ATTEMPTS TOWARDS THE SYNTHESIS OF KOSOTOXIN AND ANALOGUES

A Thesis Presented to
the School of Graduate Studies
Addis Ababa University

In Partial Fulfillment
of the Requirements for the Degree of
Master of Science in Chemistry

by
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June, 1982

To my grandmothers.

ACKNOWLEDGEMENTS

I wish to express my sincere appreciation to Dr. Ermias Dagne for his conception of this problem, for his guidance, encouragement and for creating the most favourable situation possible to do the research.

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Abbreviations

Me	=	Methyl, CH_3
Et	=	Ethyl
Al	=	Aryl
IR	=	Infrared
NMR	=	Nucles magnetic resonance
UV	=	Ultraviolet
mp	=	Melting point
lit	=	Literature
Mass spec	=	Mass spectrum
gm	=	gram
Nit.	=	Nitration
Red	=	Reduction
Hy	=	Hydrolysis
Acy	=	Acylation
OX	=	Oxidation
Concd.	=	Concentrated

Abstract

Attempts towards the synthesis of

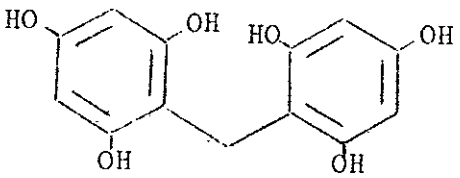
Kosotoxin and Analogues

by

Gizachew Alemayehu

Advisor: Dr. Ermias Dagne

As part of our attempts to synthesize Kosotoxin (1) simple synthetic procedures for the synthesis of related compounds A, B, C, shown below have been developed. Furthermore D and F which are key intermediates for the synthesis of Kosotoxin analogues, and F and G which are supposed to be kosotoxin analogues have also been synthesized. In addition the chemistry of unsymmetrical condensation of acylated polyhydroxy compounds has been studied.



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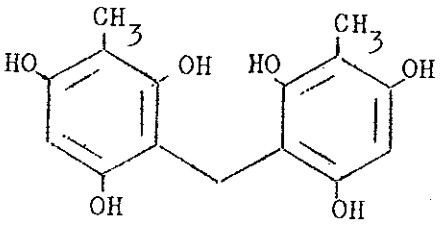

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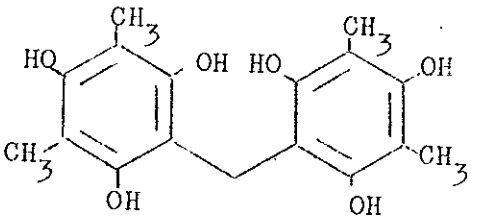

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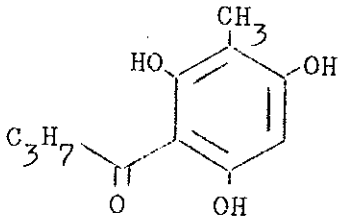

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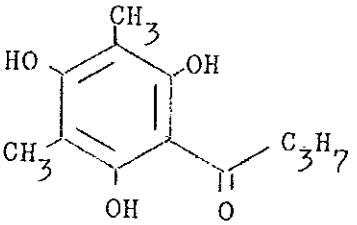

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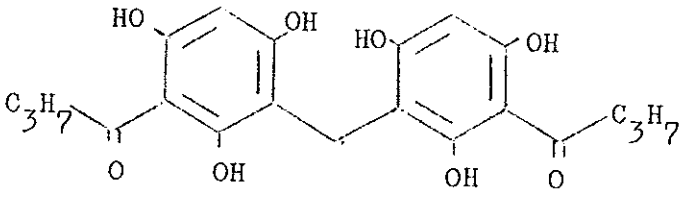

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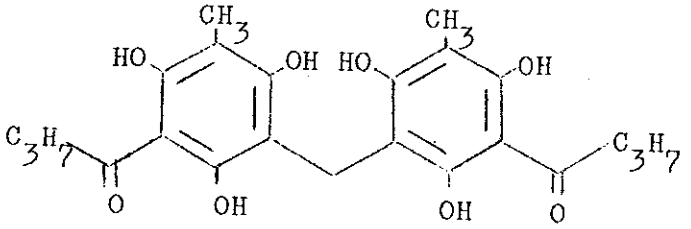


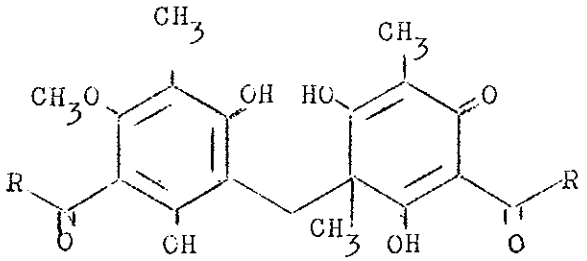
G

HISTORICAL BACKGROUND OF KOSOTOXIN (1)

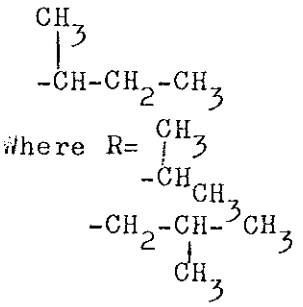
1. Introduction

Hagenia abyssinica, a slender tree which grows upto 20 m.[1] is the most widely used taenicidal plant in Ethiopia. It is a diocious tree, but only the female flowers are used as an anthelmintic in the name of 'Kosso'. The isolation and characterization of Kosotoxin started in the last century as can be deduced from papers on the subject which appeared in 1874[2] and 1893[3].

Most of the proposals for the chemical structure of the constituents of the female flowers did not stand the test of time and repeated revisions were made over the years.[4-9] The recently published work by Mauri Lounasmaa and his group presented the following structure of Kosotoxin as a result of extensive spectral analysis and examination of degradative products.[10-12]



1
Kosotoxin

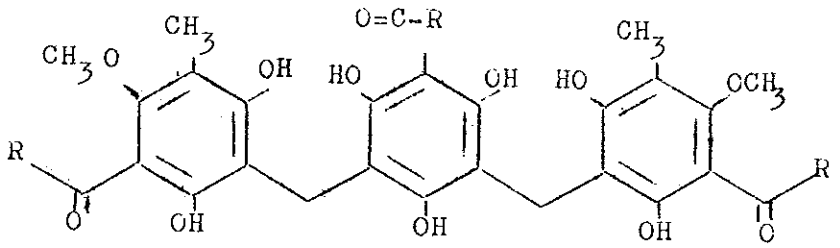


The group also reported the following physical properties: color: yellowish plates, M.P. 119 - 122° , $[\alpha]_D^{25}$ + 8.1°, λ max. 226 m (ϵ 18,900), 283 (ϵ 19300).

Kosotoxin as the name implies is a fairly toxic substance and doses as small as 4 mg are sufficiently lethal to frogs.[13] Although not yet experimentally established, this compound may probably be responsible for both the toxicity and medicinal efficacy of the female flowers. Its total synthesis has not been to date reported. In view of this, the main objective of this project was to attempt the synthesis of kosotoxin and other structural analogues, so as to be able to fully investigate their properties and potential uses.

2. Isolation and Characterization of Kosotoxin (1)

According to early investigations[14] kosso flowers contain phloroglucinol derivatives. In 1937 Hems and Todd[4] isolated from commercial 'kosso' a substance having the recorded prop rties of protokosin (2) together with some kosotoxin (1).[3] Later Birch and Todd isolated crystalline protokosin (2) and an amprphous product which was supposed to be kosotoxin (1).



2
Protokosin

Where R = $-C_3H_7$
$-C_4H_9$

In 1973, a Finnish group published the result of its investigation on the structurally related phloroglucinol derivatives in Hagenia abyssinica.[14] This group isolated the phloroglucinol derivatives with either from which were separated four crystalline compounds (K_1, K_2, K_3 and K_4) by column chromatography on silica gel and n-hexane-chloroform as eluting solvent.[14]

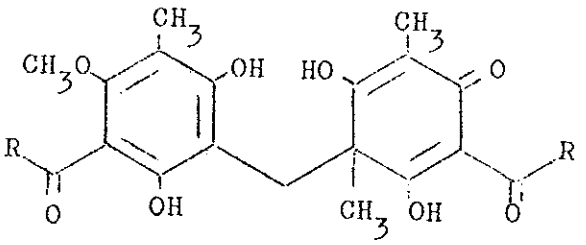
By comparing with previously reported prop rties for kosotoxin, this group concluded that K_2 is the biologically active kosotoxin.

From spectral analysis of K_2 and its degradation products, the Finnish group was able to propose, a partial structure for kosotoxin (1).

Later in 1974 the same group reinvestigated the phloroglucinol derivatives from Hagenia abyssinica. On the basis of reductive alkaline cleavages and spectroscopic evidence structure (1) was proposed for kosotoxin.[11]

According to this group, this bicyclic phloroglucinol derivative was isolated according to previously reported methods.[15] These workers, stated that, repeated recrystallization from hexane of the chromatographic fractions rich in kosotoxin gave yellowish plates, mp. 119 - 122°C, lit. 110 - 112°C. The optical activity of kosotoxin is in agreement with the asymmetric structure proposed. The products formed by alkaline cleavage also support structure (1). The mass spectrum showed peaks at M/e 488, 474, 460 corresponding to $C_{27}H_{36}O_8$, $C_{26}H_{34}O_8$ and $C_{25}H_{32}O_8$ respectively. The peaks at M/e 431 and 417 support the assumption that Kosotoxin (1) is a mixture of C_4H_9 - and C_3H_7 - side chain homologues and support structure (1). The NMR spectrum ($CDCl_3$, TMS) is also in agreement with the proposed structure (1).

In 1974 Lounasmaa and his group investigated the products formed from (1) by reductive alkaline cleavages in different experimental conditions. The group proposed the following cleavage scheme for (1)[16]



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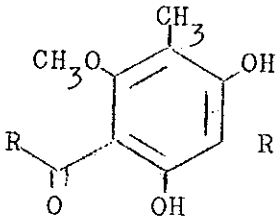

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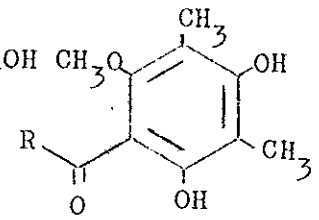

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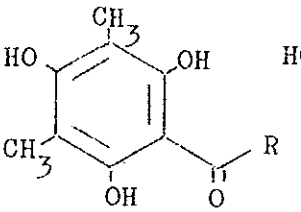

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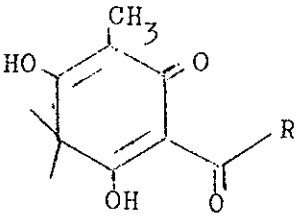

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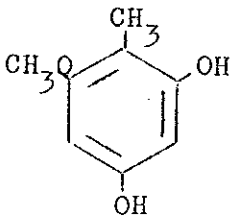

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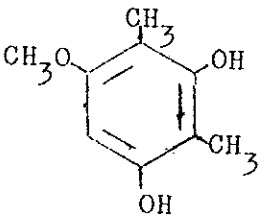

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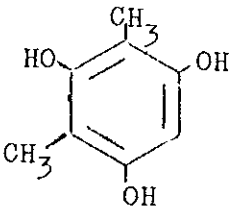

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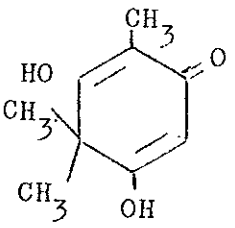
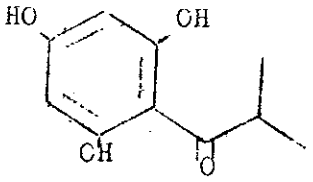


10

According to this group,[17] the second step in the decomposition of (1) could be expected to give (7), (8), (9) and (10). However none of these second step decomposition products were found after cleavage according to procedures A, B and C. Owing to this the group tried, a fourth but a much more drastic variant of alkaline cleavage, called cleavage D.[18] This time large quantities of (7), (8), (9) and (10) were detected. Most of the model compounds used for comparison were prepared by C-methylation of isobutyrophloroglucinol (11)[19]. The resulting products were mixtures separated by column chromotography on silicagel with hexane-benzene as eluent.



