.07 (m, ArH) and 10.40 (s, PhOH, exchangeable).

Found: C81.71, H12.60 and N3.56; Required for $C_{26}H_{47}NO$; C80.21, H12.08, N,3.60%.

Condensation of dist. CNSL with diethylenetriamine and formaldehyde

Reactants:

dist. CNSL	15g	(0.05m)
diethylenetriamine	5.15g	(0.05m)
35-40% aq. formaldehyde solution	4.86 g	(0.06m)



Experimental method C - The reaction mixture was heated at 80° for 3 hrs.

The red oily product (20-5g) gave a complex ^1H. NMR with δ (CCl_4) values at 0.7-1.1 (m, $-CH_3$, $ArCH_3$), 1.33 (s, $-(CH_2)_n-$), 2.10 (m, $-C{=}C-CH_2$), 2.45-2.80 (m, $-N(CH_2)_2-N$),), 3.83 (m, $ArCH_2N$), 5.10-5.60 (m, -CH=CH-), 5.80 (broad s, PhOH), 6-4-6.85 (m, ArH). $\nu_{max.}$ (Neat) 3300, 3020, 2930, 2850, 1580, 1450, 1380, 1270, 1150, 1115, 910, 870 cm^{-1}.

N.B. This experiment was repeated twice, once by pretreating the dist. CNSL with 1% w/w sodium borohydride and the second time by incorporating an antioxident, Topanol 'O', in the reaction mixture. In both cases, lighter coloured products were obtained but they became more intense in colour on standing.

Condensation of dist. CNSL with diethylenetriamine and formaldehyde

Reactants:

dist. CNSL	6.20 g	(0.02m)

diethylenetriamine	2.06 g	(0.02m)
35-40% aq. formaldehyde	1.78 g	(0.022m)

Experimental method C - The experiment was conducted in a nitrogen atmosphere. A slight excess of nitrogen pressure was maintained during the reaction. The mixture was heated for 3hrs. at 100°.

A yellow orange oily product (8.1 g) was obtained which gradually darkened on standing. The ^1H NMR and IR spectra were similar to those described before.

Condensation of saturated CNSL with diethylenetriamine and formaldehyde

Reactants:

Sat. CNSL	3.10 g	(0.01m)
diethylenetriamine	1.03 g	(0.01m)
35-40% aq. formaldehyde	0.81 g	(0.01m)

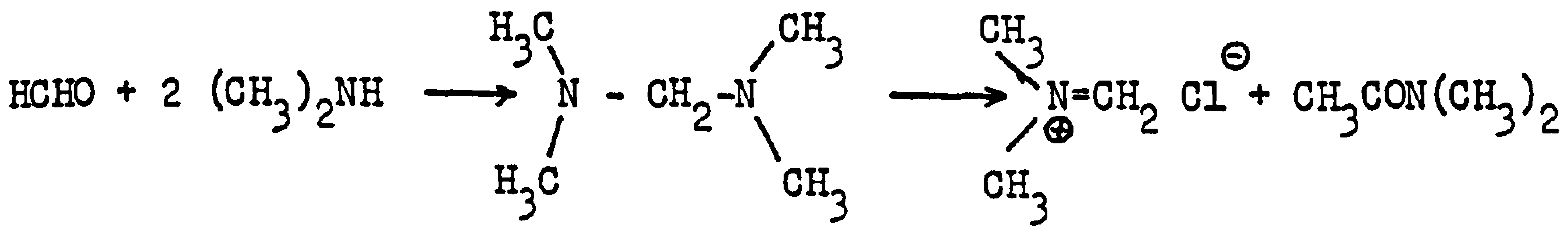
Experimental method B - The mixture was refluxed for 3hrs. Red-orange oil formed solidified on standing.

T.L.C. examination showed presence of unreacted cardanol. Separation of the pure product proved unsuccessful due to the polymeric nature of the product.

Acetylation of the Mannich base from dist. CNSL

Condensation of dist. CNSL with DETA and formaldehyde was carried out as before under nitrogen. The Mannich base was rapidly worked up and isolated as in method C and part of it (3.0 g) was treated with pyridine (18 ml) and acetic anhydride (6.0 g). The reaction mixture was kept in a stoppered flask for 24 hrs and then added to ice (30 g). On adding ether to the reaction mixture, an oily phase was formed between the water and ether layer. The oily layer (Mannich base) was isolated and the change in colour on storage was compared with that of the unacetylated product.

Preparation of N,N-dimethyl (methylene) ammonium chloride



$$HCHO + 2\,(CH_3)_2NH \longrightarrow (H_3C)_2N-CH_2-N(CH_3)_2 \longrightarrow (CH_3)_2\overset{\oplus}{N}{=}CH_2\ Cl^{\ominus} + CH_3CON(CH_3)_2$$

A solution of 35-40% aq. formaldehyde (10.11 g, 0.125M) was stirred and cooled in an ice bath. Aqueous dimethylamine (4.5 g, 0.25M) was added at a rate such that the reaction temperature was kept below 15°. The solution was stirred for 30 min. after the addition was completed, and potassium hydroxide pellets (approx. 28 g) were added in portions until the reaction mixture separated into two layers. The upper layer was separated, dried (potassium hydroxide pellets) overnight and distilled.

The product, bis-(dimethylamino) methane, was obtained in 75% yield, b.p. 80-82° (lit.[71], 83-84°), S 2.13 (12H, s, $-(CH_3)_4$) and 2.57 (2H, s, $N-CH_2-N$).

Acetyl chloride (10.92 g, 0.14 M) in ether (sodium dried) was gradually added to an ether solution of bis-(dimethylamino) methane (14.28 g, 0.14 M) in a nitrogen atmosphere. The white, N,N-dimethyl (methylene) ammonium chloride salt crystallized from the reaction solution.[72]

The salt formed was extremely hygroscopic and had to be kept in a desiccator until required.

Preparation of 3-dimethylaminomethyl indole

N,N-Dimethyl (methylene) ammonium chloride (0.94 g, 0.01 M) was suspended in anhydrous acetonitrile and stirred with a 10% excess of indole (1.23 g) for 5 min. at 22°. Both the reagents dissolved on stirring and the product, 3-dimethylaminomethyl indole hydrochloride crystallized spontaneously. The hydrochloride was filtered dissolved in water and the aqueous solution basified to give the Mannich base which was isolated, washed with water and dried.

The product (95% yield) was obtained as m.p. 129-131° (lit.[73] 128°).

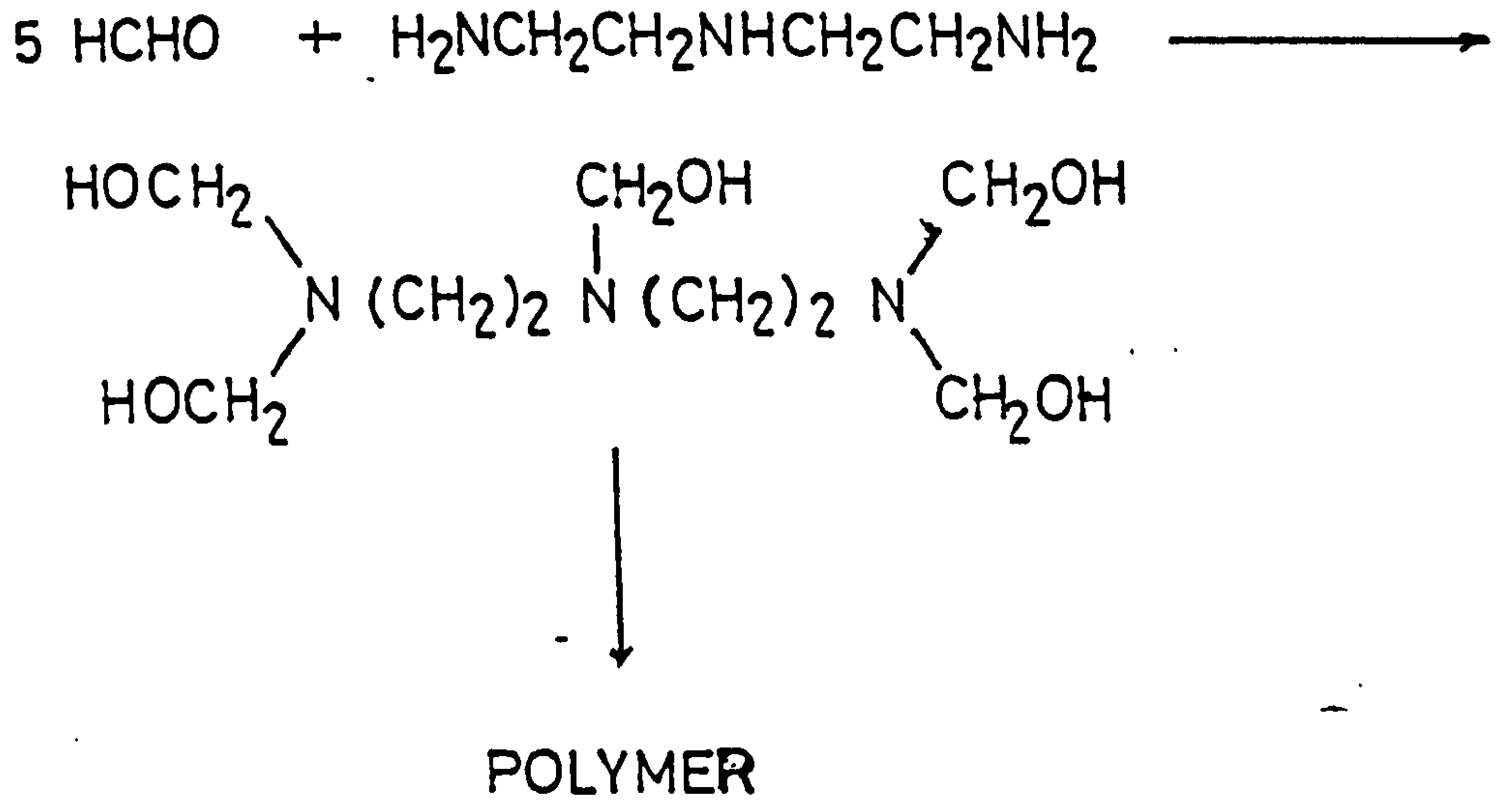
Reaction of N,N-dimethyl (methylene) ammonium chloride and phenol

A mixture of N,N-dimethyl (methylene) ammonium chloride (0.94 g, 0.01M) suspended in anhydrous acetonitrite (10 ml) and phenol (0.94g, 0.01M) was stirred at 22°C for 1 hr. and then refluxed for 2 hrs. No precipitation of the hydrochloride salt took place. The mixture was basified and extraction with ether was attempted but proved unsuccessful.

Reaction of N,N-dimethyl (methylene) ammonium chloride and resorcinol

A mixture of the ammonium chloride salt (2 g) suspended in anhydrous acetonitrile and resorcinol (1.1 g, 0.01M) was stirred at room temperature for 2hrs. Water (10 ml) was added to the dark reaction mixture. Extraction with ether and chloroform proved unsuccessful.

Reaction of diethylenetriamine and formaldehyde



A solution of 35-40% aq. formaldehyde (40.47 g, 0.5 M) was stirred and cooled in an ice bath. Diethylenetriamine (20.6 g, 0.2M) was added to this solution at a rate such that the reaction temperature was kept below 15°. The reaction mixture solidified to give a clear gel-like polymer on completion of the addition of the amine. The clear rubbery polymer turned yellow after a week.

3. ISOLATION OF COMPONENTS FROM CASHEW NUT SHELL LIQUID (CNSL)

3a. Preparative TLC of Distilled CNSL

Chloroform solutions of dist. CNSL (0.17 g, x 5) were spotted onto each of five TLC plate (20 x 20)coated with silica gel G and the plates were then developed (Solvent E). The plates were then sprayed with rhodamine 6G to visualize the different bands and the bands eluted with diethyl ether/methanol (90:10) to give the three components, cardanol, 2-me-cardol and cardol after filtration and concentration The rhodamine 6 G dye was removed from the extract by shaking the extracts in ethereal solution with dil. hydrochloric acid. The ether layer was separated, dried over anhydrous sodium sulphate and the ether evaporated.

The components, cardanol (0.52 g), 2-methylcardol (0.01 g) and cardol (0.09 g) were collected and examined for purity by analytical TLC.

3b. Isolation of polymeric material from dist. CNSL

A chromatographic column was packed with silica gel G (200 g , mesh 70-230). Distilled CNSL (10 g) was added and the column eluted with chloroform. Elution was carried out in turn, with chloroform: ethyl acetate (90:10), chloroform: ethyl acetate (80:20) and methanol to remove all of the components except brown material (polymer). The brown coloured band was then stripped off the column with glacial acetic acid. On evaporation of acetic acid a dark brown solid (0.42g) was obtained.

The ^{1}H NMR was similar to that of CNSL.

Found: C62.01 and H 8.30%.

3c. Column separation of components from dist CNSL

To a solution of dist. CNSL (5 g) in chloroform (10 mls) silica gel G (5 g, mesh 70-230) was added and the solvent was carefully evaporated. The coated silica gel was added to a column packed with silica gel G (50 g).

Column was then eluted successively with chloroform, chloroform: ethyl acetate (98:2), chloroform: ethyl acetate (95:5) and chloroform ethyl acetate (90:10) in turn . Fractions (50 ml) were collected and monitored by analytical TLC giving the results shown in the table below:

Fraction No.	Composition	Solvent
1-2	aliphatic long chain material	chloroform
3-15	cardanol	chloroform
16	cardanol+2-me-cardol	chloroform
17-19	2-me-cardol	chloroform:ethyl acetate (98:2)
20-24	2-me-cardol+cardol	chloroform:ethyl acetate (95.5)
25-33	cardol	chloroform:ethyl acetate (95:10)

yield:			
yield:	Cardanol	4.21 g	(84%)
	2-Methylcardol	0.06 g	(1.2%)
	cardol	0.33 g	(6.6%)

3d.Extraction of CNSL from Cashew nuts

Cashew nuts (350 g) were cooled with carbon dioxide/acetone coolant to make them hard but brittle. The nuts were then cracked by a smart tap with a hammer. The kernel and the brown lining were separated and weighed before placing the split shells in ether.

The shells (224 g) in ether (750 ml) were allowed to stand overnight under nitrogen. The ether was removed by filtration and the shells were disintegrated with a blender, re-extracted with ether and both the extracts combined. The ether was evaporated and the cashew nut shell liquid weighed.

Yield of natural CNSL was 79.01 g (35.3% based on weight of shells or 22.5% based on the original cashew nuts.)

Separation of Cardol from natural CNSL[54]

Anacardic acid was separated from natural CNSL by isolation of its lead salt and the remaining phenols (mostly cardol) were collected.

Lead hydroxide was prepared from lead nitrate (151g) in water (600 ml) added to sodium hydroxide (39.6 g) dissolved in water (200 ml) and the white precipitate allowed to settle for one hour. The supernatant liquid was decanted and the precipitate washed with distilled water until no longer alkaline. The slurry was stirred with IMS (1 litre) and the supernatant liquid decanted again. Natural CNSL (70.01g) in IMS (400 ml) was added to the lead hydroxide and the mixture stirred and allowed to stand overnight. The slurry was then filtered, the solid was stirred with IMS and then refiltered. The filtrate was evaporated and ether (100 ml) added to the phenolic residue. The ethereal mixture was dried (sodium sulphate) and the ether evaporated. The separation of the three phenolic materials from the residue (11.5 g) obtained from above was carried out using silican gel G (mesh 70-230) column, eluted in turn with chloroform, chloroform: ethyl acetate (95:5) and chloroform: ethyl acetate (90:10)

The fractions collected were monitored by analytical TLC and the fractions collected shown in the table below.

Fraction No	Composition	Solvent
1-10	Cardol	Chloroform
11-13	Cardanol+2-me-cardol	Chloroform:Ethyl acetate (95:5)
14	2-me-Cardol	Chloroform:Ethyl acetate (95:5)
15-17	2-me-cardol+Cardol	Chloroform:Ethyl acetate (95:10
18-29	Cardol	Chloroform:Ethyl acetate (95:10)

All the pure fractions of each phenols were combined, the solvent evaporated and the residue weighed.

Yield: Cardanol	1.2 g	(10.4%)
2-Methylcardol	0.11 g	(0.9%)
Cardol	5.2 g	(45.2%)

Hydrogenation of Cardanol[54]

Palladium 10% on charcoal (0.50 g) was added carefully to a solution of cardanol (5.0 g) in ethyl acetate (50 ml) under nitrogen. The mixture was shaken under hydrogen at 30 p.s.i. for 24 hrs. The solvent was evaporated and the solid crystalised from petroleum ether (60-80°).

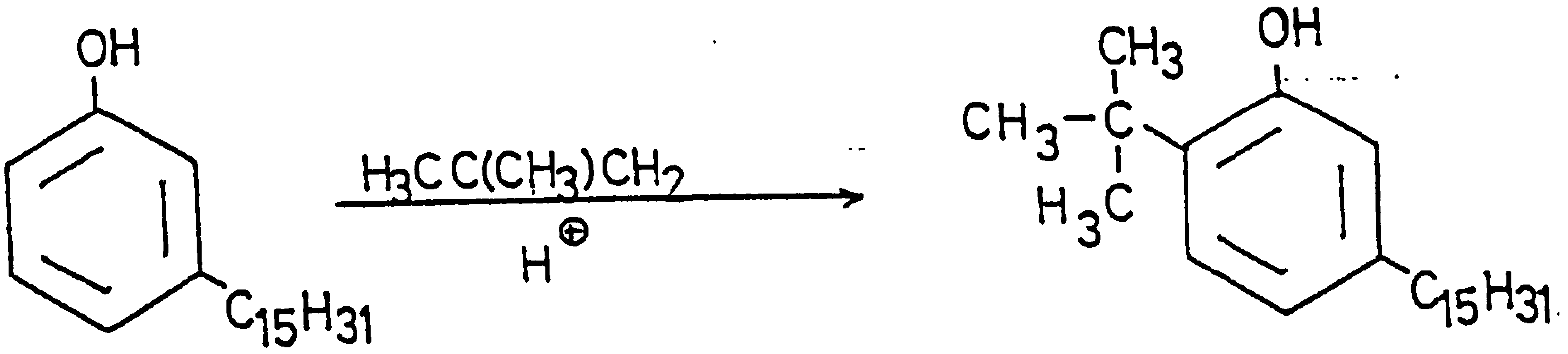
The product (98%yield), have m.p. 50-51° (lit.[54] 54°).

Hydrogenation of Cardol

Palladium 10% on charcoal (0.30 g) was added carefully to a solution of cardol (3.3 g) in ethyl acetate (30 ml) under nitrogen The mixture was shaken with hydrogen at 30 p.s.i. for 24 hrs until absorption ceased. The solvent was evaporated and the solid recrystallised from petroleum ether (60-80°).

The product, saturated cardol, was obtained in 98% yield, m.p. 86-88°. (lit.,[54] 95.5 - 96)

Preparation of 6-t-butyl-3-pentadecylphenol



Saturated cardanol (2.5 g), benzene (10 g) and conc. sulphuric acid (0.1 g) were carefully mixed in a 3-necked flask (50 ml). In to the stirred and warmed mixture at 45°, iso-butylene was slowly bubbled for 5.5 hrs while the temperature was maintained at 45°. The progress of the reaction was monitored by TLC (solvent G). Benzene was then evaporated, ether added to the residue and the ethereal solution washed first with sodium chloride solution and finally with water. The ether solution was dried (sodium sulphate) and the ether evaporated.

The product was isolated from the reaction mixture by preparative

TLC using silica gel plates (solvent H).

The product was obtained in 50% yield, m. pt 41-43°; δ (CCl_4) 0.85 (3H, m, C-CH_3), 1.32 (26H, s, -$(CH_2)_n$-), 1.40 (9H, s, ArC$(CH_3)_3$), 2.53 (2H, m, ArCH_2-), 4.47 (1H, s, PhOH), 6.60 (2H, m, ArH), 7.10 (1H, m, ArH); Found:C, 83.15; H, 12.59.

Required for $C_{25}H_{44}O$ C, 83.33; H, 12.22%.

Fractional distillation of DETA

DETA (200 g) was distilled under vacuum using a fractionating column packed with helices. Various fractions were collected and the pressure, temperature, flask variac and column variac settings were recorded for each fraction as shown below:

Fr. No.	Pressure (mm of Hg)	Temp °C	Flask variac	Column variac
1	8	70	60	40
2	8	74	60	40
3	7	76	60	40
4	8	82	60	40
5	8	82	60	40
6	8	82	60	40
7	8	83	65	40

A dark yellow residue (1.2 g) was left in the distillation flask. The fractions 4-7 were combined and examined by ^{1}H NMR and elemental analysis.

δ (CCl_4)1.22 (5H, s, -NH and $-NH_2$), 2.63 (8H, m, $-(CH_2)_4-$). Found: C, 47.78; H, 12.74; N, 40.04; Calculated for $C_4H_{13}N_3$: C, 46.60; H, 12.62; N, 40.78%.

0.1 g of each fraction from above was added to solutions of resorcinol (0.1 g) in methanol. The samples were heated on a steam bath for 2 hrs. and the intensity of the colour developed was examined Besides the residue all the other fractions gave very similar orange colours.

4. INVESTIGATION OF THE RED COLOUR FORMATION IN THE MANNICH REACTION.

4a. Qualitative reactions of the component reactants used in the Mannich reaction

1. DETA (6.18 g, 0.06M) and phenol solution (4.70 g in 10 ml water) gave an intense yellow solution on heating for 3 hrs at 85°.
2. 35-40% Aq. formaldehyde (4.05 g) and phenol (4.70 g) gave a pink solution on heating for 3 hrs. at 85°
3. DETA (6.18 g, 0.06 m) and 35-40% aq. formaldehyde (4.05 g) gave a colourless solution under similar conditions.

4b. Qualitative reactions of phenols with DETA

DETA (0.11 g, 0.001M) was added to each of the alcoholic solutions of phenol (0.1 g), resorcinol (0.12 g), 5-methyl resorcinol (0.13 g), 4-methyl resorcinol (0.13 g) 2-methylresorcinol (0.13 g), cardanol (0.3 g), 2-methylcardol (0.3 g) and cardol (0.3 g). The mixtures were then heated on a steam bath for one hour.

Phenol	Observations
Phenol	Clear solution at room temperature but becomes slightly yellow after heating for 1 hr. and intensely yellow after 3 hrs heating.
Resorcinol	Deep red colour on heating
5-Methylresorcinol	Gave deeper red colour, than other resorcinols used, on heating
4-Methylresorcinol	Deep red colour on heating
2-Methylresorcinol	Gave orange colour immediately on mixing reagents and turned red on heating.
Cardanol	Gave yellow solution on heating
2-Methylcardol	Gave red solution on heating
Cardol	Gave red solution on heating

4c. Qualitative reactions of resorcinol with amines

Ethanolamine (0.098 g), diethylenetriamine (0.096g), hexamethylenediamine (0.11 g), N-(2-aminoethyl)ethanolamine (0.096 g) and ethylenediamine (0.056 g) were added separately to methanolic solution of resorcinol (0.1 g) and left to stand for 15 days.

Amine	Observation
$(CH_2\ CH_2OH)_2NH$	produced pink colour (lighter than Resorcinol/DETA)
$(CH_2CH_2NH_2)_2\ NH$	Orange-red on standing
$(CH_2)_6\ (NH_2)_2$	Orange-red colour (similar to Resorcinol/DETA
$H_2N(CH_2)_2NH(CH_2)_2OH$	Deep red colour (darker than Resorcinol/DETA
$H_2NCH_2CH_2NH_2$	Produced Orange colour (lighter than Resorcinol DETA)

Reaction of dist. CNSL with DETA

Distilled CNSL (5.0 g: 0.0164 m) was cooled and stirred while diethylenetriamine (1.68 g, 0.0164m) was added drop wise so that the temperature did not exceed 20°. The mixture was stirred for one hour at 22° and finally heated with stirring for 3 hrs. at 70°. The product was a red oil. The T.L.C. of the product showed a red base line spot as well as a spot corresponding to cardanol. Separation of the various components was tried using a column packed with silica gel G.

The product was dissolved in $CHCl_3$ and loaded onto the column. The column was than eluted in turn with chloroform, chloroform/ethyl acetate (90:10) and methanol. The various fractions obtained were examined(analytical T.L.C.). All of the fractions obtained were mixtures.

With a second batch of DETA and CNSL mixture the removal of excess DETA was attempted by washing the mixture with water. This produced foaming and the separation of phases proved difficult. When the foam was left in contact with petroleum ether over several days the colour and the unreacted CNSL were extracted into petroleum ether layer. On evaporation of solvent a deep red oil was obtained. The oil was examined by T.L.C.

Subsequently these mixtures were separated by distillation (section on removal of cardol from CNSL).

Reactions of resorcinols with DETA

Mixtures of resorcinol (5.50 g, 0.05M) and DETA (5.15 g, 0.05M), 2-methylresorcinol (1.24 g, 0.01M) and DETA (1.03 g, 0.01M) and orcinol (1.24 g, 0.01M) and DETA (1.03g, 0.01M) in absolute alcohol were gently refluxed for $2\frac{1}{2}$ hrs. The solvent was evaporated and water (20 ml) was added to each of the residues. On leaving the solutions in stoppered flasks for one month, dark red solid was precipitated in each case. The solid was filtered, dried and analysed. On leaving the filtrates for a further month more solid was formed. The same coloured materials were formed in the absence of a solvent.

Resorcinol	Analytical data
Resorcinol + DETA	Yield 4.2 g; m. pt. $>300^{\circ}$, I.R. (KBr) 3230 broad peak), 1600, 1450, 1300, 1220, 1170, 1000, 980, 845 cm^{-1}; U.V.(1M HCl) 462, 280-258 nm; ^{1}H NMR, δ (DMSO) 2.45 (m, DMSO), 2.8-3.1

Resorcinol	Analytical data
	(m, $(-CH_2-)_n$), 5.20 (m, NH, NH_2, OH exchangeable), 6.23 (m, ArH), 6.80 (m, ArH); ^{13}C NMR ppm (D_2O) 136.84, 134.69, 133.71, 132.54, 131.97, 67.32 (dioxane), 54.23, 52.73, 52.35, 52.07, 45.53: cf with ^{13}C of resorcinol ppm (D_2O) 157.82, 131.64, 108.42, 103.52, 67.39 (dioxane) and that of DETA 67.39 (dioxane), 51.77 and 41.02; Found, C 54.86, H 5.24, N 12.29%; Repeat:C, 52.56, H 5.71, N 11.24%
Orcinol + DETA	yield 1.18 g; darkens on heating but had no definite melting point; IR (KBr) 2800 (broad peak), 1600-800 (broad peak) cm^{-1}; δ (DMSO) 2.58 (m, DMSO), 3.53 (m, $-(CH_2)_n-$), 6.20 (m, ArH), no exchangeable peaks; Found, C 57.83, H 5.71, N 12.00.%
2-Methylresorcinol + DETA	yield 0.89 g, no clear melting point.

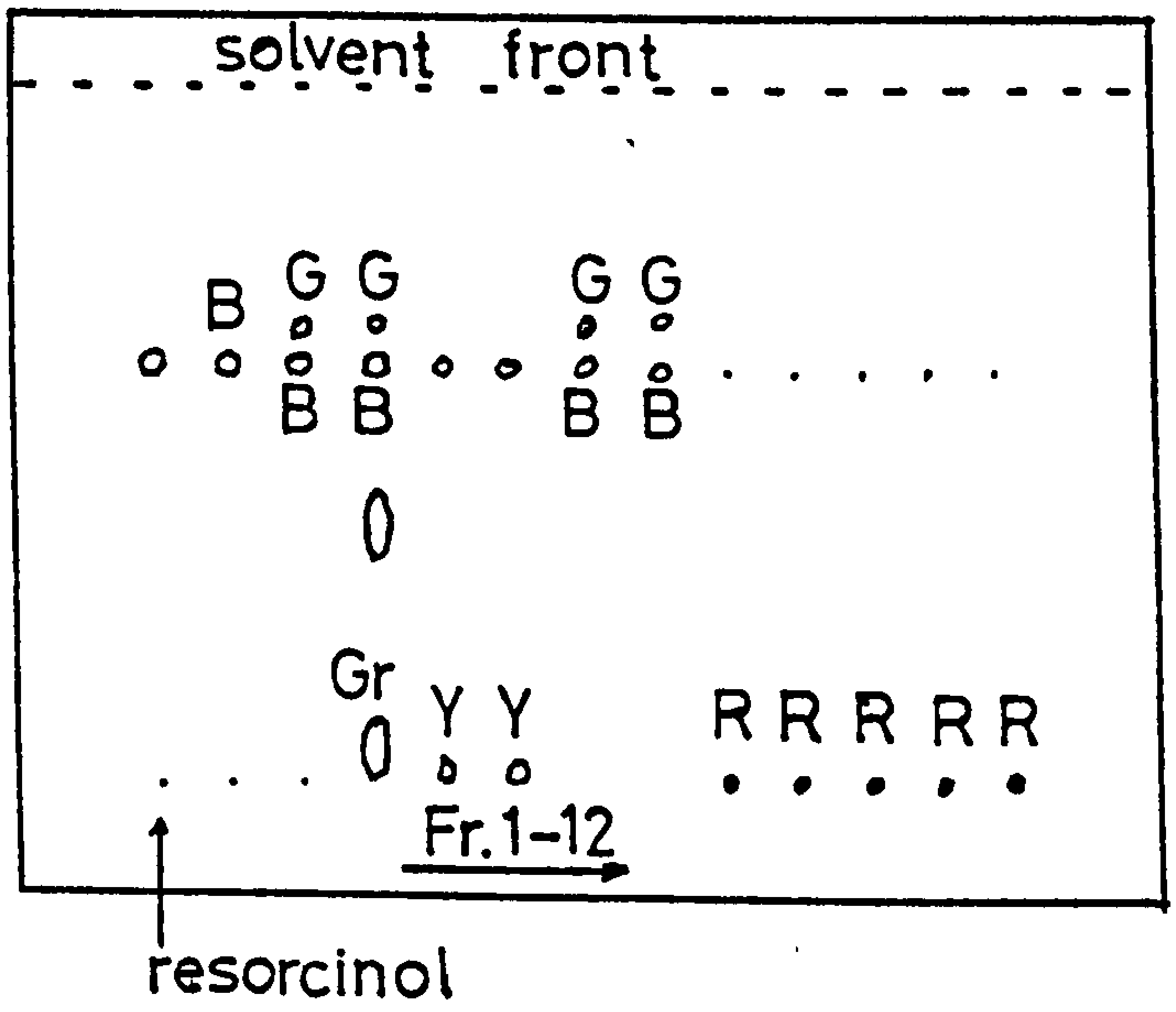
Reaction of Resorcinol with Dimethylamine

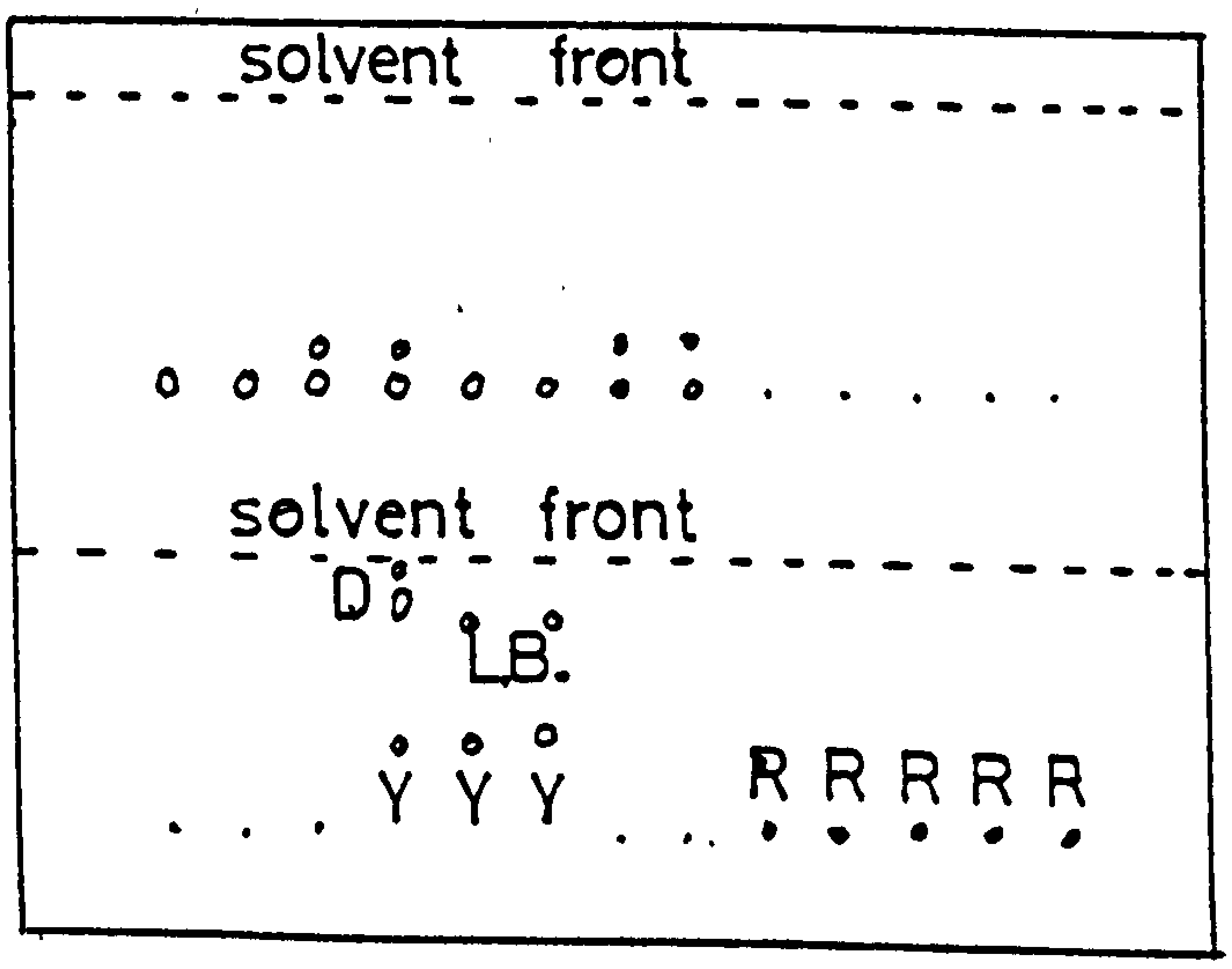
A mixture of resorcinol (5.05 g, 0.05 M) and 25% aq. dimethylamine (9.0 g, 0.05M) was heated on a steam bath for 5 hrs. The reaction mixture was periodically monitored with TLC. The water was evaporated under vacuum and the residue (6.66 g) chromatographed on a column packed with silica gel G (mesh 70-230). The column was eluted in turn with chloroform: diethyl ether (40:60), diethyl ether, ethyl acetate, acetone: methanol (80:20) and finally methanol. The column was monitored with an ultra-violet lamp. All the fractions were examined by TLC using multiple development. A schematic diagram of the devloped plate is shown below:

Plate developed
with ethyl acetate

KEY

B- Blue fluorescent
G- Green "
Gr- Grey "
Y- Yellow "
R- Red non "
D- Dark blue non "
L.B.-light blue "





Same plate
redeveloped with
acetone:methanol
(70-30)

The blue fluorescent material from fractions one and two was unreacted resorcinol (5.9 g). A dark blue material (1.2 mg) was isolated from fraction three by repeated (twice) preparative TLC using acetone: benzene (50:50) as eluant. A yellow fluorescent material (6.5 mg) was isolated by repeated (thrice) preparative TLC of fractions four and five, using acetone: methanol (70:30) as eluant.

This experiment was repeated twice using resorcinol (100 g) and 25% aqueous dimethylamine (163.6 g), but, in this case the mixture was heated for 24 hrs. and most of the unreacted resorcinol (90 g) was removed by extracting the anhydrous residue with boiling benzene. The final residue (benzene insoluble) was chromatographed on a silica gel G column followed by repeated preparative TLC of the relevant fractions. The dark blue material (7.7mg) and yellow fluorescent material (43.2mg) were collected each time. A purple material (5.2 mg) with a similar R_f value to that of dark blue material was also isolated.

Sodium borohydride reductions of the fluorescent and of the blue material led to colourless reduction products. The colour (fluorescence) was restored upon standing the sample in air.

The dark blue, purple and the yellow fluorescent material were silylated by standing each of the sample with excess of pyridine and bis-(trimethylsilyl)-acetamide for 24 hrs. The pyridine was then evaporated under vacuum and the sample analysed by mass spectroscopy.

Analytical Data

Yellow fluorescent material: no clear melting point up to 300°; R_f0.20 (acetone: methanol, 9:1); I.R.$_{max.}$ (KBr) 3440, 2930, 1631, 1580, 1515, 1470, 1397, 1290, 1210, 1170, 1120, 921 and 850 cm^{-1}; $UV_{max.}$ (MeOH) 512, 482, 324, 285, and 243 nm; δ (D_2O) 0.62 (m, solvent), 1.75 (m, solvent), 1.91 (s, = $C-CH_3$), 2.90 (m, solvent), 3.30 (d, = $\overset{\oplus}{N}{<}^{Me}_{Me}$), 4.66 (s, solvent) 6.60-6.85 (m, ArH), 7.40 (d, J 9 Hz, ArH), 8.50 (s, ArH) Found: C, 48.73; H, 5.03; N, 3.35%; repeat analysis, C, 52.50; H, 4.85 and N, 2.84%.

Mass Spectra (unsilylated)

$^m/_e$	283.0837	184.0525	137.1332	137.0015	+others
Relative intensity%	100	76.5	2.55	3.29	

Silylated

$^m/_e$	355.1245	283	256	147

Dark blue material:- no clear melting point up to 300°; IR (KBr) 3450, 1600, 1512, 1385, 1320, 1194, 1117, 985, 910, and 860 cm^{-1} $UV_{max.}$ (meOH) 608, 286, 267.5 and 211 nm; Found: C, 50.89; H, 4.47; N, 2.99%.

Mass spectra (unsilylated)

$^m/_e$	288.1556	287.1534	161.0594	138.0919	137.0840	+Others
Relative inensity%	5.65	24.25	47	100	13.72	

Silylated

$^m/_e$	863.3342	775	791	429	400	341	147	+ others

<u>Purple material</u>:- no clear melting point; UV$_{max.}$ (MeOH) 550, 297, 291 and 210 nm.

Mass Spectra (unsilylated)

$^m/e$	288.1543	287.1521	147.0438	138.0911	137.0835	+ 136.076othe
Relative intensity %	1.47	3.98	1.30	11.22	86.81	100

Silylated

$^m/e$	585	576	533.2013	503	488.2465	279	234	147	+ others

Reaction of Diethylamine with Resorcinol

A mixture of resorcinol (33 g, 0.3 M) and diethylamine (21.9 g, 0.3 M) was heated on a steam bath for 24 hrs. The water was removed under vacuum and most of the unreacted resorcinol was removed by extracting with boiling benzene. The residue was then chromatographed and a yellow fluorescent material (similar to the dimethylamine product) was isolated in the same manner to that described in the preceding experiment. An identical TLC pattern was also obtained to that of dimethylamine and resorcinol.

Photographs 1 and 3 shows two different fractions obtained from column redeveloped on a preparative TLC plate. Photograph 2 shows the base line from photograph 1 redeveloped on a TLC plate to obtain a pure sample (11 mg) of the fluorescent material. Photograph 4 shows the blue band from photograph 3 redeveloped on a TLC plate.

Analytical Data

Yellow fluorescent material: showed no clear melting point; $UV_{max.}$ (MeOH) 512, 477, 325, 283, 243 and 207 nm.

Mass spectrum (unsilylated)

$^{m}/_{e}$	397.9778	178.0631	165.0690	163.0395	149.0240	+ others
Relative intensity %	1.38	26.78	5.24	59.53	66.48	

Silylated

$^{m}/_{e}$	987.3626	933.3929	478.1968	383	357	147	+ others
Relative intensity			100	31	46	33	

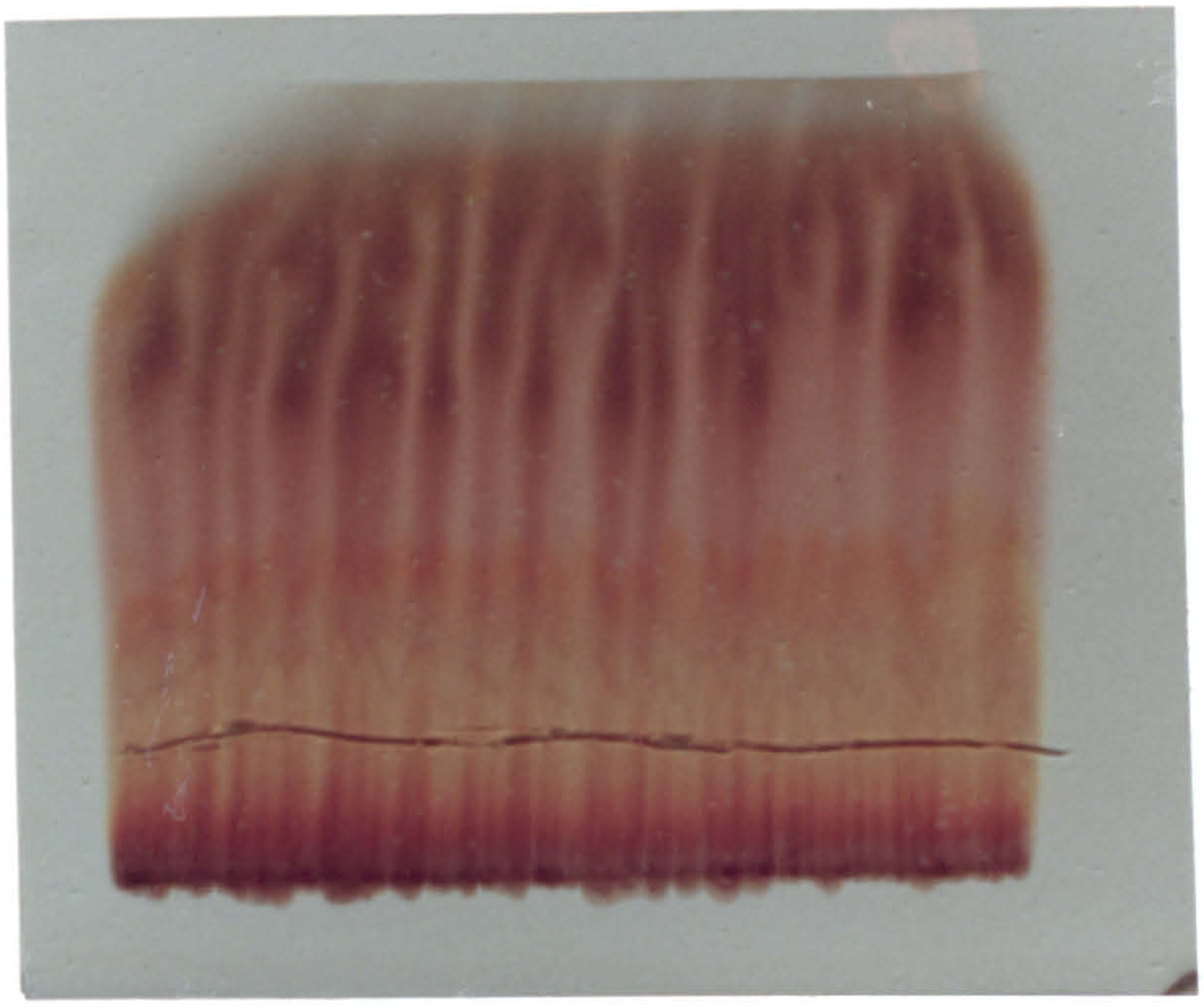
Reaction of Resorcinols with Amines

Mixtures of resorcinol, orcinol and hydroxy-β-orcinol with appropriate amine (dimethylamine, methylamine or ammonia) were allowed to stand at room temperature. The precipitate formed was filtered in each case and separation of some of the components was attempted using preparative TLC. Photographs 5-8 shows the composition of the precipitates separated by TLC using multiple development. The table on next page summarises the results obtained.

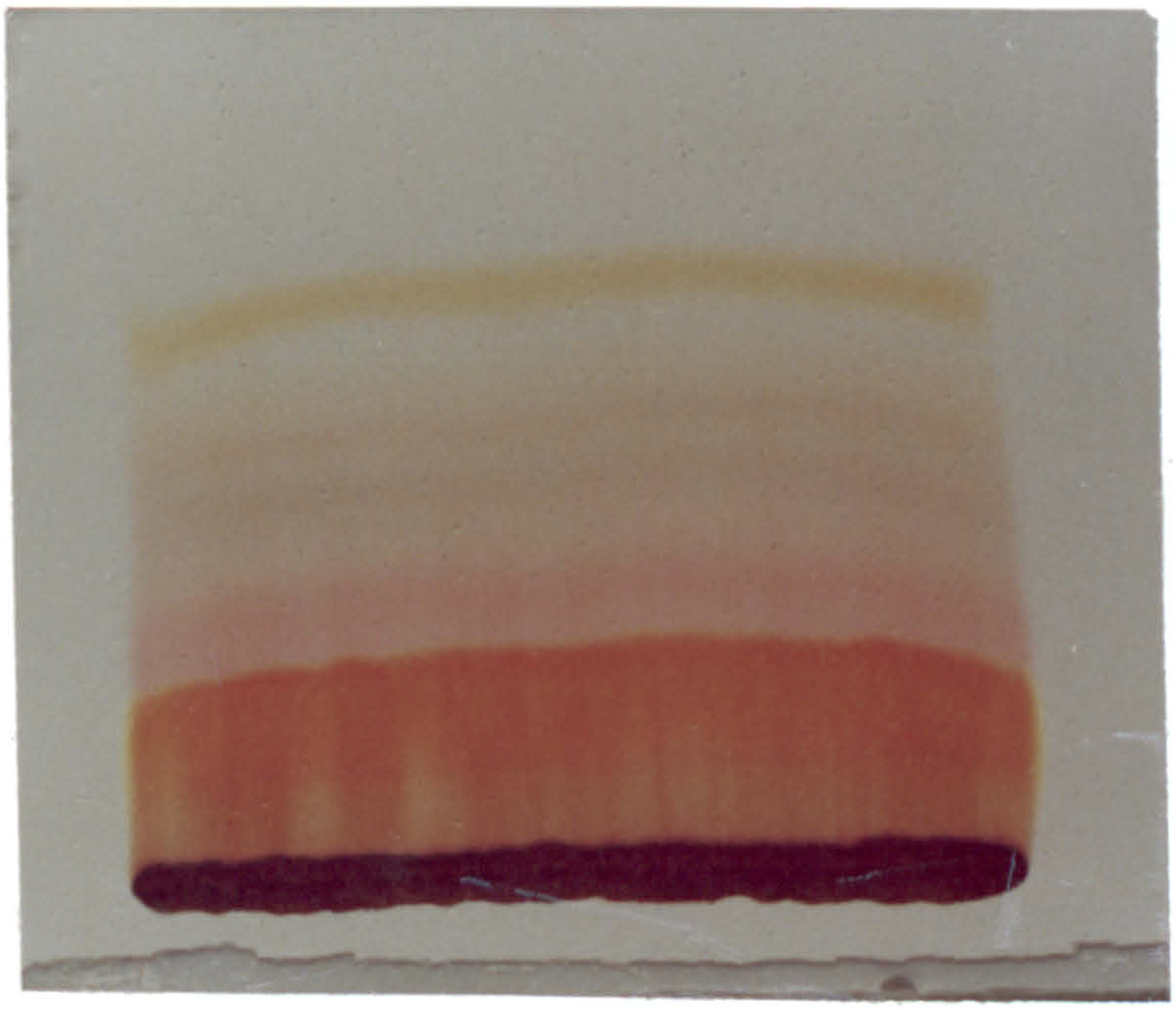
	NH_3	CH_3NH_2	$(CH_3)_2$ NH
Resorcinol	Left the mixture of resorcinol (5.05 g) and excess of ammonia solution to stand for 14 days. Dark blue precipitate (370 mg) was formed. Two components, blue (10mg, R_f0.47) and red-purple (20 mg, R_f0.15) were isolated by preparative TLC using acetone: benzene (70:30) as eluant. Blue material:- $UV_{max.}$(MeOH) 612, 292, 268 and 206nm. Red-purple material: UV_{max}(MeOH) 546, 291, 271 and 207 nm.	A dark red reaction mixture was formed on heating excess of methylamine and resorcinol (5.05 g). The mixture showed no major component.	Described previously
orcinol	Left the mixture of orcinol (3.72g) and ammonia solution to stand for 21 days. A dark blue-black precipitate (500mg) was formed. The residue showed 14 components on TLC. Two red components (R_f0.59 and 0.28, silica gel plates, ethyl acetate eluant) were isolated by TLC. Both samples were silylated and examined by mass spectroscopy. Red component (R_f0.59)-$UV_{max.}$ (MeOH) 585, 572, 538, 488, 285, 225 and 207 nm. m/e 830, 3215. Red component (R_f 0.28) - $UV_{max.}$ (MeOH) 564-532, 242 and 206nm m/e 846. 3719, 757 + others.	Left the mixture of orcinol (0.71g) and methylamine (0.62g) to stand for 7 days. A dark blue-black solid (120mg) was formed. A red-purple solid (R_f0.25) was isolated by preparative TLC (silica gel plates, acetone: benzene (7:3) as eluant). The isolated solid was silylated and examined by mass spectroscopy. Red-purple solid (R_f 0.25):- $UV_{max.}$ (MeOH) 510, 534, 277, 245,226 and 206nm. m/e 860. 3883, 771 + others; δ (d_4-methanol), 1.30 (s, -CH_3), 1.92 (d, $ArCH_3$), 2.27 (d, $ArCH_3$), 6.35 (m, ArH), 6.55 (m, ArH) -(solvent peaks not mentioned above.)	Formed red viscous oil. No separation was attempted.
Hydroxy-β-orcinol	The mixture of hydroxy-β-orcinol and ammonia when left to stand for 2 days produced a dark-blue solid. No separation was attempted. The mixture turns red-orange on acidification and red-blue on basification.	Produced a dark blue-black solid on standing the reactants for 2 days at room temperature. The dark solid turns red with acid and blue with base.	A dark blue-black precipitate was isolated on standing reactants for 2 days The dark solid turns yellow on acidification and red-blue on basification.

N.B. Trimethylamine has also been found to give coloured material with resorcinol

Thin layer chromatograms of one of the fraction obtained by column chromatography of Resorcinol/Diethylamine.

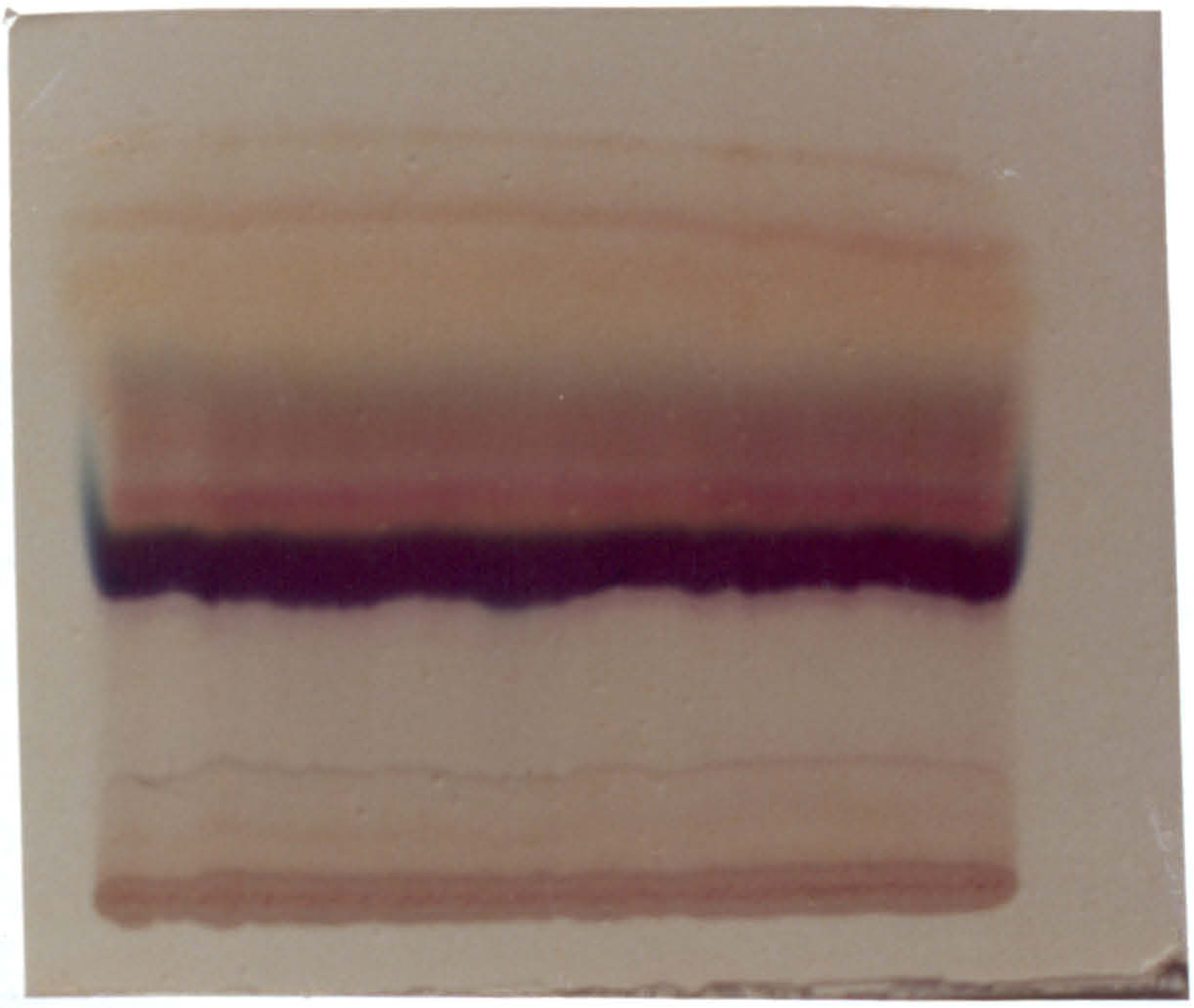


Photograph 1 - Developing solvent acetone.

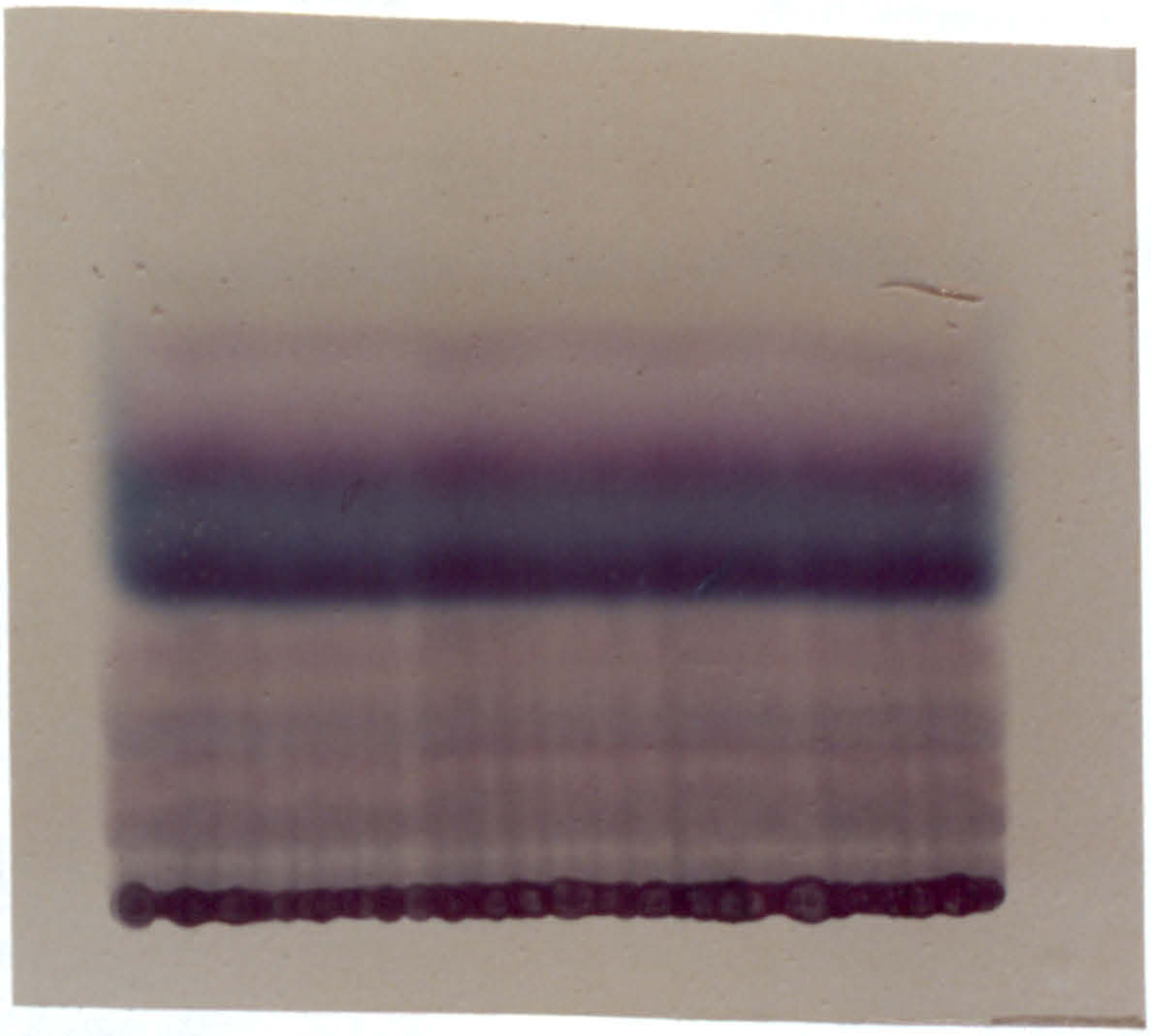


Photograph 2 - The base line from photograph 1 re-chromatographed on a different plate with acetone; methanol (95:5).

Thin layer chromatograms of one of the fraction obtained by column chromatography of Resorcinol/Diethylamine mixture.

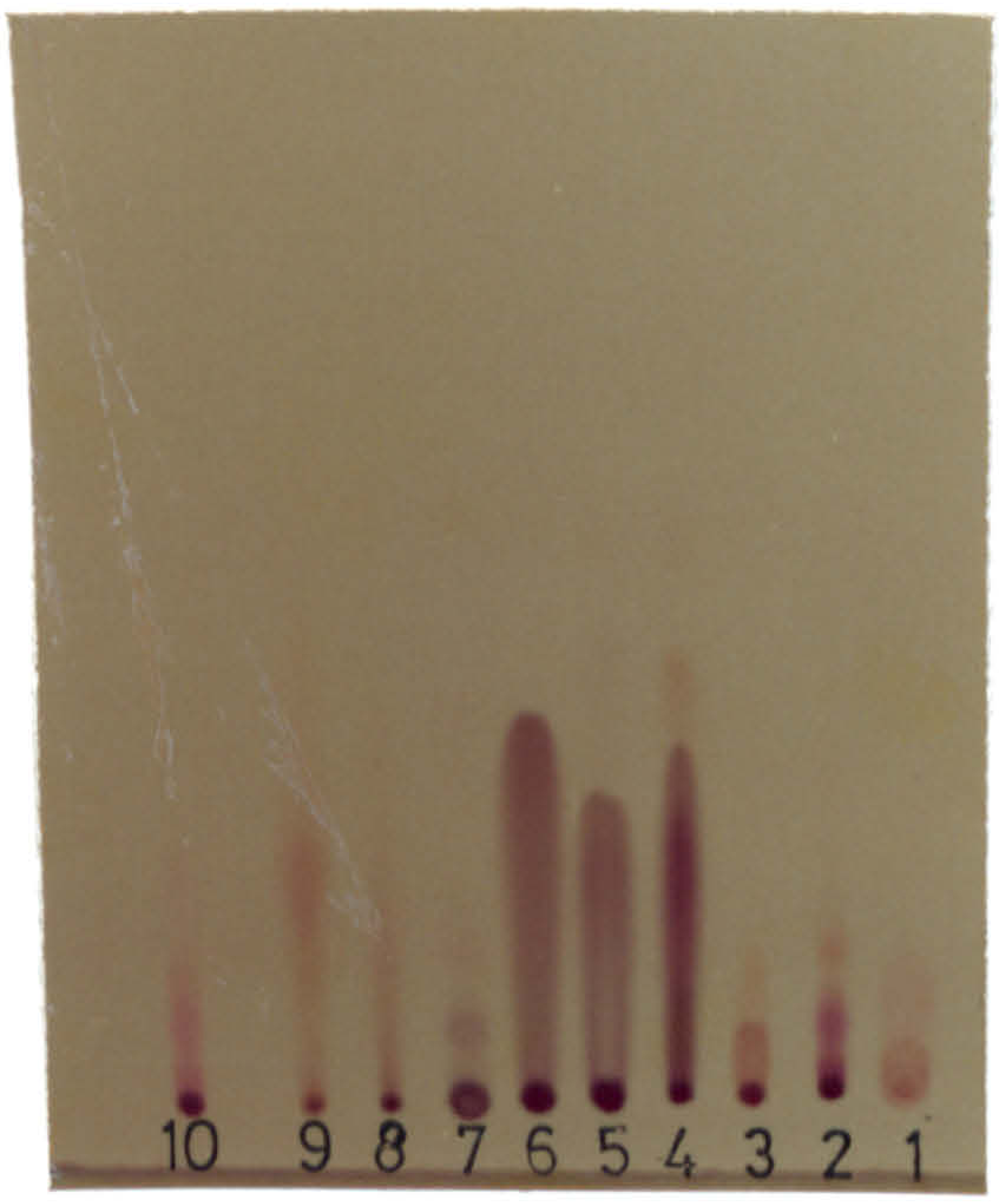


Photograph 3 - Developing solvent
Benzene:acetone (1:1).

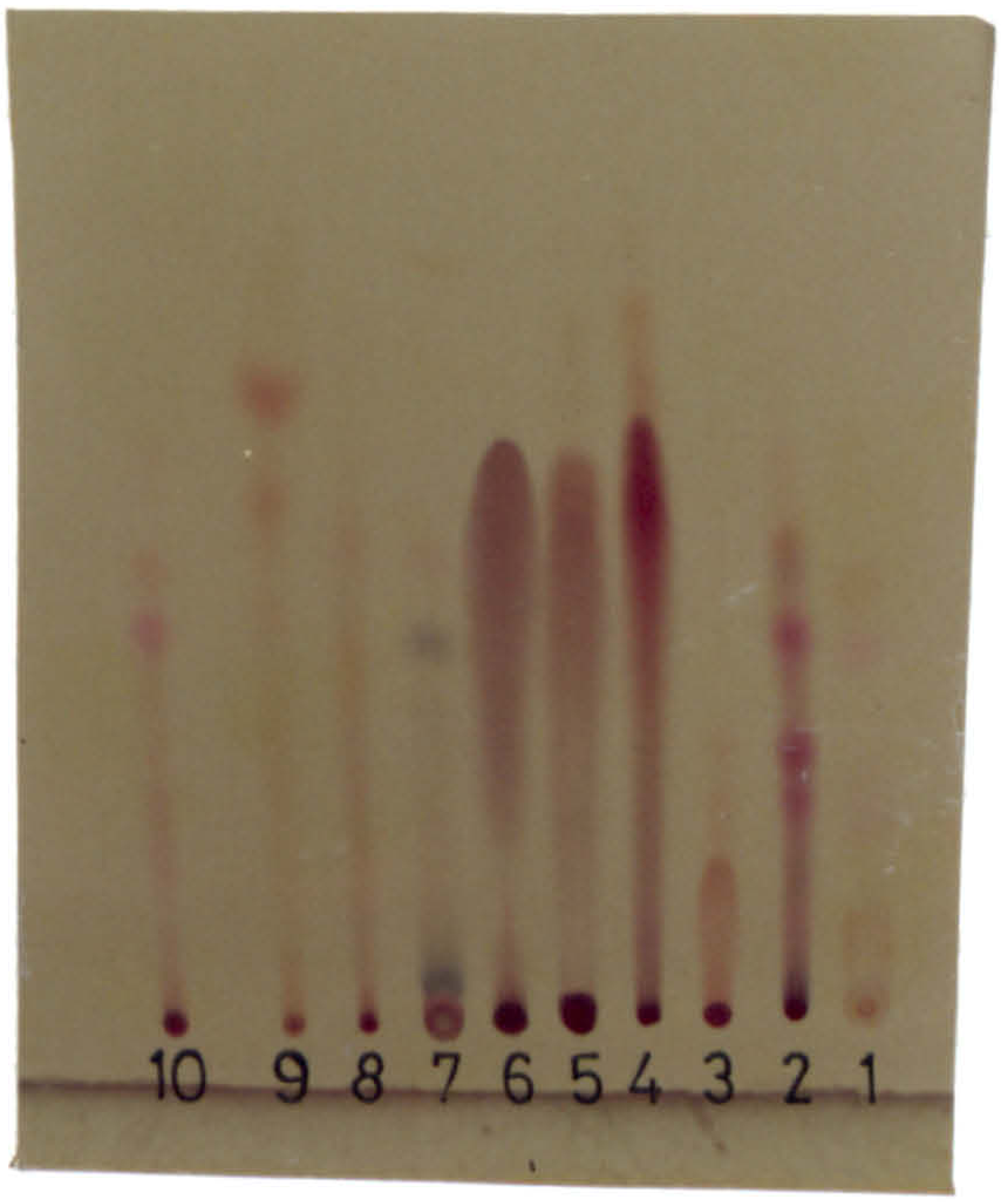


Photograph 4 - The blue band from photograph 3 re-chromatogrammed on a different plate with benzene:acetone (2:3).

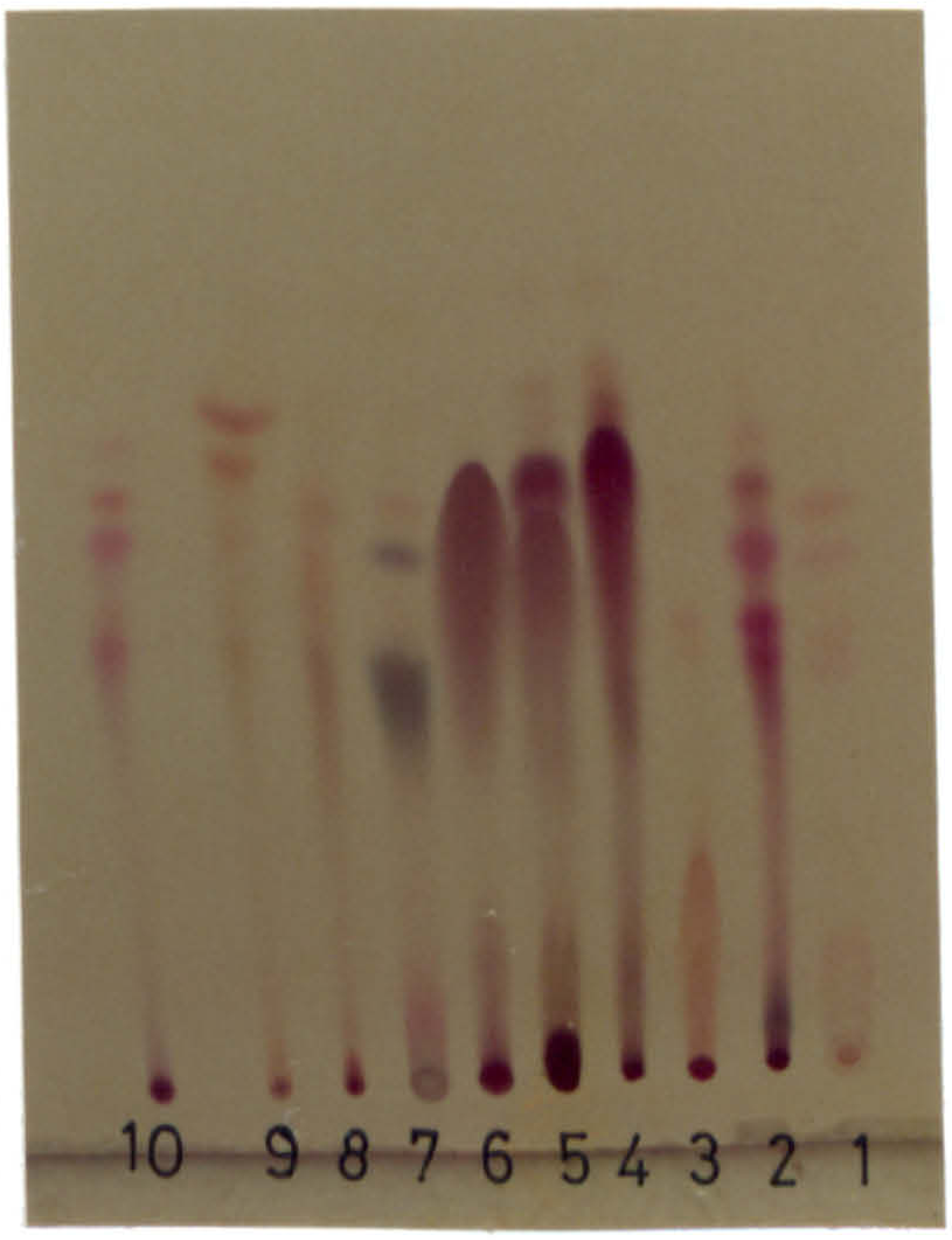
Thin layer chromatograms of Resorcinol/Amine mixture on silica gel G. Samples 1 to 10 were respectively, orcinol/ammonia, orcinol/methylamine, orcinol/dimethylamine, hydroxy-β-orcinol/ammonia, hydroxy-β-orcinol/methylamine, hydroxy-β-orcinol/dimethylamine, resorcinol/ammonia, resorcinol/methylamine, resorcinol/dimethylamine, and orceine.



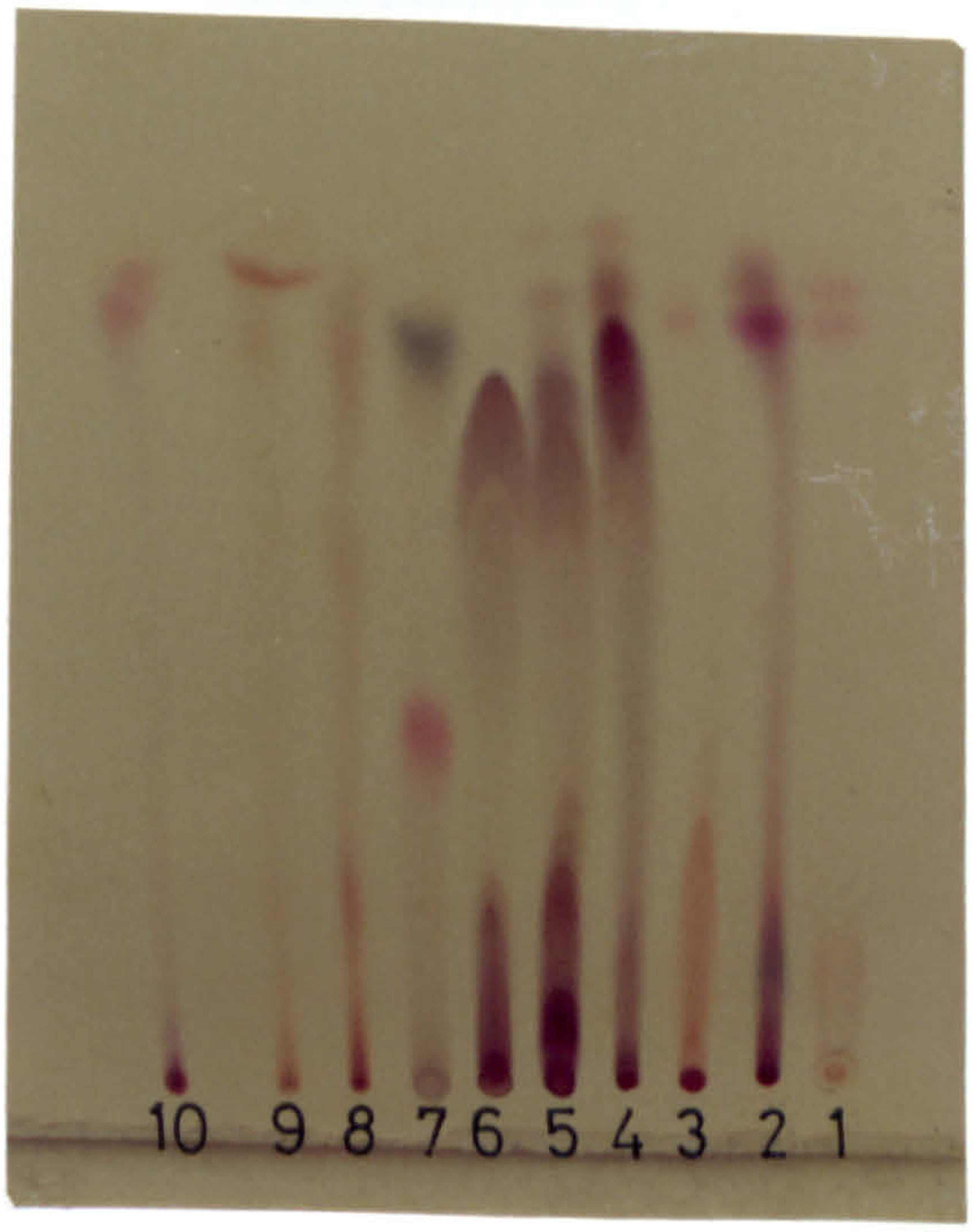
Photograph 5 - Developing solvent ether.



Photograph 6 - Developing solvent benzene:acetone (1:1).



Photograph 7 - Developing solvent benzene:acetone (1:4).



Photograph 8 - Developing solvent acetone:methanol (9:1).

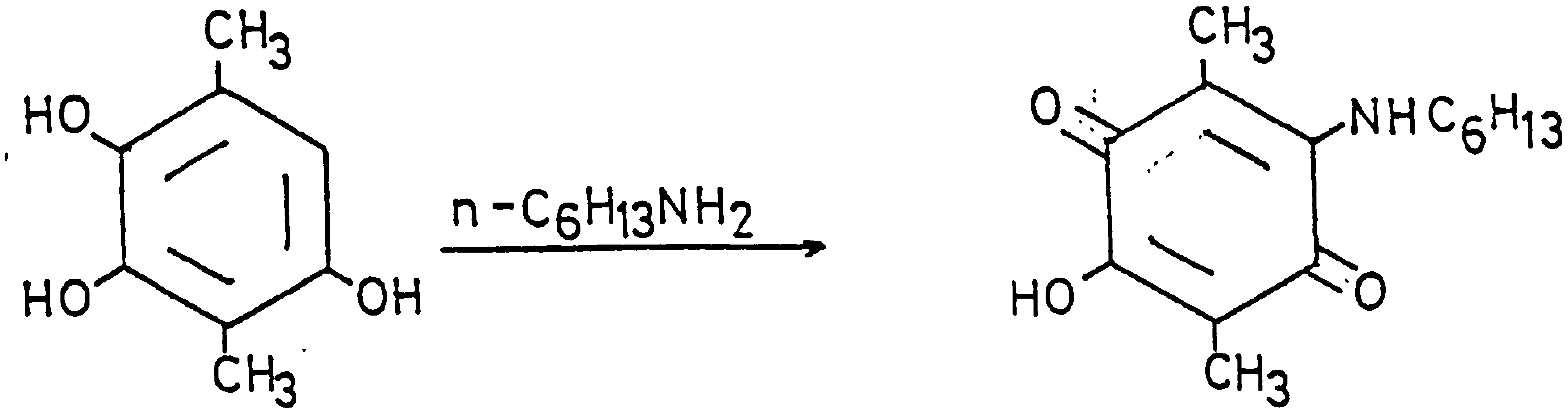
Preparation of Hydroxy-β-Orcinol

2,5-Dimethyl-p-benzoquinone (6 g), acetic anhydride and concentrated sulphuric acid (5 g) were warmed on water bath until the yellow colour of the quinone disappeared (approx. 5 min.) and poured into water. The precipitate was filtered, washed with water and dried.

The triacetate (m. pt. 106-108°, lit[74] 108°) was obtained in 98% yield.

The triacetate (8 g) in conc.hydrochloric acid (140 g) was diluted with water (140 g) and boiled for 20 mins. The reaction mixture was allowed to cool and extracted with ether. The ether was evaporated and the product recrystallised from benzene. The hydroxy-β-orcinol was obtained in 65% yield, m.p. 156-158° (lit.[74] 158°), δ(acetone) 2.11 (6H, s, $(CH_3)_2$), 6.23 (1H, s, ArH), 7.00-7.33 (3H, bs, PhOH, exchangeable)

Reaction of Hydroxy-β-orcinol with n-hexylamine (See Appendix 2)



Mixture of hydroxy-β-orcinol (0.5 g) and n-hexylamine (0.33 g) in methanol (15 ml) was allowed to stand for 3 days. The violet coloured precipitate (70 mg) formed was filtered and examined by TLC. The product was found to be TLC pure, m.p. 132-138° (lit[75] 135-143°), δ ($CDCl_3$) 0.93 (3H, m, $-CH_3$), 1.33 (10H, m, $(CH_2)_5$), 2.25 (6H, s, $2Ar(CH_3)$, 6.50 (2H, s, PhOH, exchangeable), 6.87 (1H, s, -NH, exchangeable); ^{13}C ($CDCl_3$) 181.63, 147.58, 100.71, 78.61 - 75.44 ($CDCl_3$), 44.92, 40.65, 31.38, 30.78, 26.36, 22.47, 13.92, 9.89 and 8.05 ppm; Found: C, 66.81; H, 8.78; N, 4.07%.

5. PREVENTION OF COLOUR DEVELOPMENT IN THE MANNICH REACTION

5a. The experiments to prevent formation of coloured products in the Mannich reaction by using nitrogen atmosphere, a chemical antioxidant as well as the acetylation of the Mannich base have been reported under the section on Mannich reactions.

5b. Removal of Cardol from CNSL

Different molar proportions (0.25, 0.50 and 1.0M) of diethylenetriamine (DETA) were mixed with distilled CNSL (1M) and allowed to stand for 7 days. The mixtures were then distilled under vacuum (0.1mm) and the amine and one fraction of CNSL (b.p. 180-200° at 0.1mm) were collected. The redistilled CNSL was examined by GLC.

The above experiments were repeated with technical CNSL but using higher molar proportions (1.0, 1.6 and 2.0) of DETA per mole of CNSL.

The experiments were also repeated using mixtures of technical

CNSL (1m) with N-(2-aminoethyl) ethanolamine (1.5m), diethanolamine (1.5m) as well as a mixture of technical CNSL and sodium hydroxide (2% w/w).

A further experiment was conducted in which the mixture of technical CNSL (0.03M) and DETA (0.03M) was allowed to stand for 24 hrs. prior to distillation.

Residues obtained by distillation of amine treated distilled CNSL were combined (6.78 g) and distilled under high vacuum. Two fractions were collected and examined by GLC.

Most of the distillates and the residues after silylation with bis-(trimethylsilyl) acetamide in pyridine solution were examined by GLC on a GCD apparatus equipped with an integrator upon a 3% SE 30 type column. Some of the silylated samples were also examined on a 3% PEGA column to check for the mono-, di-, and triene contents of the cardanol. In the calculation of the results, response factors have not been used and the peak areas as printed out by integrator have been normalised (expressed in % form). All the results are summarised in the tables 1 and 2.

A check on the GCD results of the residues was carried out by washing the residue with dilute hydrochloric acid and extracting with ether. The ether layer was separated, dried and evaporated. The acid washed residue was finally silylated and examined by GCD.

Conditions of GLC

3% PEGA column; 190°, recorder speed at 1 cm/min and carrier gas at 40 psi pressure. 3% SE30; 230°, recorder speed at 1cm/min and carrier gas at 40 psi pressure.

PART THREE

RESULTS AND DISCUSSION

1a Structure of Products

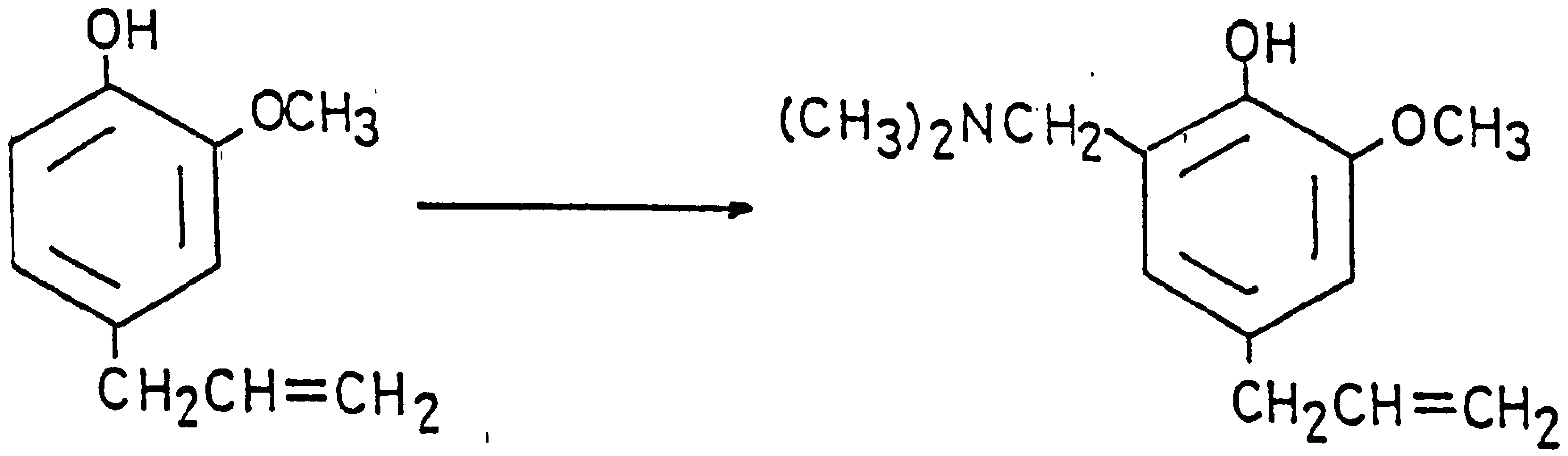
In the case of both pure and mixed products ^1H NMR spectroscopic assignments were made using the chemical shifts given in Table 3.1 and 3.2 of 'Spectroscopic Methods in Organic Chemistry', (Williams and Fleming, 2nd Edition). Calculation were made in a number of cases of the theoretically expected chemical shifts and these compared well with the practically found values.

1b Mannich Reactions with Secondary Amines

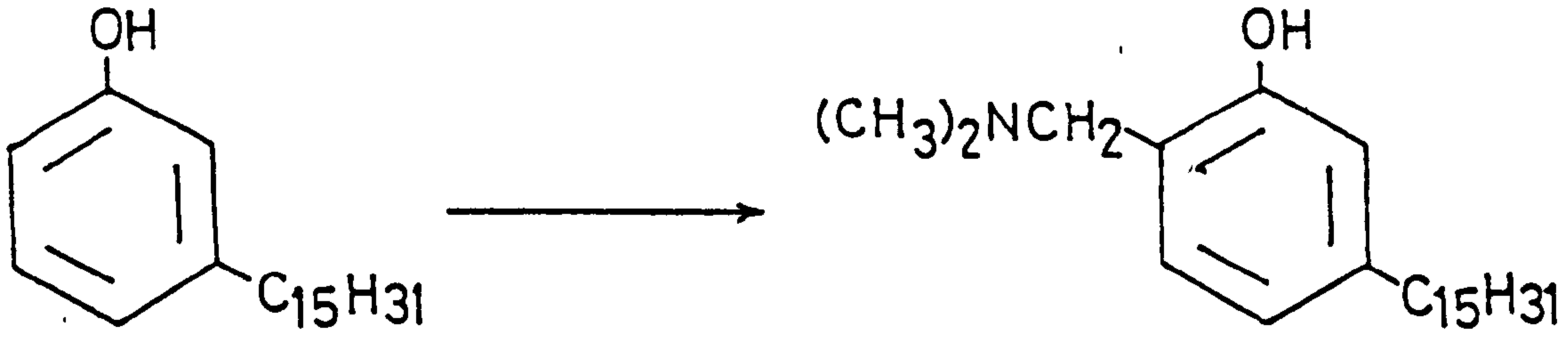
Technical CNSL being a mixture of a 3-alkyl substituted phenol, 5-alkyl substituted resorcinol and 2,5-dialkyl substituted resorcinol would be expected to give a mixture of Mannich bases. The Mannich reaction of CNSL could be further complicated due to the unsaturation of the long chain alkyl substituent. Hence Mannich reactions with formaldehyde and dimethylamine with model phenolic compounds, viz phenol, m-cresol, eugenol, p-tert-pentylphenol, p-tert-butylphenol, p-iso-propylphenol, 3,4,5-trimethylphenol and saturated cardanol were carried out in order to simplify and to establish the relationship between structural factors and colour development in the reaction.

The Mannich reaction of phenol and m-cresol with excess of dimethylamine and formaldehyde has been reported[16] to give dark red crude products which on double distillation produced an almost colourless oil in the case of phenol. The crude dark red Mannich base (b.p. 200°/ 0.5 mm) from m-cresol was not purified but reacted in situ to make 2,4,6-tris-(acetoxymethyl)-3-methylphenyl acetate. On repeating these experiments a yellow-brown oil consisting of 2,4,6-tris-(dimethylaminomethyl)-phenol and a white solid consisting of 2,4,6-tris-(dimethylaminomethyl)-3-methylphenol (m-cresol) were obtained from phenol and m-cresol respectively. The difference in the physical states of the Mannich base obtained from m-cresol on repeating the experiment and that reported by Bruson and MacMullen may be attributed to the purity of the reactants (such as the phenol and the amines) used and to the fact that they reacted the Mannich base in situ which did not allow enough time for the oil to solidify.

The Mannich bases from eugenol and saturated cardanol were a yellow oil and a white solid respectively. A comparison of ^1H NMR of eugenol and its Mannich base showed the unsaturation to be unaffected during the reaction and the introduction of one dimethylaminomethyl group.