11

Finally in 1977, Mauri Lounasmaa utilized ^{13}C NMR spectroscopy to confirm the structure of kosotoxin (1).

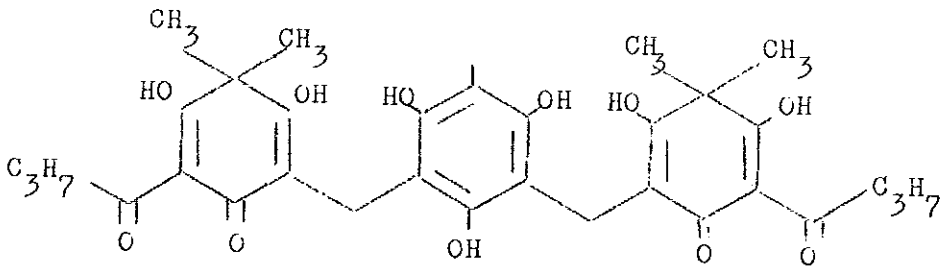
II. LITERATURE REVIEW ON PHLOROGLUCINOL DERIVATIVES

Phloroglucinol derivatives such as kosotoxin (1) and protokosin (2) were isolated from Hagenia abyssinica beginning the last century.[10]

The preparation of phloroglucinol (13) by hydrolysis of S-triaminobenzoic acid is a well established method.[22] The preparation of 2,4,6-trihydroxytoluene (14) and 1,3-dimethyl-2,4,6-trihydroxybenzene (15) by hydrolysis of the corresponding amines is recorded in the old literatures such as Beilstein.[23]

The symmetrical condensation of phloroglucinol (13)[63], methylphloroglucinol (14)[64] 1,3-dimethylphloroglucinol (16)[65] with formaldehyde is also well established.

In 1896 Boehm[25] while working on a natural product known as filicic acid (12) described its decomposition into four phloroglucinol derivatives namely phloroglucinol (13) mp 214 - 216°C, dimethylphloroglucinol (15) mp 162 - 163°C and trimethylphloroglucinol (16) mp 184°C, by using zinc and sodium hydroxide. The four phloroglucinol derivatives were separated by extraction with ether and crystallization from benzene.



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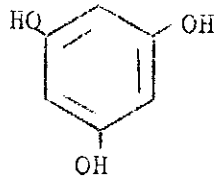

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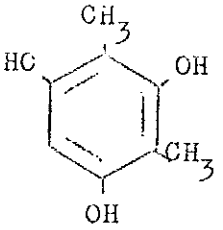

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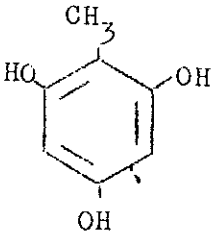

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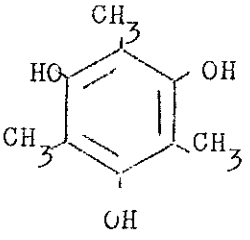
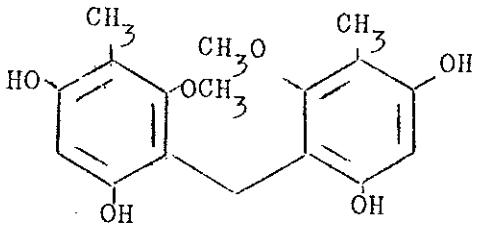


16

Riedl[26] while working on the structural elucidation of phloroglucinol derivatives obtained from plant sources observed the formation of (20) during the reduction of α-kosin (18) by sodium amalgam.



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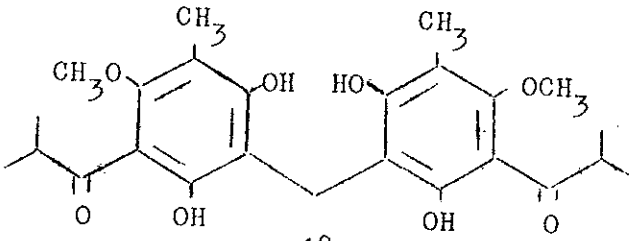

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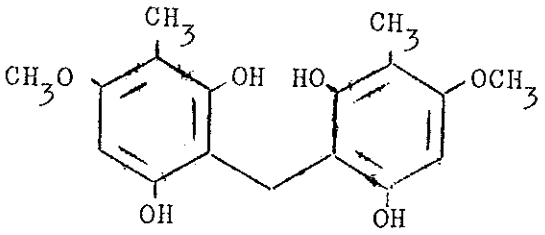
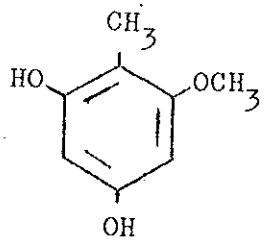


19

Riedl rationalized his observation by the cleavage of the acyl groups as isobutyryl aldehyde from (18) giving rise to (19) which isomerizes to the stable (20)

Again this worker in order to further prove the structure of ~~α~~ -kosin (18) by synthesis prepared 4,6-dihydroxy-2-methoxy-3-methyl-isobutyrophenone (22) by condensation of 2-methylphloroglucinol-1-methylether (21) with isobutyronitrile,



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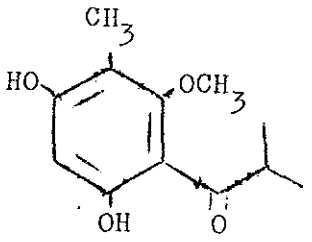
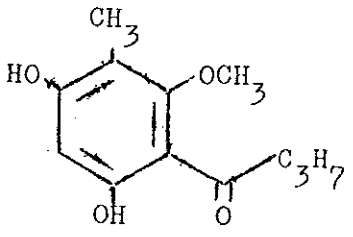


22

Later, Riedl[27] working on unsymmetrical condensation of phloroglucinol derivatives reported the synthesis of (25) and (26) by condensation of (23) and (24) with formaldehyole in alkaline solution.



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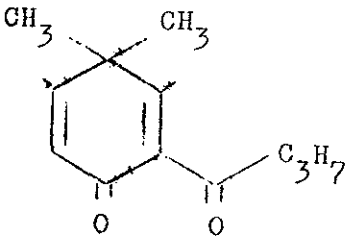

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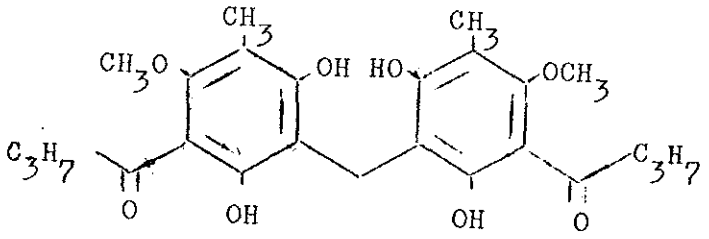

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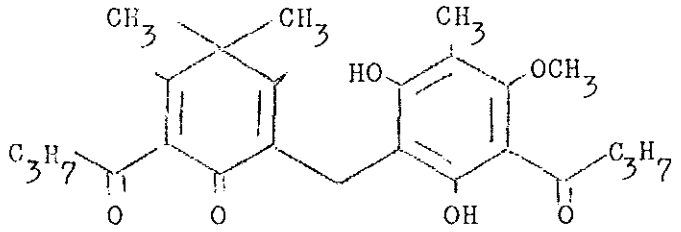

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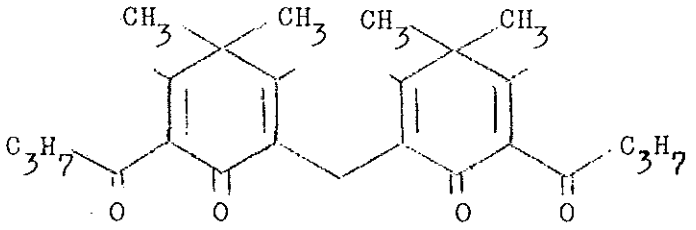
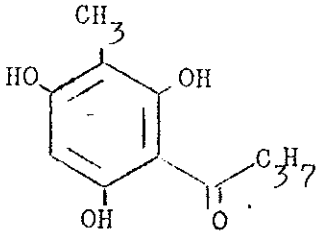


27

According to Riedl (17) was not observed because of its high alkaline sensitivity.

Riedl[27] working on the selective methylation of phloroglucinol derivatives, reported the synthesis of (31) by partial benzylation and methylation of (28). The reaction of (28) with benzyl bromide and potassium carbonate in acetone gave in small yield (7%) the dibenzylether (29) which could be methylated with dimethyl sulfate, K_2CO_3 in acetone to compound (30) quantitatively. Catalytic debenzylation (pd/c) gave compound (31) of mp 71 - 72°C.



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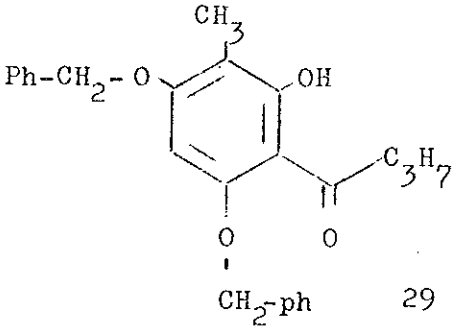

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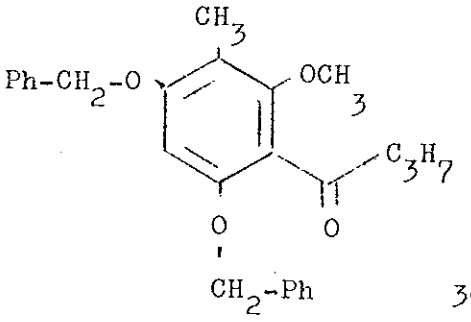

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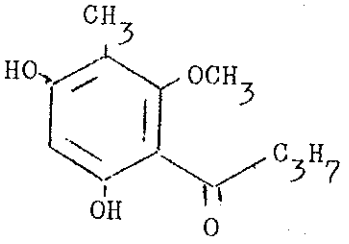

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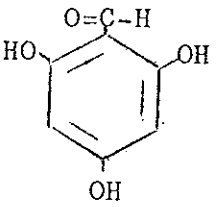
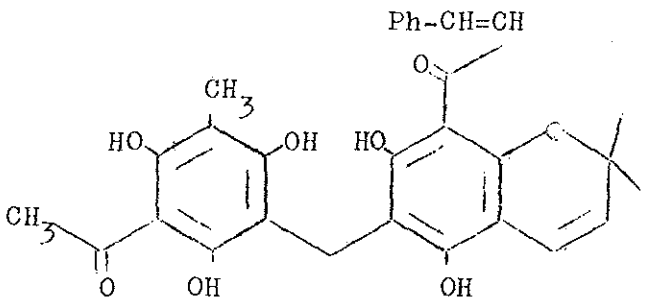


32

The acylation of phloroglucinol (13) by the Hoesch method is well known as early as 1930. In fact there is an extensive review on the scope of this method for acylation of phloroglucinol by Paul E. Spoerri and Adrien S. Dubois.[28]

The preparation of methylphloroglucinol (14) from phloroglucinol aldehyde (32) by catalytic hydrogenation at 65 lb/in^2 is also reported.[29]

In 1950, McGookin[31] et. al. investigated the disproportionation of Rottlerin (33) in basic and acidic media.



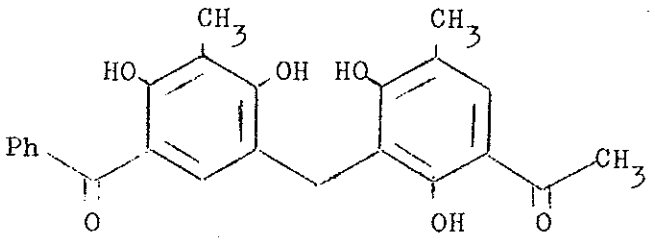
33

Rottlerin is isolated from "Kamala" an Indian coloring matter and anthelmintic drug, mp 212°C.

It has been shown by this group[31] that Rottlerin and its hydrogenation products are unsymmetrical polyhydroxy diarylmethanes of the type RCH_2R' which on treatment with warm acidic or alkaline reagents undergo disproportion according to the scheme.

$$2RCH_2R' \longrightarrow RCH_2R + R'CH_2R'$$

These workers, in addition to the synthesis of symmetrical diphenylmethanes[31] reported the synthesis of a series of unsymmetrical diphenylmethanes (34), (35), (36), (37), (38), (39), (40) from aqueous formaldehyde or paraformaldehyde and mixtures of the appropriate pair of ketones.



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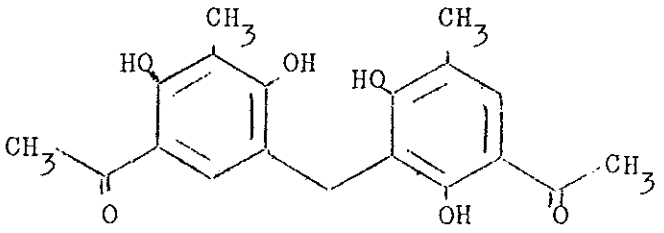

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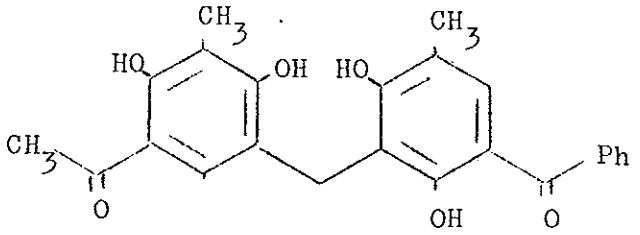

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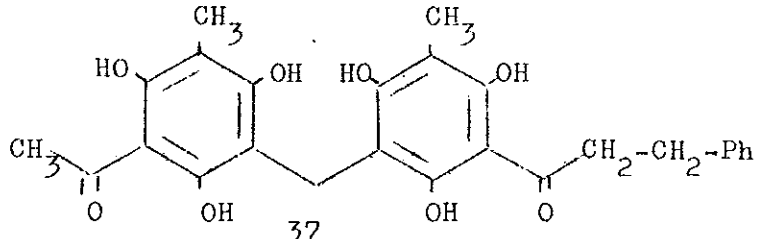

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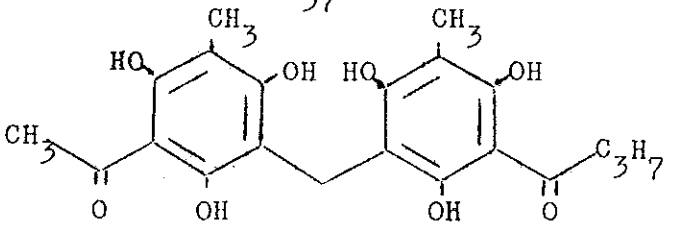

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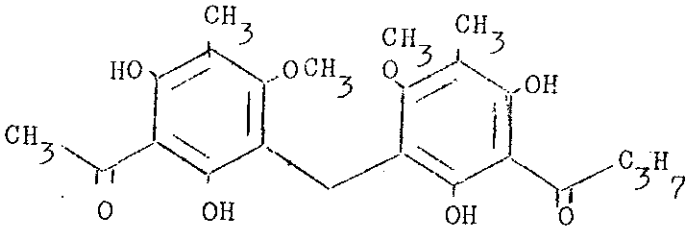

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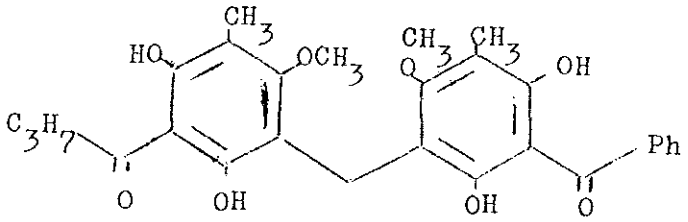
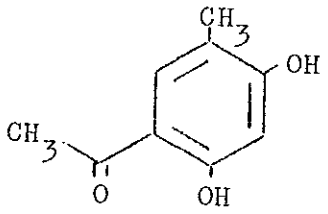


40

As expected each of the compounds was accompanied by the appropriate pair of symmetrical products.

However the group[31] found that with either of the following pair of ketones namely:-



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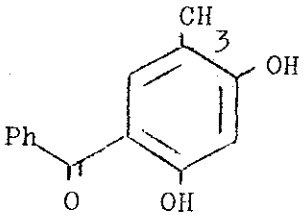

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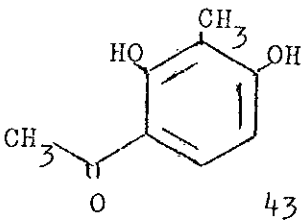

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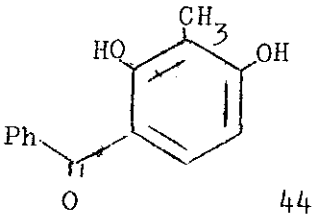

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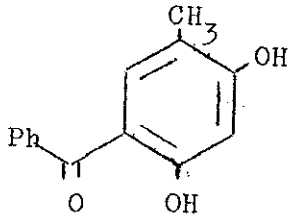

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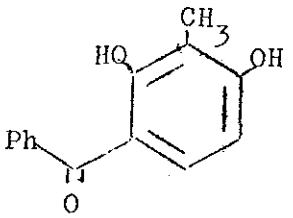

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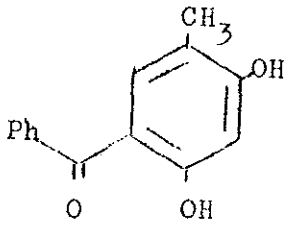

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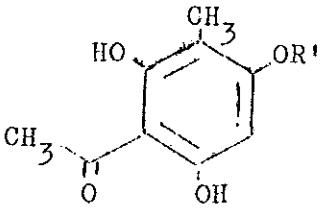

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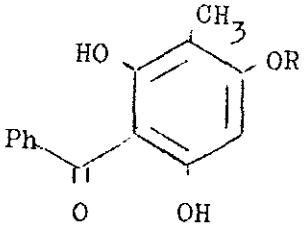

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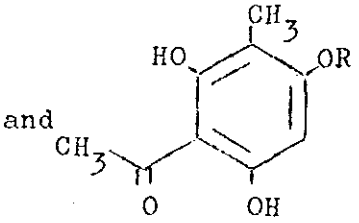

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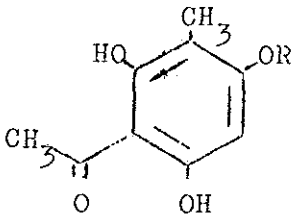

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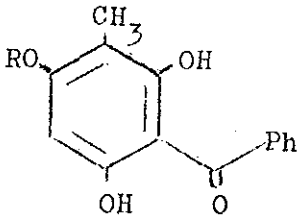

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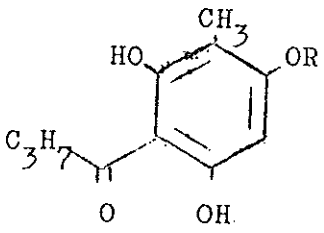

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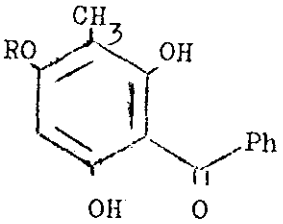


54

the unsymmetrical product was not formed in quantities detectable by fractional crystallization and chromatography. Attempts to prepare the hydroxy-benzyl alcohols from the above mentioned ketones by the alkali formaldehyde method were unsuccessful, and hence it was not possible to prepare the unsymmetrical diphenylmethanes by this route according to these workers.

From this the group concluded that certain unsymmetrical polyhydroxy-diphenylmethanes can be prepared neither by the phenol-formaldehyde reaction nor by the dispropertion method, reversing the rotelerone change.

The workers pointed out that the disproportionation reaction is clearly a reversible hydrolysis, and may be represented thus:

a) $RCH_2R' + H_2O \longrightarrow RCH_2OH + R'H$

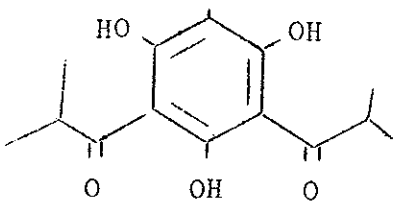
b) $RCH_2R' + H_2O \longrightarrow R'CH_2OH + RH$

c) $RCH_2OH + RH \longrightarrow RCH_2R + H_2O$

d) $R'CH_2OH + R'H \longrightarrow R'CH_2R' + H_2O$

Of the steps (c) and (d) it is clear that if one is much more rapid than the other the final product of the forward reaction will be almost wholly a symmetrical compound involving the more reactive phenol. The group maintained that it seemed likely that a polyhydroxy diphenylmethane formed from a less reactive phenol should be completely decomposed on being heated with a more reactive phenol.

In 1972, T. Meikle and R. Stevens, reported that treatment of a mixture of anhydrous phloroglucinol (13) and isobutyric acid with borontrifluoride yielded diisobutyryl-phloroglucinol (55) which was methylated with an excess of methyliodide-soduim ethoxide to give diisobutyryl filicinic acid (56).



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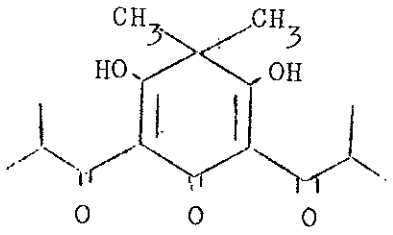
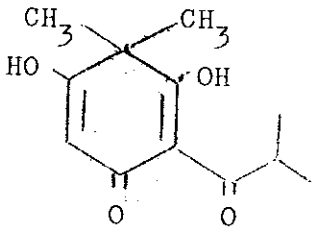


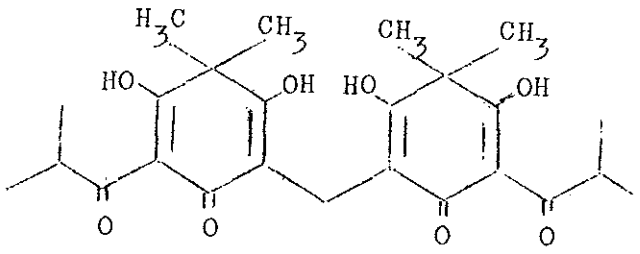
56

According to this workers, selective deacylation of (55) with 80% sulfuric acid gave monoisobutyryl filicinic acid (56).



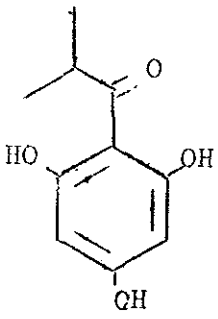
57

Condensation of (57) with formaldehyde afforded (i B i B) (58).



58

Alkylation of phloro-isobutyrophenone (59) with 1-Bromo-3-methyl-but-2-ene (60) (1 mole equivalent) gave mono-iso-pentenyl phloroisobutyryl phenone (60)



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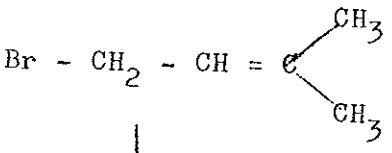

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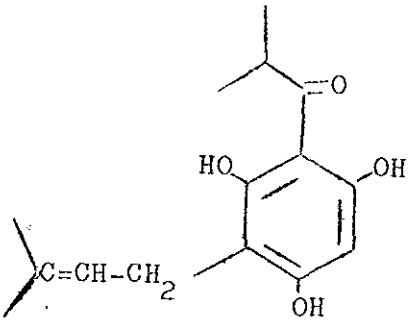
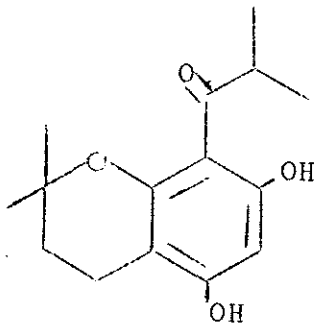


61

Treatment of (61) with toluene-p-sulfonic acid gave a mixture of (62) and (63) mp 145°C and 142°C respectively, and separated by fractional crystallization.