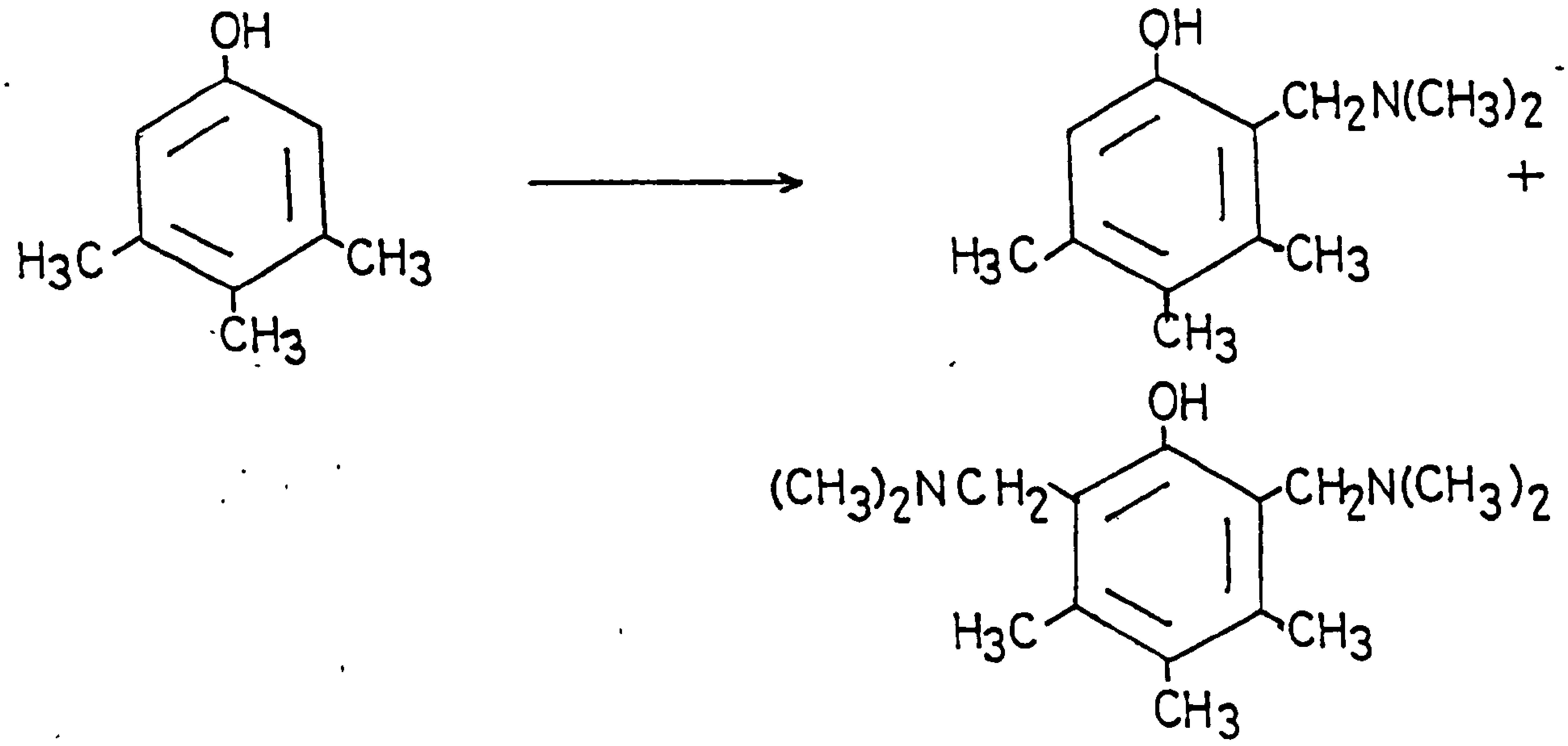
The ^1H NMR spectrum of the Mannich base from the reaction of saturated cardanol with excess of dimethylamine and formaldehyde indicated only a mono-dimethylaminomethyl substituted product as compared with a tri-substituted product from m-cresol.



The 2- and the 4- positions of cardanol may be sterically hindered by the bulky m-substituent. The condensation of cardanol with fromaldehyde in basic medium was studied by Bakshi and N. Krishnaswamy.[76] They isolated 6-methylol, 4-methylol and 4,6-dimethylol derivatives of cardanol. The absence of 2-methylol derivative was attributed to steric hindrance due to the bulky m-substituent. The absence of 4-dimethylaminomethyl derivative in the case of the Mannich base may be due to the larger substituent group involved compared with the methylol group.

The Mannich reactions with p-tert-pentylphenol, p-tert -butylphenol and p-iso-propylphenol produced 2,6-bis(dimethylaminomethyl) derivatives which indicated that the branched chain had no steric effect on substitution.

The Mannich reaction of 3,4,5, trimethylphenol produced both the mono and disubstituted products. This again indicated the importance of the chain length of the m-substituent since 3- and the 5-methyl groups showed no steric hindrance towards substitution at the o-positions.



The Mannich reaction of distilled CNSL with secondary amines having a sum of more than six carbon atoms in the dialiphatic group, for e.g. diamylamine and dilaurylamine, and formaldehyde to obtain yellow-to-brown oily Mannich bases in 98 to 100% yields has been reported by Revukas and Cranford.[77] On repeating these experiments with dimethylamine, CNSL and formaldehyde a red-brown oily condensation product was obtained. The examination of the Mannich base by analytical TLC showed the presence of unreacted cardanol while the 2-methylcardol and cardol components were absent. This indicated the reaction of dihydric phenols to be faster than that of monohydric phenols.

1c Mannich reaction of Resorcinol with Secondary and Primary Amines

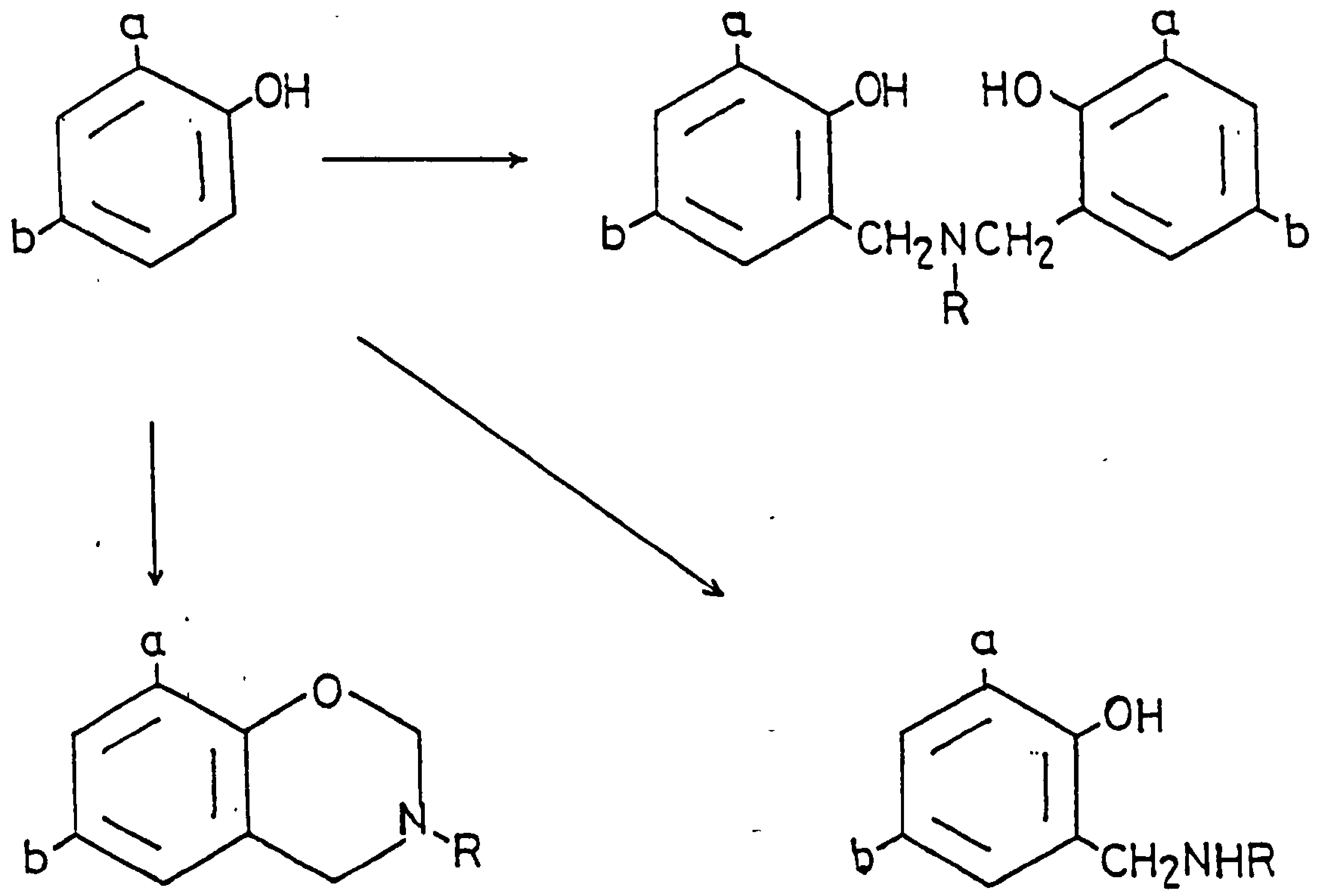
A Mannich base from resorcinol, formaldehyde and dimethylamine hydrochloride has been reported by Decombe[78] but a repetition of this experiment with excess of dimethylamine gave a dark red polymeric material. When the reaction was repeated again using molar proportions of reactants and milder conditions, it again failed to yield the Mannich base and instead a red solid was isolated.

Ebers[79] and Gils[80] also found that polymers and resins of low solubility were formed in the reaction of resorcinol, formaldehyde and a primary or a secondary aliphatic amine. The resin was found to remain in solution if at least 0.65 mole of amine was present for each mole of formaldehyde which combined with the resorcinol.

Gils gathered information on the reaction mechanism by measuring the heat of reaction of formaldehyde and ammonia and, subsequently, of mixtures of formaldehyde and resorcinol to which varying amounts of ammonia were added. In a very fast reaction ammonia was said to react with formaldehyde to form an unstable intermediate, trimethylolamine, which then reacted further with resorcinol to form tris-(dihydroxybenzyl)-amine. This intermediate reacted with more ammonia and formaldehyde to give a Polymer. Primary amine and secondary amines were also said to react in a similar manner to ammonia.

1d With Primary and Polyamines

Primary Amines: Mannich reactions of primary amines with phenols have been described to a very limited extent. Burke[22,23] has shown the reaction of 2,4-substituted phenols with formaldehyde and primary aliphatic amines to produce three different products depending on the molar proportions of the reactants used. The usage of disubstituted phenols precluded the formation of polymers. The three products isolated were 3,4-dihydro-(3,6-disubstituted)-1,3, 2H-benzoxazines, 2-alkylaminomethylphenols and N,N-bis-(2-hydroxybenzyl)-alkylamines. The reaction scheme showing the formation of the three products is given on next page.



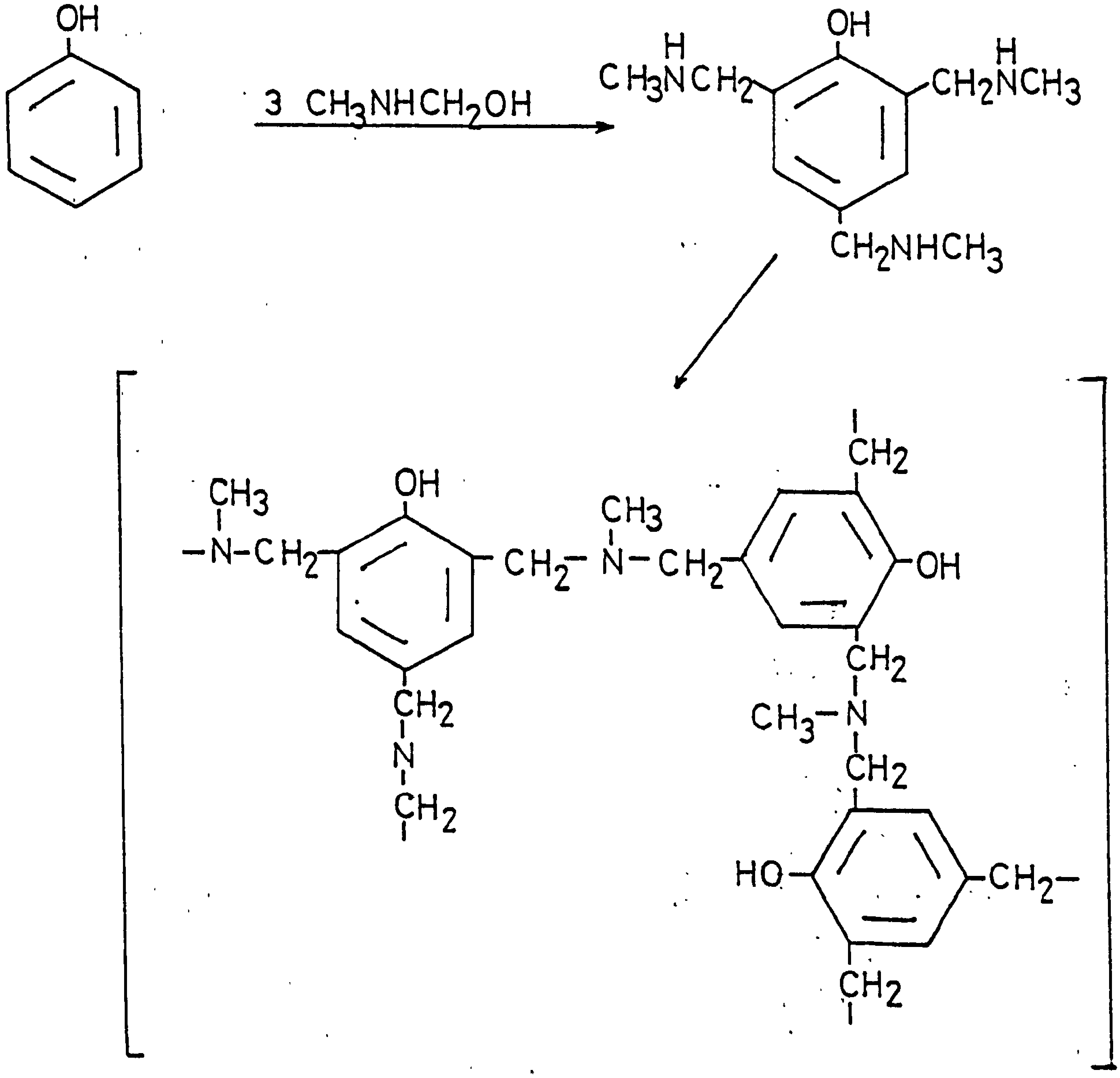
RNH_2 = benzyl, cyclohexyl or methylamine

a = CH_3 , $C(CH_3)_3$, or Cl

b = CH_3 or $C(CH_3)_3$

On repeating the above experiment with phenol and excess of methylamine and formaldehyde a solid white polymer was isolated from the reaction mixture. The first stage in the formation of polymer could be the formation of tris-(methylaminomethyl)-phenol. The secondary amine thus formed may react further with a molecule of formaldehyde and of phenol to give a Bakelite-like polymer. A possible scheme for this reaction is outlined on next page.

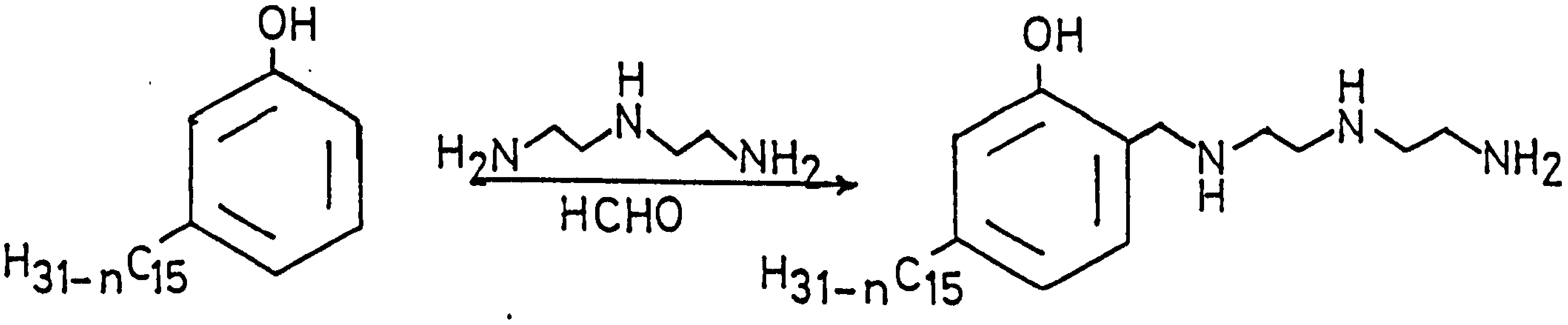
$$CH_3NH_2 + HCHO \longrightarrow CH_3NHCH_2OH$$



When molar proportions of reactants and milder reaction conditions were used it was possible to isolate the monomers methylaminomethylphenol and methylaminomethyl-m-cresol.

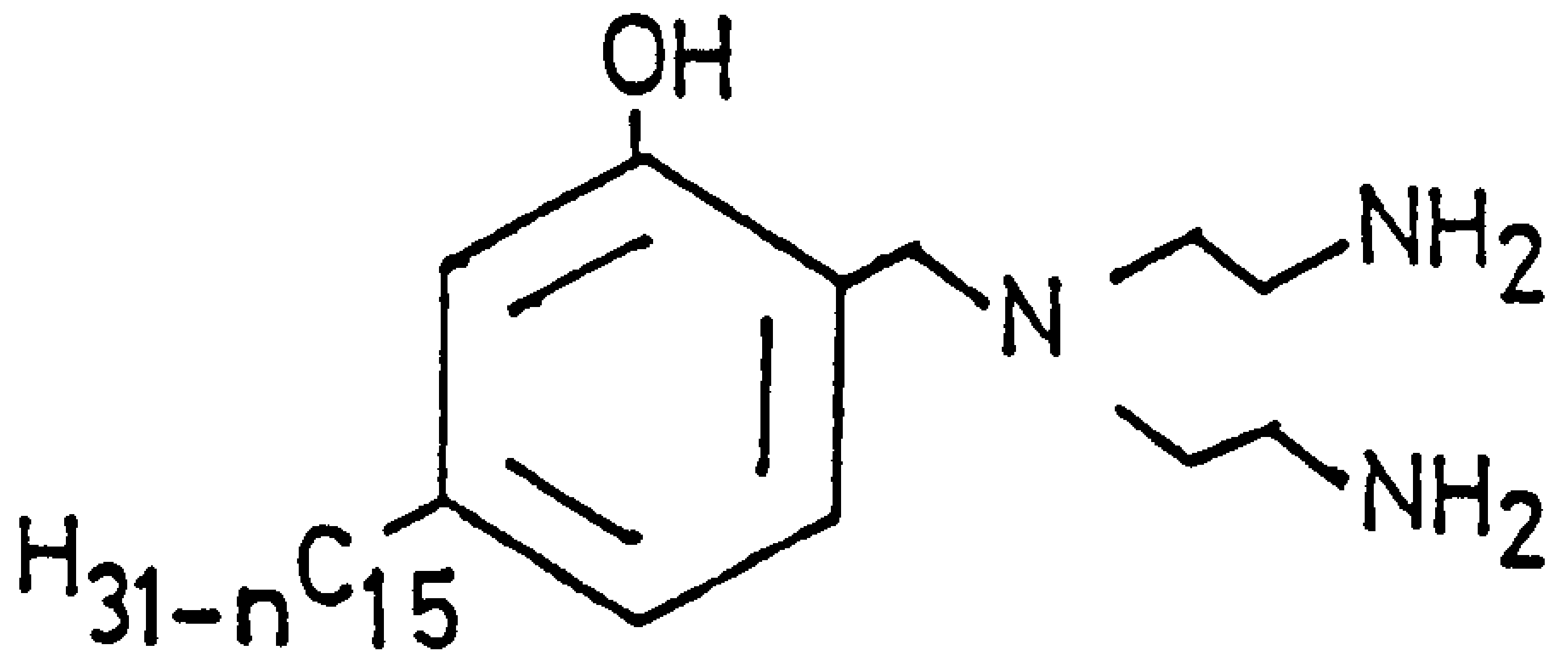
Polyamines: The reaction pathway with diethylenetriamine ($H_2N(CH_2)_2NH(CH_2)_2NH_2$), formaldehyde and cardanol will be likely to be complex with probable formation of mixture of products, depending on the molar ratio of the reactants used.

With a 1:1 molar ratio of reactants it is possible that primary amine may react first giving the material (I) or the secondary amine giving the material (II) and so mixtures of product are always possible The degree of polymerisation with cardanol would be less compared with phenol due to steric hinderance by the bulky m-substituent in the former case.



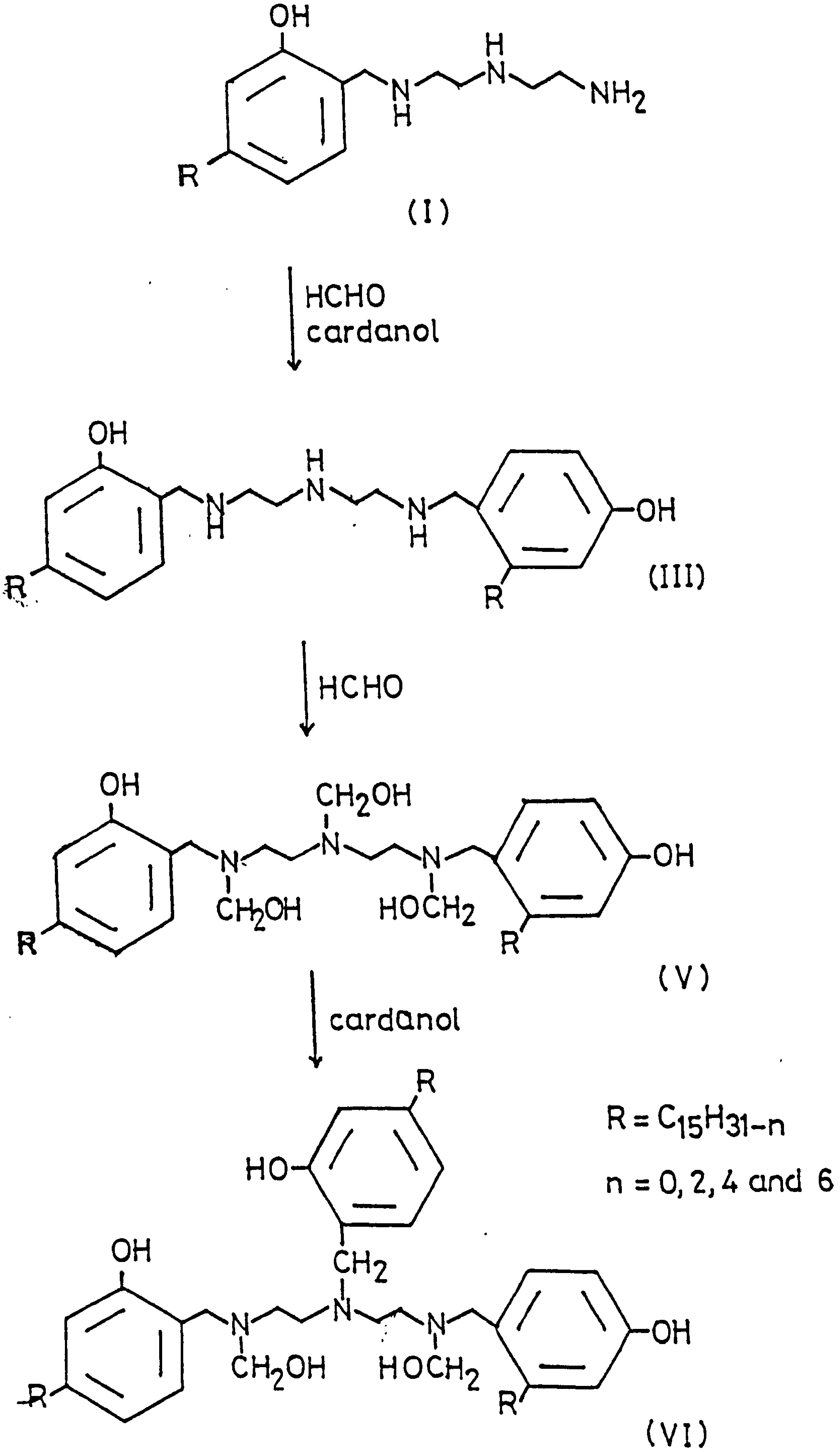
(I)

or/and



(II)

As the reaction proceeds further, substances (I) and (II) could react with another molecule of formaldehyde and cardanol to



(I)

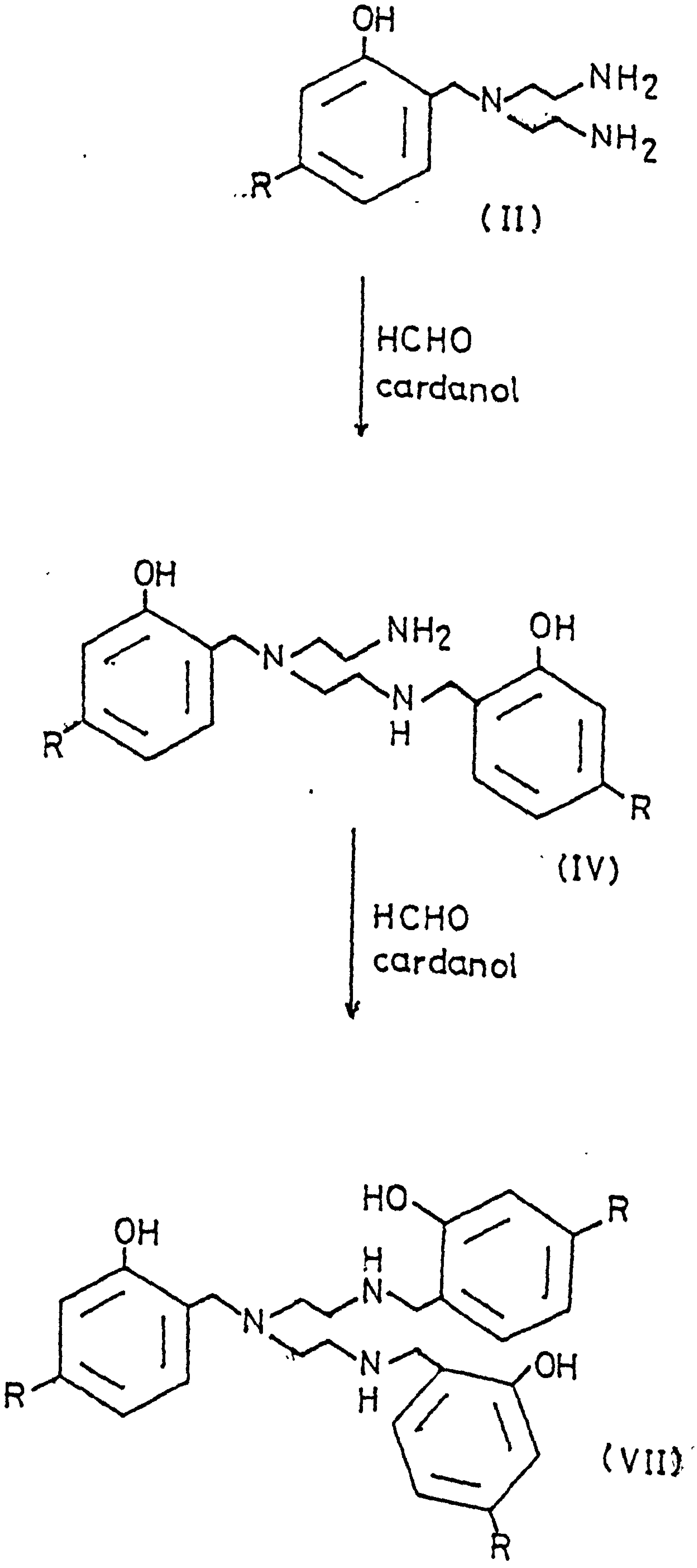
(III)

(V)

(VI)

$R = C_{15}H_{31-n}$

n = 0, 2, 4 and 6


OH
R
N
NH2
NH2
HCHO
cardanol
OH
N
NH2
NH
OH
R
R
HCHO
cardanol
HO
R
OH
HN
N
NH
OH
R
R

(II)

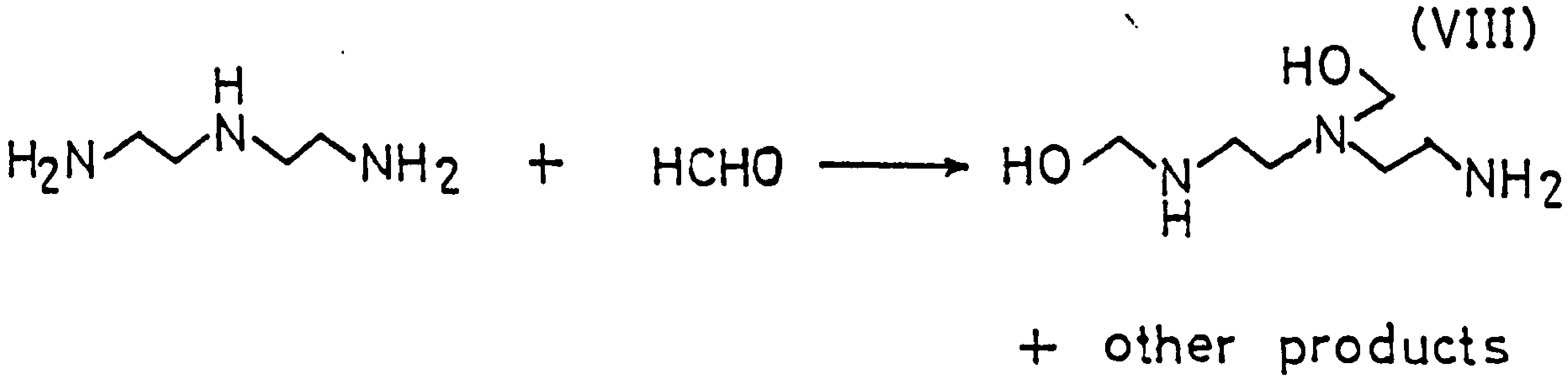
(IV)

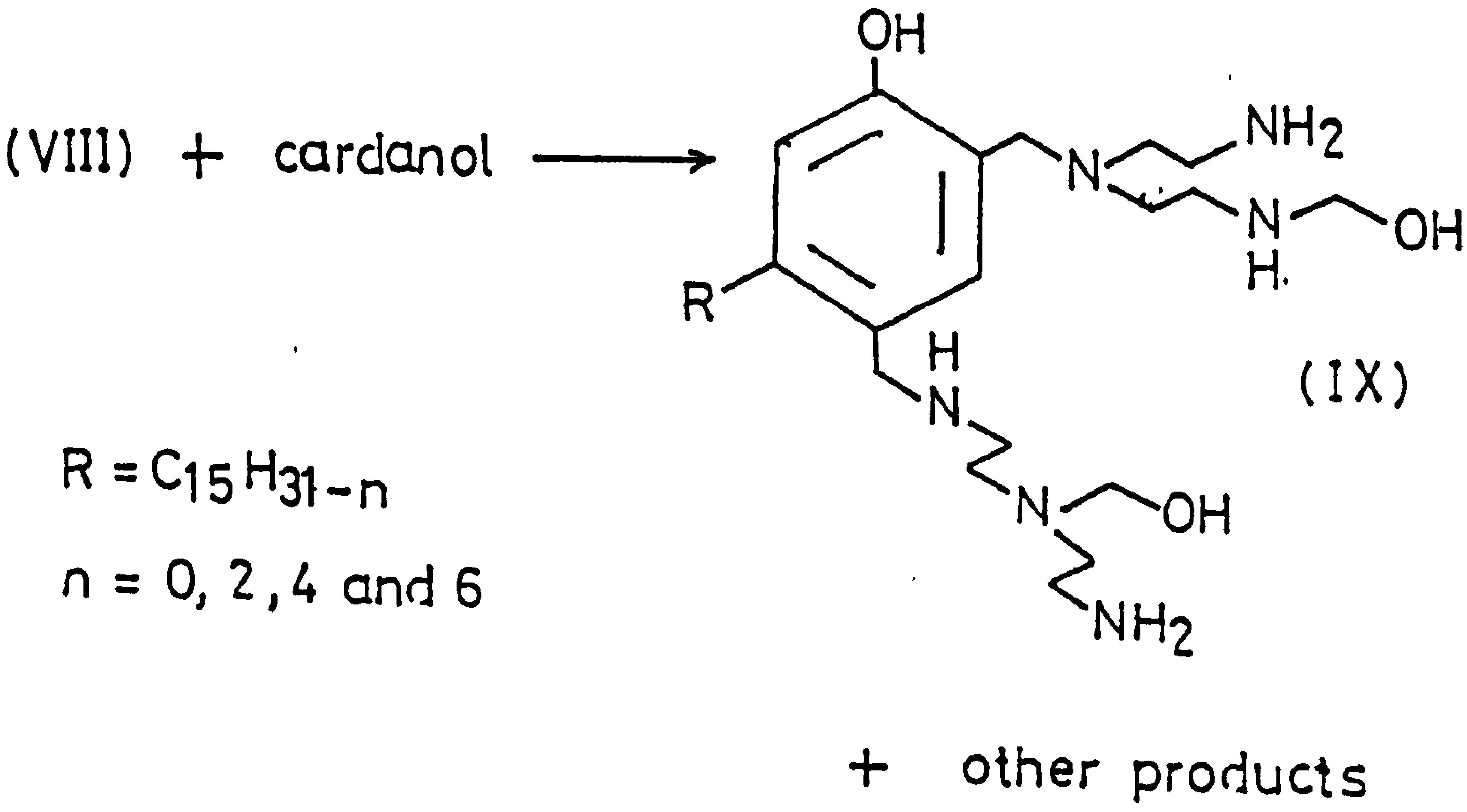
(VII)

give 'dimers' (III & IV) The substances (III) and (IV) could react again with formaldehyde to give a methylol derivative or could proceed further to give Mannich products.

There would be other structures possible besides those considered due to attacks on both the 6 and 4 positions of cardanol depending on the proportions of the reactants employed.

An alternative mode of the reaction could be via a methylol derivative of (IX) which would eventually give similar products to those previously outlined but would explain the presence of unreacted cardanol during the reaction when 1:1:1 molar proportions of reactants were used.





R = $C_{15}H_{31-n}$

n = 0, 2, 4 and 6

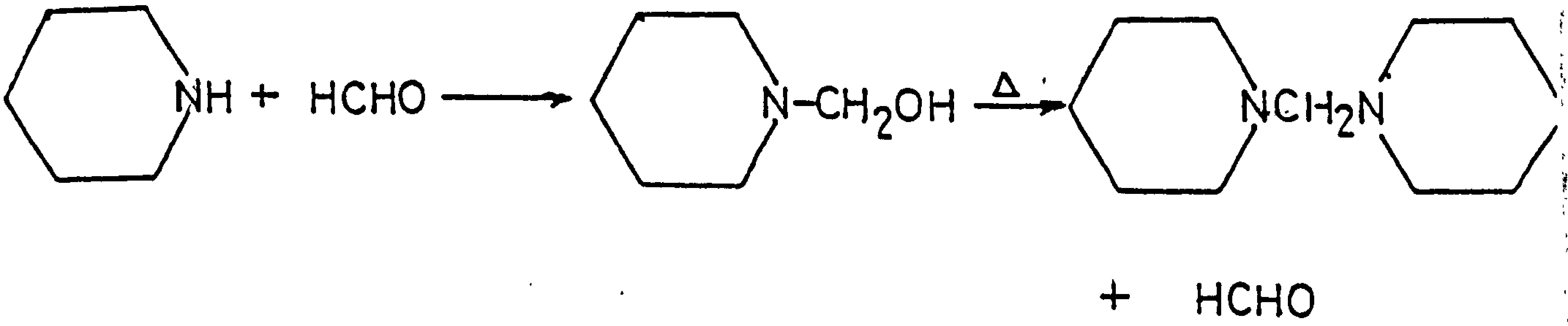
A detailed study of the mechanisms of Mannich reaction is outlined in the next section.

1e Mechanisms

The mechanisms of the Mannich reaction have been studied by several workers[27-43] and conflicting as well as comparable mechanisms have been proposed. In essence two different mechanisms can be operative , one for acidic and the other for the basic media.

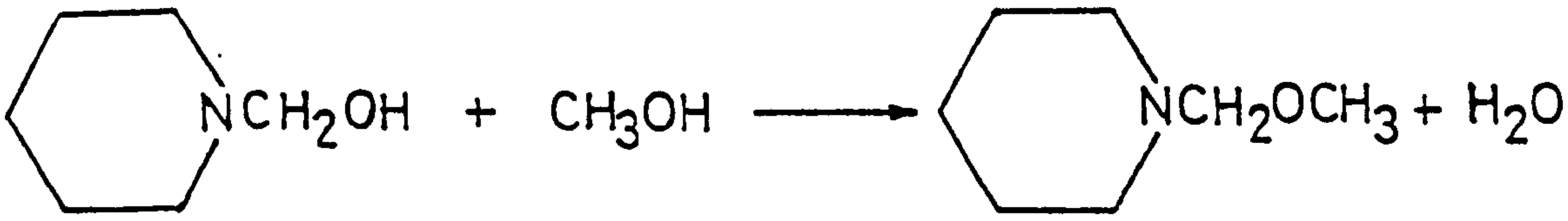
Acidic Conditions

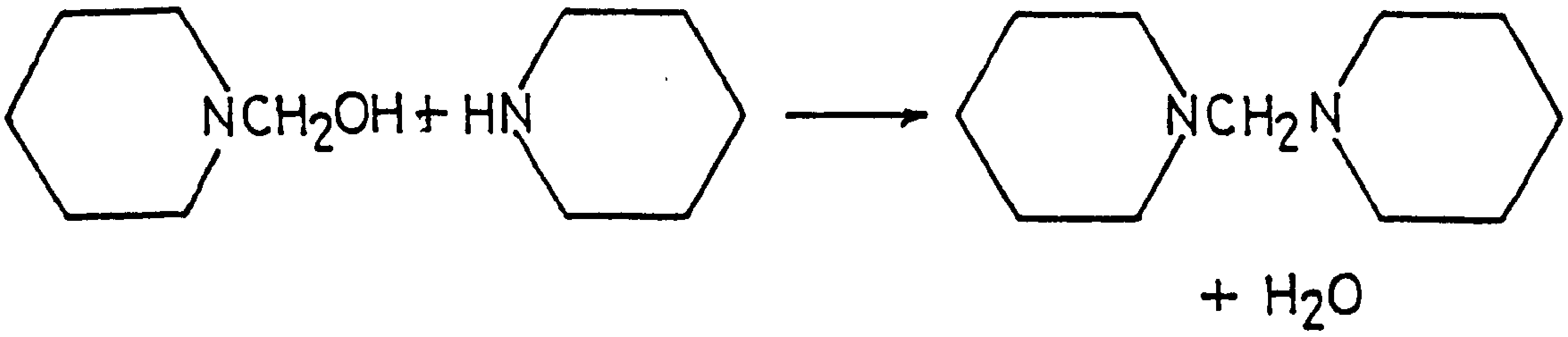
The initial stage in the condensation is considered to be the interaction of formaldehyde with the amine. Several different intermediates are possible depending on the operating conditions. The N-hydroxymethylamines, as reported by Henry[81] in 1897, may be obtained from aq. formaldehyde and the amine with cooling. These oily, nondistillable N-hydroxymethylamines are difficult to purify, and exist only in the cold. Warming causes decomposition to formaldehyde and free amine along with some recondensation to form a methylenediamine, as shown below in the scheme:-



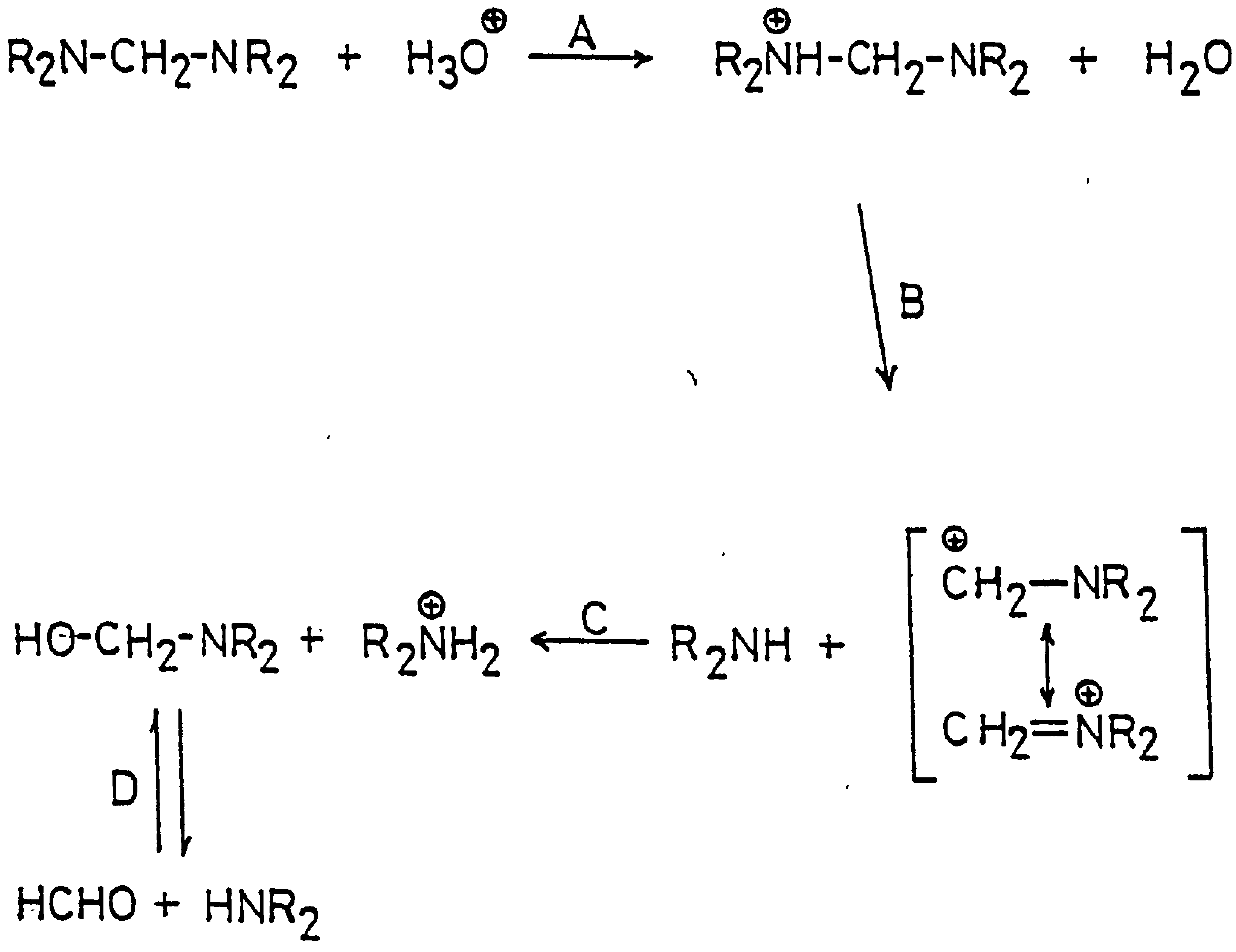
Methylenediamines are formed exclusively when formaldehyde and amine are allowed to react without cooling.

By contrast with oxygen hemi-acetals, nitrogen hemi-acetals are converted to O,N-acetals with alcohols or to N,N-acetals (methylene-diamine) with amines without added catalysts. For example:



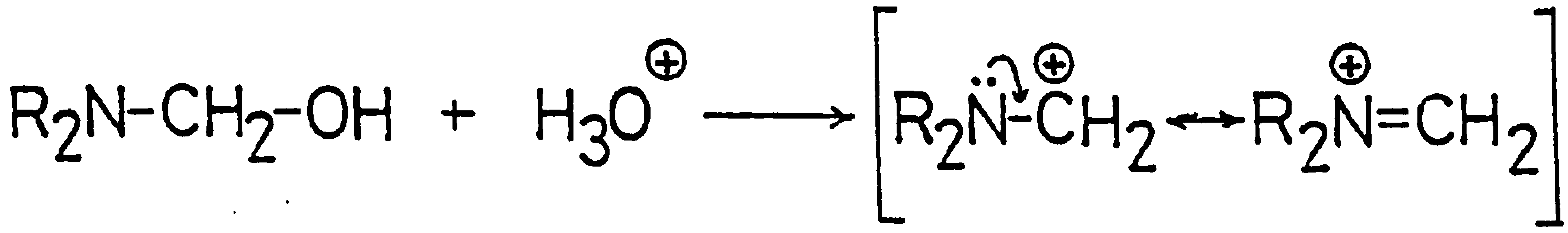


The members of both these compound classes are very acid-sensitive and follow a well-defined reaction course in acid hydrolysis,[42] as illustrated below:



$$\begin{tikzcd}
R_2N\text{-}CH_2\text{-}NR_2 + H_3\overset{\oplus}{O} \arrow[r, "A"] & R_2\overset{\oplus}{N}H\text{-}CH_2\text{-}NR_2 + H_2O \arrow[d, "B"] \\
HO\text{-}CH_2\text{-}NR_2 + R_2\overset{\oplus}{N}H_2 \arrow[d, shift left, "D"'] & R_2NH + \left[\overset{\oplus}{C}H_2\text{—}NR_2 \leftrightarrow CH_2\text{=}\overset{\oplus}{N}R_2\right] \arrow[l, "C"'] \\
HCHO + HNR_2 \arrow[u, shift left] &
\end{tikzcd}$$

The ammonium salt of methylenediamine which formed in step A decomposes immediately in water to form an aminomethyl carbonium ion (reaction B). The acid in this system may react further to neutralize the free amine formed in equilibrium (D) or it may act directly on the intermediate, N-hydroxymethylamine. The latter action was discussed by Stewart and Bradley[42] who reported that addition of an N-hydroxymethylamine to a solution of aqueous acid followed the course outlined below:



$$R_2N\text{-}CH_2\text{-}OH + H_3O^{\oplus} \longrightarrow \left[R_2\ddot{N}\text{-}\overset{\oplus}{C}H_2 \longleftrightarrow R_2\overset{\oplus}{N}{=}CH_2\right]$$

The reverse order of mixing appeared to favour formation of the salt of the free amine.

Liebermann and Wagner[33] concluded that the aminomethyl carbonium ion formed as above is the final electrophilic intermediate and that it reacts with a carbanion which arises from the acidic or labile hydrogen compound undergoing the Mannich reaction.

Alexander and Underhill[34] put forward a mechanism which involved N-hydroxymethylamine as the intermediate and in which the acidic hydrogen compound was suggested to react in the enol form rather than to ionize as Liebermann and Wagner proposed.

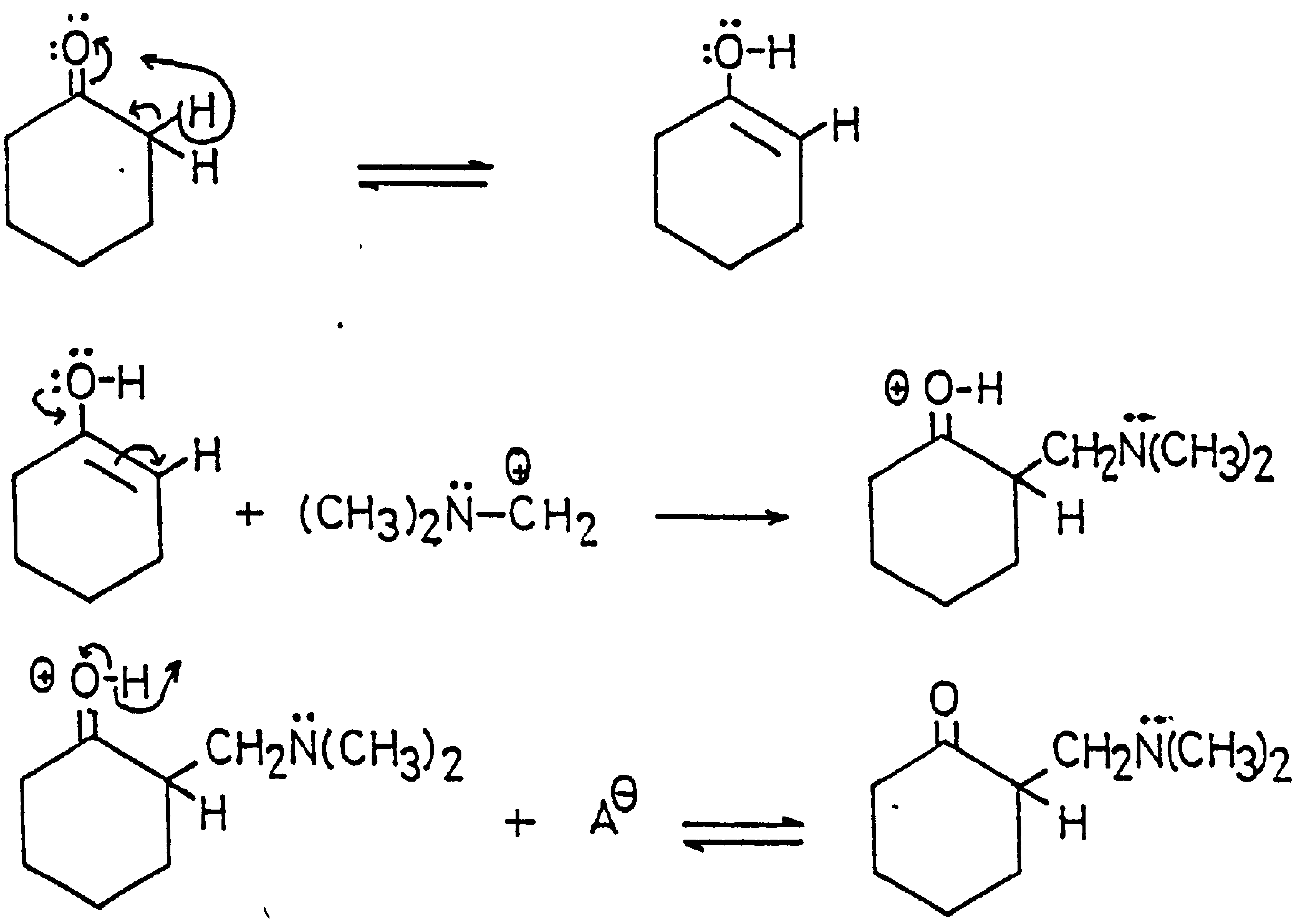
Based on extensive experimentation carried out, Hellmann and Opitz[29] concluded that rather strong inductive effects must be operating in order to activate the labile hydrogen compound sufficiently for it to react as a carbanion, or that there must be enol formation in the absence of strong inductive effects.[39] The proposed mechanism offered was quite similar to the mechanism in acid medium of Cummings and Shelton[30] and represents an elimination mechanism.

The mechanism proposed by Cummings and Shelton for cyclohexanone in acidic media is outlined below:

$$(CH_3)_2\overset{\oplus}{N}H_2 \quad + \quad \overset{\ominus}{A} \rightleftharpoons (CH_3)_2NH \quad + \quad HA$$

$$(CH_3)_2NH \quad + \quad HCHO \rightleftharpoons (CH_3)_2N-CH_2OH$$

$$(CH_3)_2N\text{-}CH_2OH \quad + \quad HA \rightleftharpoons (CH_3)_2\ddot{N}-\overset{\oplus}{C}H_2 + H_2O + A^{\ominus}$$

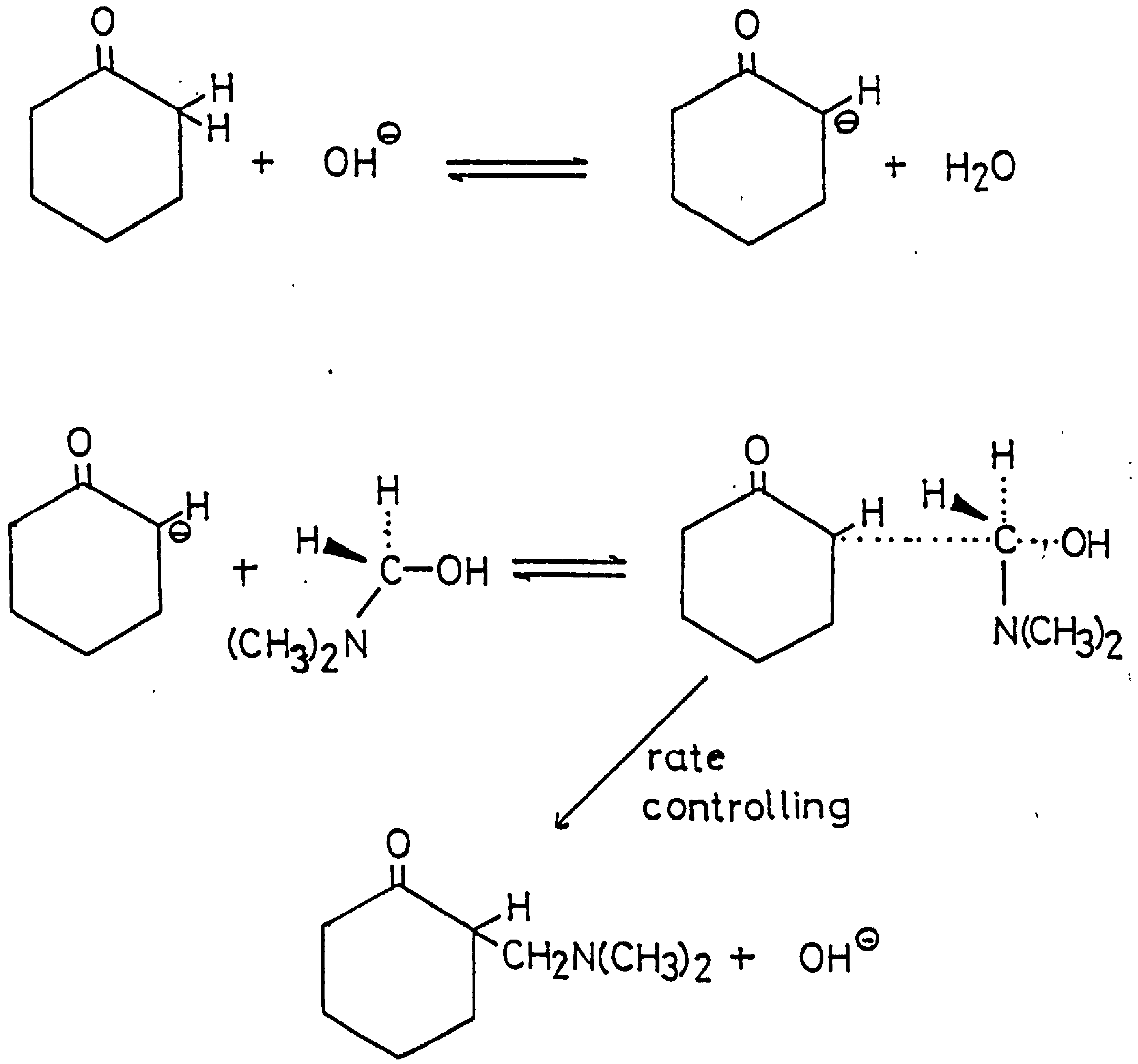


Basic Condtions

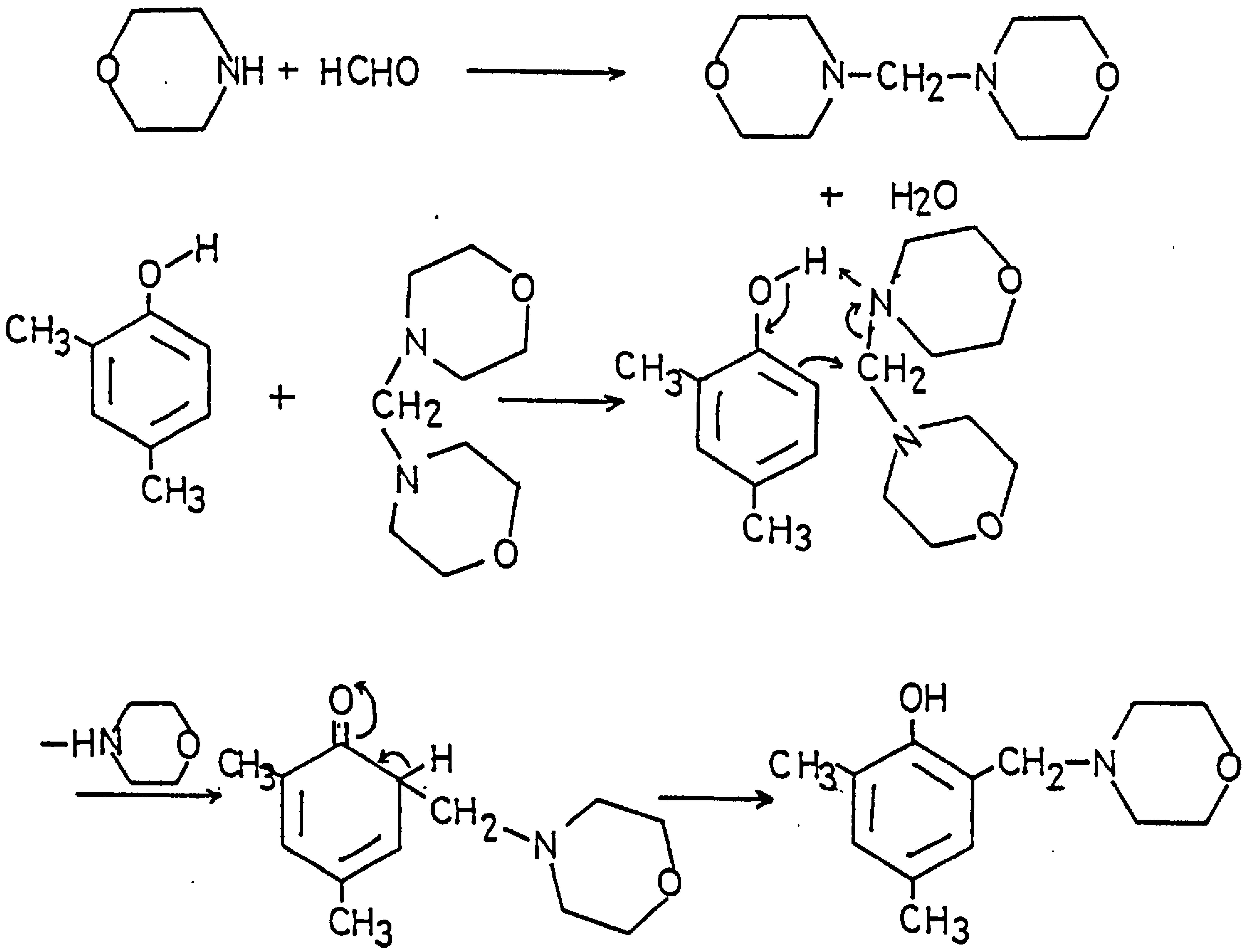
The intermediates, N-hydroxymethylamine, N-methoxymethylamine and methylenediamine formed in the course of the Mannich reaction do not undergo further reaction in basic media so they act as the reacting species.

Cummings and Shelton conducted a kinetic study in basic media on the Mannich reaction of cyclohexanone. They suggested dimethylaminomethanol as the intermediate on which an S_N2 displacement of $OH^{\ominus}$ by the cyclohexanone carbanion takes place. The appropriate carbanion presumably arises by base attack on the reactive α-protons of cyclohexanone. The suggested reaction scheme is outlined below:

$$(CH_3)_2NH + HCHO \rightleftharpoons (CH_3)_2NCH_2OH$$

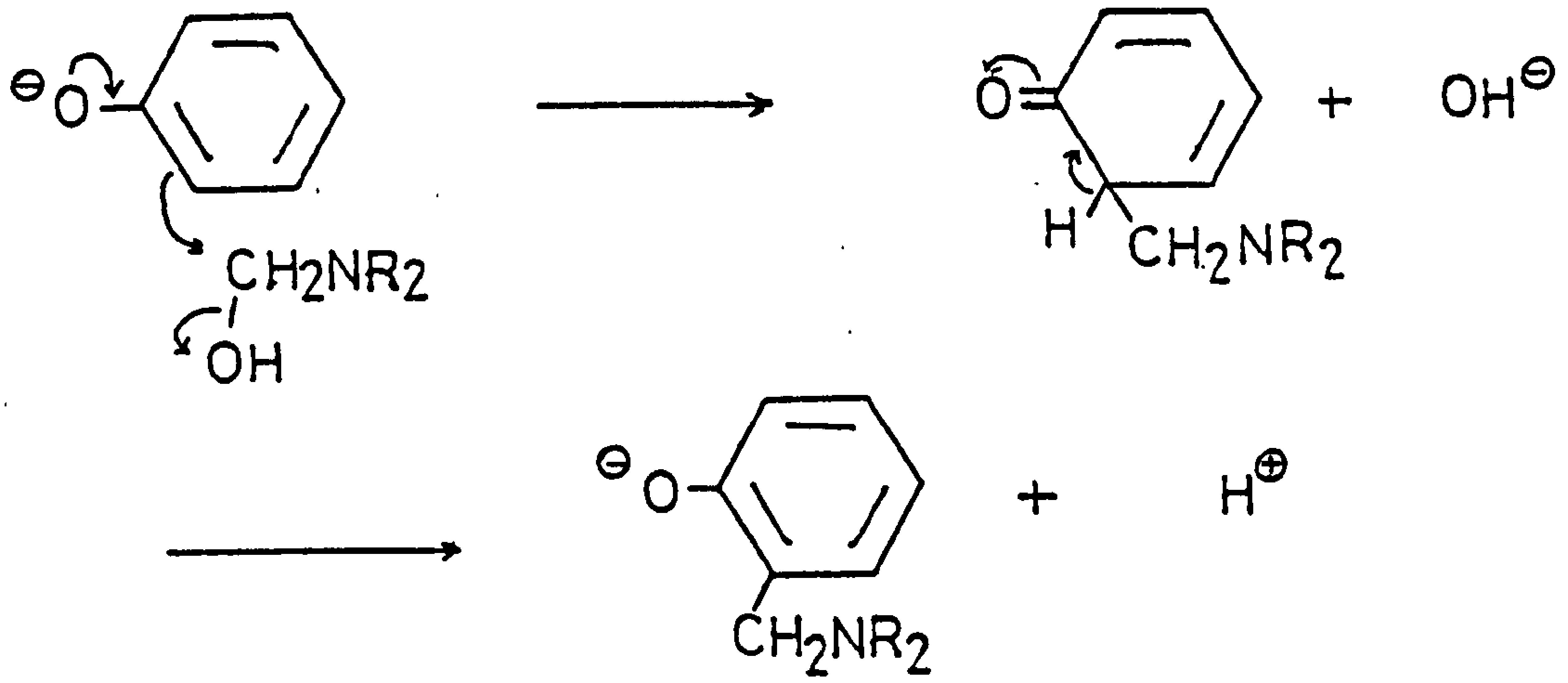


In the mechanistic and kinetic studies carried out in basic media by Burckhalter and co-workers,[27,35] the rate of condensation of formaldehyde and morpholine with 2,4-dimethylphenol was controlled by the formaldehyde if the concentration of formaldehyde was less than half the morpholine concentration. Conversely, the morpholine concentration was critical if it was less than twice the formaldehyde concentration. This suggests the participation of methylene-bis(N-morpholine) as an intermediate. A pure sample of this compound gave data kinetically indistinguishable from those of the formaldehyde and morpholine mixture. An explanation of the fact of preponderant ortho-substitution was offered by the formation of a quasi six membered chelate ring. The suggested reaction mechanism is outlined below:



Hydrogen bonding between the phenolic hydrogen and the basic nitrogen of the Mannich reagent, methylene-bis(N-morpholine) would be expected to precede the formation of the associated intermediate which would then bring the reactive methylene group into position for electrophilic attack on the aromatic ring in the o-position.

Miacque,[4] in a recent review outlined an alternative mechanism which is given below. The cleavage of -C-OH to give OH$^{\ominus}$ however seems very unlikely.



Both above mentioned mechanisms would be plausible in the cases of eugenol, para branched chain phenols as well as cardanol. In the main, the formation of N-hydroxymethylamine, N-methoxymethylamine and methylenediamine are considered to be the rate determining steps depending on the molar ratios involved. Further proof of this was given by Terenter et al[82] who reacted several methylenediamines with phenols to obtain Mannich bases in good yield.

When an alternative way for aminoalkylation was tried in the present work using N,N-dimethyl(methylene) ammonium chloride it was found to be unsuccessful with phenol and resorcinol while it worked extremely well with indole. This may be due to a different mechanism being involved with phenols compared with ketones, aldehydes and other compounds with reactive α-hydrogen. The phenols are usually aminoalkylated under basic conditions while the aldehydes and ketons are usually aminoalkylated under acid medium when aminomethyl carbonium ion is the reactive species.

2 NATURE OF COLOURED PRODUCTS IN THE MANNICH REACTION

To define the conditions for formation of coloured materials, the reaction conditions of the Mannich were simplified. At the outset it seemed unlikely that the colour arose from the Mannich bases since these always contain an insulating group, the methylene adjacent to the ring. It was possible that all the reactants were involved or only two. Accordingly, mixtures of phenol/formaldehyde, formaldehye/amine and amine/phenol were examined. Only in the last case were colours consistently formed, which qualitatively resembled those in the Mannich reaction itself. Results of model small scale experiments carried out to define, if possible, the structural conditions necessary for orange/red colour formation from amine/phenol interactions are summarized in the table:-

PHENOL	AMINE	OBSERVATIONS
Phenol	DETA	Intense yellow colour on heating mixture for 3hrs at 85°C.
Resorcinol	DETA	Deep red colour on heating for ½ hr. on steam bath.
5-Methylresorcinol	DETA	Produced deeper red colour than other resorcinols on heating for ½ hr.
4-Methylresorcinol	DETA	Deep red colour on heating for ½ hr.
2-Methylresorcinol	DETA	Gives red colour immediately on mixing reagents and darkens on heating.
Dist. CNSL	DETA	Produced red-orange colour on heating for ½ hr.

Phenol	Amine	Observation
Cardanol	DETA	Produced yellow colour on heating
Cardanol	DETA	Produced red-orange colour
2-Methylresorcinol	DETA	Produced red-orange colour
Resorcinol	Ethylenediamine	Produced orange colour (lighter colour than DETA/Resorcinol)
Resorcinol	Ethanolamine	Produced pink colour (lighter colour than DETA/Resorcinol).
Resorcinol	N-(2-Amino-ethyl)-ethanolamine.	Produced deep red colour (darker colour than DETA/Resorcinol.
Resorcinol	Hexamethylene diamine	Produced red-orange colour.

The orange-red colour may be initially formed due to molecular complex formation followed by autoxidation of the resorcinols under basic conditions. Giles, Rose and Vallance[83,84] reported formation of hydrogen bonded complexes of diethylamine-phenol (1:1), diethylamine-resorcinol (1:1, 1:2 solid colourless complex) and phenol-triethylamine (1:1), however no mention was made concerning the colours of the complexes.

A crystalline product was isolated by Potapov et al.[85], from a reaction of equimolar amounts of resorcinol and hexamethylenetetramine in aqueous solution at room temperature. The composition of the crystalline product corresponded to an addition compound. The IR spectrum showed new bands compared with those in the reactants and the product had an identical U.V. spectrum to the mixture of the reactants.

2a Oxidation of Resorcinol and its Derivatives

Resorcinol has been reported[86] to develop brown-red colour on storage for 3.5 months while phenol showed yellow-brown colouration under the same conditions Quantitative data for the rate of oxidation of several phenols with atmospheric oxygen in aqueous alcoholic alkali hydroxide (fig 1)[87] show that monohydric phenols and resorcinol react much more slowly than hydroquinone and pyrocatechol and that the reaction rate of phenol increases with increasing alkyl substitution.

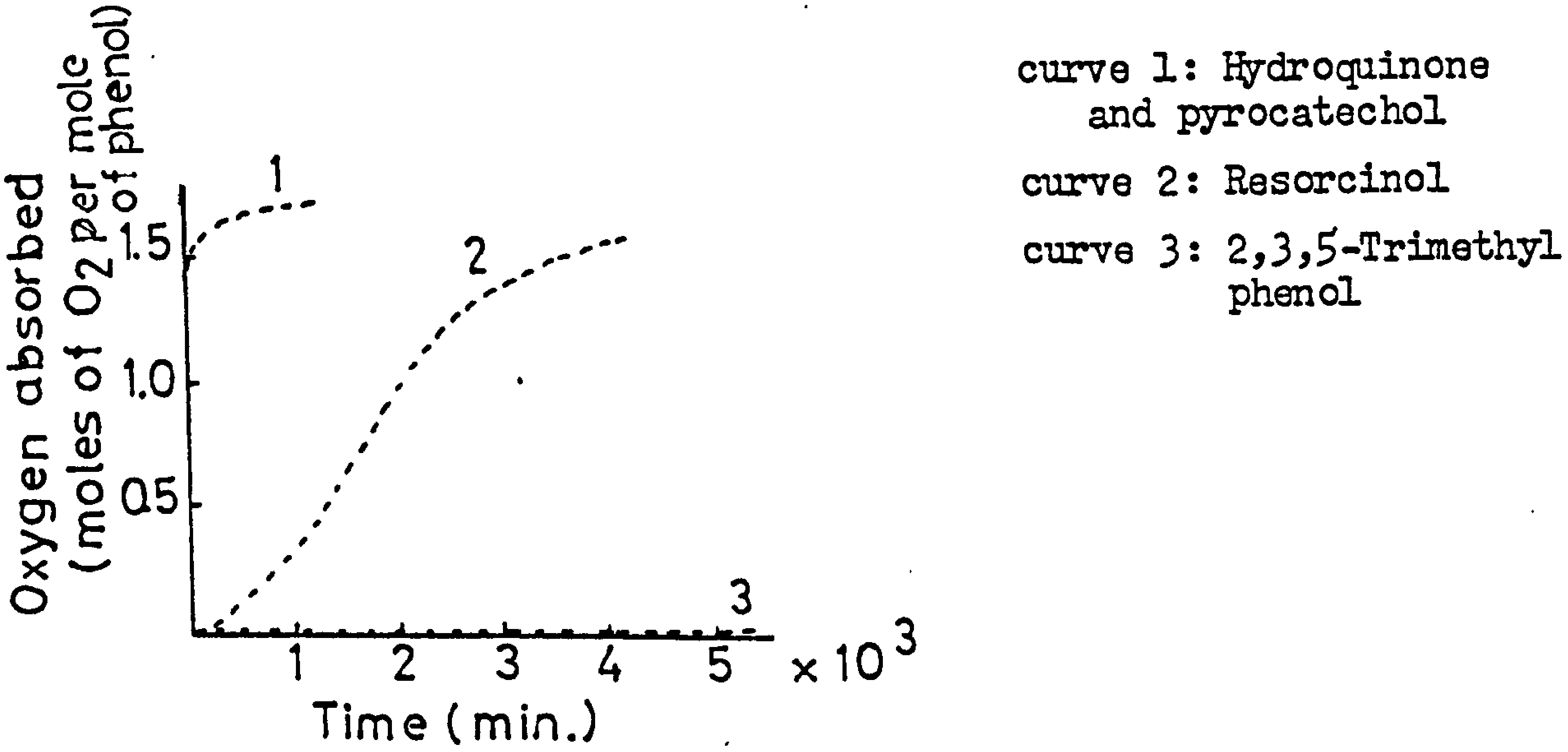
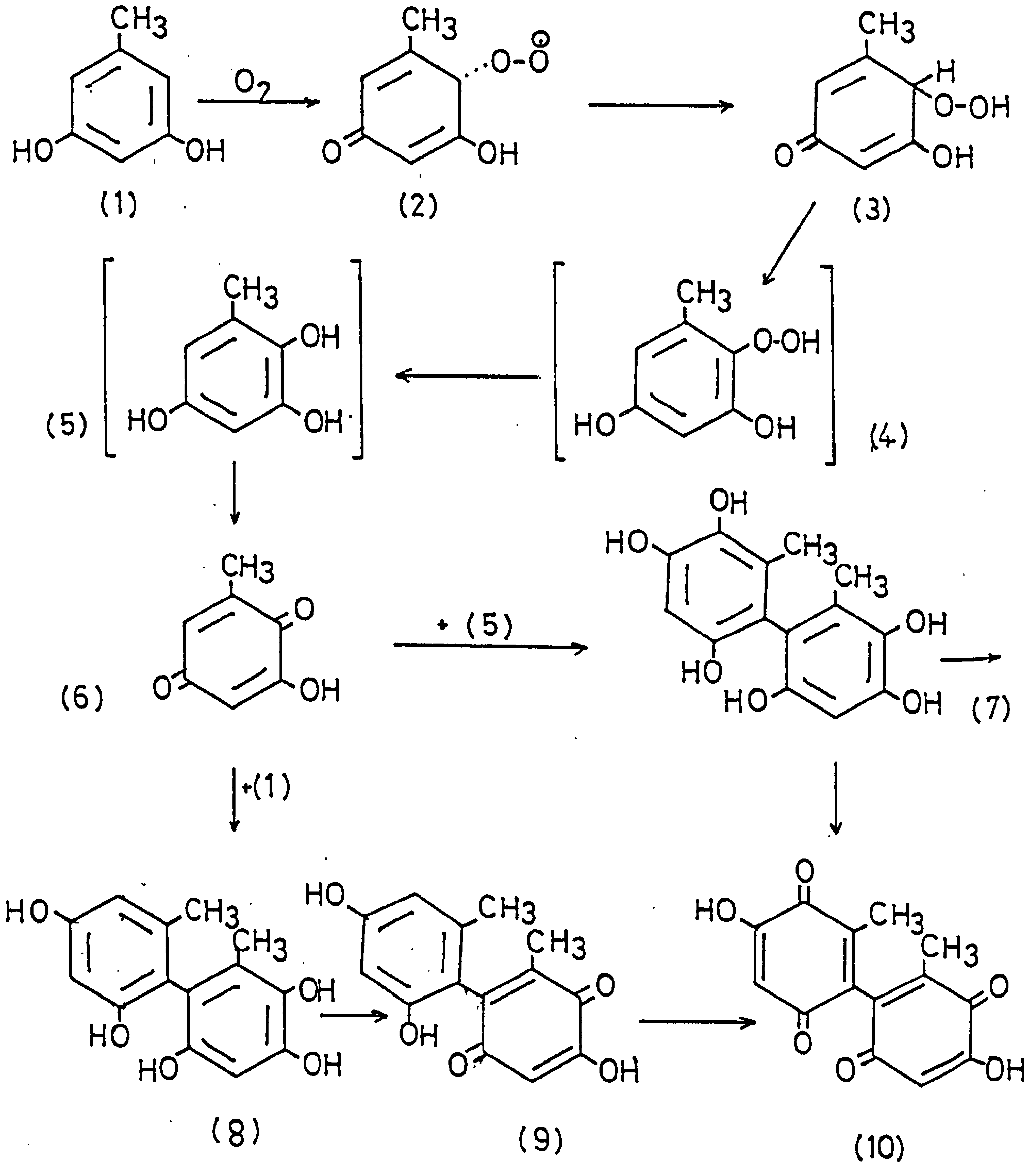


Fig 1 - Rate of autoxidation of phenols in methanol/water (1:1) at pH 13

The oxidation of resorcinol derivatives has been studied for a long time in connection with the formation of orceine and litmus dyes from orcinol. The structure of these products and the mechanism of their formation, however, have only recently been elucidated.[88]

Since resorcinol cannot give rise to o- or p-quinonoid products on removal of two electrons, its behaviour in the first oxidation step is that of a monophenol whose oxidation potential is lowered by the second hydroxy group.

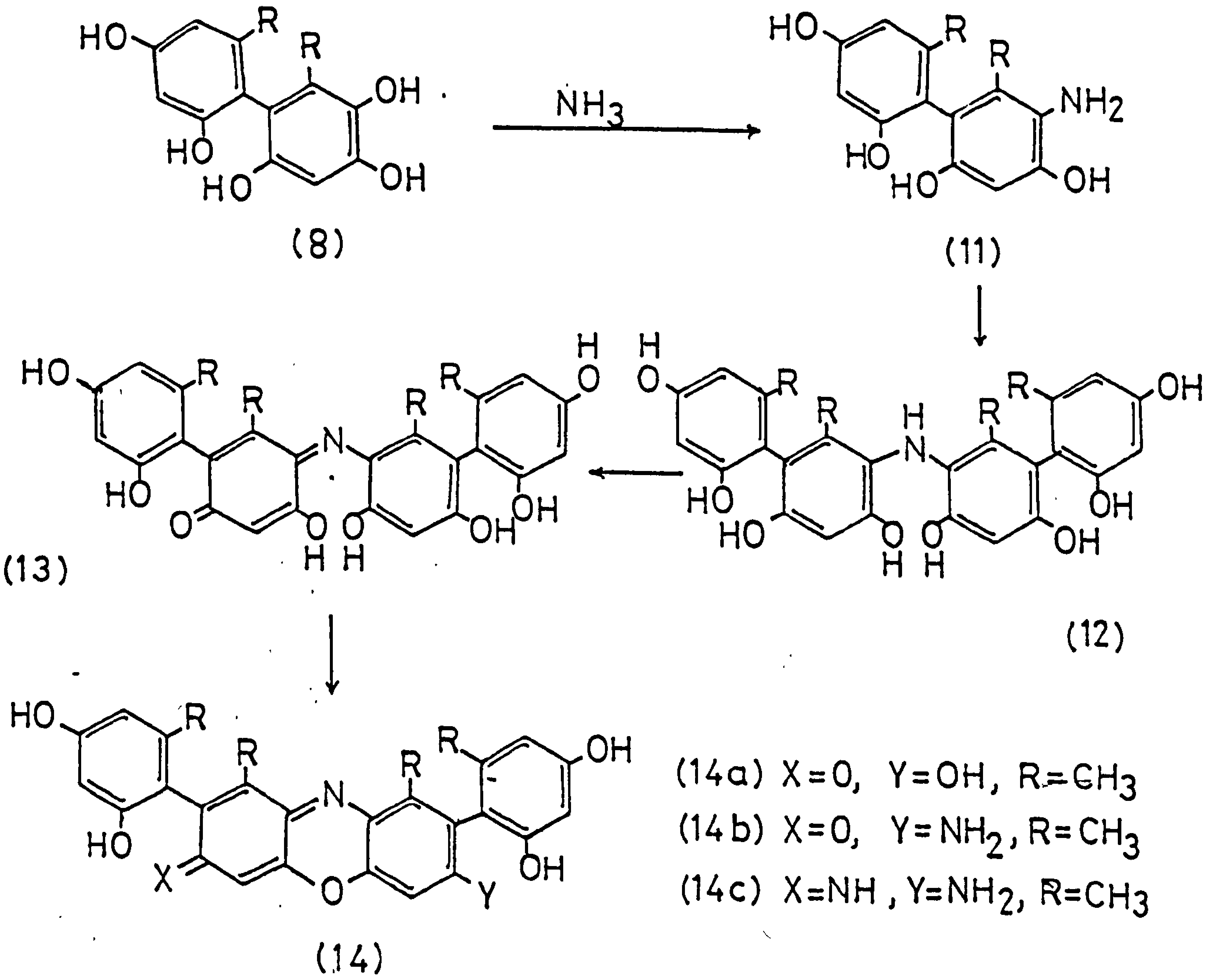
Oxidation of orcinol (1) with oxygen has been reported[89] to give a mixture of more than 50% of the dimeric monoquinone (9) plus the dimeric diquinone (10). A reaction scheme showing the formation of the two quinones is shown below:



The occurence of the hydroperoxide intermediate (3) has not been demonstrated directly but an analogous product from oxidation of 4,6-di-t-butylresorcinol was isolated. Whether the intermediates (4) and (5) were also formed in the case of orcinol has not been determined. Similarly the formation of coloured polymeric products from cardol can be envisaged (see Appendix 3).

2b Reaction of Resorcinols in the presence of Ammonia

Autoxidation of orcinol in the presence of ammonia affords orceine and litmus dyes. The former consists of mixtures of 7-hydroxy and 7-aminophenoxazones of type (14) and (18).[88]

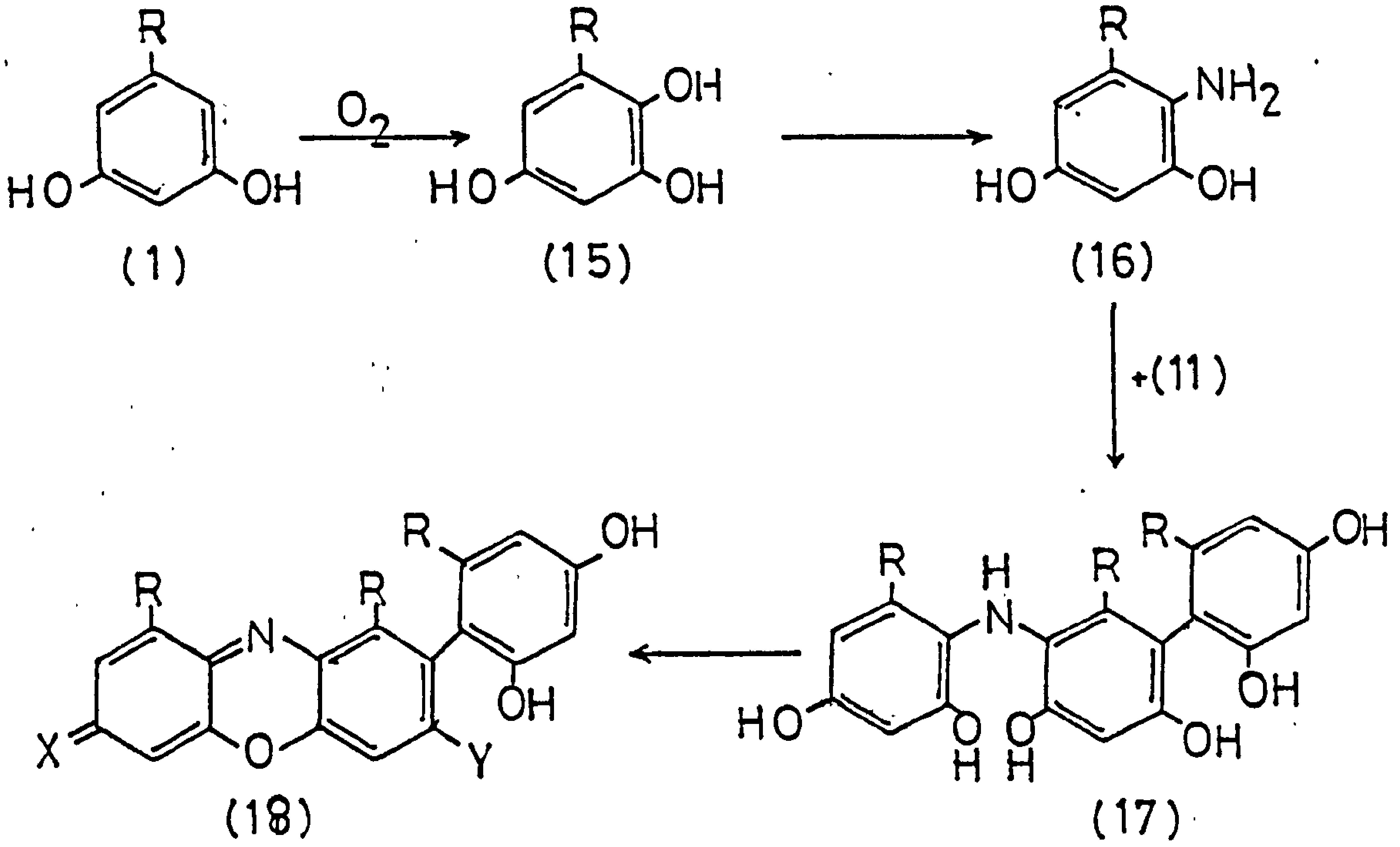


(8) (11) (12) (13) (14)

(14a) $X=O$, $Y=OH$, $R=CH_3$

(14b) $X=O$, $Y=NH_2$, $R=CH_3$

(14c) $X=NH$, $Y=NH_2$, $R=CH_3$

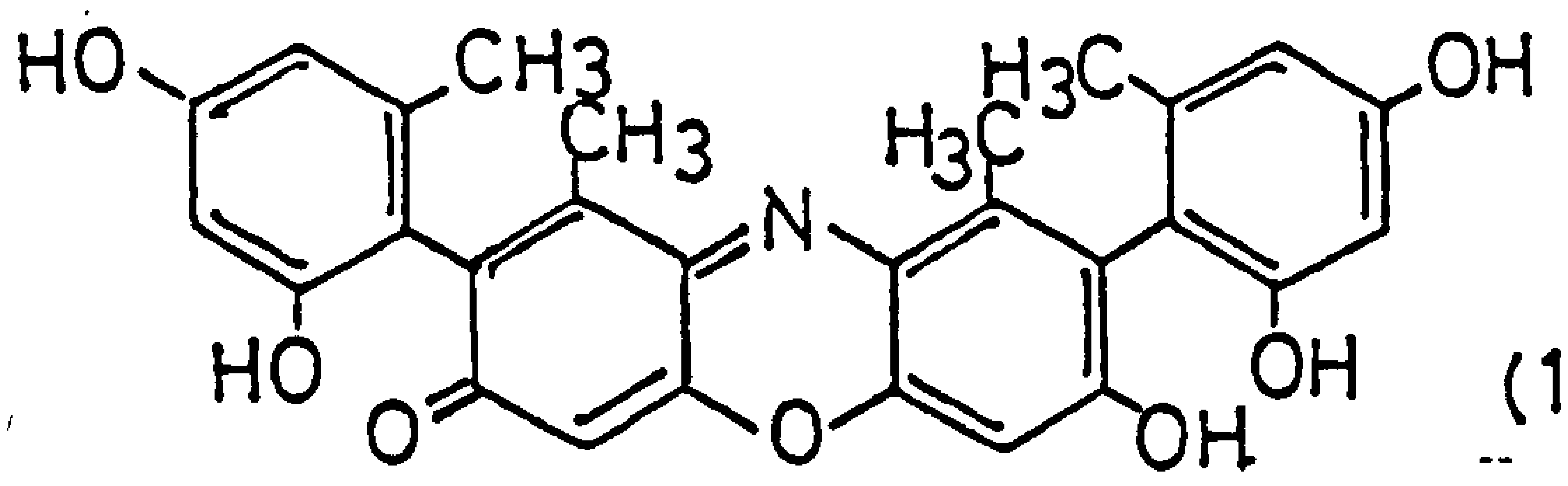


(18a) X=O, Y=OH, R=CH_3
(18b) X=O, Y=NH_2, R=CH_3

Ammonia participates in the autoxidation of resorcinol derivatives by replacing a hydroxy group of the hydroxyhydroquinone intermediate (8), thus affording (11) and (12). After the diphenylamine derivative (12) has been oxidised to the indophenol (13), ring closure to the orceine dye (14) can take place. The autoxidation of resorcinol[90] and 2,5-dimethylresorcinol[91] proceeds analogously.

To compare the products from resorcinol and orcinol with ammonia with those from the methylamine, the former were used as model compounds for the examination of the application of different spectroscopic and chromatographic techniques.

Two phenoxazines with similar R_f values were isolated from orcinol/ammonia oxidation products during the present study. These compounds were silylated and examined by mass spectroscopy. The samples were silylated to try and enhance the molecular ion. Major ions of mass 846 and 830 were obtained for the two compounds. The mass spectrum of the compound with mass 846 had other peaks at 830, 757, 73 and 75. The peak at 757 can be attributed to the loss of - O Si $(CH_3)_3$ and the peaks at 73 and 75 are due to -Si $(CH_3)_3$. The only possible phenoxazone (from those mentioned above) which fits the mass spectral data is the trimethylsilyl derivative of compound 14a.