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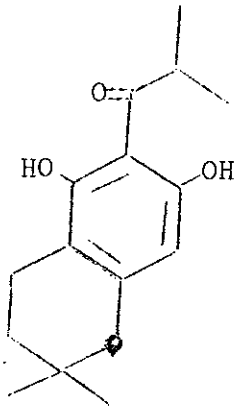
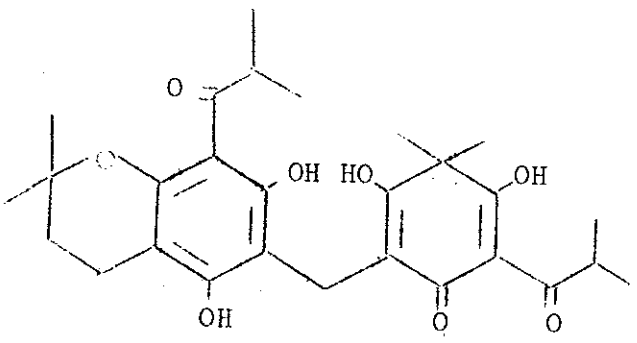


63

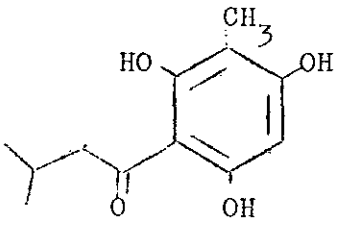
The group[32] ascertained that attempts to effect mixed condensation of (61), (62) or (63) with (57) gave mixtures from which only symmetrical products could be isolated. However the group also pointed out that treatment of albaspidin (iB iB) (58) with an excess of the disodium salt of (62) in methanol under reflus afforded dihydrovliginosin B (64) in 80% yield.



64

In 1956, Japanese workers[33] led by Isao Inagaki, reported the synthesis of a series of phloroglucinol derivatives of the type: 2,1,3,5-RCO $C_6H_2(OH)_3$ where R is n-C_7H_{15}-, n-C_4H_9-, n-$C_{10}H_{21}$, n-$C_{11}H_{23}$, $Me_2CHCH_2CH_2$-, P-OH $C_6H_4CH_2$-, P-$O_2NC_6H_4CH_2$-, and Me (RCO) C_6H $(OH)_3$, where R stands for n-C_5H_{11}-, Me_2 CH CH_2-CH_2-.

This group also reported the condensation of (65) in 2N NaOH and 7 ml of water mixed with 0.05 ml of 26.5% formalin, letting it stand for 15 minutes, acidified with 2N HCL, heated a while on a water bath, and the product recrystallized from 98% EtOH to give methylene bis-(isovaleryl methyl phloroglucinol) (66) needles mp 260 - 2°C.



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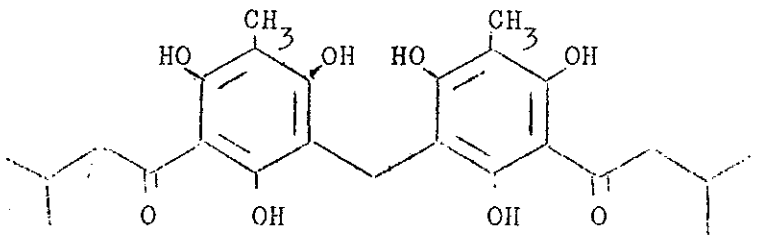
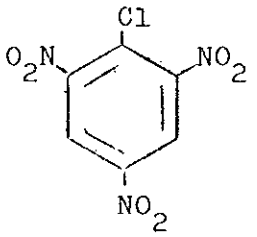


66

In 1959, P.M. Heertjes et al.,[34] described various methods for the preparation of phloroglucinol (13) from picryl chloride (67).



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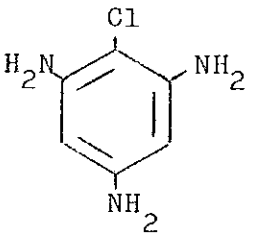


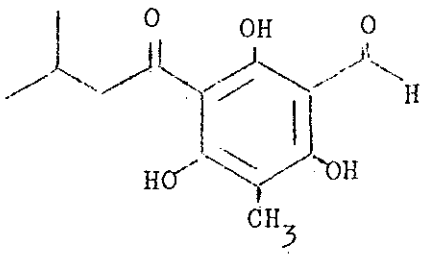
68

The reduction of (67), the group stated, with tim and HCl gave 40% 2,4,6-triaminochlorobenzene (68), which afforded 82% (13) on prolonged boiling in aqueous HCl, Reduction of (67) with Fe, according to this workers, was not satisfactory. An electrical method is also described for the reduction of (67) to 2,4,6-triaminochlorobenzene (68) followed by hydrolysis to (13) in 93% over all yield.

In 1963, Kalle[35] et al. observed that the hydrolysis of S-triaminobenzene to trihydroxy benzene is catalized by Cu or CuCl. Thus, according to this workers refluxing under inert gas of 2,4,6-triaminobenzoic acid, Cu. H_2SO_4 (P^H1) gave 80% of phloroglucinol (13).

In 1968, another group[36] prepared (13) by catalytic hydrogenation of trinitrobenzene or trinitrobenzoic acid 60 lb/in^{2}H pressure and 85°C, followed by hydrolysis in 69% yield.

In 1978, Francisco et al.,[37] reported the synthesis of grandinol (69), a root inhibitor from the adult leaves of Eucalyptus grandis, by reduction of 2,4,6-trinitrotoluene (83) with Sn and HCl (32%), followed by hydrolysis to give 2,4,6-trihydroxytoluene which after Friedl-Crafts acylation with isovaleryl chloride (23%) and formylation gave grandinol (69) in 25% yield.



69

In 1979, Heikki Pysalo et al.[38] described the application of glass capillary gas chromatographic methods, for structural determination of naturally occurring bicyclic and tricyclic phloroglucinol derivatives.

According to earlier papers[39,40] the decomposition reactions of naturally occurring polycylic phloroglucinol derivatives can be divided into the following three steps:

(1) $2ACH_2B \longrightarrow ACH_2A = BCH_2B$

This is the so called rottlerone change, which is a typical behaviour of methylene-bis-polyhydroxy-phenols (polyhydroxy-diphenylmethanes). This reaction type has been observed in both alkaline and acidic medium and by gentle heating of the polyclic

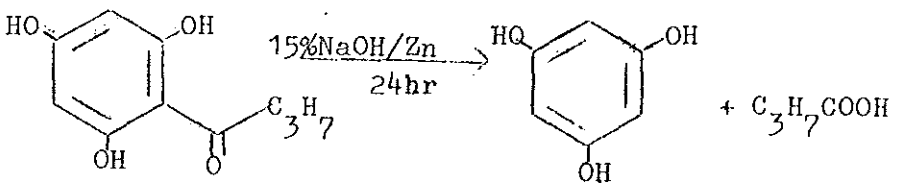
phloroglucinols in their melting range. It also occurs in the ionization chember of a mass spectrometer at high vacuum.[38]

(2) Cleavage of the methylene bridge between the rings:

$$A\text{-}CH_2\text{-}B \xrightarrow[5\ min]{} A + CH_3B + A\text{-}CH_3 + B$$

A and B are acylphloroglucinol derivatives. This reaction occurs on heating polycyclic phloroglucinols for short period with dilute lime (NaOH) under reductive conditions and leads to the formation of several different monocyclic acylphloroglucinol derivatives. Some rottlerone change may also occur as a side reaction.

(3) Cleavage of the acyl side chain of the phloroglucinol rings.[38]

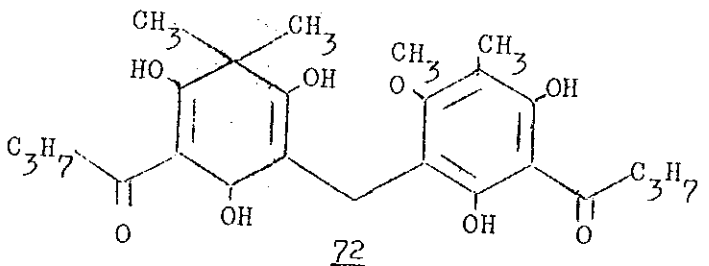


70 71

This reaction occurs on heating acylphloroglucinol with more concentrated lime (NaOH) under reductive conditions for several hours.

Pysalo[38] reported that, when P-aspidin (72) was silylated and injected into the chromatograph decomposition according to scheme 2 mainly occurred, and aspidinol B (75) and 3-methylbutyryl

filicinic acid (76) were observed among the decomposition products. However, the group pointed out, that butyryl filicinic acid (73) was not observed.



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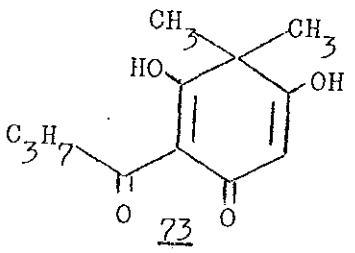

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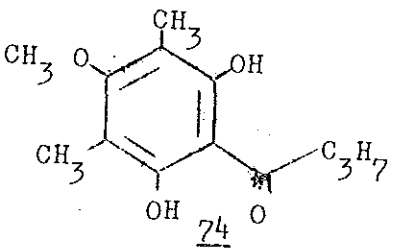

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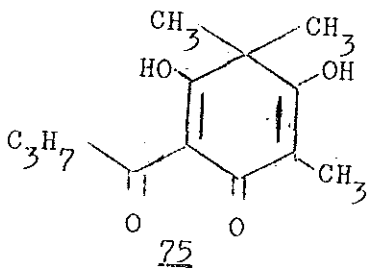

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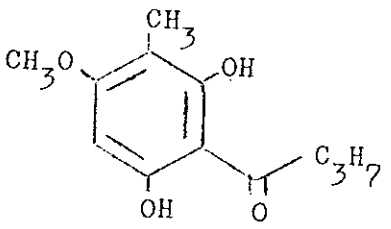
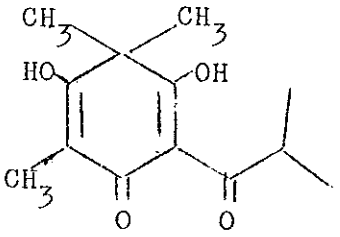


76

Later, according to this group, upon reductive alkaline cleavage of the methylene bridge between the rings of (72) and silylation of the products formed, butyryl filicinic acid (73) and Aspidinol B (76) were detected.

In 1980, Widen et al.[42] reported the separation of a series of naturally occurring Drypteris, Hagenia, and Mallotus, compounds and several artefacts by reversed-phase high performance liquid

chromatography. According to these workers the easily occurring decomposition of polycyclic phloroglucinols during chromatography would be totally avoided using slightly acidic conditions. By this method, the group reported, the investigation of the following phloroglucinol derivatives (77), (78), (1), (79), (80), (28) and (2)



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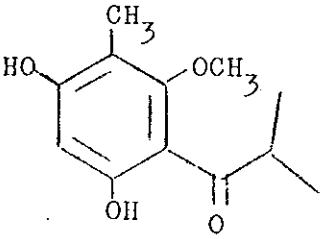
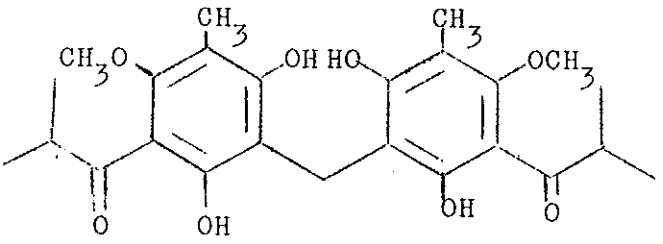


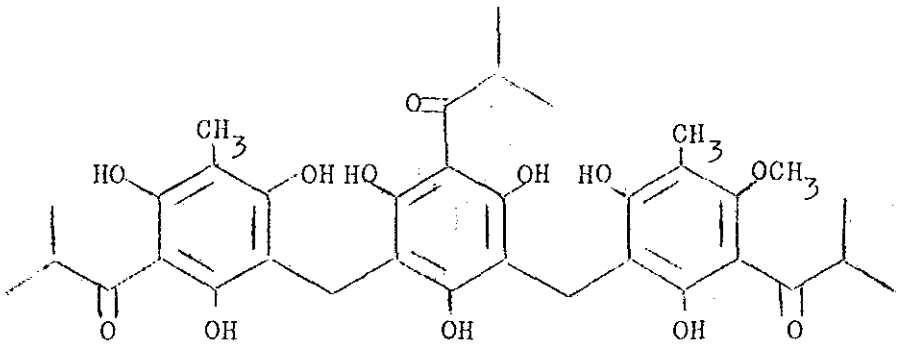
78

3-methylisobutyryl filicinic Pseudo-aspidinol iB (iV,2MeB) acid



79

(1) - Kosin iBiB(iV,2MeB)



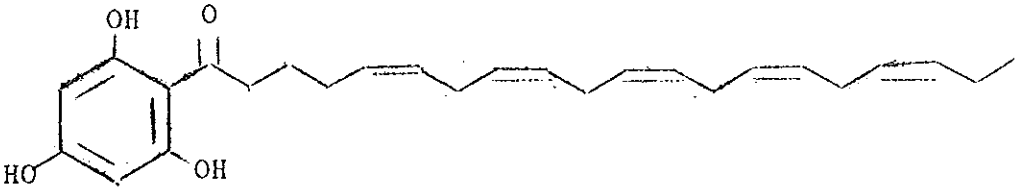
80

Tripseudo-aspidinol iBiBiB (iV,2MeB)

The group stated[42] that these compounds can be well separated in HPLC system, however owing to the existence of homologues (iB,iV,2MeB) the peaks of the naturally occurring kosotoxin (1) and protokosin (2) are broad and show minor side peaks. In TLC separation of these two compounds has not been achieved.[43] In 1977, E. Dagne[77] and his co-worker, while working on the comparative study of the male and female flowers of Hagenia abysinica, reported the same R_F value for kosotoxin (1) and protokosin (2) in different solvent systems.

In 1981, Vincenzo et al.,[45] reported the isolation and characterization of a phloroglucinol derivative (81) from the brown alga zonaria tournefortii.

Zonaria Tournefortii is a brown see weed, occuring in the mediteranean waters.



81

Using the above survey as a background material, we set out to synthesize kosotoxin. However first of all we focused our attention on the development of facile synthetic methods for the synthesis of the not readily available starting materials namely the substituted trihydroxybenzenes.

Our main approach then would center around the synthesis of the two halves of kosotoxin followed by coupling these halves to give rise to the desired natural product (1).

III. RESULTS AND DISCUSSION

The synthesis of kosotoxin and its structural analogues demanded phloroglucinol derivatives as starting materials. Phloroglucinol is commercially available, where as methyl phloroglucinol and dimethyl phloroglucinol are not. As a result considerable effort was made to develop simple methods of synthesizing these starting materials. Schemes 1 and 2 show the reaction sequence followed.

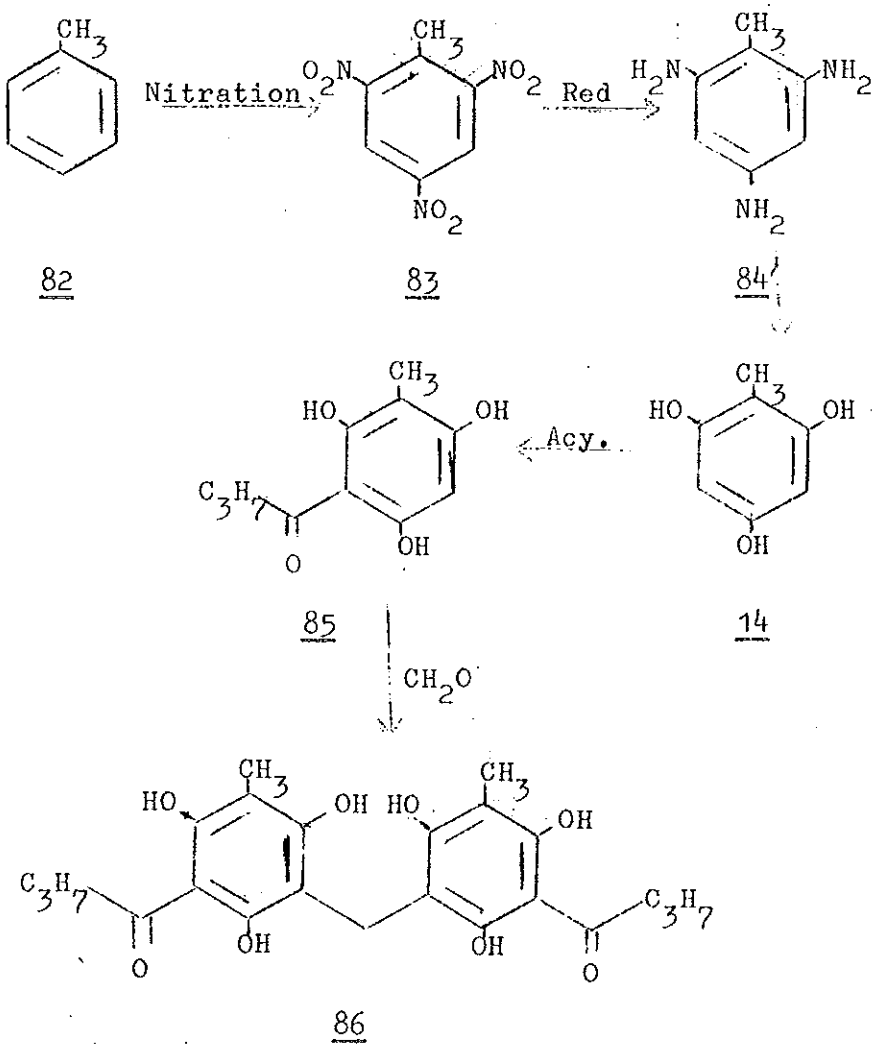


Fig.2 Scheme for the synthesis of (86)

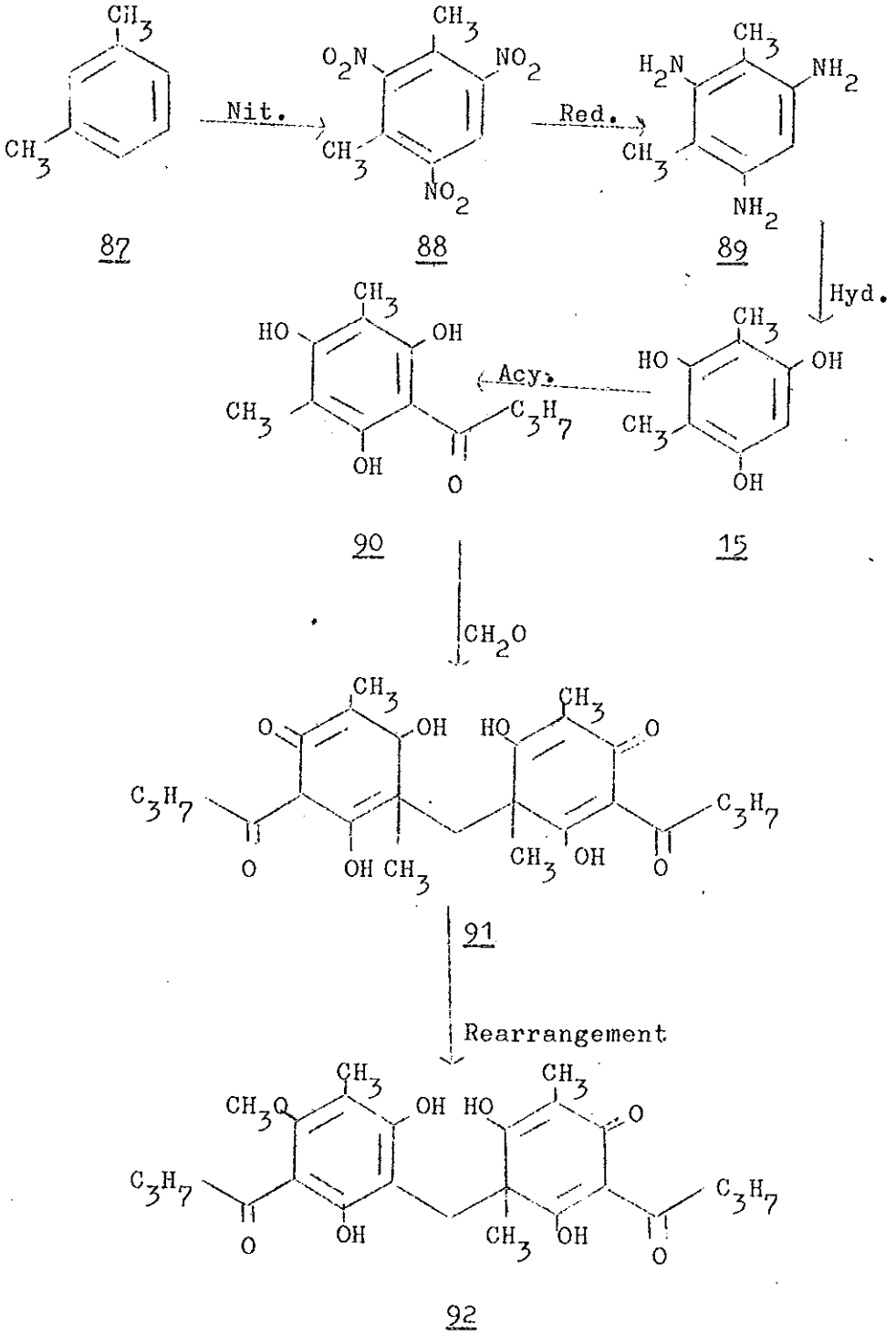
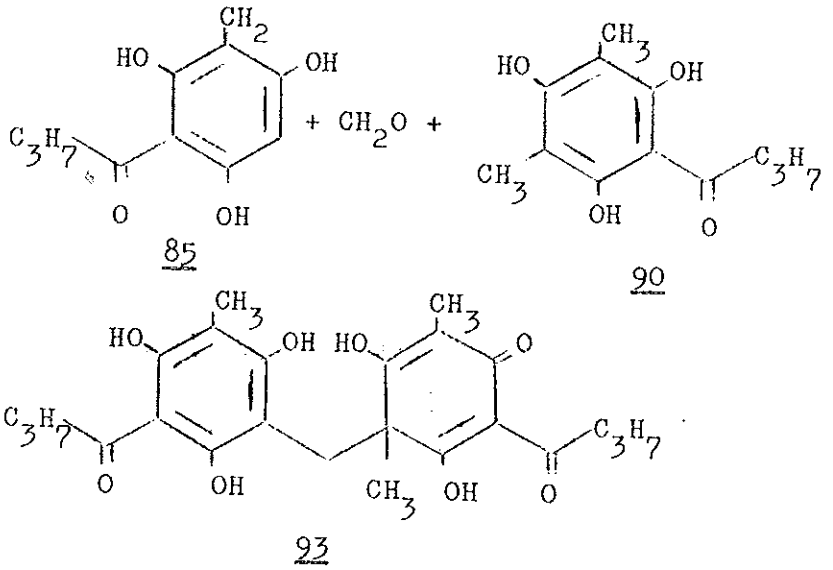