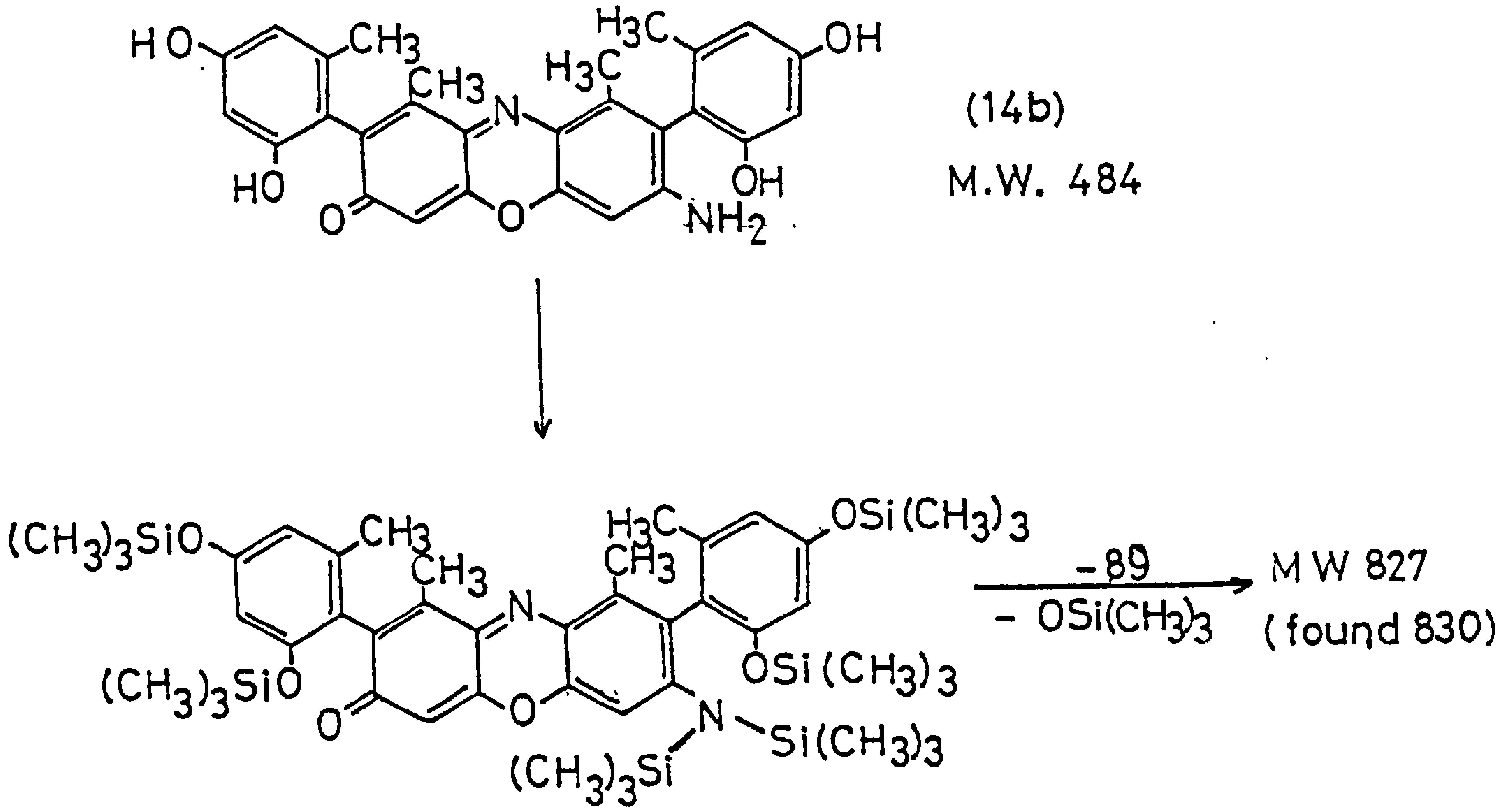
(14a)

M.W. 485

$$\downarrow + 5\ [-Si(CH_3)_3] - 5H$$

M.W. 845

The mass of 830 with the second compound may be explained by the following scheme:


(14b)
M.W. 484

Although the major peaks were at 830, 73 and 75 there were other peaks at 919, 847 and at 758. The peak at 847 would be due to the presence of the trimethylsilyl derivative of 7- hydroxyphenoxazone (14a) impurity and the peak at 758 would be due to loss of - O Si $(CH_3)_3$ grouping from (14a). The possibilities of small errors due to miscounting cannot be excluded with masses in the range being examined.

2c Reaction of Resorcinols with Methylamine*

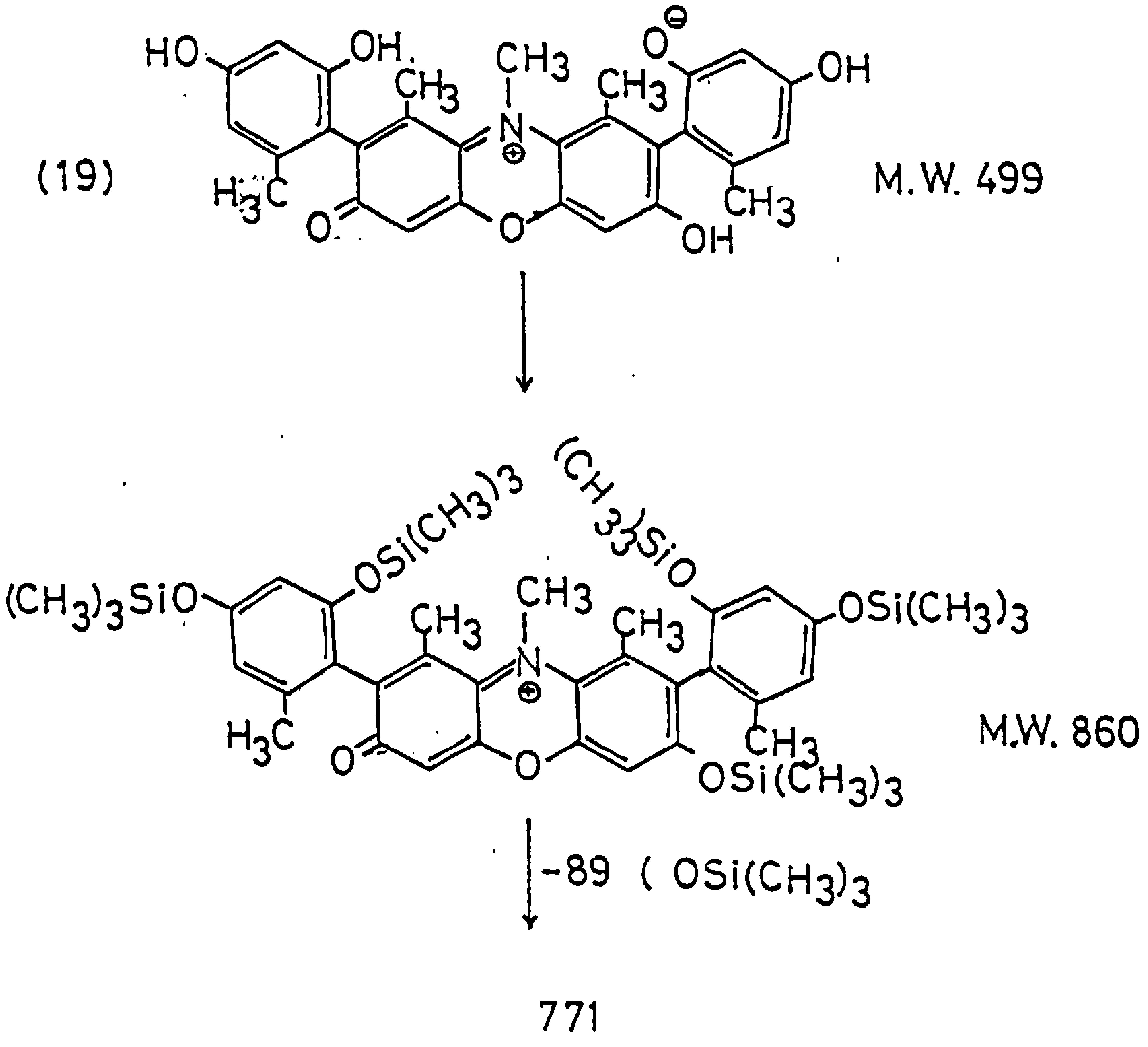
The autoxidation product of orcinol with methylamine produced a similar reaction mixture to that of orcinol/ammonia with similar litmus-like properties. Only one pure product was isolated from the mixture. This was examined by ^1H NMR and the trimethysilyl derivative by mass spectroscopy.

---

* The reaction of organic bases has remained apparently uninvestigated until the present work.

The mass spectrum showed major peaks at masses 860, 771, 73, 75, as well as two peaks of doubly charged ions at masses 429 and 430. Upon silylation with bis-(trimethylsilyl)acetamide the negative charge is removed (acetamide may be the new counter ion) and upon electron removal, a doubly charged positive ion can result. A similar fragmentation pattern as that of orcinol/ammonia material i.e. the peak due to loss of one - OSi $(CH_3)_3$ group and peaks at 73 and 75 due to the - Si $(CH_3)_3$ group was shown. A similar molecular weight to that of compounds (14 a) and (14 b) is apparent and the structure of the unknown compound appears likely to be as shown below (19). The negative charge could be on any one of the oxygen atoms.

(19)



The structure (19) also accounts for the several types of CH_3-C bonds in the NMR spectrum. The aromatic protons would be expected to be similar.

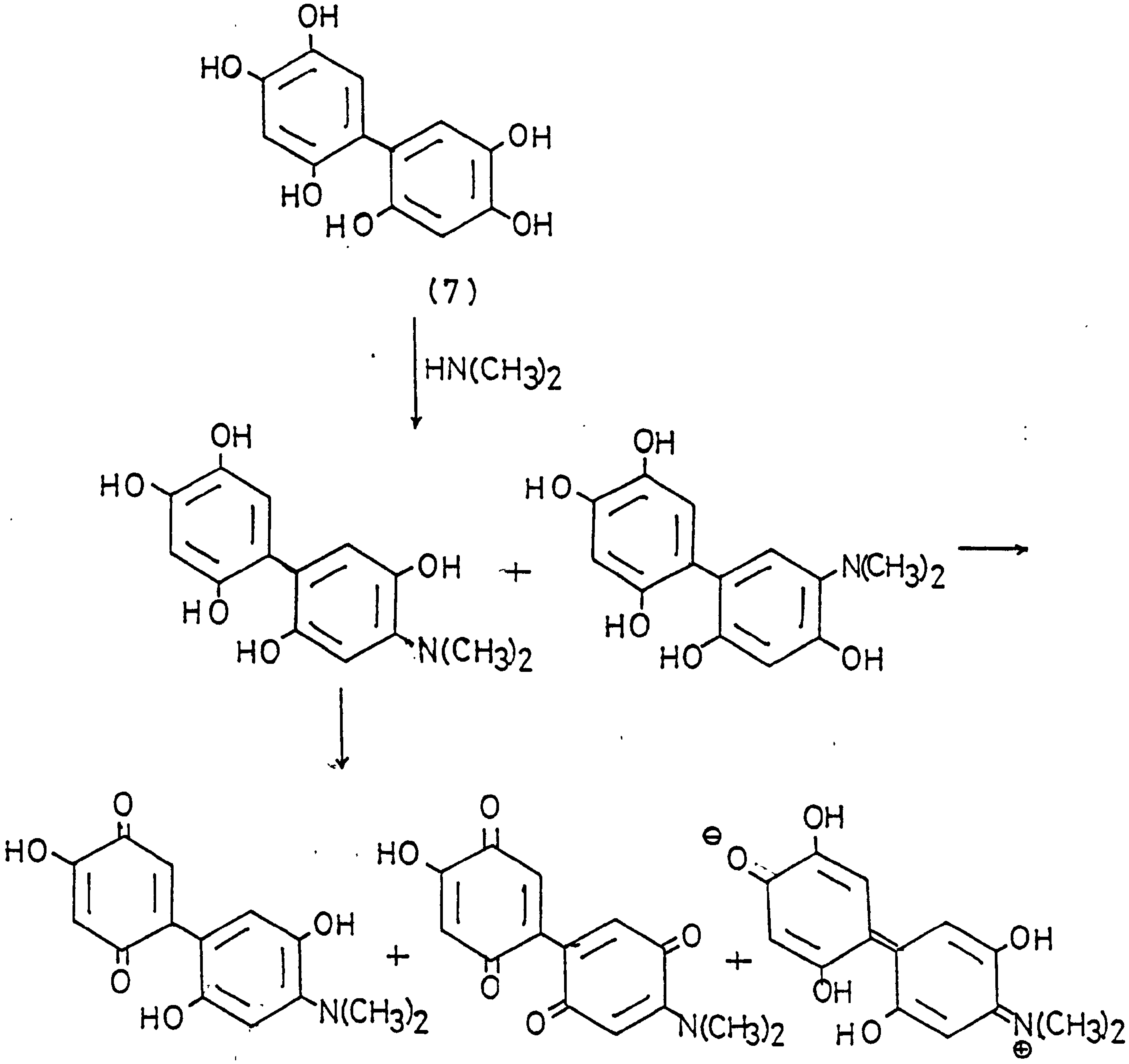
The reaction mixture from resorcinol/methylamine produced red products but it was not possible to isolate any component due to the complexity of the mixture and the small quantities involved.

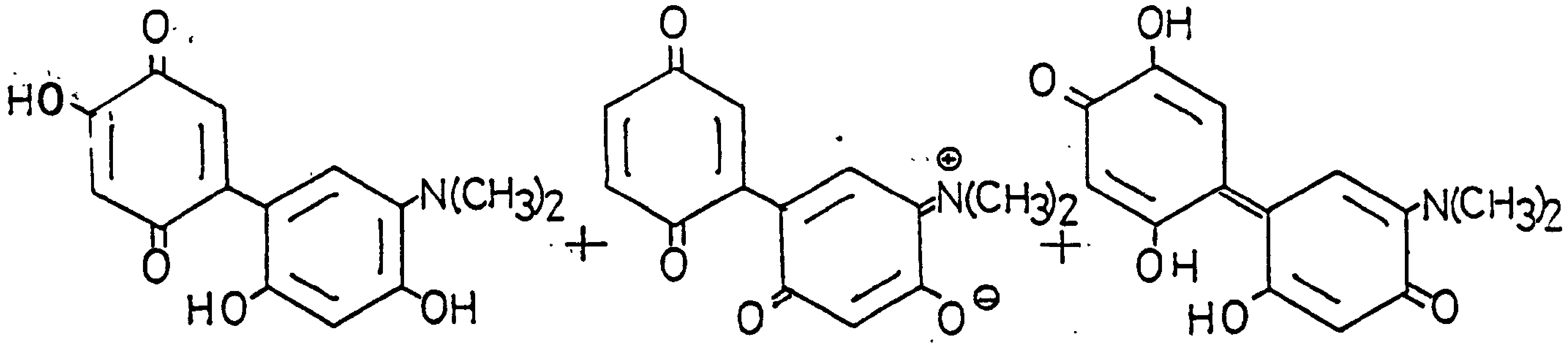
2d Reaction of Resorcinols with Dimethylamine and Diethylamine

From a red-coloured concentrate (obtained by heating resorcinol and aqueous dimethylamine followed by removal of the unreacted resorcinol) three products, a red solid which showed yellow fluorescence in solution, a blue solid and a purple solid were isolated.

The yellow fluorescent material had a similar U.V. spectrum to that of rhodamine 6G. (λ_{max} for Rhodamine 6G at 526, 494, 346.5, 294, 277, 248, 223, 205 nm and that for the unknown at 512, 482, 324, 285, 243, 210 nm). The elemental analysis for the unknown showed the following composition:- C 52.50, H 4.845, N 2.836, a repeat analysis showed C 48.73, H 5.02, and N 3.35%. A corresponding reference analysis for Rhodamine 6G was found to be, C 67.21, H, 6.41 and N 5.40 % (expected C 69.26, H 5.99 and N 6.22%). The difference between the original and the repeat analysis showed a considerable difference which may be due to the high melting point ($>300^{\circ}$) and hence the difficulty in fully combusting the unknown compound. This may also explain the rather low figure found for the carbon analysis. The mass spectrum showed the molecular weight to be 283. This mass of 283 could be made up from two molecules of resorcinol, one molecule of dimethylamine and one molecule of water which would give a molecular formula of $C_{14}H_{21}NO_5$ (283). This could however be fortuitous.

However, reaction schemes were devised to account for the structure of this fluorescent material as well as the other large number of products formed as shown by TLC.

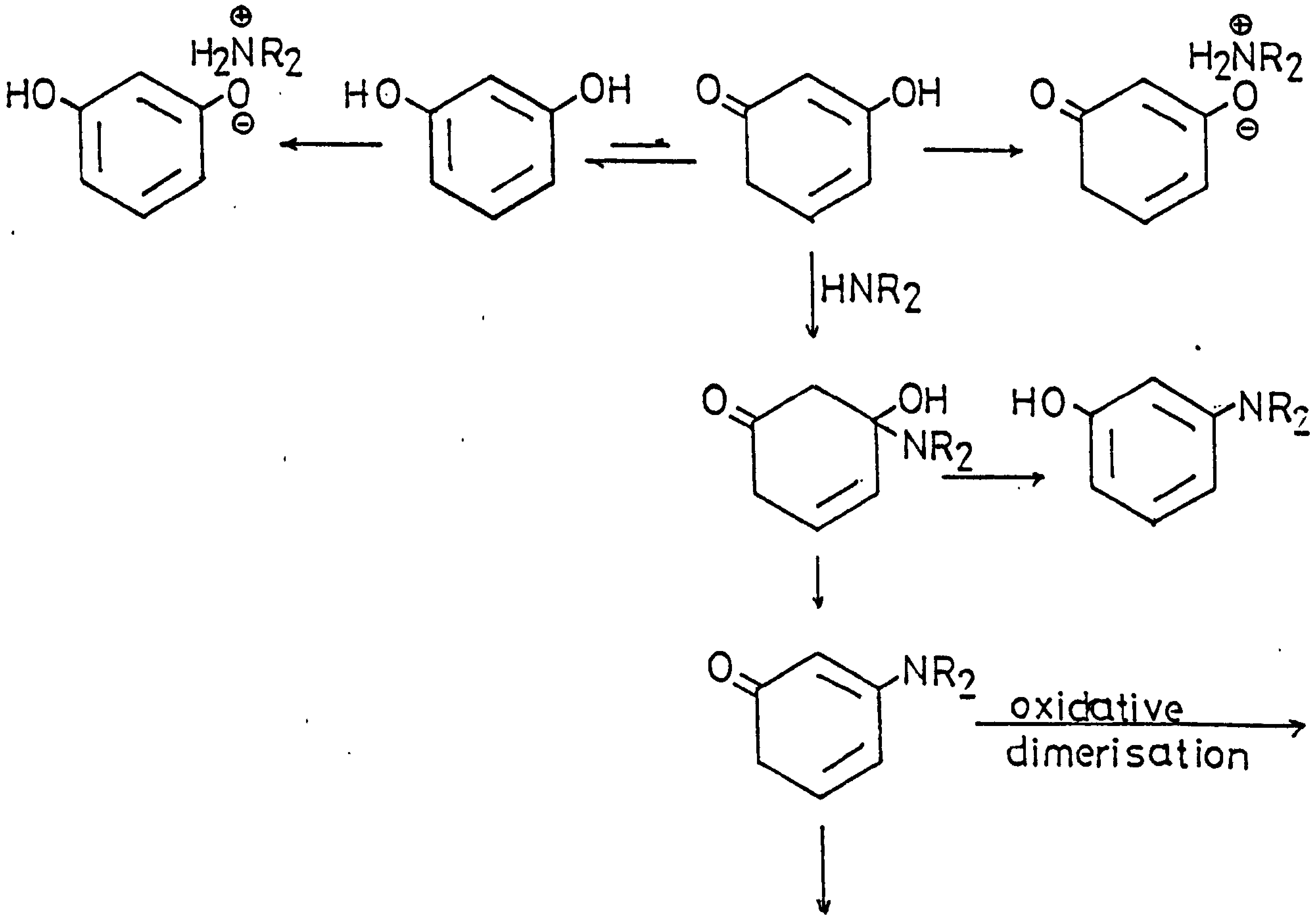

(7)

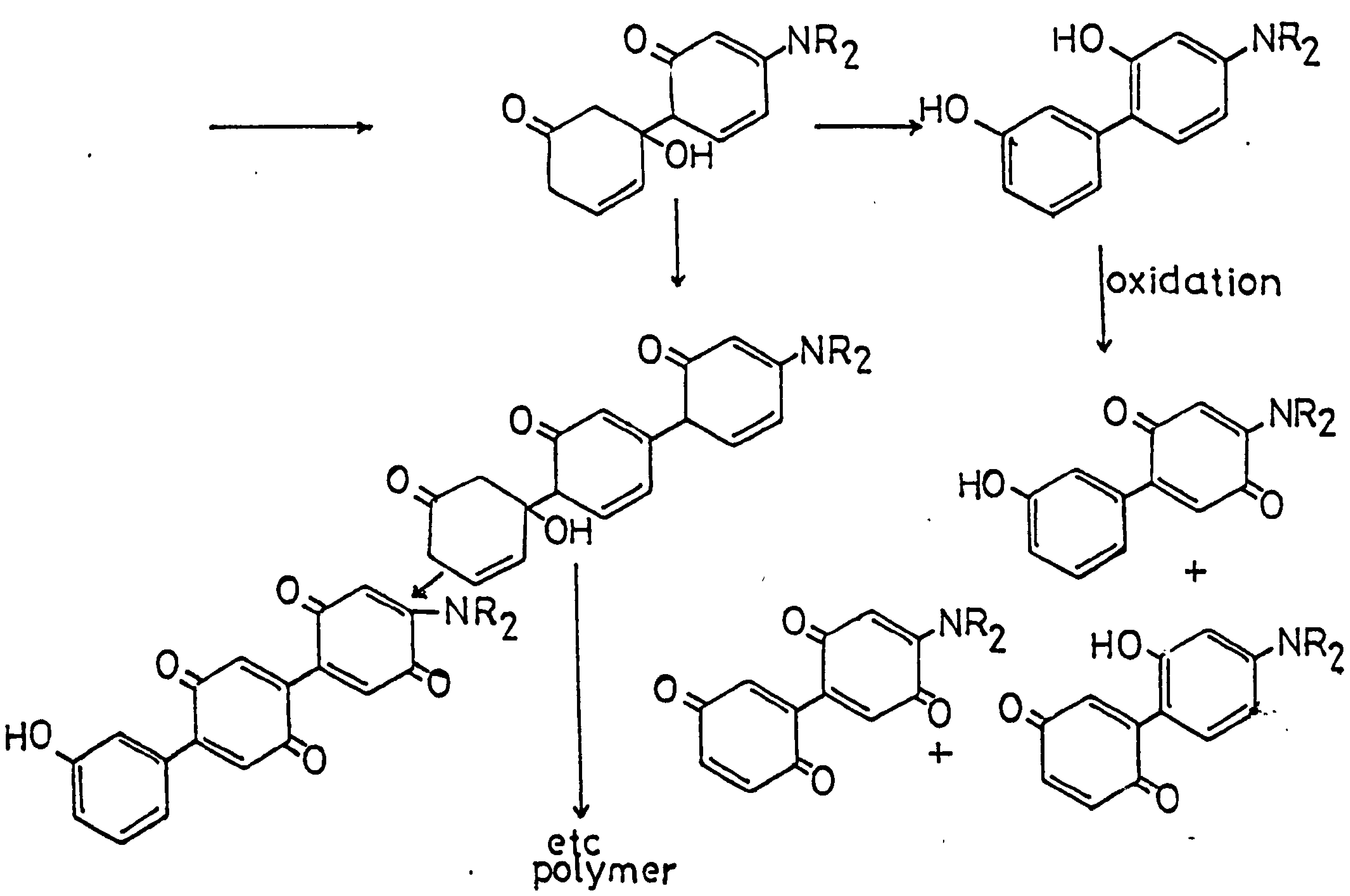


It was believed possible that the fluorescent compound would be related to one of the structures above.

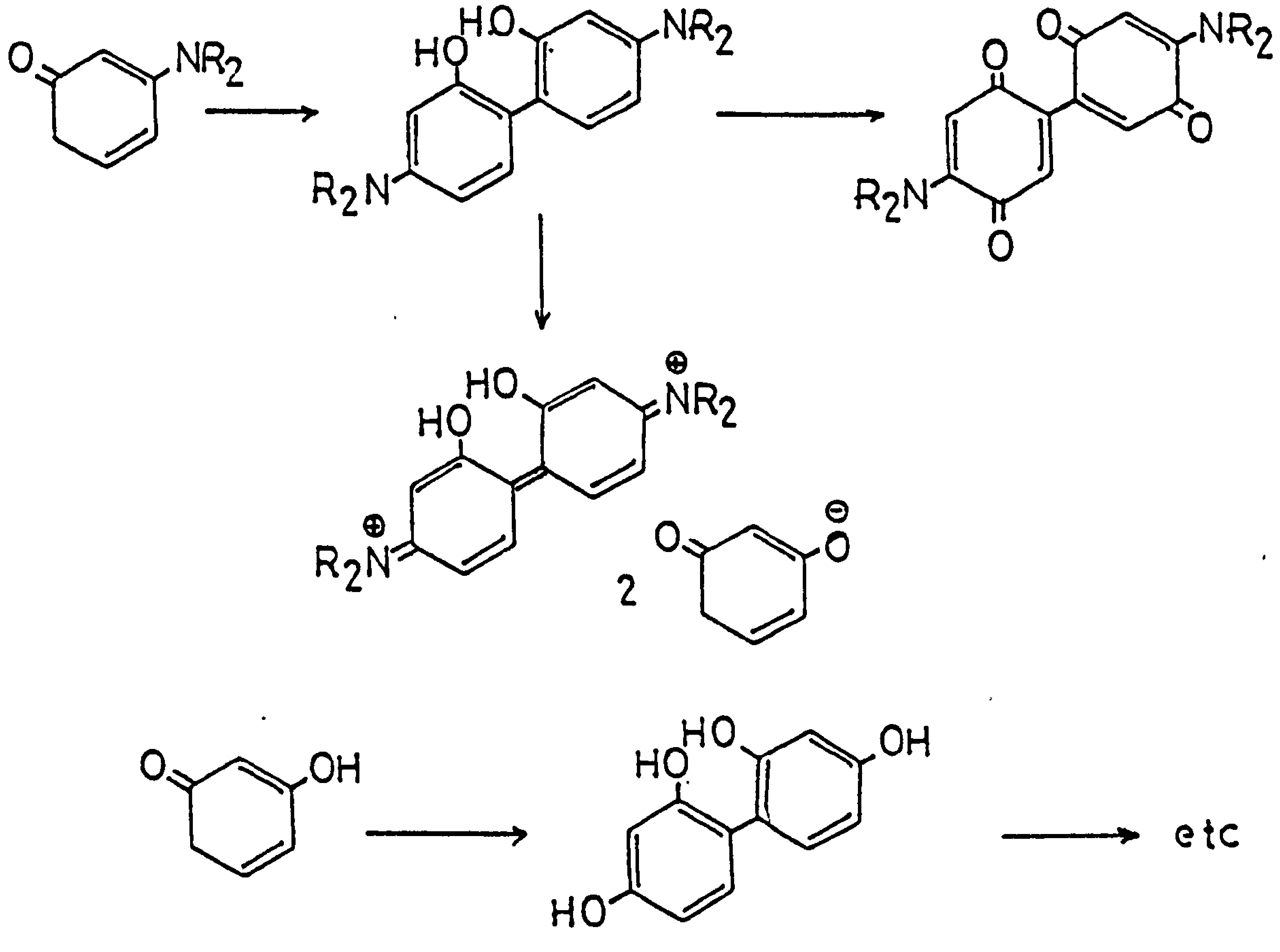
It was also thought conceivable that a large number of products, similar to those given above would be formed by the reaction of the ketoform of resorcinol to give a series of oxidative dimerisation, additive reactions, and possibly Diels – Alder reactions.

Dimerisation, Trimerisation reactions

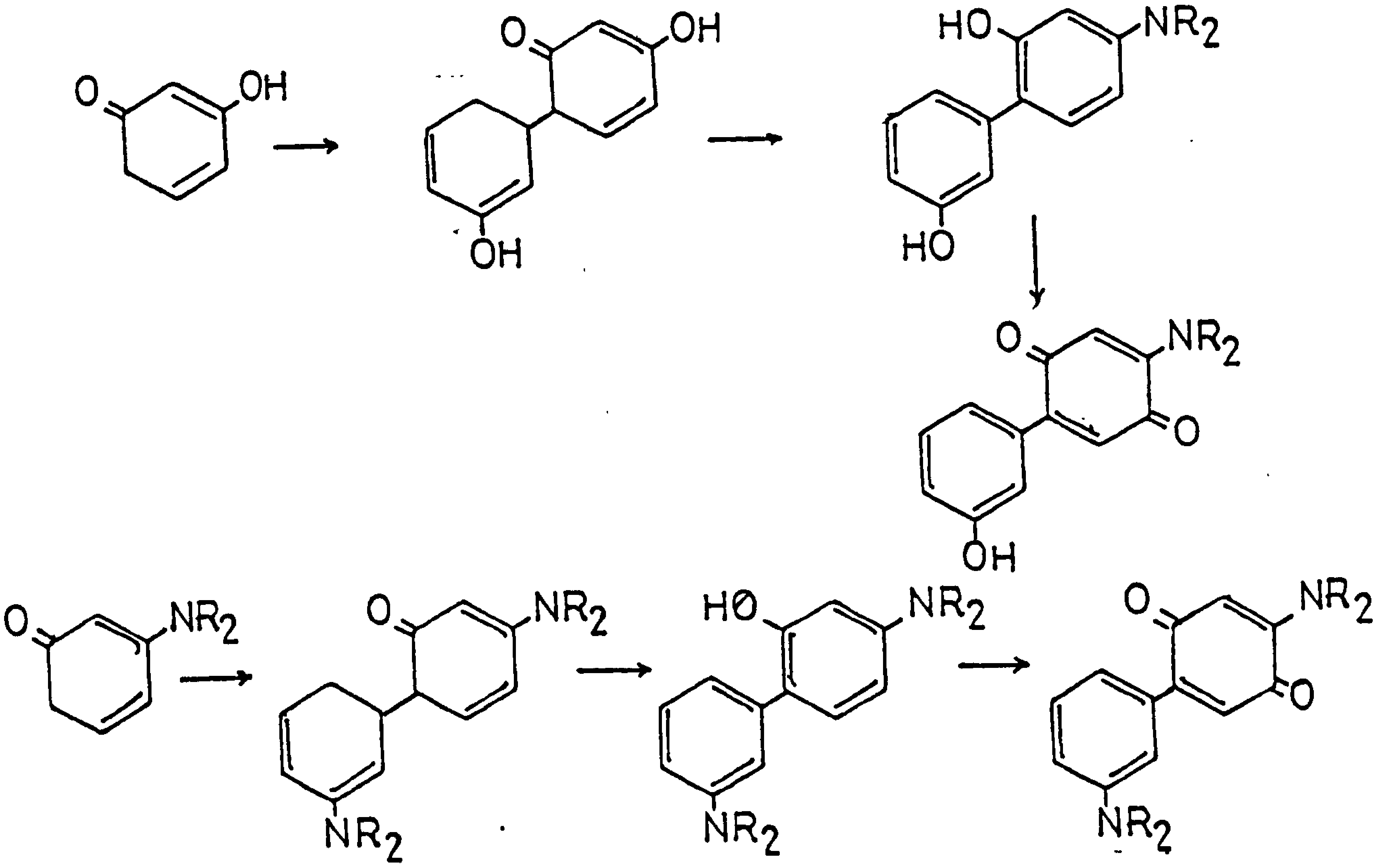




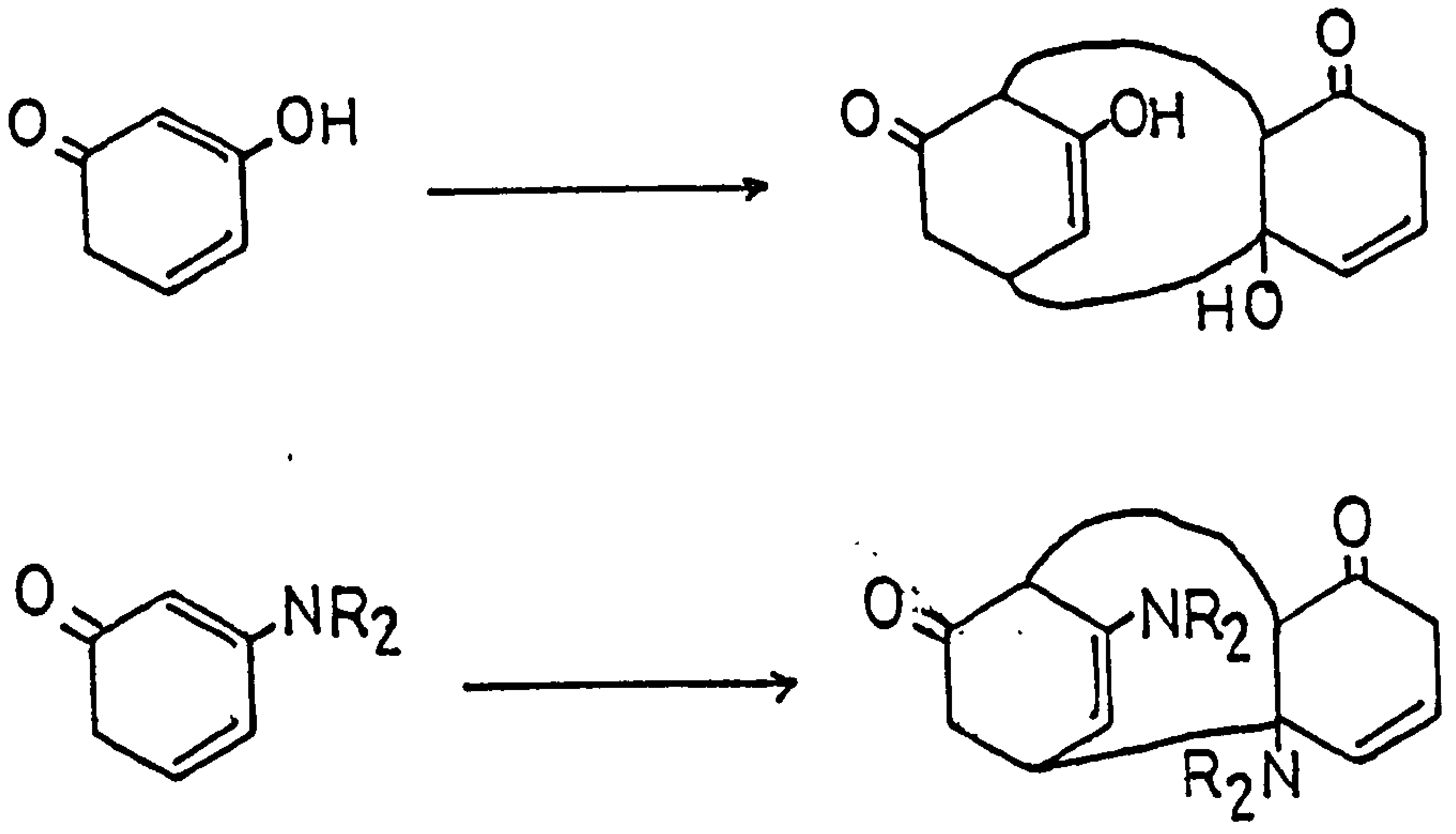
Oxidative dimerisation



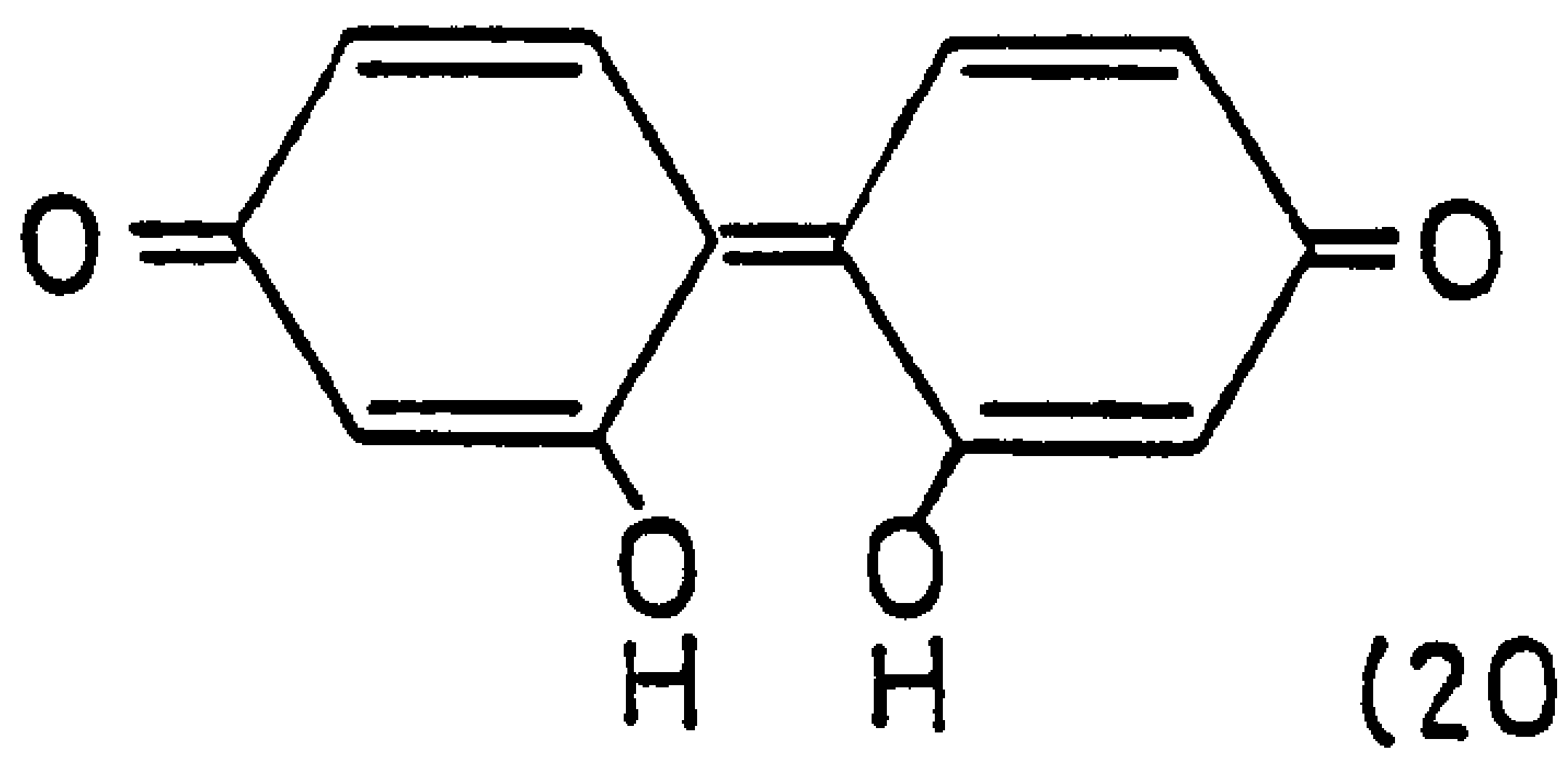
Claisen condensation



Diels-Alder products



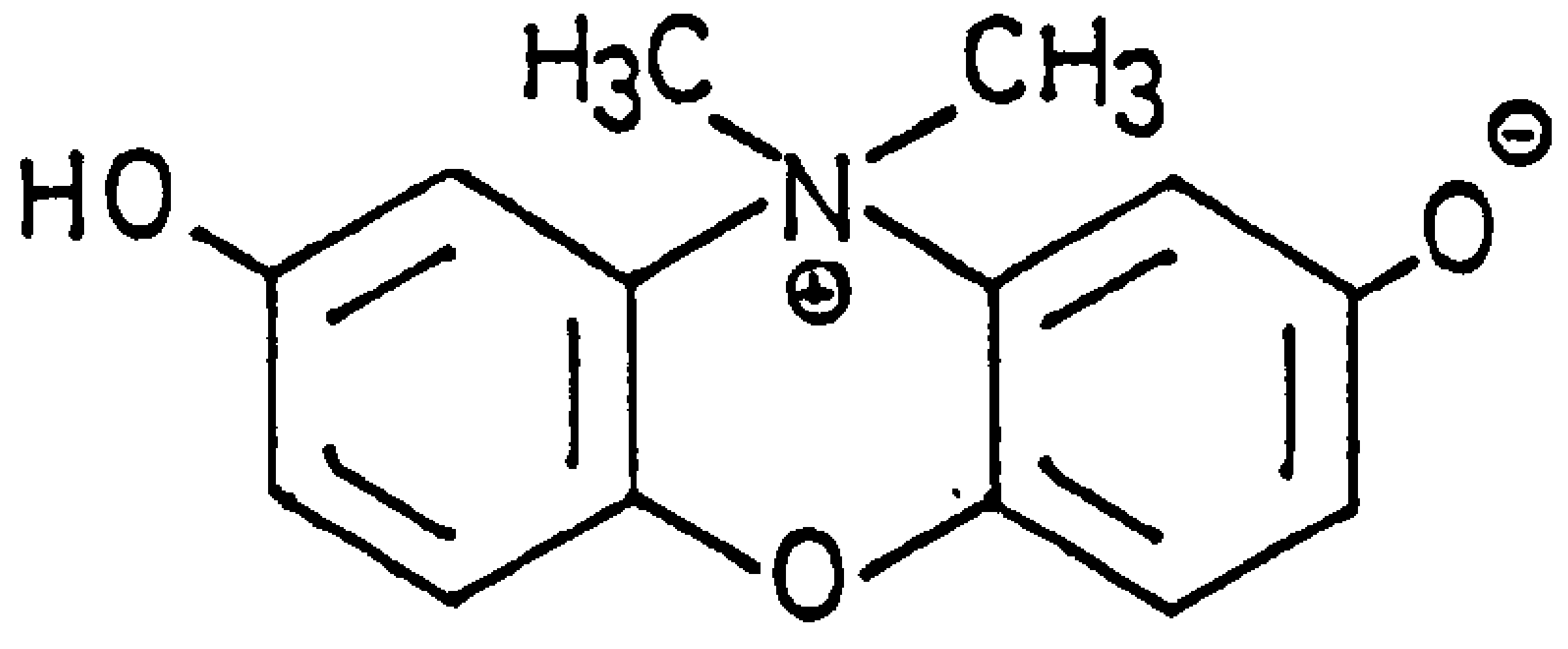
In fact such products as (20)^{92} have been isolated from oxidation of resorcinol with barium hydroxide and atmospheric oxygen



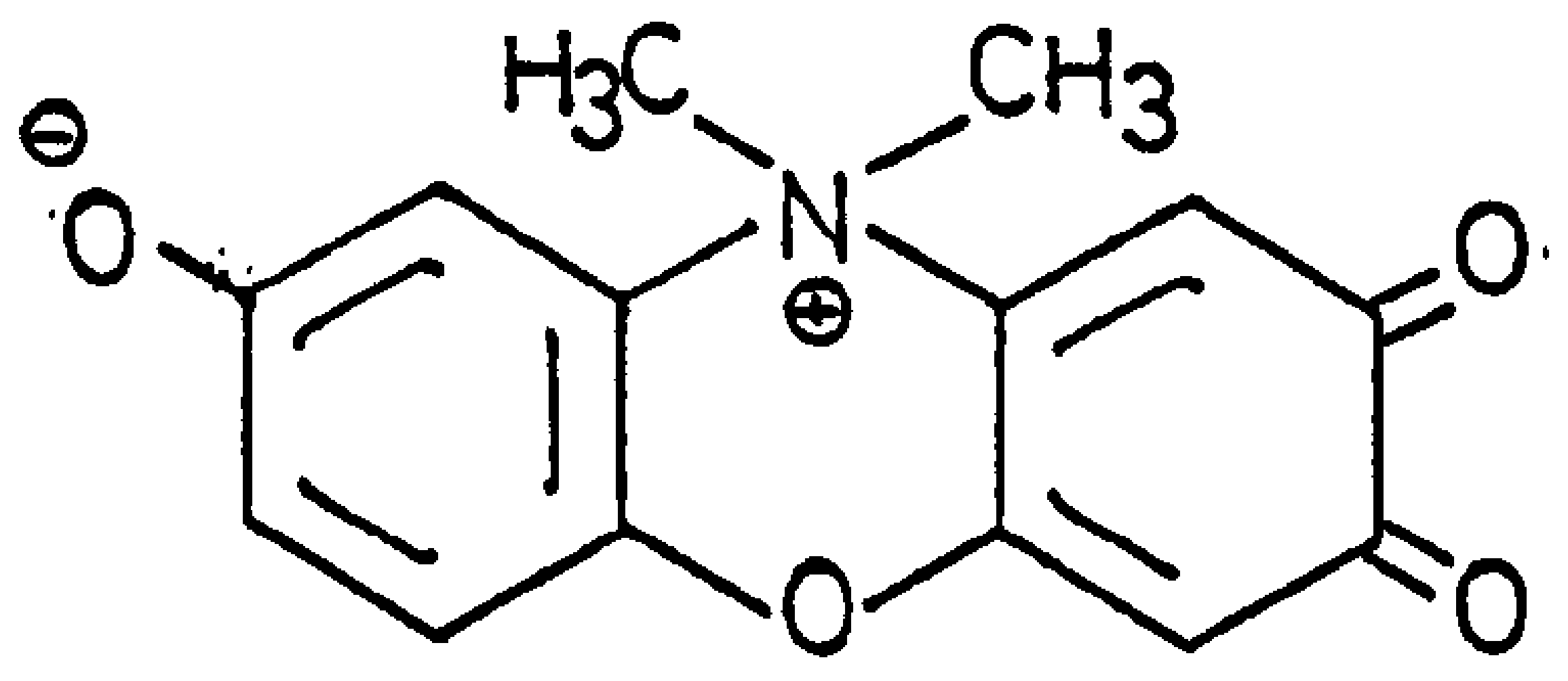
(20)

The difficulty with these various formulations is that the IR and ^{1}H NMR spectra of the yellow fluorescent material did not match the various groups in the speculative structures (see later).