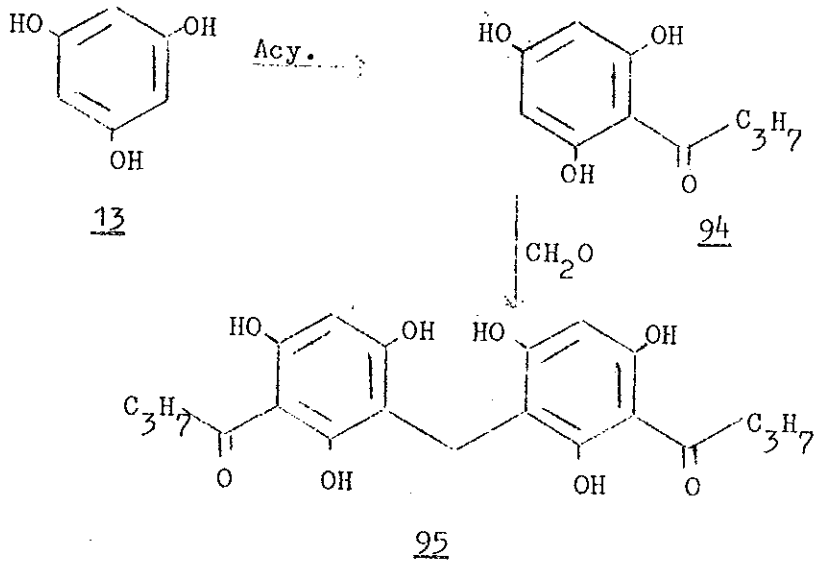
Fig. 3 Scheme for the attempted synthesis of (92)

Unsymmetrical condensation of 2,4,6-trihydroxy-3-methyl-butyrophenone (85) and 2,4,6-trihydroxy 3,5-dimethyl-butyrophenone (90) with formaldelyde



85 90 93

Fig. 4 Scheme for the attempted synthesis of (93)



13 94 95

Fig. 5 Scheme for the synthesis of (95)

1. Synthetic Route Towards Compound (86)

a) Nitration of Toluene (82)

Nitration of organic compounds, a reaction discovered in 1834, is one of the most common and important reactions in organic chemistry.[44] Nitric acid is usually employed for the introduction of the nitro group into organic compounds. The number of nitro groups entering the organic molecule depends on the concentration of the acid used, on temperature, the duration of the process and on the nature of the substance to be nitrated.

In the course of nitration the main reaction is accompanied by side reaction which diminish the yield of the main product. The oxidizing effect of nitric acid is responsible for one of these undesirable side reactions, which is enhanced by rises in temperature. Under very drastic condition of nitration a breakdown of the organic molecule may occur, as for example in the preparation of trinitrobenzene where tetra-nitromethane is formed as a by-product. The introduction of a nitro group into an organic molecule is accompanied by the formation of a molecule of water. The accumulation of water in the reaction mixture lowers the concentration of nitric acid. If nitric acid alone is used as a nitrating agent, the lowering of its concentration below a certain limit leads to practical cessation of the reaction. Hence in practice a mixture of nitric acid and sulfuric acid is used for nitration. This is the so called "nitration mixture".

However in the process of nitration sulfuric acid does not act merely as a dehydrating agent.

The formation of by-products in the course of nitration has long been known. Usually as a result of side reactions hydroxy nitro-compounds are obtained during nitration indicating simeltaneous introduction of hydroxy and nitro groups into the organic molecule. Thus for example in the nitration of nitrobenzene the side product is 2,4,6-trinitroresorcinol. In the nitration of trinitrobenzene there is an interaction between the organic and not the nitrogen but the positively charged oxygen of the nitrating agent, leading to the formation of nitro-phenol in the first place. As a result of subsequent nitration 2,3,4,6-tetranitrophenol is obtained in which the nitro group at position 3 is known to be very mobile and whose substitution by a hydroxyl group gives 2,4,6-trinitroresorcinol.

The temperature at which nitration is carried out is a very important factor affecting the course of the process.[74] Nitration is an exothermic reaction and when a mixture of nitric and sulfuric acid is used in the nitration of aromatic compounds a large amount of additional heat is given off by the dilution of sulfuric acid with water formed in the reaction. Hence it is usually necessary to use external cooling and to mix the reagents gradually. Variation in temperature not only affects the number of nitro groups entering a molecule but also

the position at which the nitro group enters.[41] It is self-evident that, therefore, for each particular nitration there is an optimal temperature.

Spindler investigated the nitration of benzene, chlorobenzene, bromobenzene and toluene with nitric acid of different concentrations.[44] Nitration was carried out by slow addition of the substance to be nitrated to an excess of nitric acid. No formation of nitro-compounds has been observed on attempts to carry out nitration with dilute nitric acid (5 to 10 vol. of H_2O to 1 vol. of HNO_3) by heating the reaction mixture on water bath for 120 hrs. Analysis of the products showed that under these condition the reaction tended towards oxidation. Spindler[44] in his comparative studies of experimental data on nitration of benzene, toluene, chlorobenzene and bromobenzene with acid of the same concentration concluded that the presence of a halogen or a methyl group in the aromatic ring enhances the yield of nitro derivatives on nitration. Thus toluene and xylene can be nitrated with nitric acid even at room temperature.

However the most wide spread method for nitrating aromatic compounds uses a mixture of nitric acid with concentrated sulfuric acid.[74] This mixture is a more powerful nitrating agent than nitric acid alone. The presence of sulfuric acid not only contributes to its dehydrating proporties but also enhances the nitrating action of nitric acid by diminishing its oxidizing

properties. Moreover sulfuric acid serves as good solvent for many nitro compounds.

Direct nitration of benzene to trinitrobenzene is considerably more difficult to accomplish than that of its homologues, such as toluene.

In this work, the preparation of trinitrotoluene was done in three steps according to reference 46. Nitrotoluene was prepared by using 55.4% nitric acid and 98% sulfuric acid at about 40°C in 69% yield. Dinitrotoluene was prepared by adding a mixture of fuming nitric acid and concentrated sulfuric acid gradually while stirring, to nitrotoluene at 50°C and then refluxing it at 90 - 95°C for ½ hr, in 96.8% yield. Trinitrotoluene was prepared by adding a mixture of fuming nitric acid and 15.7% oleum to dinitrotoluene, while stirring and then refluxing at 97 - 100°C for 4 hrs in 61.7% yield.

The structure of the compound (83) was confirmed by its melting point (79-81°C, lit. 82°C) and Infrared spectrum which showed strong absorptions peaks at 1540 and 1365 cm^{-1} for the asymmetric and symmetric streching frequencies respectively of the NO_2 group, and at 3100 for the aromatic C-H streching frequencies.

Fuming nitric acid was obtained by reacting sodium nitrate and sulfuric acid in 81% yield.

b) Preparation of S-triaminotoluene (84)

The most important method for preparation of aromatic amines is the reduction of nitro compounds. The reduction of nitro-compounds to an amine occurs through various intermediate stages. In acid solution a nitroso compound is first formed, followed by a hydroxylamine derivative and finally the amine.

$$RNO_2 \longrightarrow RNO \longrightarrow RNHOH \longrightarrow RNH_2$$

In alkaline solution the reduction takes the same course initially, nitroso and hydroxylamine derivatives are formed. These however then condense to form azoxy compounds because the combination takes place more rapidly than their further reduction. Azoxy compounds give hydrazo compounds by further reduction and these are oxidized by atmospheric oxidation to azo compounds or on the other hand by the action of a further reducing agent, are reduced to the corresponding amines.

$$RNO + RNHOH \longrightarrow R-N=N-R \longrightarrow R\text{-}NH\text{-}NH\text{-}R \longrightarrow 2RNH_2$$

$$R-N=N-R \quad (O) \qquad R\text{-}NH\text{-}NH\text{-}R \xrightarrow{OX.} R-N=N-R$$

Azoxy compound

Azo compound.

Reduction by dissolving metals is a well known method for the reduction of nitro compounds to the corresponding amines. Usually either tin, zinc, or iron and hydrochloric acid are used.[75]

It is also known that, like polyphenols, polyamines are difficult to prepare and handle since they are readily oxidized. Polyamines cannot therefore be kept indefinately in air but soon become colored and decompose. Their salts are more stable.

Clark and Hartmann[47] described the reduction of trinitrobenzoic acid as a preliminary step in the preparation of phloroglucinol. This was effected by taking a suspension of trinitrobenzoic acid in hydro-chloric acid and adding tin in small portions gradually so that the reaction proceeds briskly. No attempt was made to control the temperature and isolate the product.

Palmer and Brenke described the reduction of trinitrodibromotoluene with tin and hydrochloric acid.[48]

Hein and Wagner[48] stated that the reduction 2,4,6-trinitrotoluene by means of tin and hydrochloric acid is unsatisfactory because of losses due to hydrolytic cleavages and sensitivity of the product to oxidation.

Later, John Krueger[48] in a patent revealed that the condition of reduction of symmetrical trinitrobenzene compounds with tin and hydrochloric acid, notably the acid strength and reduction temperature very materially influence the character of the reduction products and the yield. For example, according to Krueger, when trinitrobenzene is reacted with tin and hydrochloric acid at boiling temperature following the direction of Hepp, and the resulting amines precipitated as their tin

double salts; their aqueous solution, freed from tin by means of hydrogen sulfide and evaporated to dryness in vacuo at room temperature yielded a mixture of hydrochlorides. Krueger ascertained that the latter, by treatment with sodium carbonate, be resolved into bases namely 1,2,5-triaminobenzene and 1,3,5-diaminophenol, a very substantial proportion being the latter base.

John Krueger also found that when a temperature of approximately 60°C to 80°C is used in carrying out the reduction of symmetrical trinitrobenzene compounds such as trinitrotoluene with tin and hydrochloric acid, particularly a large excess of such acid, a double salt which is obtained contained only the single base, triaminobenzene in the form of the hydrochloride. However when the aqueous solution or said base hydrochloride is freed from tin by means of hydrogen sulfide and evaporated to dryness at room temperature in vacuo pursuant to earlier procedures the said triaminobenzene hydrochloride is converted to a mixture of triaminobenzene hydrochloride and diaminophenol hydrochloride.

According to earlier methods[48] for the recovery of the triaminobenzene trihydrochloride from the reduction mixture, the reduction solution was filtered or decanted from the unused tin and the tin chloride triaminobenzene hydrochloride complex or double salt was recovered; as for example by precipitation with hydrochloric acid. The resulting complex or double salt

was then dissolved in water and thus freed from tin with hydrogen sulfide. The treatment with hydrogen sulfide caused the formation of hydrochloric acid which prevented complete precipitation of the tin sulfide. Hence several precipitations were necessary and the solution was required to be evaporated in vacuo at low temperature between precipitations with hydrogen sulfide. Such process for the recovery of the triaminobenzene hydrochloride free from inorganic salts, has been exceedingly tedious and costly.

However John Krueger[48] eliminated the slow and combersome methods of the previous procedures which utilize hydrogen sulfide, instead the tin is removed by means of a strong solution of sodium carbonate, the double salt of the tin and the triaminobenzene hydrochloride being decomposed thereby.[48] The precipitate of the tin salt which results from the treatment with sodium carbonate is then filtered off and the triaminobenzene hydrochloride substantially free from tin, may be precipitated by means of strong hydrochloric acid, particularly HCl gas. The free triaminobenzene base may be recovered from the triaminobenzene hydrochloride by adding a strong solution of an alkali carbonate followed by an extraction with an organic solvent.

In light of the above findings the preparation of 2,4,6-triaminotoluene (84) was attempted following the methods of John Krueger.[48] According to this workers, the tin double

salt which precipitated was filtered off and was treated with 135 ml of 20% sodium carbonate solution, the tin oxide was filtered off and the filterate was extracted fourteen times with 150 mls of chloroform. However this procedure gave a low yield inspite of the reported 66% yield by Krueger. This is probably because of the loss of the amines by oxidation during the tedious extraction caused by the formation of emulsion with chloroform and the high solubility of the triamino-compound (84) in water. Instead the following modified procedure gave a better result. 135 ml of 20% sodium carbonate was added to the double salt, separated by filteration, until the bulk of the solid comes into solution, to which is added dry sodium carbonate until the solution was dry. The triamino compound (84) was extracted from the solid mass with chloroform. This method gave the triamino compound (84) in 60% yield. The identity of the compound was proved on the basis of its mp (109 - 113°C, lit. 121 - 122°C), IR spectrum: 3350 - 3400 cm^{-1} (NH_2 strech), 3100 cm^{-1} (Aromatic C - H strech), 2950 cm^{-1} (Methyl C - H strech) 1620 cm^{-1}, 1510 cm^{-1} (Benzene ring vibrations C···C) 1480 cm^{-1}, 1380 cm^{-1} (methyl C - H deformations), and NMR spectrum ($CDCl_3$, TMS) δ = 5.5 ppm S(aromatic H) integrating for 2H, δ = 3.5, b(NH_2) integrating for 6H, δ = 1.9 ppm (Ar - $\underline{CH_3}$) integrating for 3H.

The relatively high depression of the mp is indicative of the unstability of the amines.

Another synthetic method employed for the preparation of polyamines was catalytic hydrogenation. Catalytic reduction of symmetrical aromatic trinitro-compounds in ethylacctate solution, using Raney Nickel as catalyst has been described by J.E. Gill et al. to be a convenient method for the preparation of symmetrical aromatic triamines.[49]

This group stated that the preparation and isolation S-aromatictriamines have in the past proved difficult and before the present work the only amine of this type reported have been 2,4,6-triaminotoluene and 2,4,6-triamino anisole.[50] The workers working on the reduction of trinitrotoluene and trinitroanisole had trouble in isolating the amines which they prepared by catalytic reduction of the corresponding nitrocompounds in ethylalcohol solution and all their manipulations had to be carried out in an oxygen free atmosphere.

According to J.E. Gill,[49] aliphatic alcohols are not good media for the reduction of polynitro compounds as they are poor solvents for the nitro compounds, but when diluted with the water formed during the reaction they are very good solvents for the amines; and isolation is correspondingly difficult. When Ethyl acetate is employed as solvent in the hydrogenation method, with Raney Nickel as catalyst, a number of new S-triamino compounds have been isolated without difficulty in good yield. For example, the preparation of S-triamines of toluene, ethylbenzene, chloro-benzene in yields ranging from 60 - 80%

has been reported.

Following the procedure of J.E. Gill,[49] the reduction of 2,4,6-trinitrotoluene (83) was attempted using W_2 Raney Nickel, which is the most commonly used catalyst. The reaction time was varied from 2 hrs which is recommended by the group, to 5 hrs, but in both cases only the starting material was isolated. W_2 Raney Nickel was prepared using the procedure of Augustine.[51] A second trial was made using W_6 Raney Nickel, which is the most active of all the Raney Nickel catalysts[32,40] but prepared according to the procedure given in organic synthesis[52] and reaction time of 3 hrs. To our dismay the reaction was not successful. A third attempt was made using W_6 Raney Nickel again, but prepared according to the procedure of Augustine,[51] and a reaction time of 48 hrs. Indeed the reaction was promising in that, upon cooling the solution, crystals of 2, 4,6-triaminotoluene (84) separated mp 118 - 121°C, lit. 121 - 122°C (benzene). However no attempt was made to isolate all the product, to avoid its loss by oxidation. Instead, it was isolated as its trihydrochloride salt, which is to be used for subsequent reactions, by adding hydrochloric acid. The yield of the salt of (84) was 83%.

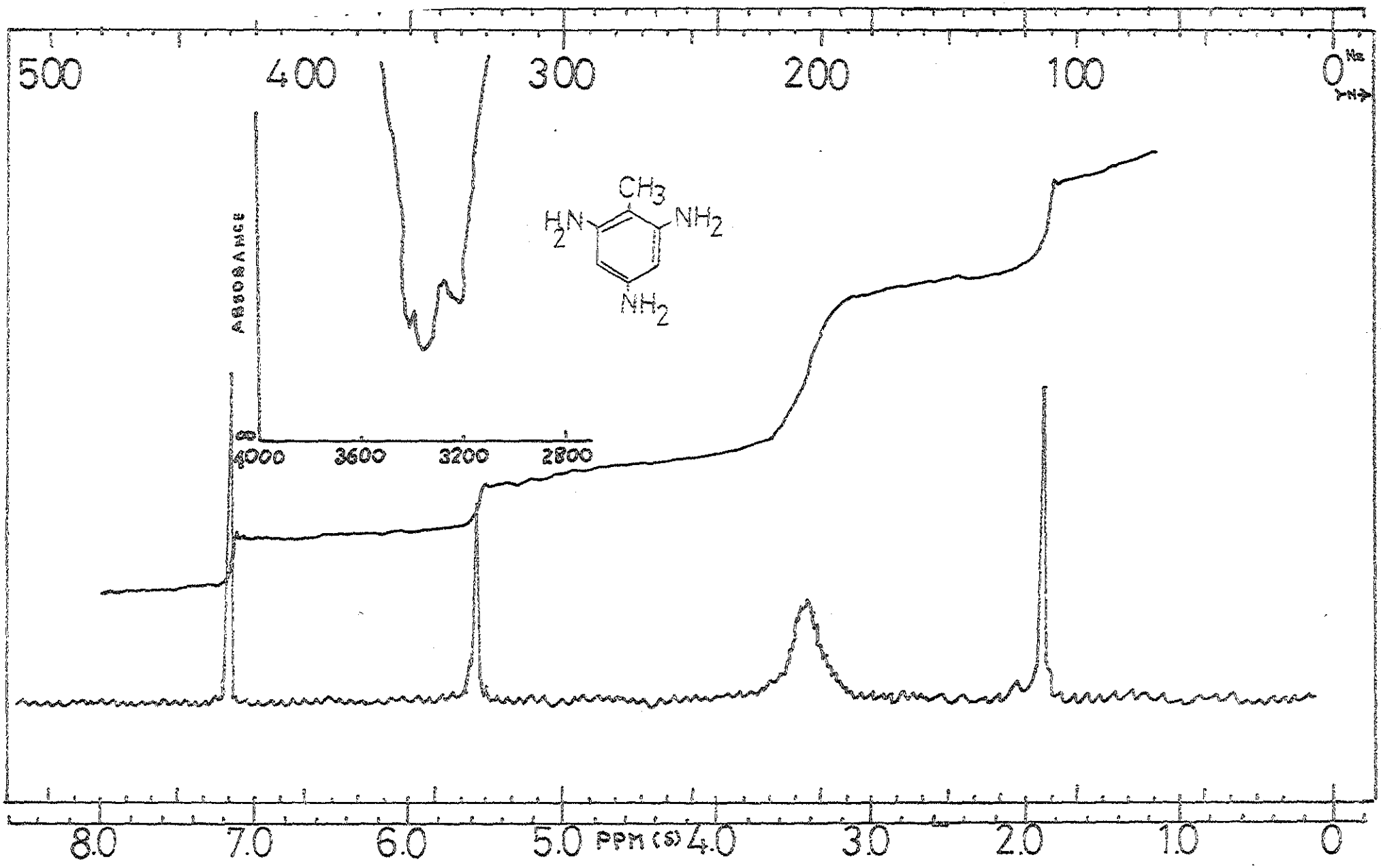

500
400
300
200
100
0
ABSORBANCE
4000
3600
3200
2800
CH3
H2N
NH2
NH2
8.0
7.0
6.0
5.0
PPM (S)
4.0
3.0
2.0
1.0
0

FIGURE:6

c) Preparation of 2,4,6-trihydroxy toluene (14)

It was observed that when benzene sulfonic acid was fused with alkali phenol, resorcinol and phloroglucinol were the major products.[53] This reaction is not useful since separation of the mixture is difficult. The only synthetically useful method, in the literature, for the preparation of polyphenols is the hydrolysis of aromatic polyamines. For example Clarke and Hartman[53] reported the preparation of phloroglucinol by refluxing triamino benzoic acid with dilute acid in an atmosphere of coal gas for 20 hrs. It is also reported[23] that when triaminotoluene hydrochloride was refluxed with water in an atmosphere free of air for about 30 hrs, it decomposes to trihydroxy toluene and ammonium chloride.

Recently, Francisco et al[37] working on the synthesis of grandinol (69), a new root inhibitor from the adult leaves of Eucalyptus grandis, reported the preparation of 2,4,6-trihydroxy toluene (14) by reducing trinitrotoluene with tin and hydrochloric acid, the tin precipitated with sodium hydroxide and boiled under a stream of nitrogen, in 32% yield; mp 210 - 211°C.

In 1981, the preparation of phloroglucinol from triamino-benzene obtained by amination of 3,5-diaminochlorobenzene was reported.[21]

In the course of this work efforts were made to prepare 2, 4,6-trihydroxy toluene (14) from 2,4,6-trinitrotoluene (83) via 2,4,6-triaminotoluene (84) following the information of Beilstein.[23]

First the hydrolysis reaction was attempted on the solution obtained by reduction of trinitrotoluene (83) after removing the unreacted tin by filteration.[48] Second the hydrolytic reaction was tried on the double salt obtained by adding concentrated hydro-chloric acid on the solution obtained after reduction. Both reactions were not successful.

Later the reaction was done on the triaminotoluene obtained after removing the tin as tin oxide by adding 20% sodium carbonate solution.[48] Fortunately this reaction was successful but the yield was very low. The reaction was done several times in view of improving the yield, paying attention to the factors that could destroy the unstable polyamines, which we feel is the main reason for the low yield. Indeed we have observed that, traces of acids (HNO_3,H_2SO_4) in 2,4,6-trinitrotoluene and long exposure of the 2,4,6-triaminotoluene (84) during the tedious filteration on the tin oxide do affect the yield of the product. It was a common observation to see the filterate containing the triamino compound (84) getting darker and darker in the course of filteration. Another factor is the concentration of hydrochloric acid in the reduction step. It was noted that the use of hydrochloric acid from a bottle which was opened for a long time resulted in unsuccessful reactions. However, several washings of the trinitrotoluene (83), filteration under nitrogen atmosphere imporved the yield only to 22.0%. In all cases the hydrolysis

reaction was done under nitrogen atmosphere.

Later a better yield of 35% was achieved by reducing 2,4, 6-trinitrotoluene (83) with W_6 Raney Nickel,[51] separating the triamino compound (84) as its hydrochloride salt from ethyl acetate and refluxing it with water under nitrogen atmosphere for 30 hrs.

The identity of the product (14) was confirmed on the basis of its mp 210 - 213°C, lit 214 - 216°C, IR spectrum (pellet, KBr): 3200 - 3500 cm^{-1} (OH) 2900 cm^{-1} (CH_3), 3000 cm^{-1} (Ar - H), 1620 and 1580 cm^{-1} (Ar - ring vibration), 1380 and 1450 cm^{-1} (CH_3 bending) and NMR spectrum (DMSO - d_6, TMS) 5.7 ppm (Aromatic H) integrating for 2H and 1.8 ppm (Ar - CH_3) integrating for 3 H.

Another reaction which was investigated was hydrolysis of diazonium salts. The preparation of polyphenols by this method is not reported in the literature, but an attempt was made to adapt procedures given for the preparation of phenols[52] and the results in the diazotization of triamines to yield trihydroxybenzenes was not encouraging.