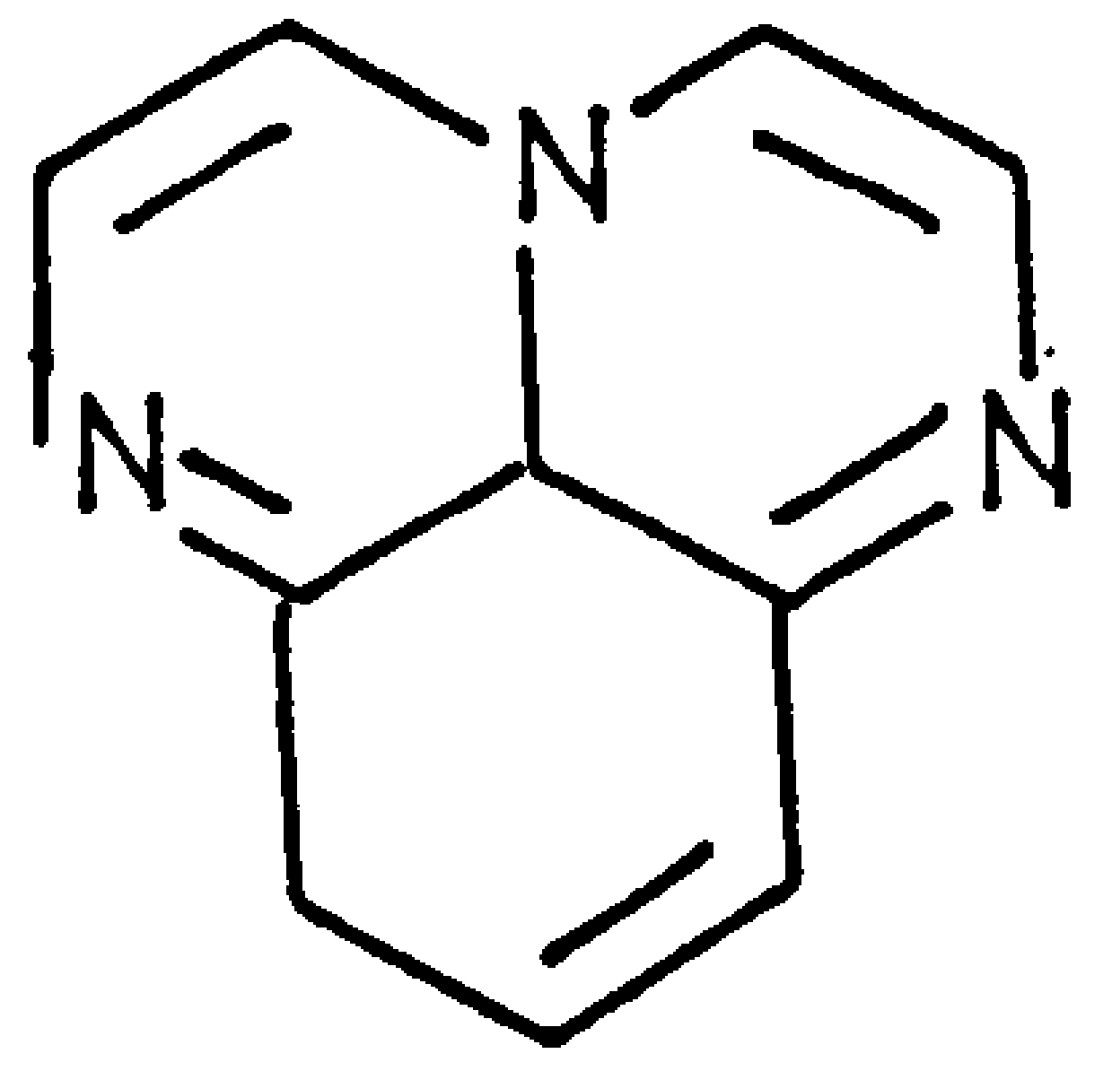
Further speculative structures in the case of resorcinol/dimethylamine such as the dimethyl cationic structures shown seemed unlikely to possess sufficient conjugation to explain the deep colour and pronounced fluorescence of the product isolated.

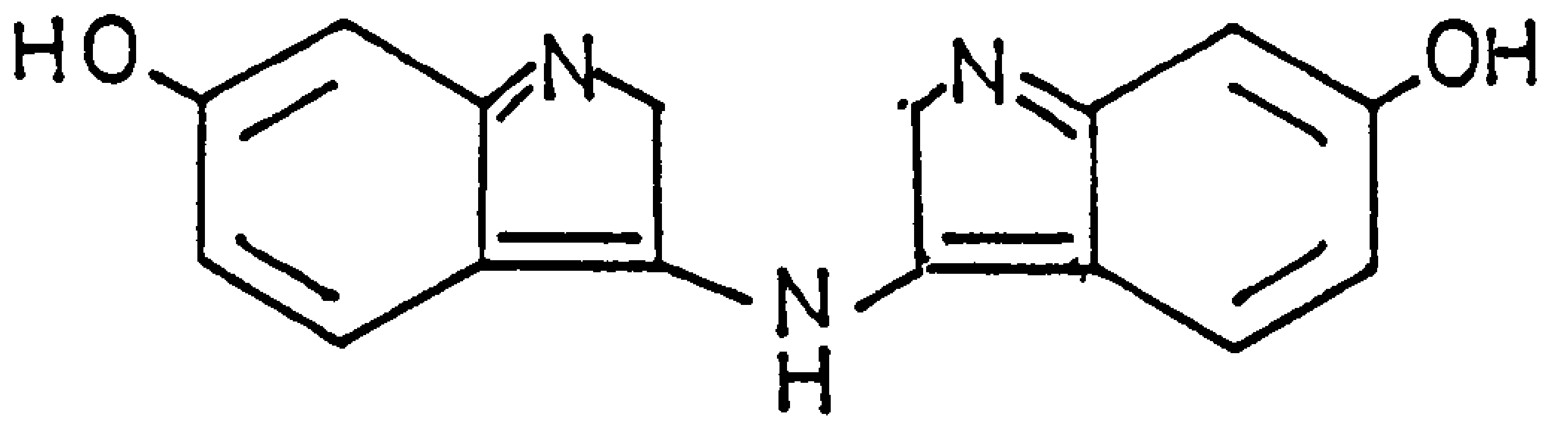


or



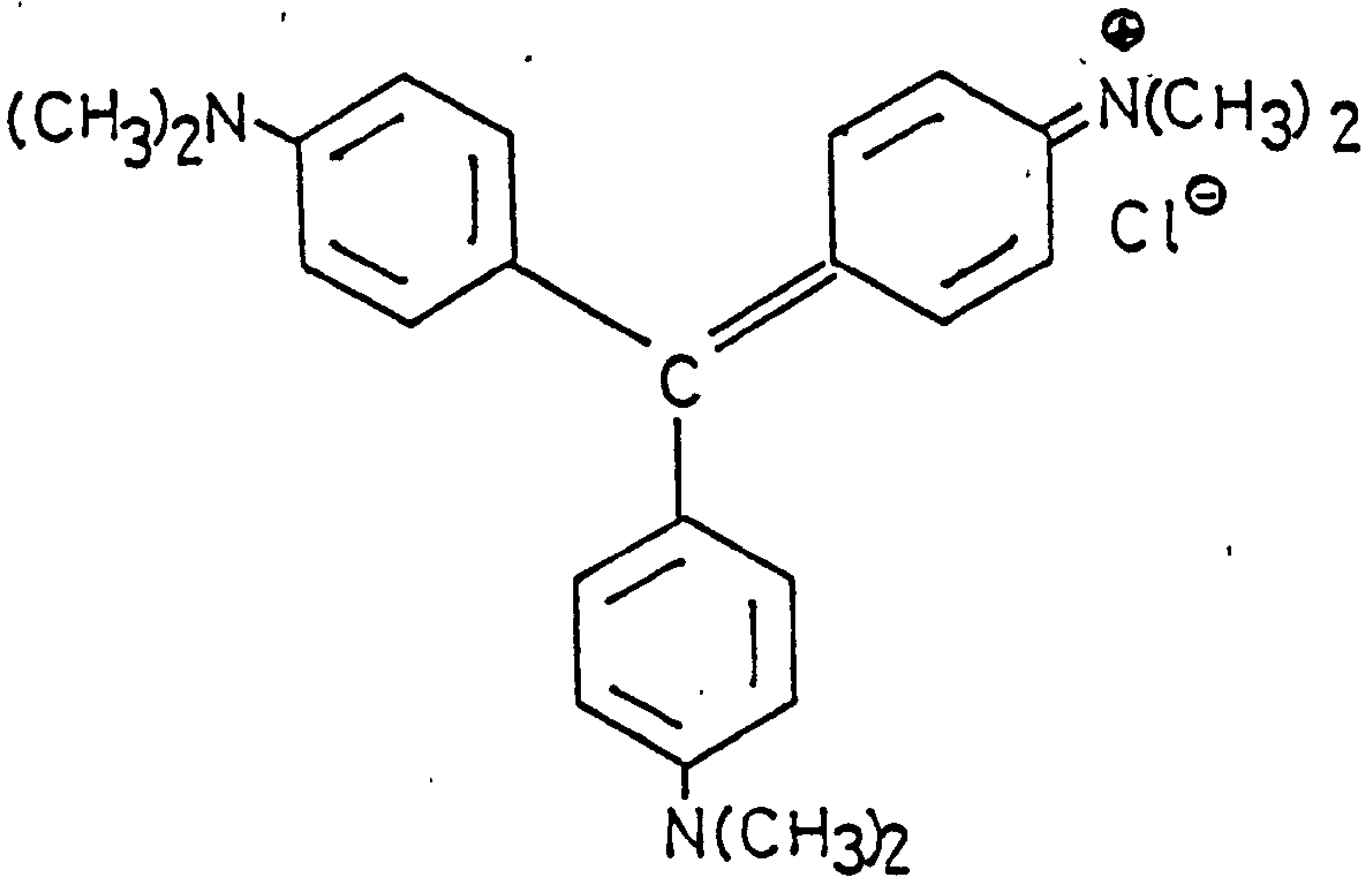
In the case of diethylanetriamine/resorcinol products the formation of unusual hetrocyclic seemed possible but they were again unlikely to explain all the facts.



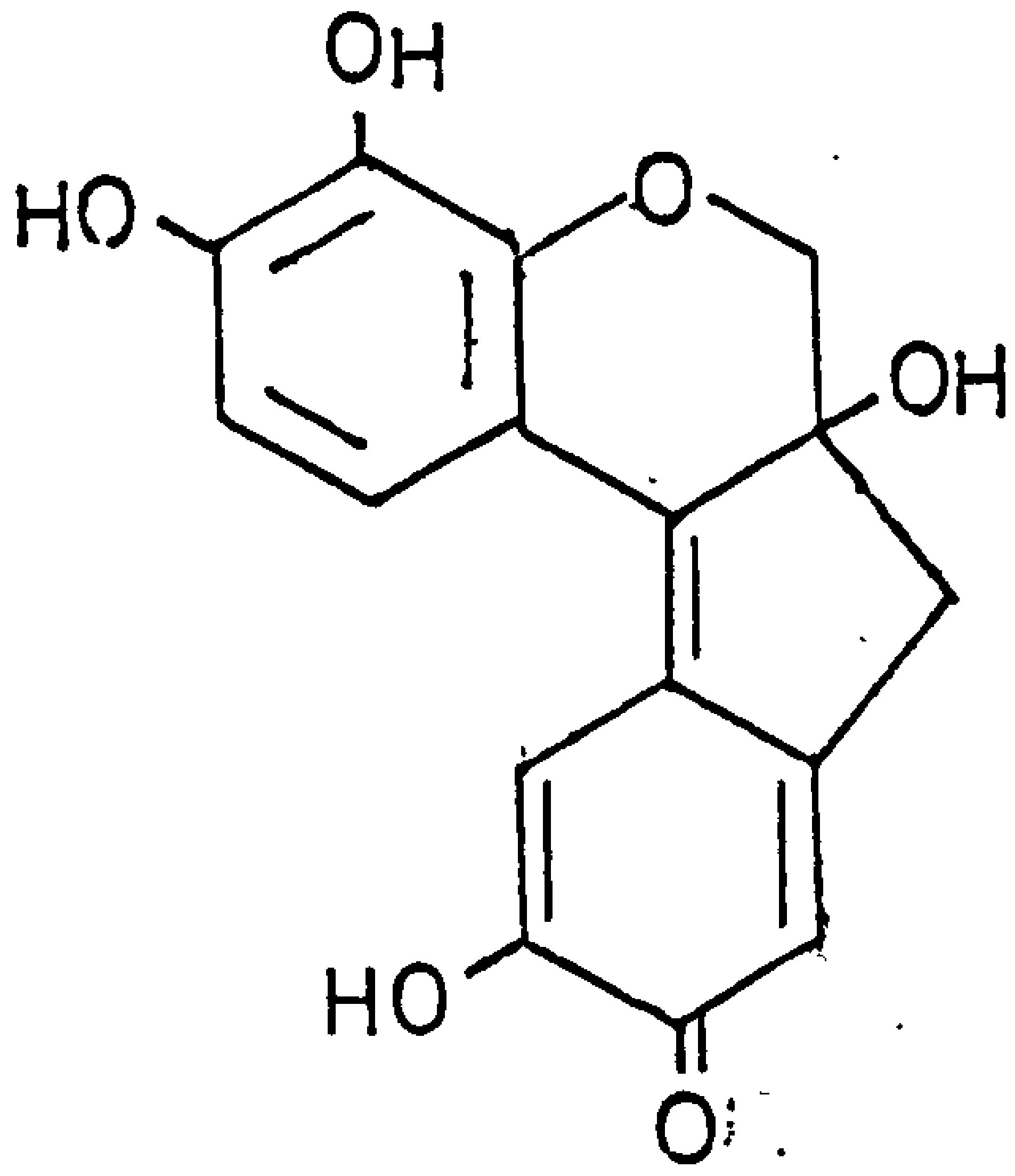


Additionally the absence of oxygen in the molecules was difficult to account for.

Accurate remeasurement of the mass of the product with yellow fluorescence showed the compound to have the molecular formula $C_{16}.H_{13}\ NO_4$ (283.0837). The other major peaks were at 239, 213, (212), 211, 184 and 155. The peak at 239 would be due to loss of one $-N(CH_3)_2$ group. The silylated derivative showed major peaks at 355(356, 357), 283, 256, 147, 73 and 75. The difference of 72 between the parent ion mass of the silylated and the unsilylated ion indicated the presence of only one -OH or $-O^{\ominus}$ group in the fluorescent material. The I.R. spectrum showed only a weak absorption at 3440cm^{-1} but strong absorptions at 1631 and 1580 cm^{-1}. The I.R. spectra of Crystal Violet (ν_{max} KBr) 3440, 1590, 1485, 1370, 1298, 1175, 948, 917, 840, 810 and 730 cm^{-1}) and of haematin (ν_{max}(KBr) 3420, 1610, 1512, 1295, 1212, 1086, 1060, and 870 cm^{-1}) were also recorded for reference purposes. The absorption of a strongly conjugated carbonyl group in a quinonoid structure evidently is shifted well below 1700 cm^{-1}.



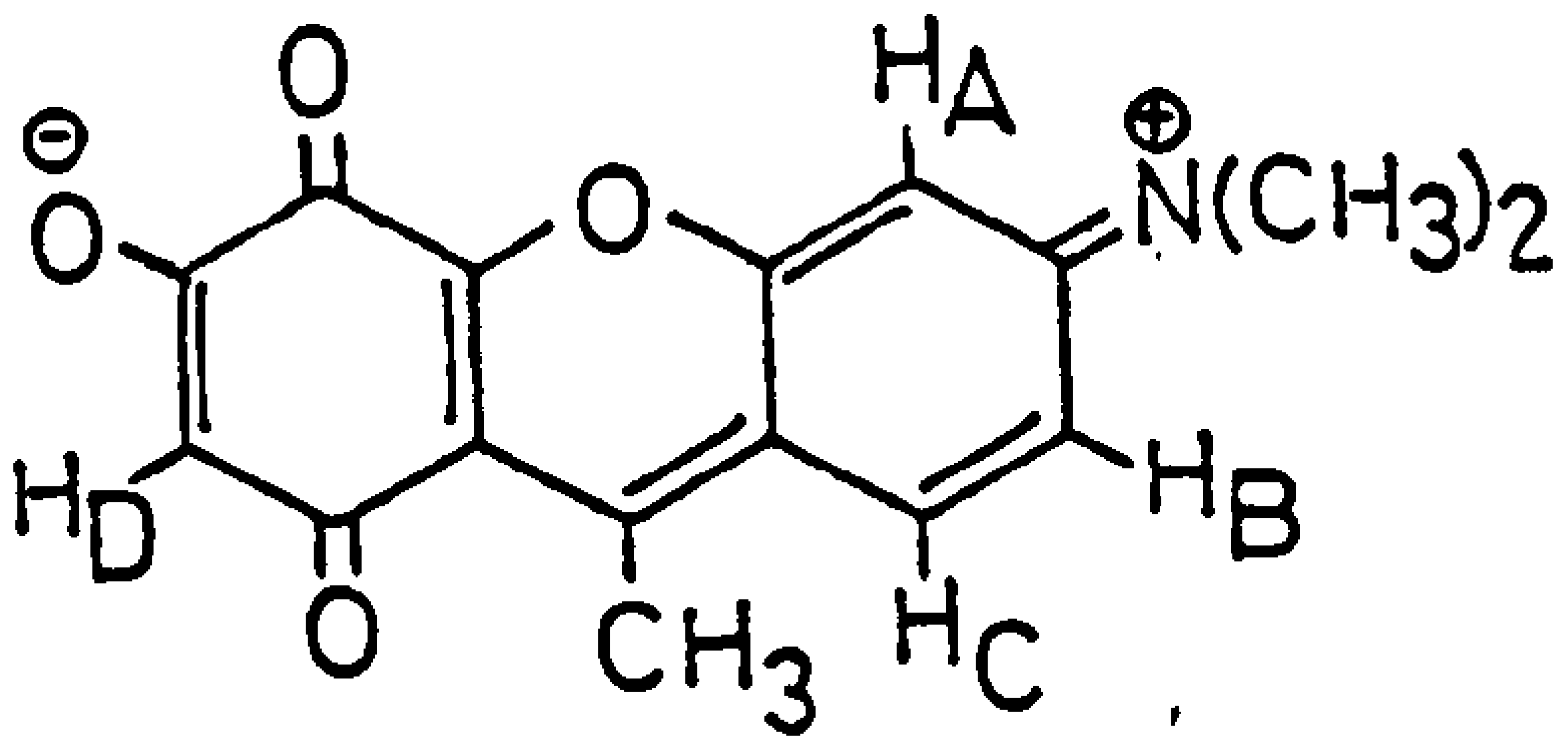
crystal violet



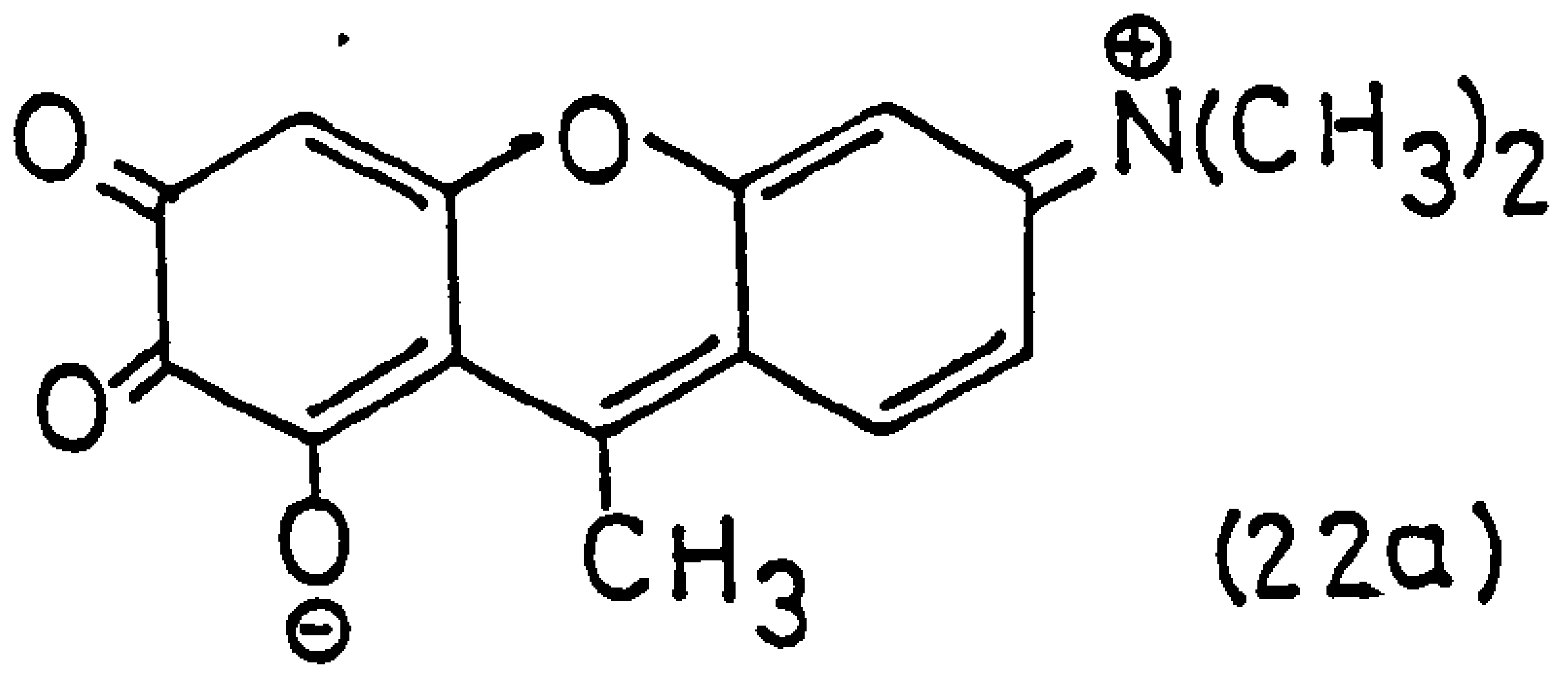
haematin

The ^1H NMR spectrum gave a better indication of the structural features of the unknown compound. The spectrum showed a singlet at δ 1.91 ($=C-CH_3$) and a doublet at δ3.30 ($=\overset{\oplus}{N}\genfrac{}{}{0pt}{}{Me}{Me}$) and several peaks due to aromatic protons. The aromatic protons indicated by chemical shifts and coupling constants observed were two o-protons and a third in the m-, p- positions relative to the two former.

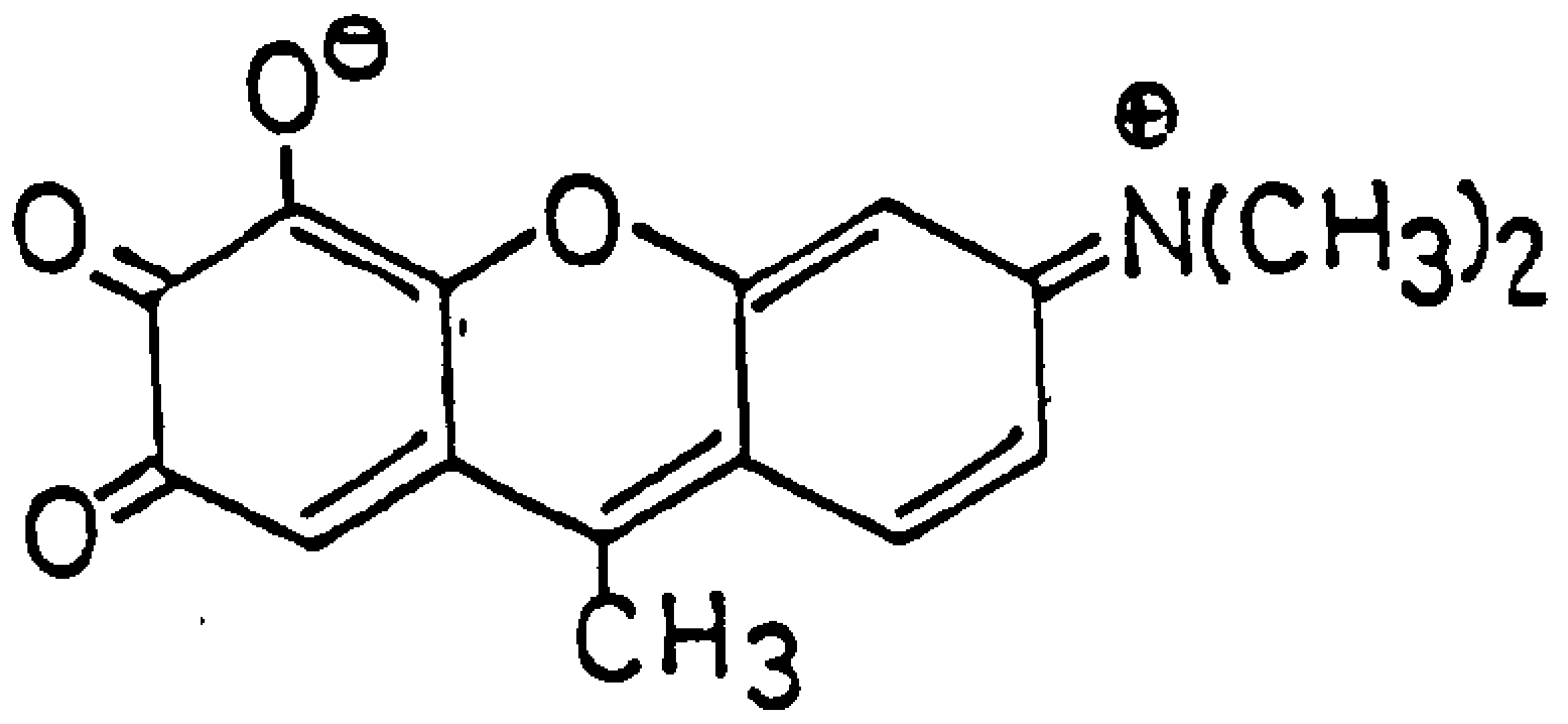
The examination of the analytical data obtained so far indicated the structural formula of the yellow fluorescent material to be probably one of the following:



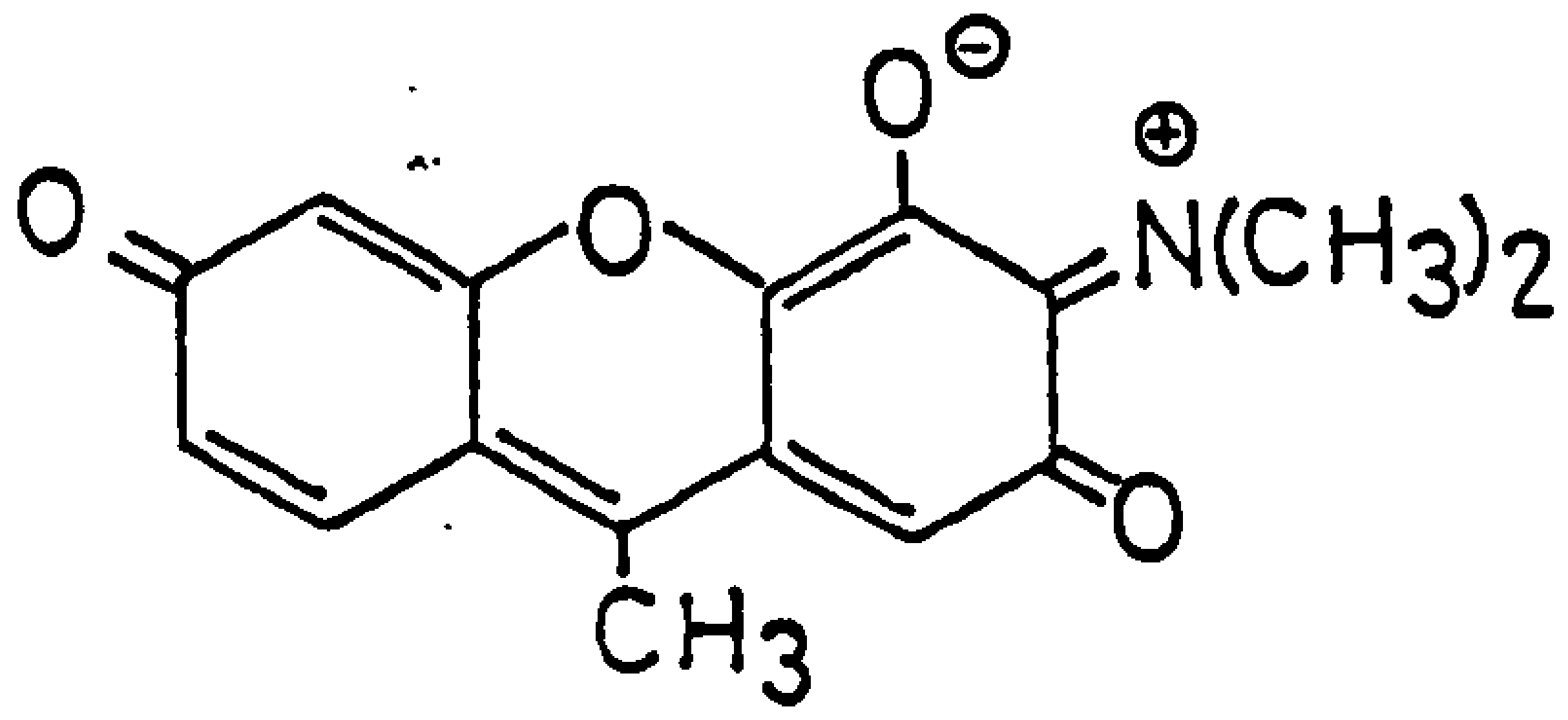
(21)



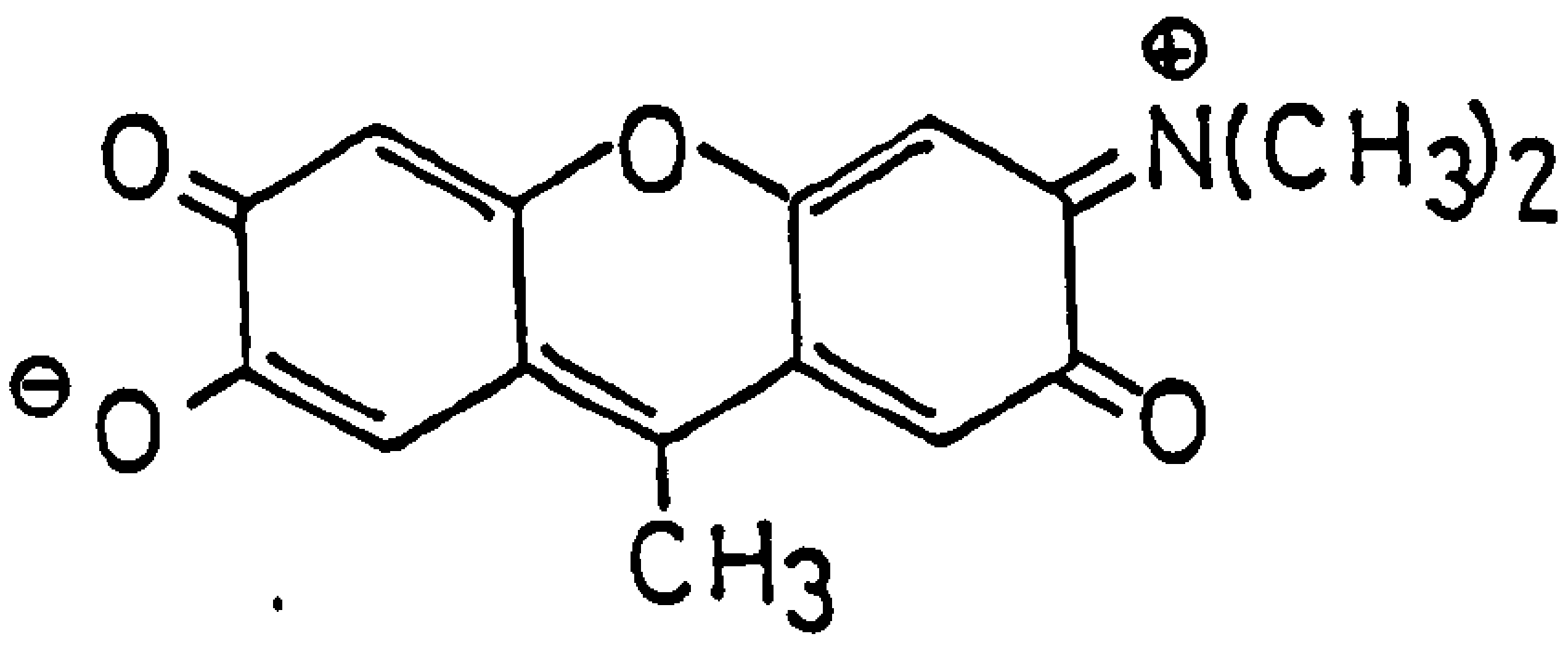
(22a)



(22b)



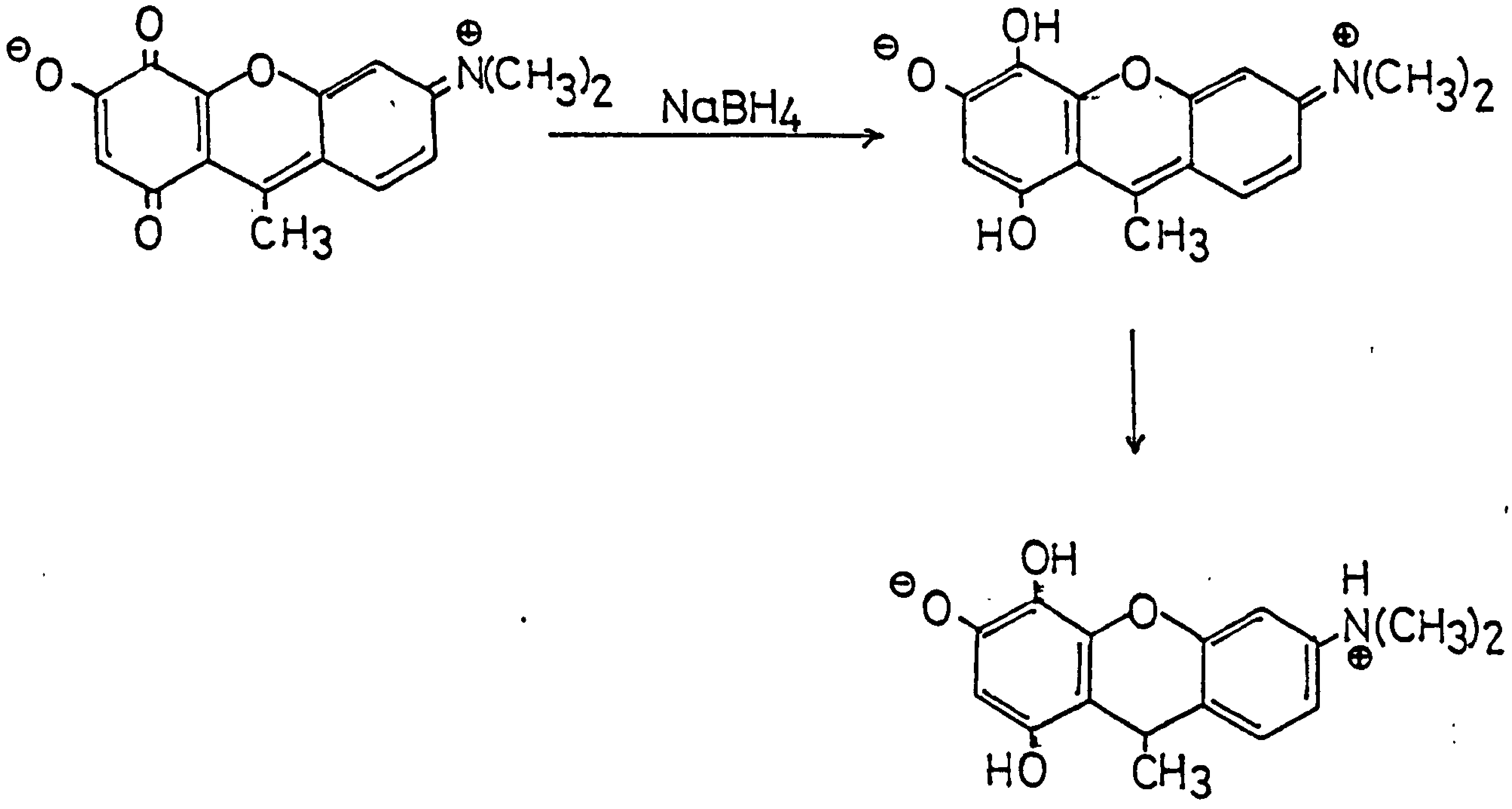
(23)

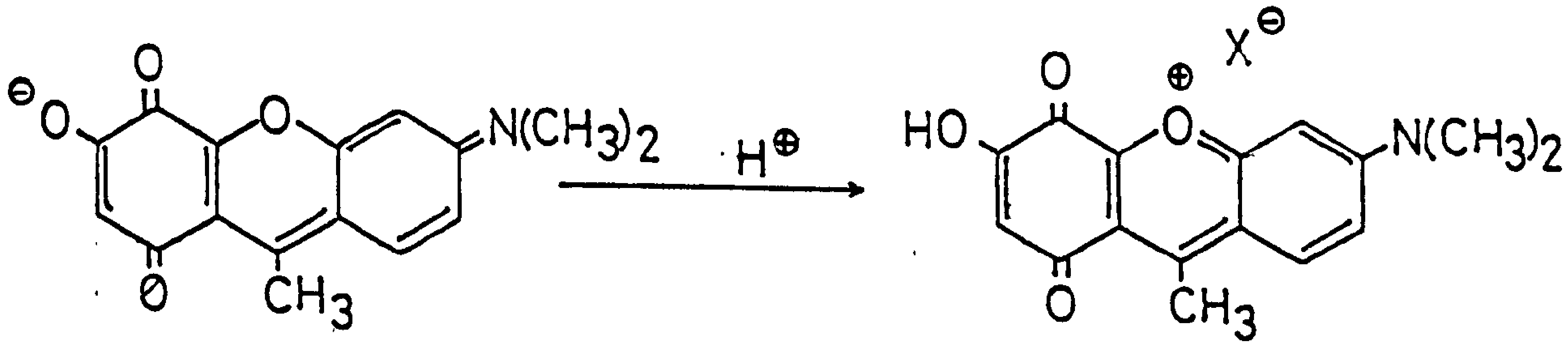


(24).

The structures (21), (22) and (23) meet the ^{1}H NMR spectral requirements and (24) with only para protons can be ruled out since there are no ortho coupled protons present. It was of interest to calculate the chemical shifts for the 4-aromatic protons (see Appendix 4) under consideration using the chemical shifts in Table 3.6 (Spectroscopic methods in Organic Chemistry, Williams and Fleming). The calculated values for 3 protons H_A, H_B, H_C, in the structures 22a, 22b and 23 appear to agree with those observed. However no calculated value for the isolated fourth H_D proton appears to accord with the observed value at δ 8.5.*

The loss of the fluorescence by sodium borohydride reduction, by silylation and by dilute acid can be explained by the following reactions, exemplified for structure (21).





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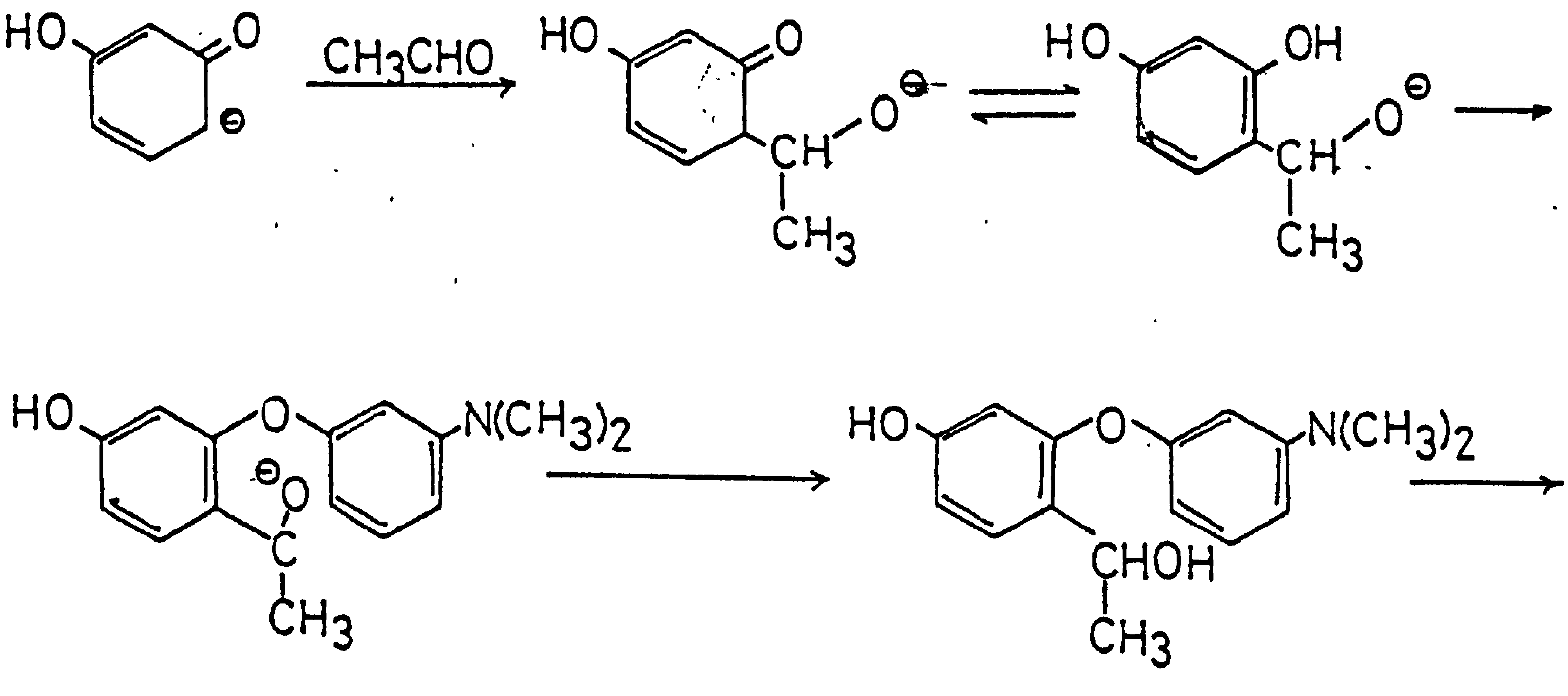
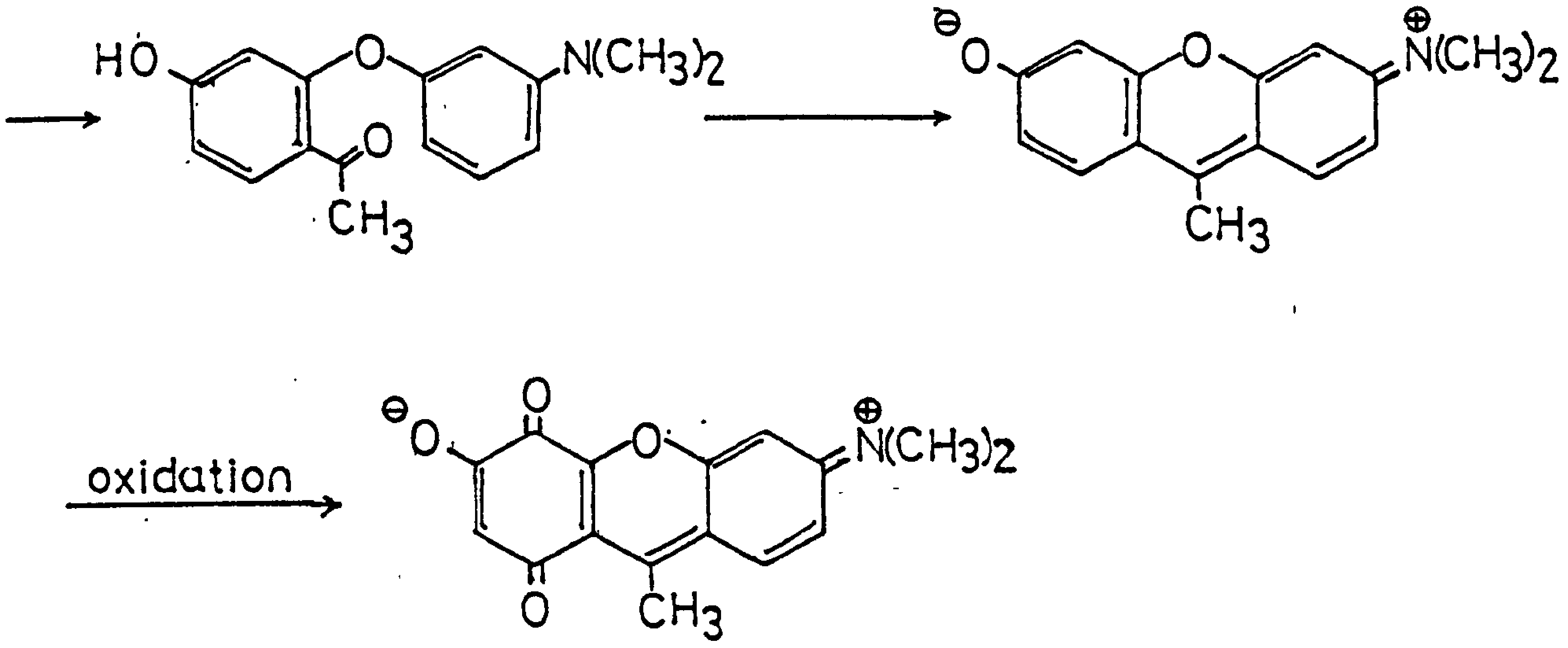
* A difficulty however is that theoretical chemical shits are not available in Table 3.6 referred to, for all the structural features in (21), (22) and (23).

Of the three structures possible it seems highly likely in view of the close similarity of the fluorescence of the resorcinol/dimethylamine product and that of Rhodamine 6G that the substitution in the ring containing the dimethylamino group is possibly the same. Thus structures (21), (22a) and (22b) appear to be more acceptable than (23) and (24). Of these the one in which the calculated H_D value is more downfield is (22b). The major difficulty in the calculation of chemical shifts is that of finding values for actual structural features in the molecule under consideration. Structures 23b could arise like the others proposed by autoxidation at reactive positions ortho and para to OH groups. Unfortunately insufficient time was available for the synthesis of some of the possible structures to be undertaken. (see Appendix 5).

A scheme envisaged for the formation of the product such as(21), is outlined below and would involve the participation of acetaldehyde (as discussed in the next section). Similar schemes involving different oxidation could be involved for (22a) (22b) and (23).



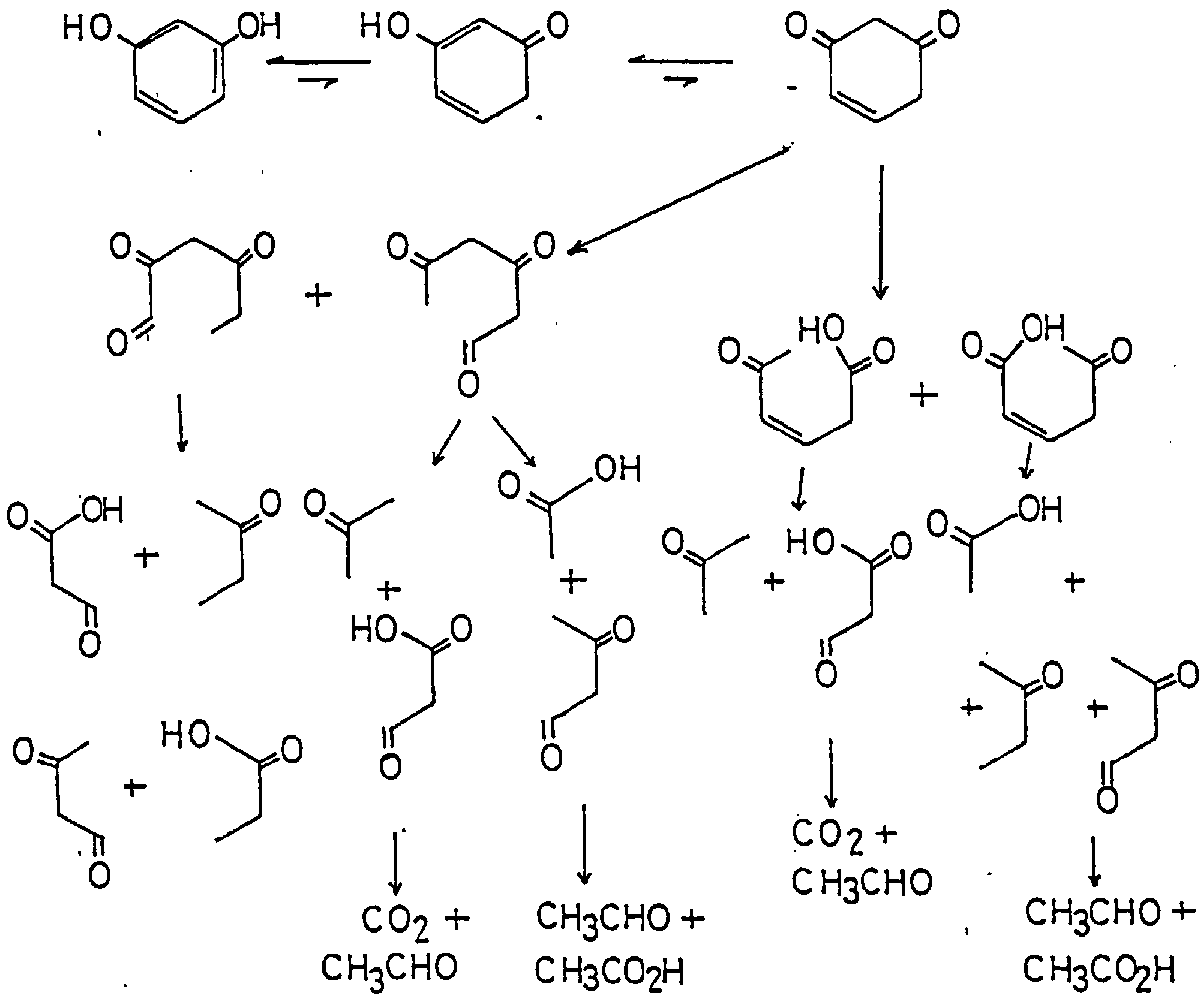


The proton H_D in (22b) in somewhat sterically hindered and this could possibly explain its resistance to oxidation to give a p-quinone and for the alternative o-quinone to be formed.

Formation of Acetaldehyde

The acetaldehyde may be presented as an impurity in the reactants or more likely may be formed in situ by the fragmentation of the resorcinol molecule as outlined. Acetyl acetone is known to readily yield acetone and acetic acid upon hydrolysis. Resorcinol is known to be capable of reacting in a diketo form,* so the following equilibra are possible:-

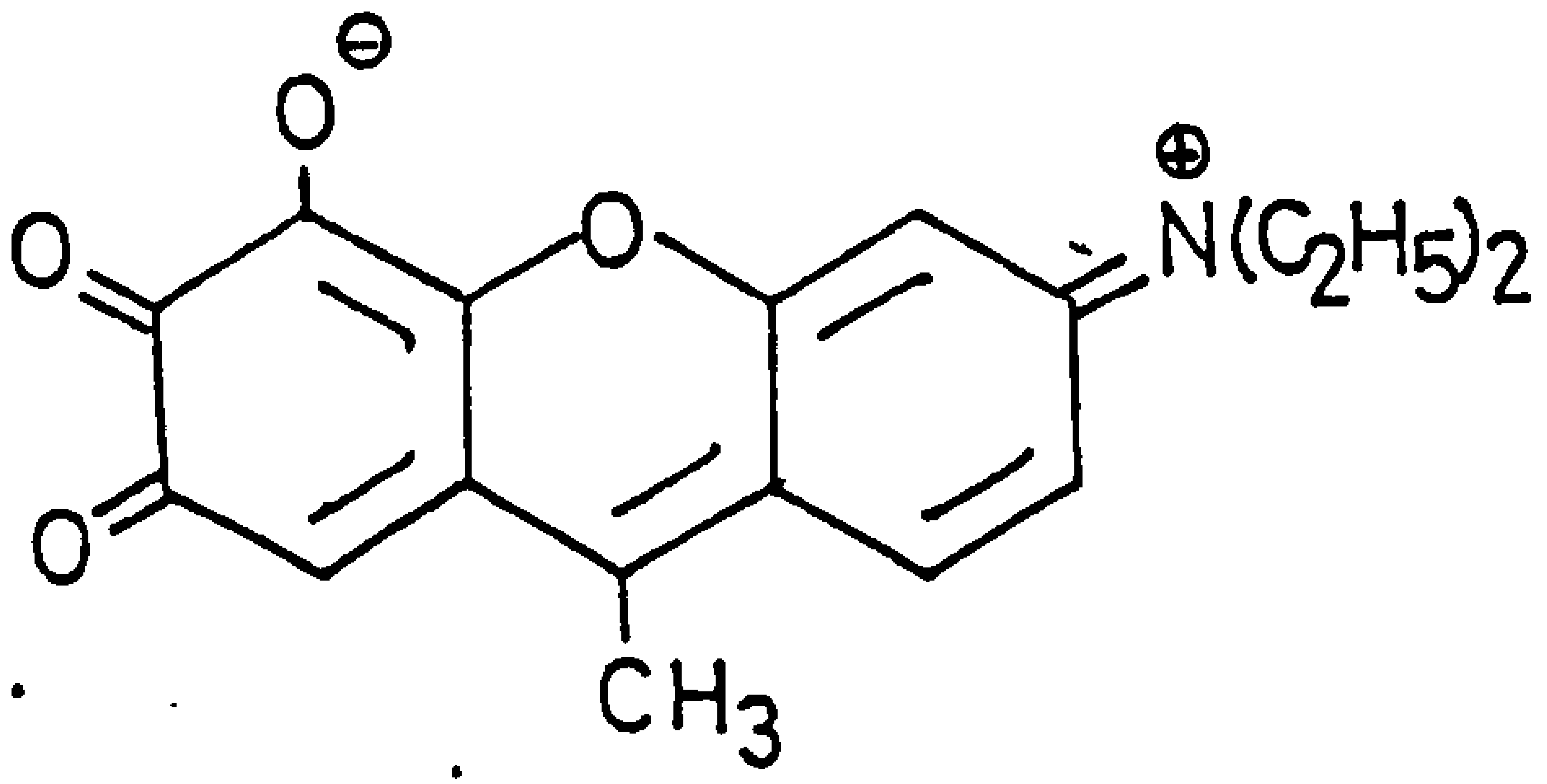
* W. Fuchs and Elsner, Ber., 53, 886 (1920); 57, 1225 (1924)



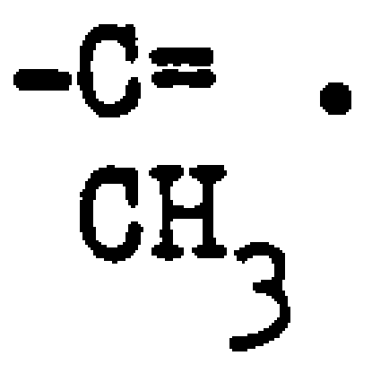
In four of the above pathways, the formation of acetaldehyde can occur by way of decarboxylation and hydrolysis. Retroaldol reactions of Claisen condensation products are also well known. e.g. cinnamaldehyde is known to give benzaldehyde and acetaldehyde.

Resorcinol/Diethylamine product

An analogous product from diethylamine and resorcinol showed similar fluorescence (U.V.) as well as the expected mass spectrum for the homologous compound. The mass spectrum of the silylated material had major peaks at 383, 357 (small peak at 311 due to parent compound), 285, 254, 239, 147, 75 and 73. The spectrum also had small peaks at much higher masses (933 and 833) which are probably due to impurities. (The photographs (1-4) of the preparative plates show the complexity of the mixture involved and hence the difficulties in obtaining pure compounds in large enough quantities for analysis). The formula thus appears to be likely to be,

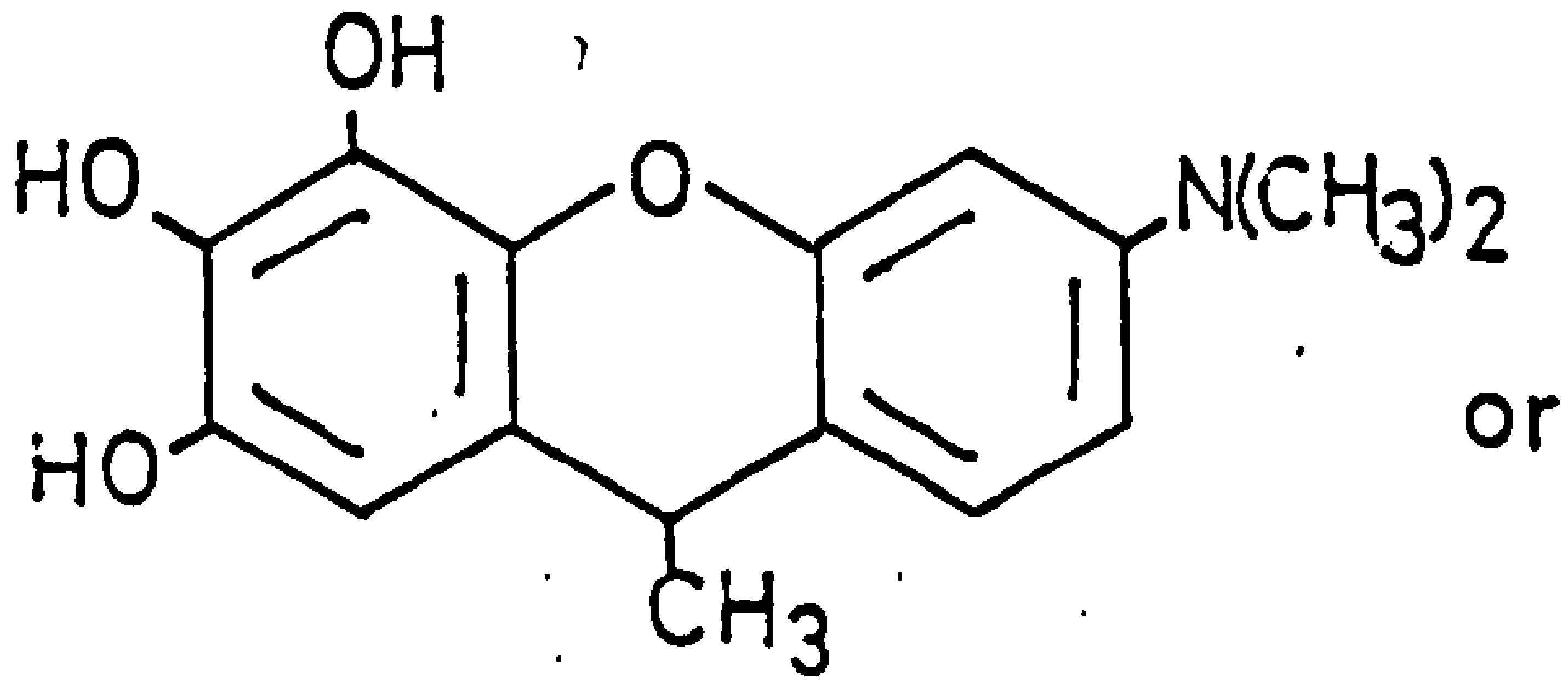


or related compound to 21 and 22a

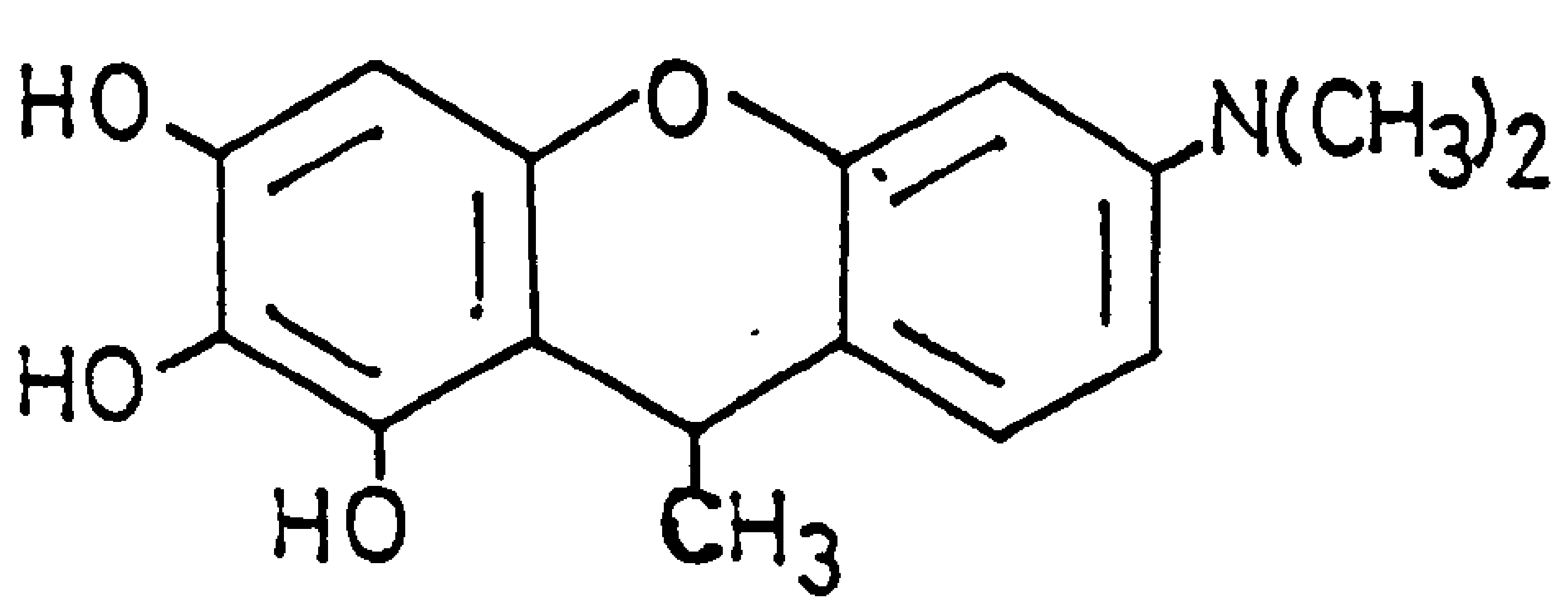
The question may well arise as to whether similar compounds bearing a $-\underset{CH_3}{C}=$ linking group can be formed in the reaction of resorcinol and of orcinol with ammonia and methylamine. The considerably greater basic strength of dimethylamine compared with ammonia may be the reason for the hydrolysis of resorcinol with the organic amine. If any appreciable percentage of such materials were present in the products they would be revealed as bands in TLC separation or as peaks in mass spectral examination. Such products if they existed would give parent ions at 11 m/e units higher than the corresponding phenoxazines. They have not been detected although in the orcinol/methylamine product the ^1H NMR spectrum contains a doublet for the grouping  $\underset{CH_3}{-C=}$. However in view of the number of closely related and non-equivalent methyl groups attatched to aromatic rings and to double bonds of quinonoid systems this evidence must be accepted with reserve. The mass spectral evidence is lacking for the existence of such bridged-type materials.

Other products from Resorcinol/Dimethylamine reaction

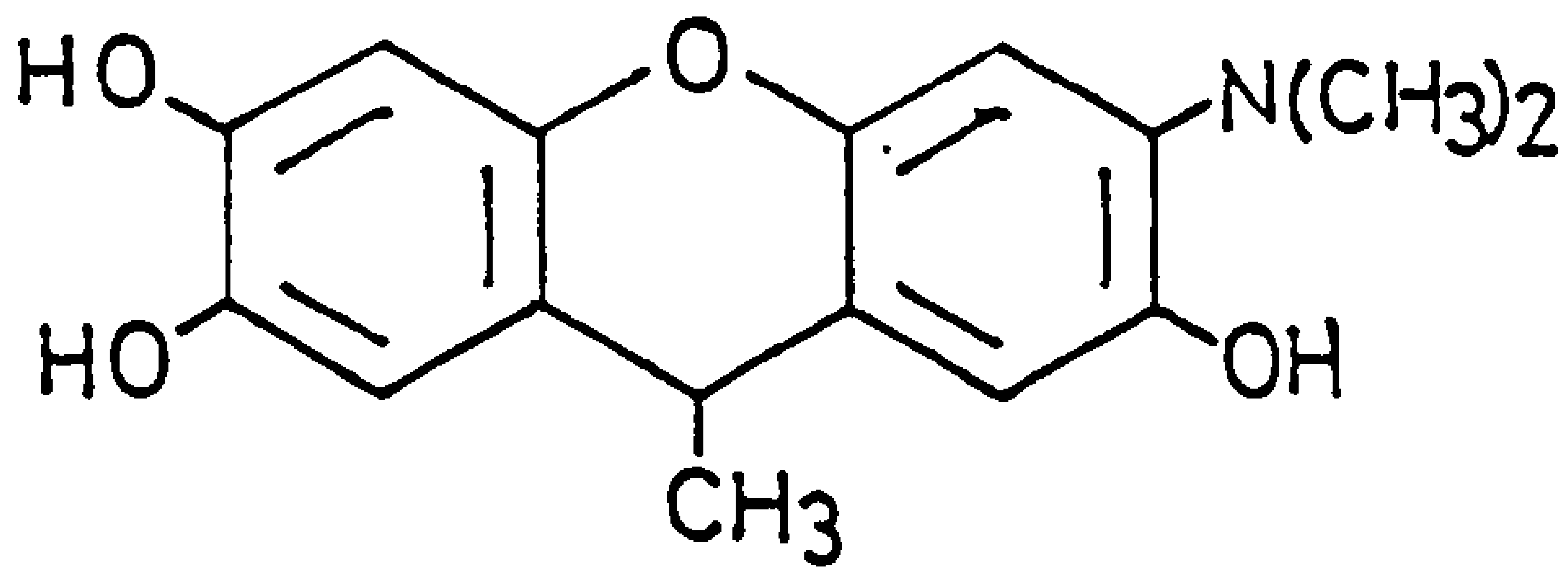
The I.R. spectrum of the blue material showed absorption bonds at 3450 (strong), 1600 (strong), 1512, 1385, 1194, 1117, 985, 910 and 860 cm^{-1}. The mass spectrum of the material showed the parent ion to have a mass of 287 i.e. 4 units more than that for the fluorescent material. The material could be related to the fluorescent compound in which case it would probably have one of the structures below. The coloured materials may well be 'leuco' forms which are intermediates in the general formation of more complex coloured products.



or



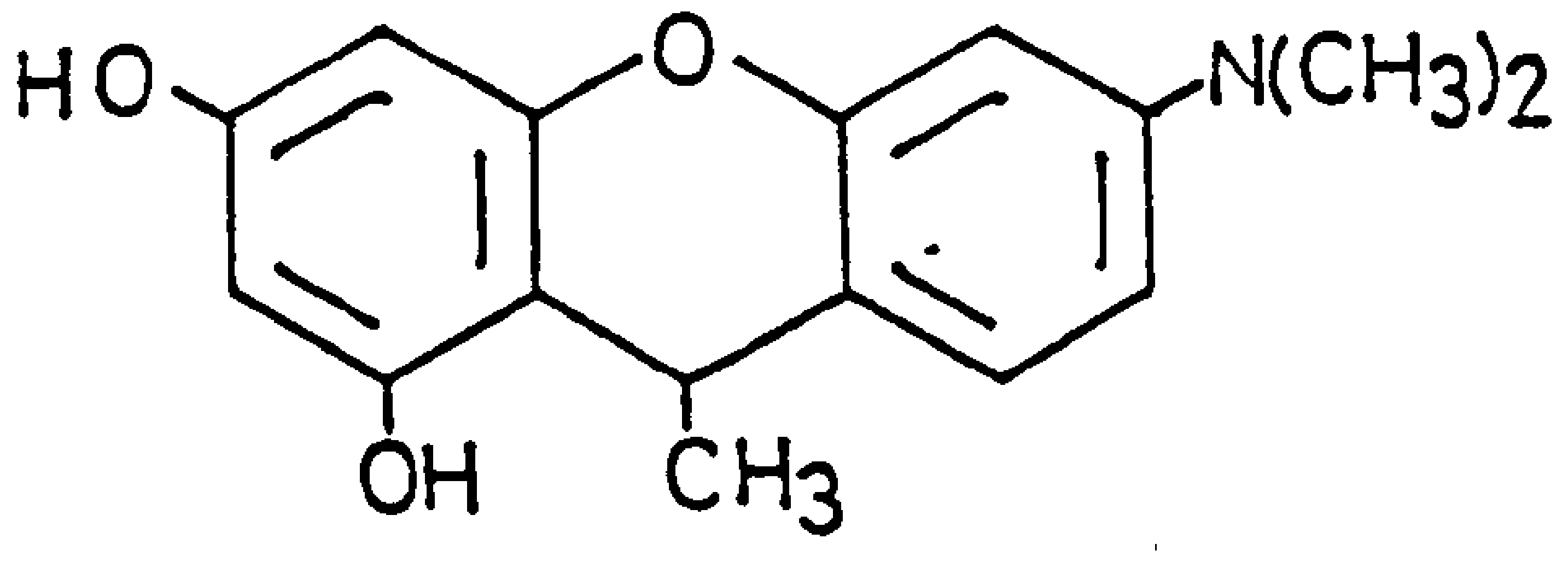
or



The above structures would also account for a very strong -OH absorption in I.R.

However a mass of 863 for the silylated blue material indicated an increase of 576 ie the weight increase expected when eight -OH groups are replaced by -Si $(CH_3)_3$ groups. It seems that dimerisation could occur. The dimethyl amino group could also possibly interact with the silylating agent leading to the total up take of 8 - $Si(CH_3)_3$ groups.

The purple material gave a similar mass spectrum to that of the blue material. It also had peaks at mass 287 as well as a peak at 272. The silylated material had peaks at 503 and 416 corresponding to addition of 3 and 2 silyl groups respectively. The possible molecular formula revealed,namely $C_{25}H_{42}NO_3Si_3$ after removal of $C_9H_{27}Si_3$ and addition of 2H., leaves $C_{16}H_{17}NO_3$. The peaks at 287 and 503 could be due to impurity (blue material). The purple material with 2 -OH could have a related structure as shown.



$(C_{16}H_{17}NO_3)$

The difficulty in analysing all the materials in this work arose due to their non-volatility and the problem in isolating pure materials, due to the presence of oligomers and to the labile character of the materials as a general class.

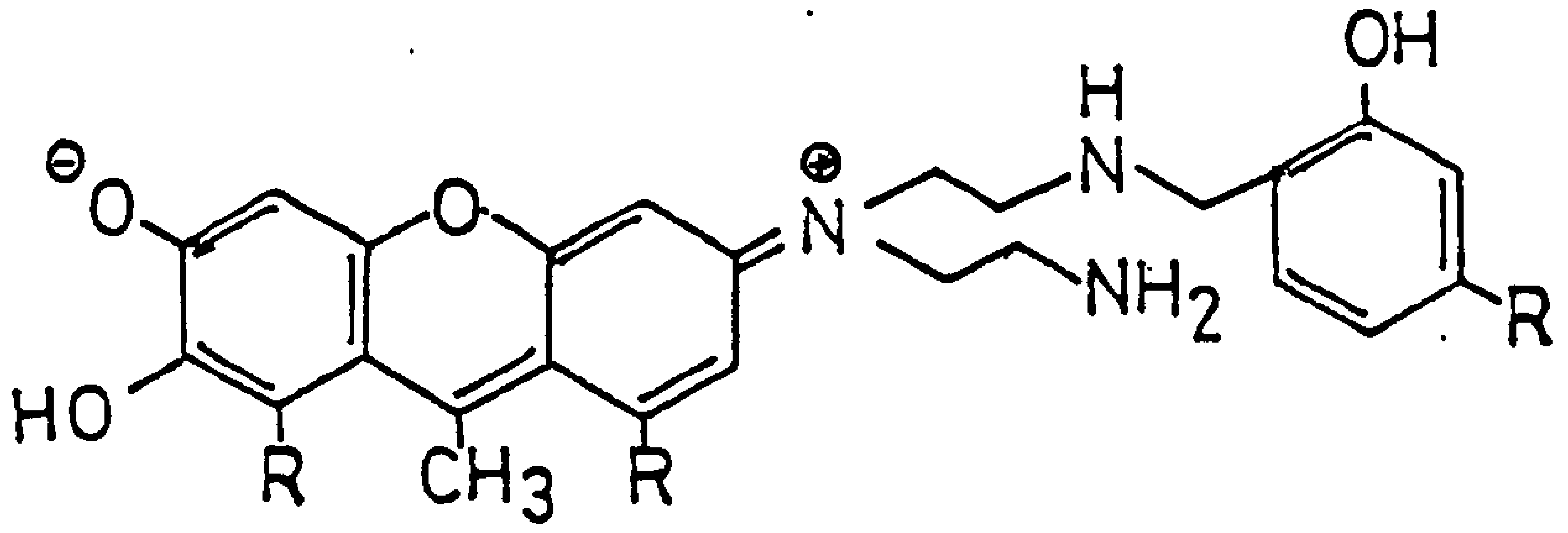
2 e Reactions of Resorcinols with Diethylenetriamine

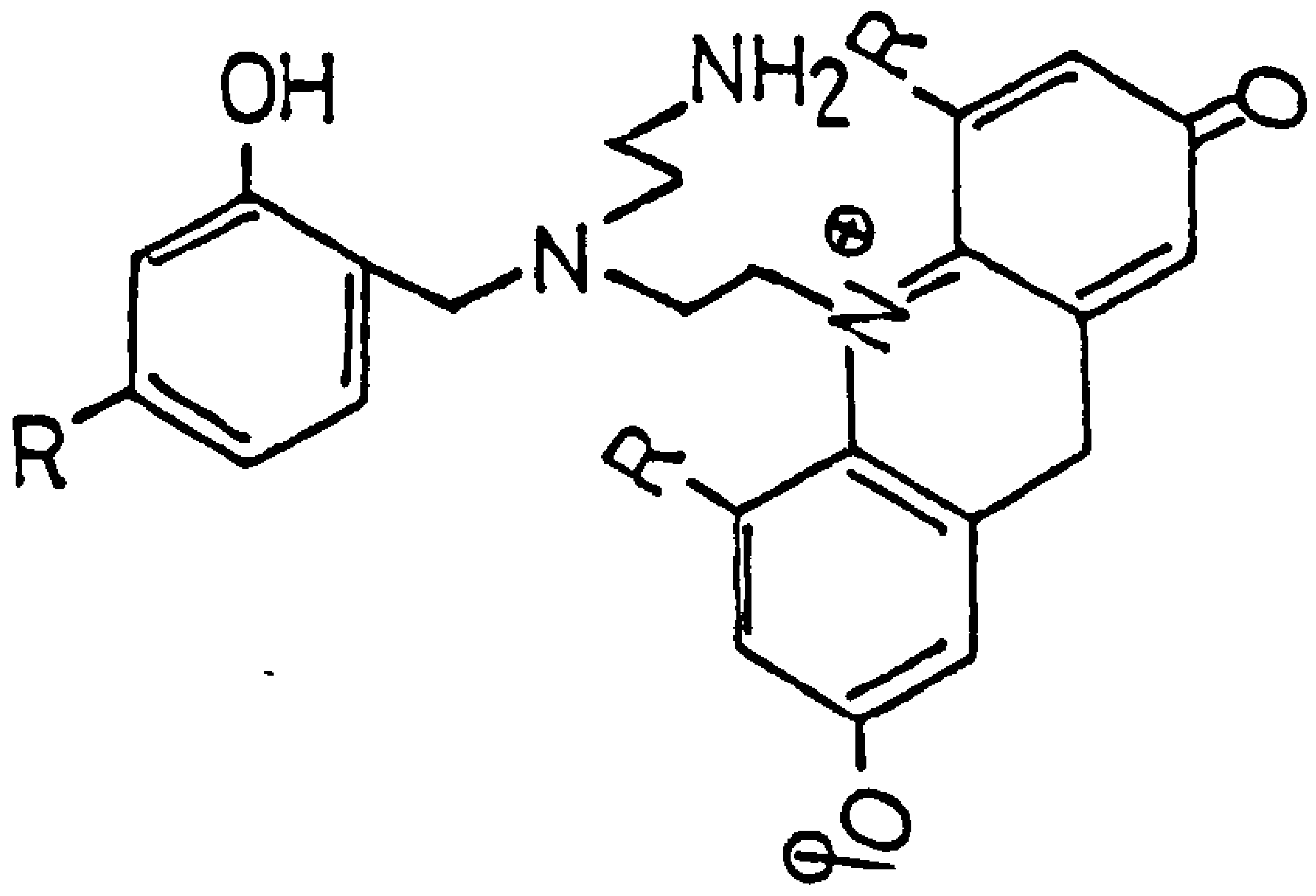
Each of the mixtures of resorcinol, 2-methyl resorcinol and 5-methylresorcinol and of cardol with DETA produced red coloured products. The quantity of product formed depended on the length of time the mixtures were left to stand.

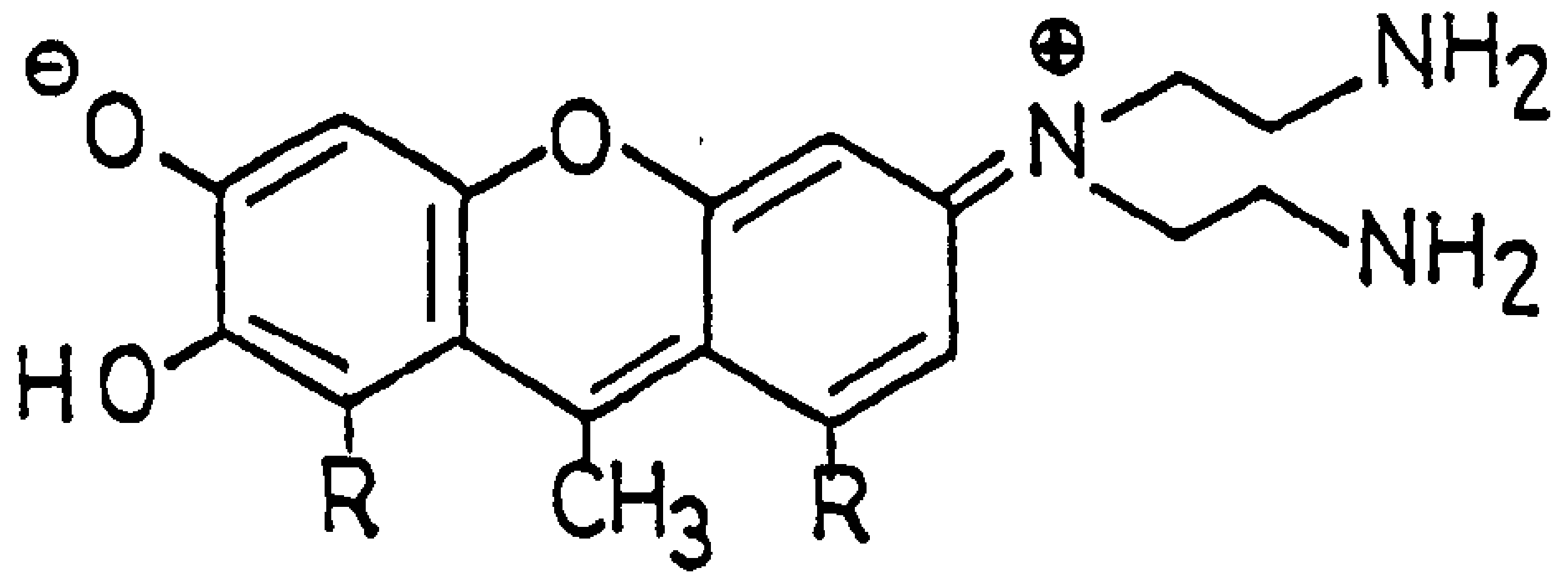
The ^{1}H NMR spectrum of the resorcinol DETA product showed a broad N-CH_2-CH_2-N band, a broad exchangeable band (-NH, -NH_2, -OH) and bands for aromatic protons. The elemental analysis suggested an empirical formula of $C_{10}H_{12}N_2O_4$ but a repeat analysis suggested the formula to be $C_{10}H_{14}N_2O_4$. The product was slightly soluble in dimethyl sulphoxide and water, insoluble in methanol and soluble in dilute acid. A product with -NH, -NH_2 and -OH group would be expected to be soluble in methanol and so the insolubility may be due to the polymeric nature of the product. It was soluble in acid probably due to salt formation.

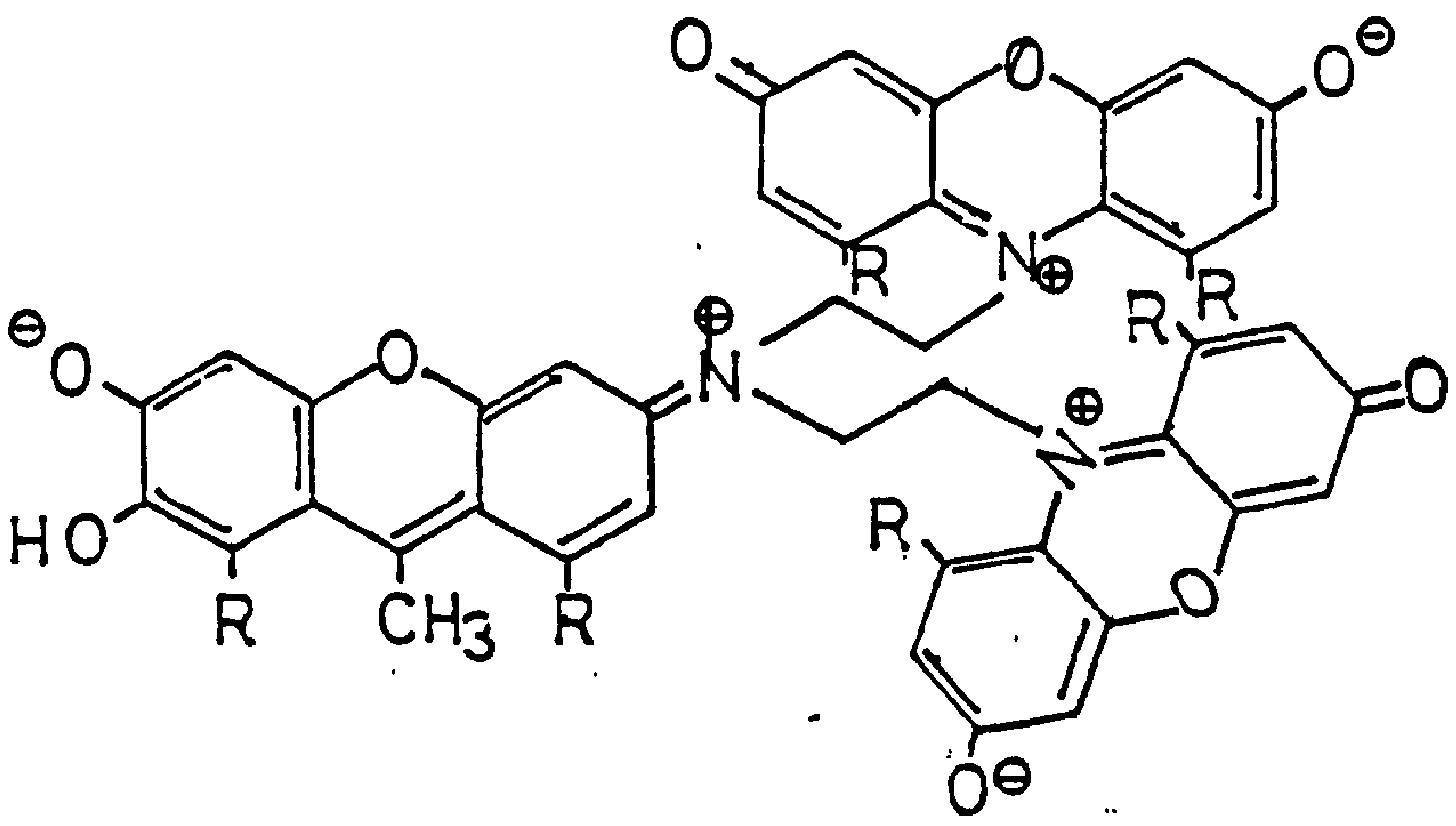
The structures of the compound would probably be derived from the resorcinol/primary amine and resorcinol/secondary amine pathways including 5-substituted resorcinols together with oxidation. The Mannich bases may well also be present in the structures. (see Appendix 6)

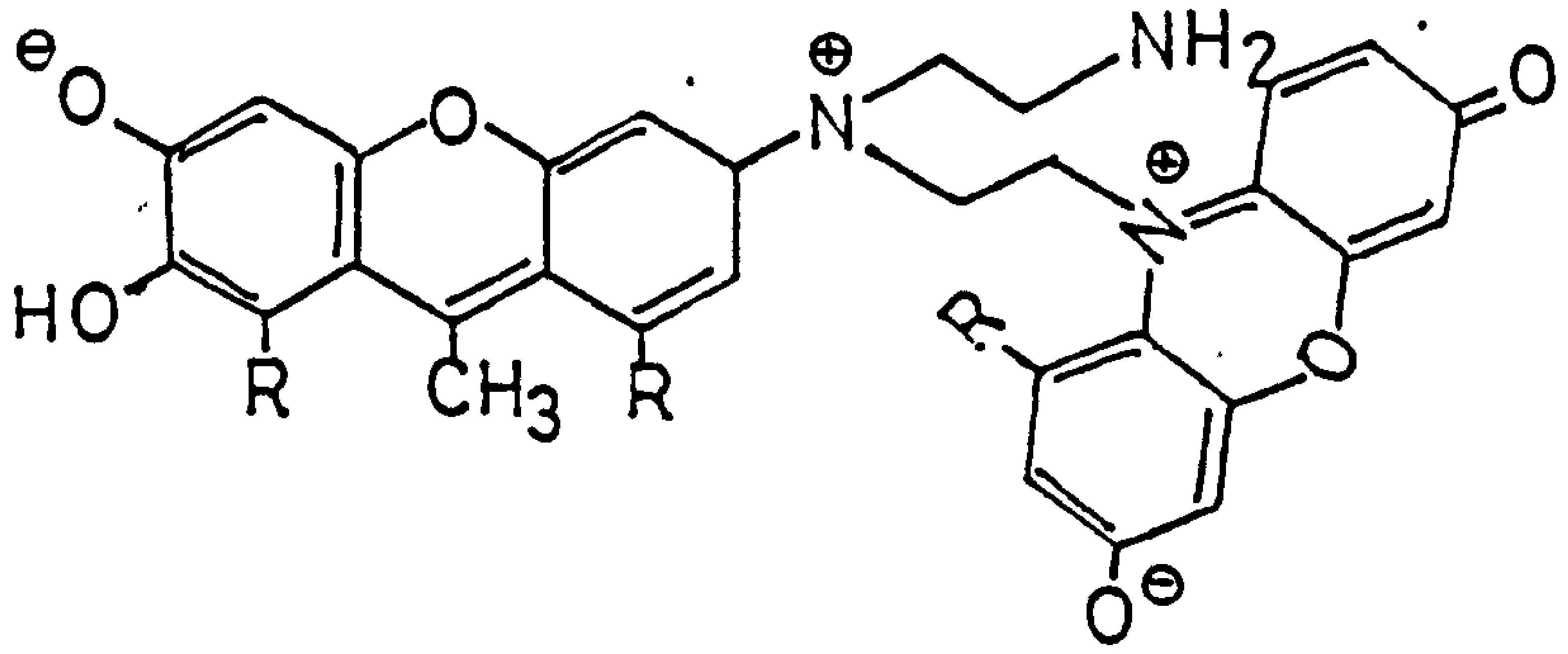
Spectulated structures for CNSL/DETA are given below

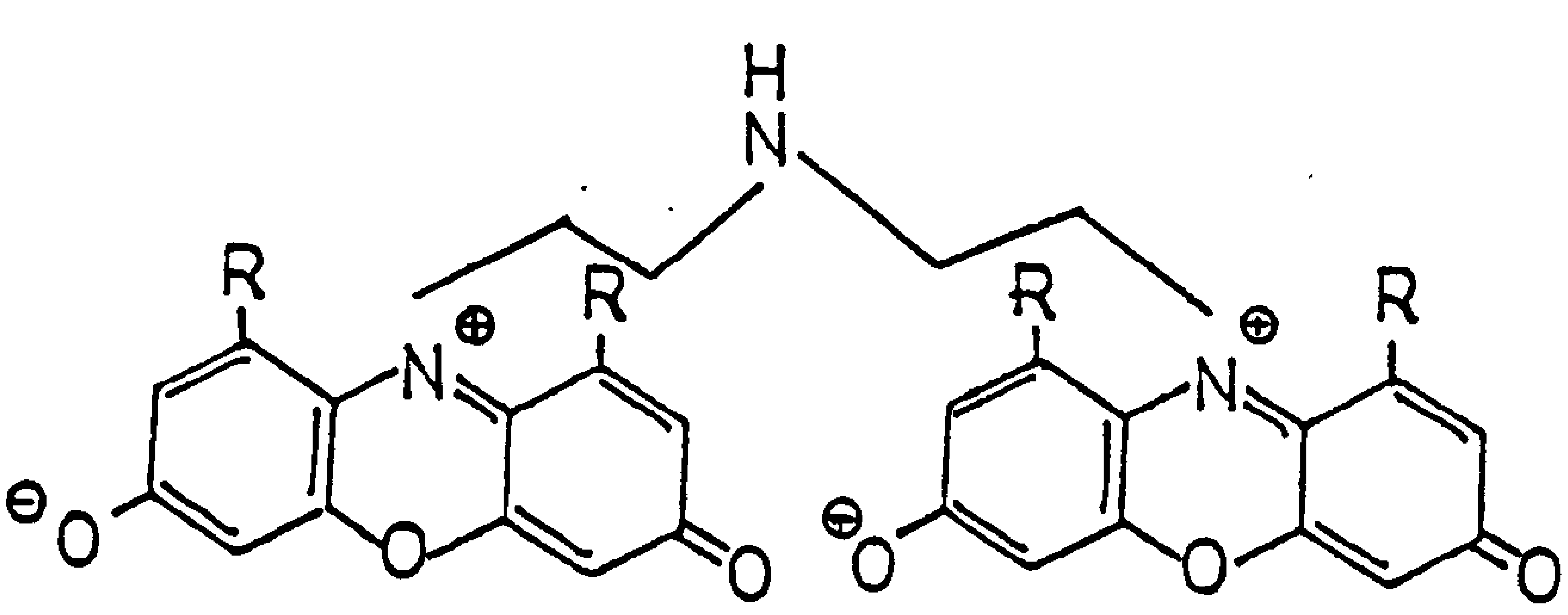












$R = C_{15}H_{31-n}$

$n = 0, 2, 4,$ and 6

3 PREVENTION OF COLOUR DEVELOPMENT DURING MANNICH REACTION

3a Simple experiments were carried out to prevent oxidation of reaction mixture after the finding that the red-coloured material formed during Mannich reactions were mainly due to oxidation followed by a probable further reaction of the amine (e.g. DETA) with CNSL, in particular with the cardol component of the CNSL.

The use of sodium borohydride, inert atmosphere as well as a combination of inert atmosphere and anti-oxident incorporated in the Mannich mixtures all proved useful in giving pale coloured reaction mixtures. On standing these mixtures in air they all turned dark red. To prevent this darkening of colour on storage the pale Mannich base prepared as above was immediately acetylated so that the reactive OH groups was blocked and hence the formation of quinonoid structures by oxidation would be stopped. This method proved useful but was abandoned as it was thought that the removal of the OH group would adversely affect the surface properties of the Mannich product and also because the displacement of the tertiary amino group by the acetoxy group may occur as reported by Bruson and MacMullen.[16]

3b Removal of Cardol from CNSL

As the formation of colour in the Mannich reaction was associated with the resorcinol component, cardol, its total removal by an effective means was desirable.

Technical CNSL can be distilled under high vacuum with wide bore distillation or by molecular distillation[93] to yield cardanol/cardol possessing a pale yellow colour but reversion of colour occurs on standing. In general all fractions contains both cardanol and cardol and the separation of the two is low. A slightly greater separation can be achieved by molecular distillation but the % of pure cardanol recovered is low.

Murthy et al[94] have submitted CNSL to specific treatments prior to distillation and obtained pale coloured distillate with improved yields. In some cases the pale distillates obtained under went slight reversion but analysis of samples has not been reported.

Misra and Pandey[95] investigated recovery of cardanol from CNSL in terms of residence time, pressure and temperatures but the analysis of distillates has again been omitted.

As stated the removal of cardol from technical CNSL by distillation, even under conditions where an apparatus having a number of theoretical plates is used, is relatively inefficient. Hitherto pure cardanol free of cardol has only been obtained by coloumn chromatography,[96] method however not readily applicable on a larger scale.

3c Recovery of cardanol from CNSL by vacuum distillation in the presence of base.[97]

A preliminary experiment on the possible use of a molecular association of cardol with DETA to separate the cardol component from CNSL was conducted by allowing a mixture of dist. CNSL and DETA to stand for a week to allow the molecular association to take place. The mixture was then vacuum distilled. On examination of the distilled CNSL by TLC, no spots for cardol and 2-methylcardol were observed. This selective removal of dihyric phenols was investigated further to find the optimum conditions as well as the affect of base strength, for obtaining pure cardanol.

The results from the experiments with technical CNSL and amines as well as with technical CNSL and sodium hydroxide are shown in Table 1 and from distilled CNSL and amine (DETA) in Table 2. The control experiment showed that in the absence of amine the percentage cardol was halved as a result of distillation, but with DETA, N-(2-aminoethyl)-ethanol amine and sodium hydroxide the cardol was further reduced directly from ca. 19% to ca. 5%. A one molar proportion of base to CNSL was sufficient to achieve this with bases mentioned above but similar treatment of tech. CNSL with even a 50% excess of diethanolamine prior to distillation showed only a 50% reduction of cardol concentration i.e. the same level of concentration as that obtained without amine treatment. Later experiments by Durrani[98] have shown ammonia to be ineffective in separating cardanol from cardol. This suggested the amine/cardol interaction to be dependant on the base strength.

The analytical results of the distillates show a ca. 93% pure cardanol which may be the optimum level attainable by this method when starting from technical CNSL. As Table 2 shows, when distilled CNSL was subjected to base treatment, 95-98% pure cardanol was obtained by this method.

3d Effect of length of time of base treatment

When a mixture of technical CNSL and DETA (1 molar proportions) was allowed to stand for 24 hrs. cardanol of 92% purity was obtained compared with 93% pure cardanol obtained when the mixture was allowed to stand for seven days prior to distillation. The rate of amine/cardol interaction was apparently slow in the case of organic bases due probably to the reaction taking place in a non-aqueous system. However, in the case of sodium hydroxide the reaction would by very fast. A further advantage of using sodium hydroxide would be that it would not react further with the distillate to produce red coloured materials although it is possible that conjugation would still take place. The disadvantage of using aqueous sodium hydroxide was that water had to be removed prior to distillation since otherwise manipulative difficulties due to foaming would occur.

The incorporation of a few theoretical plates as with Vigreux type column did not lead to a significant difference in the purity of the cardanol.

3e Effect of treatment with DETA and distillation upon the unsaturated composition

The triene content of cardanol in CNSL usually decreases on distillation of CNSL but an examination of the distillate obtained from base treated technical CNSL showed only a small drop in the triene content. This may be due to the useful affect of the amine in preventing polymerisation leading to an increased yield of cardanol. The large variation in the yield of cardanol obtained in the present series of experiments may be due to the difficulty in consistently maintaining a low vacuum and also due to the visual monitoring of the end point of distillation.

3f Recovery of phenols from the residues obtained from distilled CNSL

The analysis of residues showed an increased concentration of cardol and a similar result was obtained when an acid-washed residue was analysed. As demonstrated in the case of the combined residues from base treated CNSL, the residues can be further distilled to obtain concentrates of cardanol and cardol. The latter fraction could be used as a source of cardol or the residue could be used for reaction with formaldehyde. A prolonged heating of the residue would lead to polymerisation.

3g Effect of base strength upon the separation of cardanol from cardol.

It was clear from the use of the three organic bases of different strengths that the level of basicity had to be high. It was first thought that the minimum requirement would be to use an aliphatic diamine but in a parallel study by 3M Ltd. piperidine has been shown to give very satisfactory results. There may be a minimum base strength required such as that of diethanolamine or ammonia but this physical property may not be as important, since the amine/CNSL interaction occur in a non-aqueous system. The K_b values [99] of a number of bases are shown on the next page together with, where possible, their usefulness in the cardol/cardanol separation.

Base	K_b*	Effectiveness (in cardol removal)
+ Piperidine	1.6×10^{-3}	Excellent
N-(2-Aminoethyl)-ethanolamine		Excellent
Ethanolamine	2.77×10^{-5}	-
Ethylenediamine	8.5×10^{-5}	-
Triethylamine	4.37×10^{-4}	-
Diethylamine	1.26×10^{-3}	-
DETA	probably 8.5×10^{-5}	Excellent
Diethanolamine	probably 3×10^{-5}	not effective
Ammonia	1.8×10^{-5}	not effective

* Value from $K_b = \frac{(BH)(OH)^{\ominus}}{(B)}$

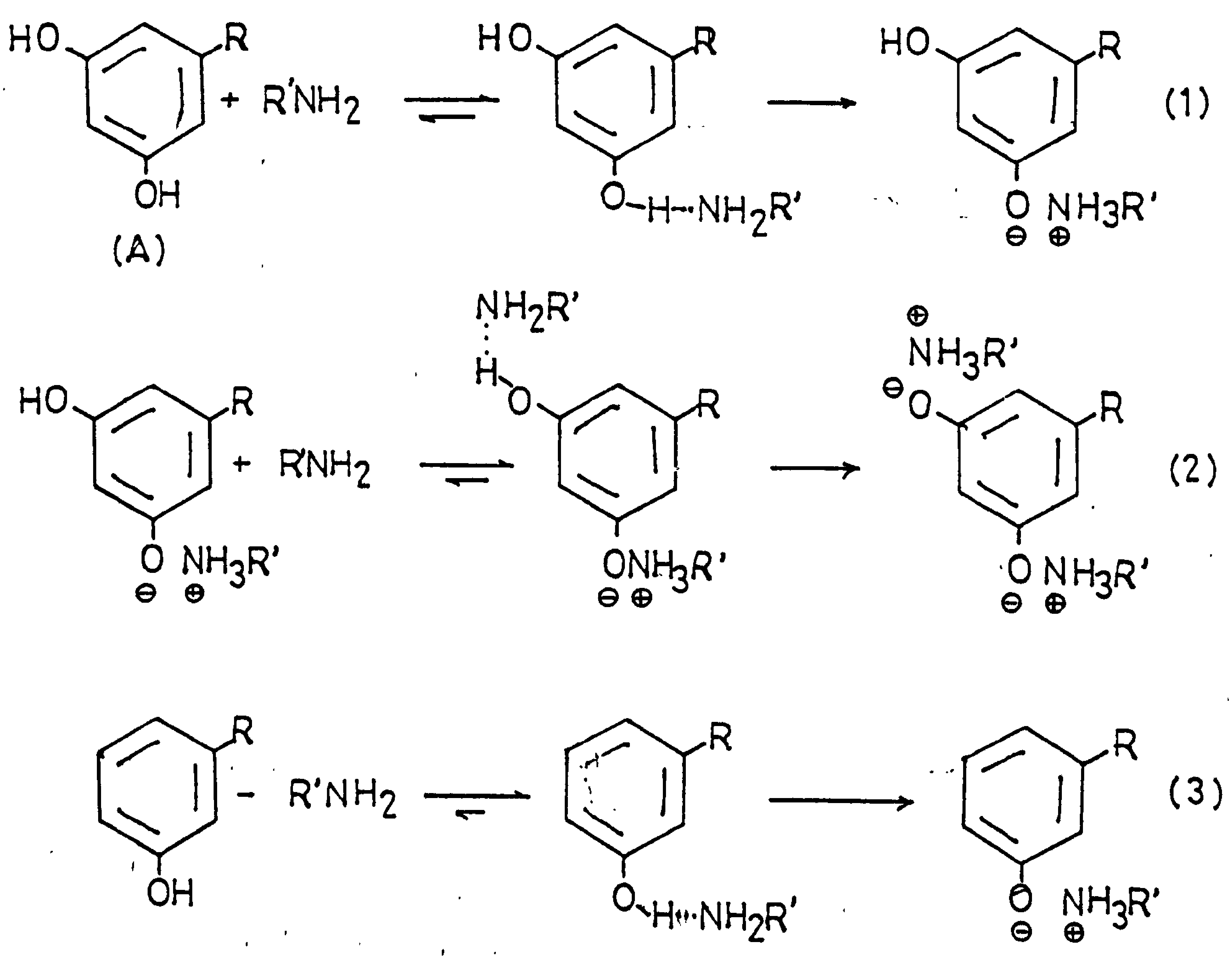
\+ Result reported by 3M Ltd.

The ineffective compounds have low K_b values than the other (effective) compounds.

In all the cases the recovery of the base was excellent but it was apparent that the unrecovered portion may well be present in the distillation residue as a salt or a hydrogen bonded complex of the dihydric phenols. In further work by Duranni[98] the base (DETA) was not detected in a free state in the residue.

3h Mechanism of the reaction

The first step is probably a 1:1 interaction of an acidic centre with a strongly basic centre. In the competition between cardol and cardanol, the former with its high first dissocation stage would be expected to combine with the amine in the following way.



$R = C_{15}H_{31}{-n}$ n = 0,2,4 and 6

R' = alkyl

N.B. Ka for phenol 1.1×10^{-10} at 25°C

Ka for resorcinol 3×10^{-10} at 25°C

At ambient temperature the equilibrium of (1) is probably well to the right and (2) may be a relatively minor reaction. (A 1:2 solid complex from resorcinol and diethylamine has been isolated by Giles, Rose and Vallance.[85]) The equilibrium of (3) would be expected to lie perhaps equally balanced between the phenol and the salt. Under distillation conditions the effect of (1) is to reduce the partial pressure P_A of cardol to a low level whereas that of cardanol P_C is probably the major contribution to the total pressure, after the free amine has been completely removed.

In the absence of the amine the partial pressure of the cardol is simply a product of its vapour pressure at that temperature and its molar fraction. Similarly that of cardanol is related to its vapour pressure and its corresponding molar fraction. Under these circumstances it is evident that P_A is much higher than when the amine is present and hence the success of the method in separating cardanol from cardol.

This technique of facilitating the separation of one component of a mixture, otherwise non-separable, by the addition of a second component with which it forms some molecular association has been used in the process of extractive distillation.[100] The addition of furfuraldehyde to a mixture of the C_4 hydrocarbons, butadiene, butylenes and the butanes enables the butadiene component to be selectively removed.

Products from the Mannich reaction of cardanol obtained in the preceding way were pale in colour and did not darken on storage.

Table 1

Distillation of technical CNSL treated with Amines

% composition of Technical CNSL - Cardanol 77.1% (Monoene 32.62%)
(diene 19.70%)
(triene 47.68%)
Cardol - 18.8%
2-Methylcardol 4.1%
(9.18 g of tech. CNSL was used with different molar proportion of the Amines)

Amine (Base)	% of CNSL recovered	% of amine recovered	% composition of distillate			% Residue	% composition of residue		
			Cardanol	Cardol	2-methyl-cardol		Cardanol	Cardol	2-methyl-cardol
Blank(no amine)	51.4	-	86.4 (93.6)^{xxx}	9.7 (7.0)	3.9 (0.5)	45.5	59.8 (70.4)	32.3 (27.8)	7.9 (1.8)
DETA (1M)	18.5	-	93	5.1	1.9	75.2	85.6	11.2	3.2
DETA (1.6M)	48.8	87	91.1	6.8	2.1	46.8	75.1	21.7	4.2
DETA (2M)	62.2	93	93.1	5.8	1.1	42.4	63.2	29.1	7.6
*DETA (1M)	47	80	92.05 monoene 33.9% diene 20.4% triene 45.7%	6.2	1.8		44.3 (47.1)$^{+}$	45.1 (42.5)$^{+}$	10.6 (10.3) +
**DETA(1M)			91.7 monoene 33.8% diene 23.0% triene 43.2%	6.6	1.6				
Diethanolamine (1.5M)	56.4	80	88.0 (93.6)	9.7 (6.0)	2.3 (0.4)	42.5	55.7 (68.3)	33.9 (130.9)	10.4 (1.6)

Table 1 contin...

Amine (base)	% of CNSL recovered	% of amine recovered	% of composition of distillate			% Residue	% of composition of residue		
			Cardanol	Cardol	2-methyl-cardol		Cardanol	Cardol	2-methyl-cardol
N-(2-Aminoethyl)-ethanolamine (1.5M)	18.3	83	92.4 (93.4)	5.3 (6.6)	2.3	70.1	75.5 (83.0)	19.8 (15.9)	4.7 (1.0)
NaOH (2% w/w)	29	-	93.7	4.7	1.6		71.0	22.9	6.1

* Distillation carried out using Claisen-Vigreux flask

** The mixture was stored for only 24 hrs. prior to distillation

*** Results obtained with a different GCD and integrator are shown in the brackets.

\+ Results for acid washed residue.

Table 2

Distillation of distilled CNSL treated with DETA

Composition of dist. untreated CNSL - Cardanol 86.9% - monoene 47.3%
- diene 29.9%
- triene 31.81%

Cardol 10.3%
2-Methylcardol 2.8%
(9.18 g dist. CNSL was used with different molar ratio of DETA)

Amine	% of CNSL recovered	% composition of distillate		
		Cardanol	Cardol	2-Methylcardol
DETA (0.25M)	53.3	95.4	3.9	0.7
DETA (0.50M)	62.3	97.7	2.0	0.4
DETA (1.0M)	26.1	93.8 monoene 46.7 diene 21.6 triene 31.7	4.2	2.0
DETA* (1.0M)				

* In this case a Claisen-Vigreux flask was used for distillation

CONCLUSIONS

1. Reaction conditions and structural considerations have been examined for obtaining Mannich bases from long chain phenols. Essentially the introduction of one aminomethyl group per phenol molecule appears to take place.

2. The coloured products which occur with CNSL in the Mannich reaction arises from the dihydric phenols present. The structures of some of the coloured products have been found. By using the simpler model compounds, resorcinol and the primary and secondary monoamines, it has been found that rhodamines and phenoxazines of new structural types are formed.

3. Colour formation in the Mannich reaction of CNSL may be very greatly reduced by removal of the cardol from the CNSL. This can be achieved by a process of extractive distillation in which an organic base of sufficient strength or an inorganic hydroxide is used to form a salt with the cardol whereby cardanol, which does not similarly react can be removed by distillation.

Proposals for further work

1. Structural work on the Mannich bases from CNSL phenol with DETA and TETA.

2. Isolation of further coloured materials from dihydric phenols with organic amines by using HPLC combined with TLC.

3. Examination of reaction mixtures by (i) gas chromatography/mass spectrometry (ii) TLC combined with silylation and mass spectrometry.

4. Studies of rates of reaction and proportion of different structures formed.
5. Synthetic work with a view to exploiting the fluorescence and dye properties of by-products in the Mannich reactions.

APPENDIX 1

Summary of Mannich Reactions of Phenols with Amines and Formaldehyde

Phenol	Amine	Product
Phenol	25% Aq. Dimethylamine	2,4,6-Tris(dimethylaminemethyl)-phenol
m-Cresol	" "	2,4,6-Tris(dimethylaminomethyl)-m-cresol
2-Methoxy-4-allylphenol (Eugenol)	" "	2-Methoxy-4-allyl-6-dimethylaminomethylphenol
3-Pentadecyl phenol(Saturated cardanol)	" "	3-Pentadecyl-6-dimethylaminomethylphenol
4-Isopyopylphenol	" "	2,6-Bis(dimethylaminomethyl)-4-isopropylphenol
4-Tert. butyl-phenol	" "	2,6-Bis(dimethylaminomethyl)-4-tert- butylphenol
4-Tert amylphenol	" "	2,6-Bis (dimethylaminomethyl)-4-tert-amylphenol
2,4,5-Trimethyl-phenol	" "	2-Dimethylaminomethyl-3,4,5-trimethylphenol and 2,6-Bis(dimethylaminomethyl)-3,4,5-trimethylphenol
Tech. CNSL	" "	6-dimethylaminomethylcardanol
3-Pentadecyl-phenol	Diethylamine	3-Pentadecyl-6-diethylaminomethyl-phenol
Resorcinol	Dimethylamine	Polymer
Phenol	Ethylendiamine	Rubbery polymer

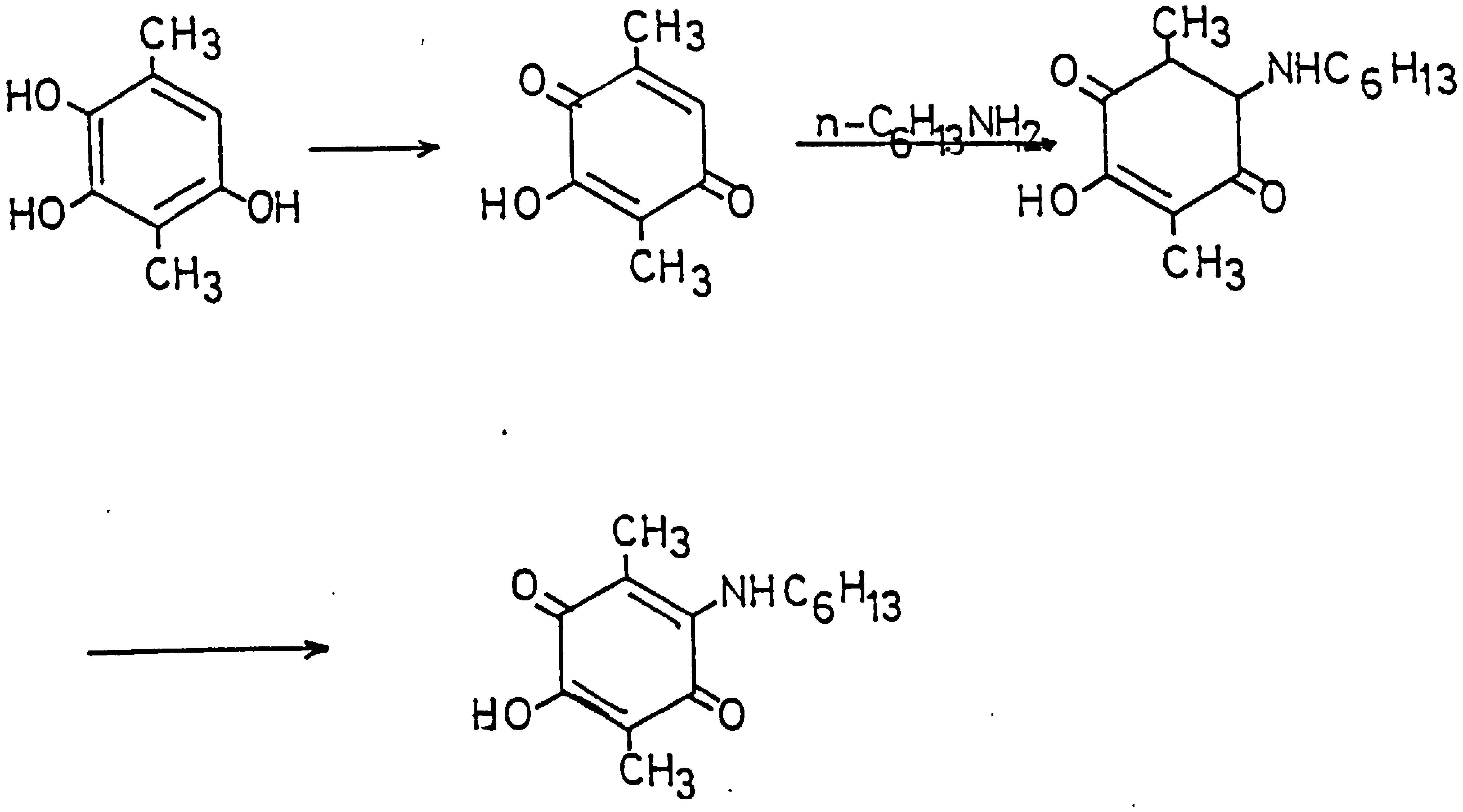
Appendix 1 cont/.

Phenol	Amine	Product
Phenol	Methylamine	Polymer with excess of reagents
m-Cresol	"	Polymer as well as 2-methylaminomethyl-m-cresol
Phenol	Diethylenetriamine	Polymer (resins)
m-Cresol	"	"
Saturated CNSL	"	"
Distilled CNSL	"	"

APPENDIX 2

Reaction of n-Hexylamine with Hydroxy-β-orcinol

The reaction product from the elemental analysis appears to have the molecular formula $C_{14}H_{21}NO_3$ (reqd. C, 66.94; H, 8.37; N, 5.58%). rather than $C_{14}H_{21}O_2N$ (reqd. C, 71.48; H, 8.94; N, 5.96%). The formation may well proceed as follows:



Small differences in the exchangeable protons may well be explained by the presence of some of the trihydroxy starting materialor of water of hydration.

A somewhat different pathway is given by the Japanese authors[75] since in the abstract of their paper the formation of 2-hydroxy-6-n hexylamine-p-xyloquinone is stated to have occured,2,6-substitution and a p-quinone structure are mutually incompatible however. Possibly

Appendix 2 continued:

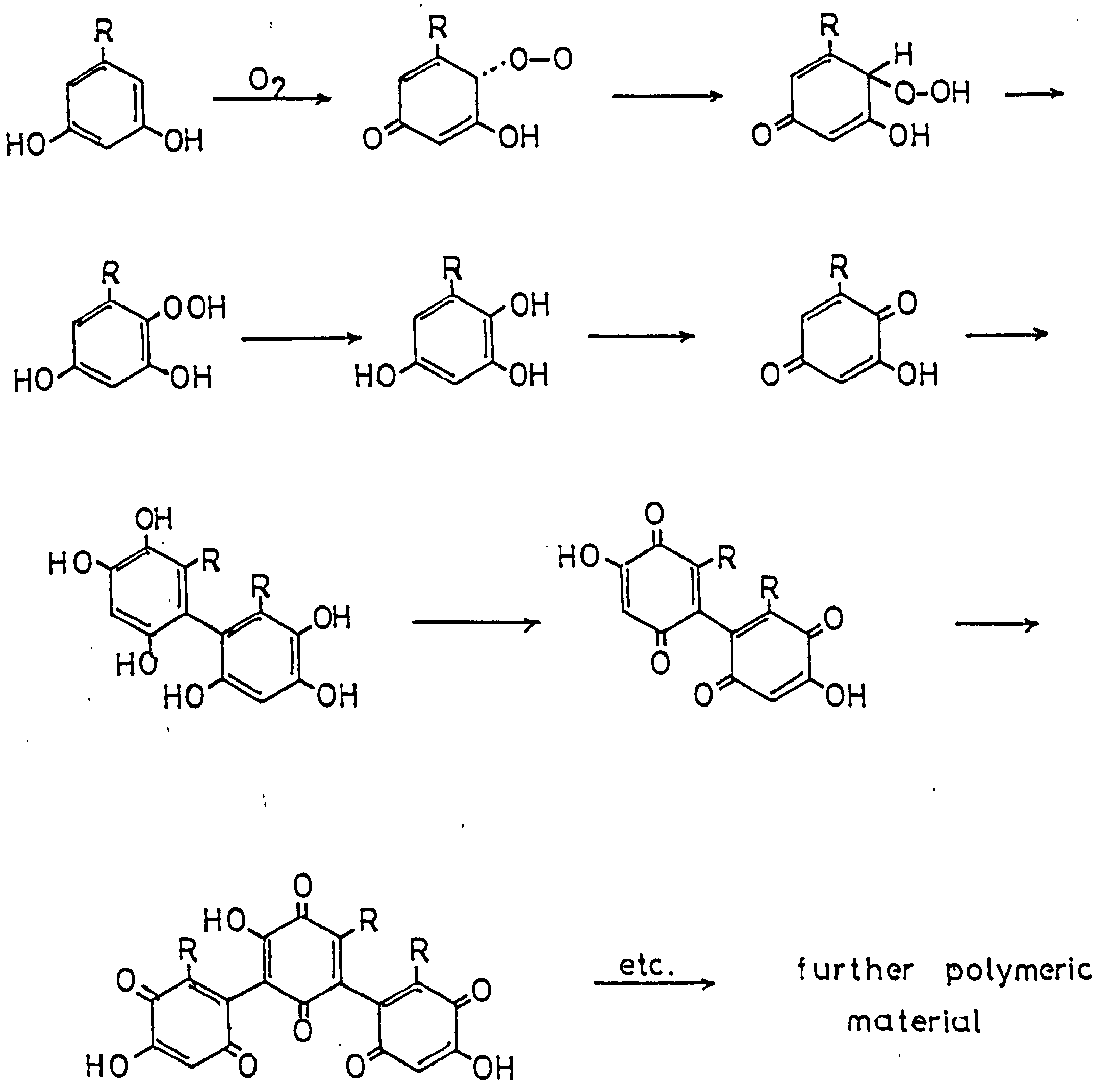
there may be an error in the Abstract.

The course of the reaction involving β-addition to a quinone followed by oxidation is equivalent to the process of direct nucleophilic substitution of an aromatic hydroxyl group

APPENDIX 3

Nature of polymeric material in CNSL

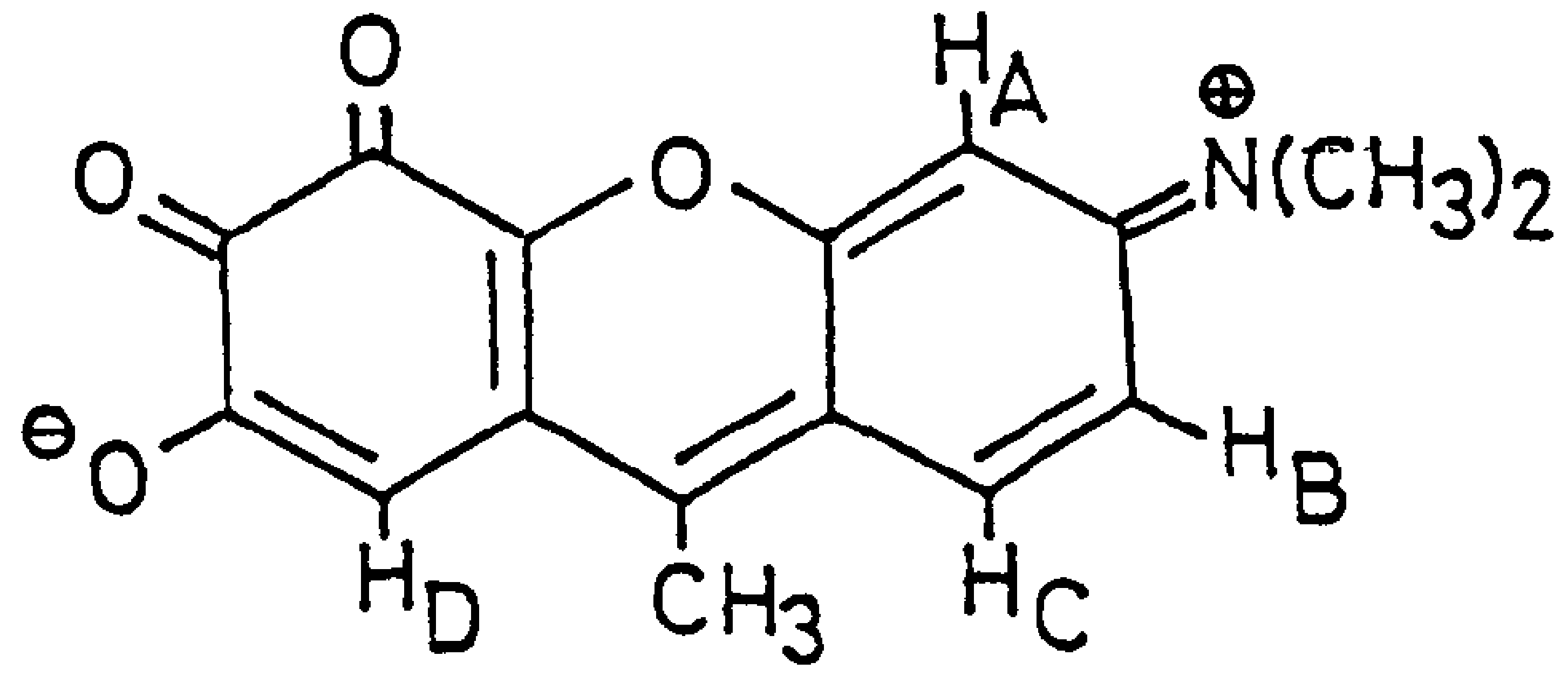
Polymeric material in CNSL appers to consist of colourless dimeric material probably formed by Diels Alder reactions and coloured materials formed by oxidation process. For cardol (R = C_{15}) such a sequence could be as follows:



APPENDIX 4

Calculation of chemical shifts for aromatic protons

The values used in calculation are taken from Table 3.6 in 'SPECTROSCOPIC METHODS IN ORGANIC CHEMISTRY by Williams and Fleming, 2nd Edition'.



$\delta\ H_A = 5.25 - 0.60 + 1.06 - 0.05$

$= 5.6$

$\delta\ H_B = 5.25 + 0.05 + 1.10$

$= 6.35 - 0.85$

$= 6.3$

$\delta\ H_C = 5.25 + 0 + 1.24 + 0.70$

$= 7.19$

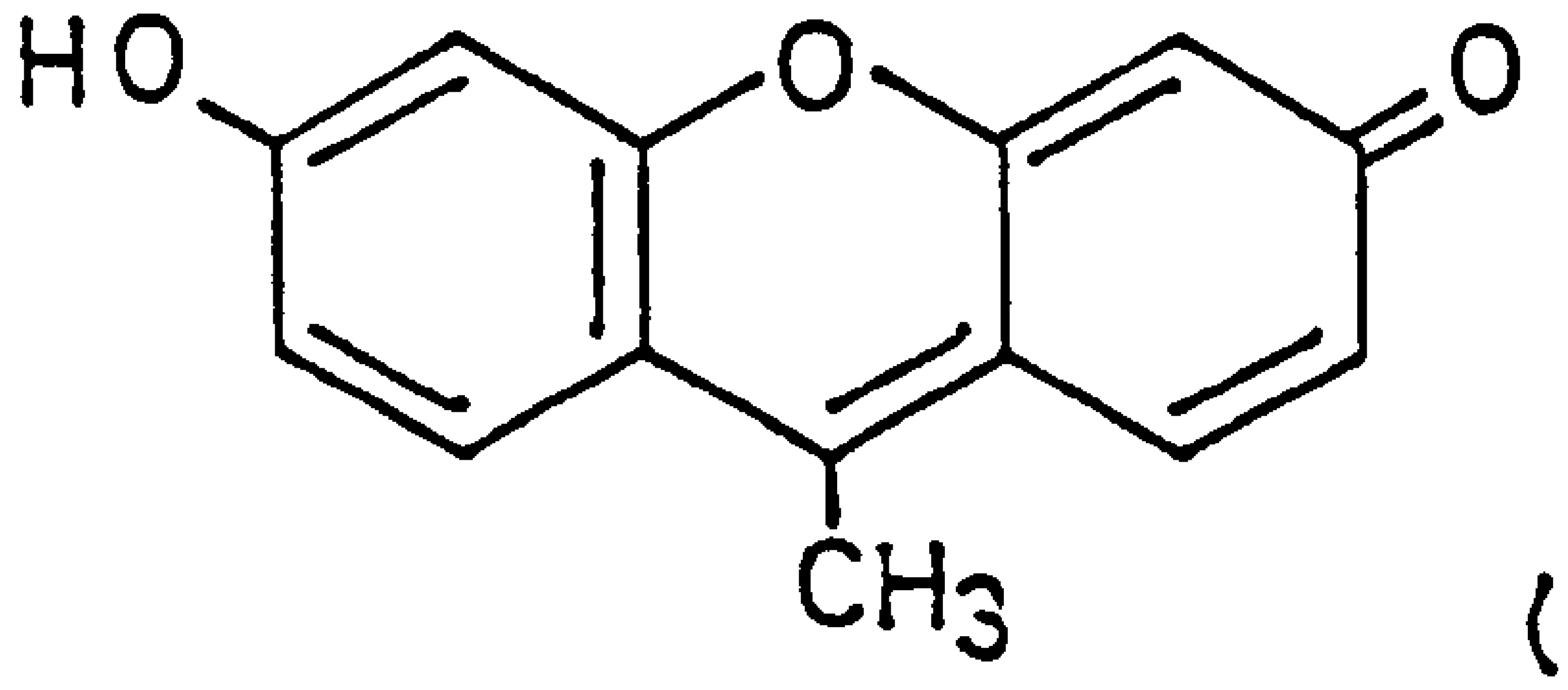
$H_D = 5.25 + 1.06 + 0.02 + 0.7$

$\doteq 7.03$

No values for C=N are given, values for C=O have been used.

APPENDIX 5

Structures of the type belived to be present could be formed by the dehydration of a mixture of resorcinol, 3-dimethylaminophenol and acetaldehyde under acidic-conditions. Indeed the interaction of resorcinol and aldehyde to give compounds such as (I) under acidic conditions has



(I)

been described by R.N. Sen and N.N. Sinha J. Am . Chem. Soc., 1923, 45, 2984. The compound shown is stated to have a green fluorescence.

Under basic conditions the mode of formation of the compounds (NMe_2 and NEt_2 ~~members~~) isolated in the present work may well proceed differently from the above as shown earlier.

APPENDIX 6

It has been reported (original research proposal from 3M Ltd, Chemical Resources Division, St. Paul, Minnesota, U.S.A.) that Mannich reactions with CNSL and ethylene diamine, 1,3-diamine propane, triethylene tetramine, N-aminoethylpiperazine all gave deep red coloured products. The nature of the these could be explained in structural terms similar to the DETA coloured products.

Lighter Mannich bases were obtained when either there was less dihydric phenol present or a nonylphenol was used. 'Purified' CNSL with ethylene diamine gave a lighter product than with DETA. This may suggest that the coloured material is derived rather more from the secondary amine character of DETA than the primary amine.

The external position of the salt forming secondary amino group rather than the eventual internal position of the primary amino group may be a factor in the relative abundance of the two types of coloured product .

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Errata

Page 1	line 6	subtituted should be substituted
Page 6	line 4	Mechanisms of Mannich Reaction should be Mechanism of Mannich Reactions.
Page 11	line 4	kernal should be kernel
Page 16	line 3	di-olefine should be di-olefin
16	line 14	major coponents should be major components
Page 20	line 1	the best conditions should be the best reaction conditions.
20	line 21	(iii) should be (ii)
20	last line	antioxident should be antioxidant
Page 22	line 6	rhodamine 6G should be Rhodamine 6G
Page 24	line	Infra-red should be Infrared
24		Ultra-Violet should be Ultraviolet
24		Hydrogenation should be Hydrogenations
Page 25		Aqueous solution should be An aqueous solution
Page 28		(yellow-organge) should be (yellow-orange)
Page 32		N, 1074 should be N, 10.74
Page 33	last line	Ethenediamine should be Ethylenediamine
Page 47	last line	rhodamine 6G should be Rhodamine 6G
Page 48	line 2	2-me-cardol should be 2-methylcardol
Page 49	Table	2-me-cardol should be 2-methylcardol
Page 50	line 22	using silican should be using a silican
Page 51	Table	2-me-cardol should be 2-Methylcardol
Page 54	line 16-17,	5-methyl resorcinol (0.13g), 4-methyl resorcinol should be 5-methylresorcinol (0.13g), 4-methylresorcinol
Page 67	line 1	Resorcinol/amine mixture should be Resorcinol/Amine mixtures
Page 70	line 21	by GCD should be GLC

Page 77	last line	of mixture should be of a mixture
Page 78	line 6	steric hinderance should be steric hindrance
Page 88	line 7	para branched should be para-branched
Page 88	line 19	ketons should be ketones
Page 98	line 12	rhodamine 6G should be Rhodamine 6G
Page 103	line 9	hetrocyclic should be heterocyclic
Page 113	line 4	ie should be i.e.
Page 114	line 2	due to should be from
Page 115	line 6	Spectualted should be Spectulative
Page 117	line 2	mixture should be mixtures
Page 118	line 1	contains should be contain
Page 118	last line	dihyric should be dihydric
Page 119	line 1	affect should be effect
P. 120	line 12	with Vigreux should be with a Vigreux
P. 120	line 18	affect should be effect
P. 121	line 12	3M Ltd. should be 3M Ltd.,
P. 121	line 16	occur should be occurs
P. 125	Table 1	insert figures for DETA* 1.0M, 93.5, 5.4, 1.1%
P. 126	Table 2	last line (130.9) should be (30.9).
P. 128	line 1	considerations should be requirements
P. 129	line 1	proportion should be proportions
p. 130	line 2	(dimethylaminemethyl) should be (dimethylaminomethyl)
p. 130	line 9	2,4,5-Trimethyl-should be 3,4,5-Trimethyl-
p. 130	line 6,	4-Isopyopylphenol should be 4-Isopropylphenol
p. 130	line 7,	7,4-Tert. butyl should be 4-Tert-butyl

Page 130	line 8	4-Tert amylphenol should be 4-Tert-amylphenol
Page 140,	Ref 66,	Inustrial should be Industrial
Page 138	Ref 4,	M. Miocqus should be M. Miacque
Page 139	Ref 36	J of pharm. sci., should be J. Pharm. Sci.,
Page 141	Ref 76	Ind. J. Chem., should be Indian J. Chem.,
Page 141	Ref 79	p. 4003i should be P4003i
Page 27	line 16	$(N-(CH_3)_2)_2$, 3.25 (3H, s, $ArCH_3$), 3.43 (2H, s, $ArCH_2$), 3.50 (4H, s, should be $(N-(CH_3)_2)_2$), 2.82 (3H, s, $ArCH_3$), 3.25 (2H, s, $ArCH_2$), 3.43 (2H, s, $ArCH_2$), 3.50 (2H, s, $ArCH_2$),
Page 51	Table	1st line Cardol should be Cardanol
Page 73	line 3	fromaldehyde should be formaldehyde
Page 103	line 8	diethylanetriamine should be diethylenetriamine
Page 107	Foot note	chemical shits should be chemical shifts
Page 117	line 8	anti-oxident should be anti-oxidant
Page 118	line 6	distillate should be distillates
	15	cobumn should be column
	16	method not should be a method not
Page 122	line 1	low K_b values should be lower K_b values
Page 103	line 9	hetrocyclic seemed should be heterocyclic systems seemed