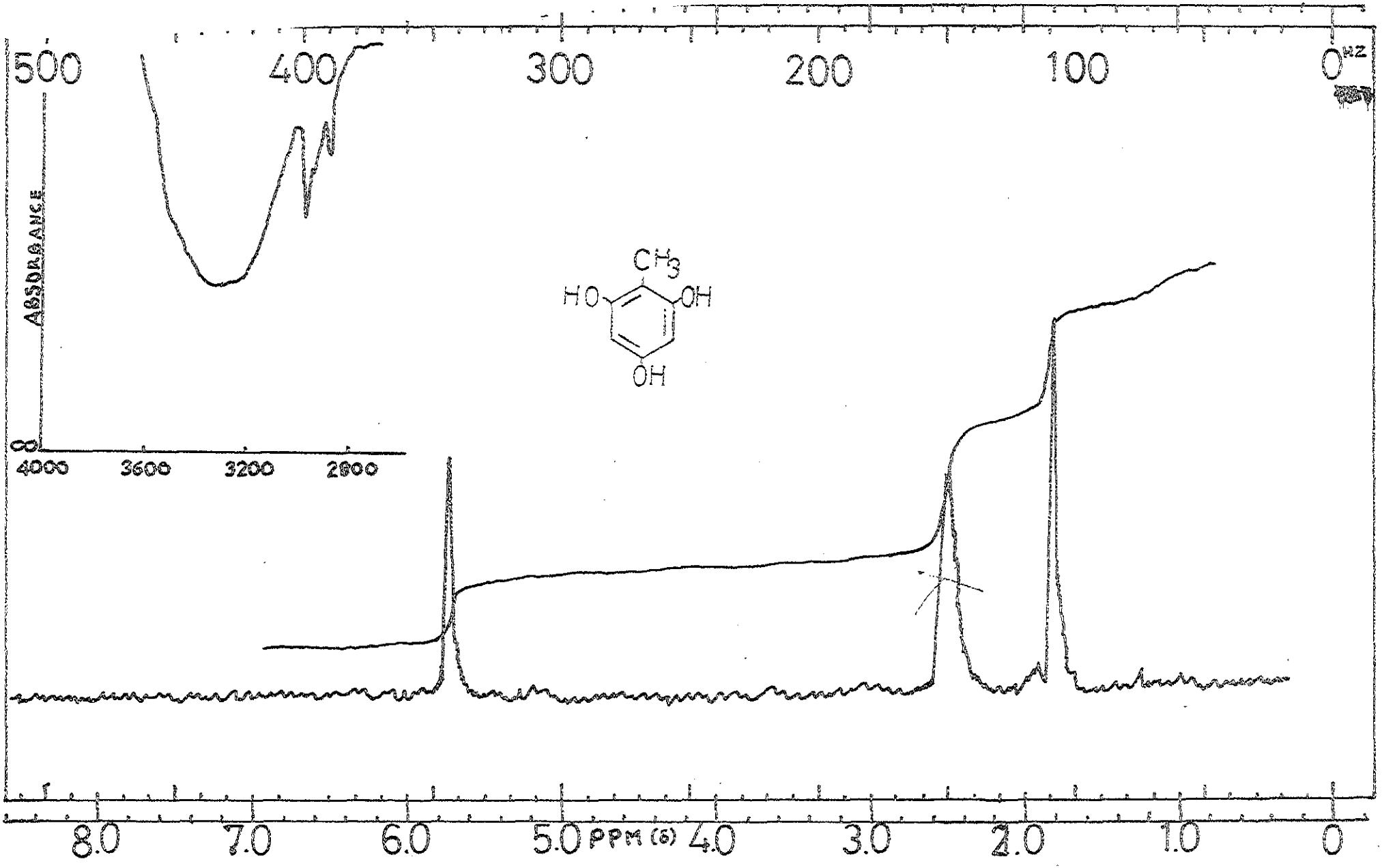

500
400
300
200
100
0
HZ
ABSORBANCE
0
4000
3600
3200
2800
CH3
HO
OH
OH
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

FIGURE: 7

d) Preparation of 2,4,6-trihydroxy-3-methyl butyrophenone (85)

The most important method for the preparation of acylketones is known as Friedl-Crafts acylation.[55] The reaction is of a wide scope, but with amines and phenols there may be competition from N-or-O-acylation. However O-acylated phenols can be converted to C-acylated phenols by Fries rearrangement.

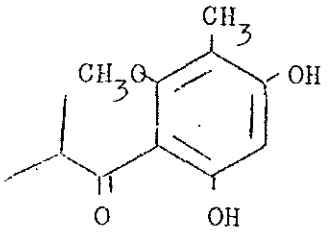
The mechanism of Friedl-Crafts acylation is not completely understood, but at least two mechanisms probably operate depending on conditions. In most cases the attacking species is the acyl cation, either free or as an ion pair formed by:

$$RCOCl + AlCl_3 \longrightarrow RCO^+ + AlCl_4^-$$

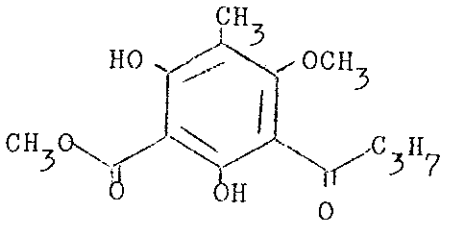
If R is tertiary, then RCO^+ may lose CO to give R^+, so that in such cases the alkylarene is often a side product or the main product. In the other mechanism an acyl cation is not involved but 1:1 complex ($R-\underset{\underset{Cl}{|}}{C}=O \longrightarrow AlCl_3$)

The relative rates for the acylation of benzene with solution of some typical acid chlorides and aluminum chloride in nitromethane are: CH_3COCl (1.00), C_2H_5-COCl (0.92), n - C_3H_7COCl (0.34) $CH_3-\underset{\underset{CH_3}{|}}{CH}-COCl$ (0.20), C_6H_5-COCl (0.06).[56]

Riedl[27] synthesized 2,4-dihydroxy-5-methyl-6-methoxy-isobutyrophenone (96) and 2,6-dihydroxy-5-methyl-3-butyro-4-methoxy-methylbenzoate (97) from the corresponding hydroxy compounds by Friedl-Crafts method using $AlCl_3$ as a catalyst.



96



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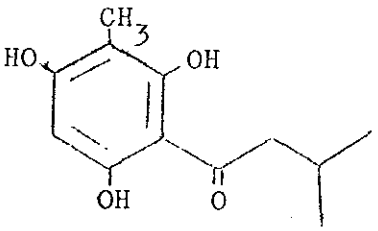
We were not able to repeat this reaction for the acylation of phloroglucinol (13) and 1,3-dimethylphloroglucinol (15) and hence was not used for the acylation of methylphloroglucinol (14).

Recently, Francisco et al. reported the synthesis of 2,4,6-trihydroxy-3-methyl isovalerophenone (98) by Friedl-Crafts acylation of 2,4,6-trihydroxytoluene (14) (1 eq of isovaleryl chloride and 10 eq $TiCl_4$ in 1:1 CH_2Cl_2-CS_2 at 25°C), in 23% yield.



98

Another important method for the preparation of arylketones is the Hoesch's method. The Hoesch's synthesis consists in the condensation of a nitrile with phenol or p lyhydric phenol or phenolic ether to form a hydroxyaryl or alkoxyaryl ketone.[28] Usually equimolar quantities of the reactants are dissolved in dry ether, preferably in the presence of a catalyst such as zinc chloride and dry hydrogen chloride is introduced.

When phenols are used imino ether hydrochlorides are some times formed as by products.

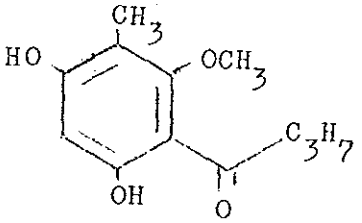
$$RCN + C_6H_4(OH)_2 \longrightarrow R-\underset{\underset{O}{\|}}{C}-C_6H_3(OH)_2$$

$$RCN + C_6H_5OH \longrightarrow R-\underset{\underset{NH.HCl}{\|}}{C}-O-C_6H_5$$

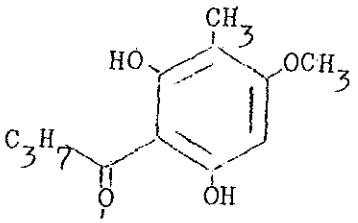
According to Hoesch, the reaction involved three separate steps: the formation of imino chloride, interaction of the imino chloride with phenols to give ketimine hydrochloride and hydrolysis of the ketimine hydrochloride to ketones.

Even though there are no ample literature informations on the acylation of methylphloroglucinol as that of phloroglucinol, by this method, there are some reactions preported.

For example, Riedl prepared 4,6-dihydroxy-3-methyl-2-methoxy butyrophenone (99) and 2,6-dihydroxy-3-methyl-4-methoxy-butyrophenone (100) by acylation of 3,5-dihydroxy-2-methyl-phenyl-methylether (101) using butyronitrile.



99



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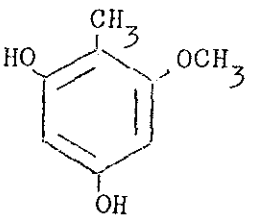


101

The preparation of 2,4,6-trihydroxy-3-methyl-butyrophenone (85) from 2,4,6-trihydroxytoluene (14) and butronitrile is also reported.[57]

Following the direction of Hoesch[58] and using ammonia[57] as catalyst in the hydrolysis step, we attempted the acylation of 2,4,6-trihydroxytoluene (14) with butyronitrile. The reaction was successful but the maximum yield achieved by carefully drying the ether, $ZnCl_2$, reactants, bubbling dry HCl for 10 hrs and keeping the mixture for 5 days in a fridge was 50%.

The mp of the product 154 - 156°C, lit 154 - 155°C and IR spectrum 1660 cm^{-1} (-C-) 1380, 1450 cm^{-1} (CH_3 bending), 3400b (OH), 1580, 1450 cm^{-1} (Aromatic ring) proved the structure.

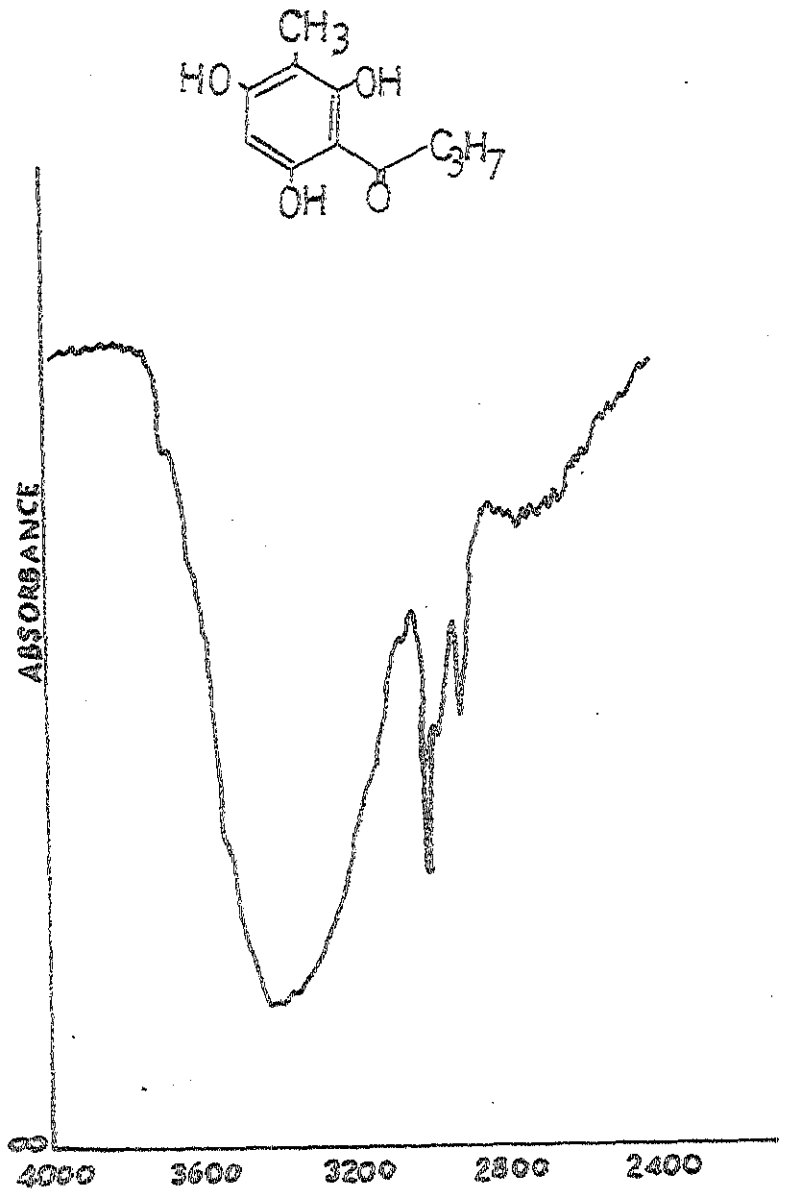
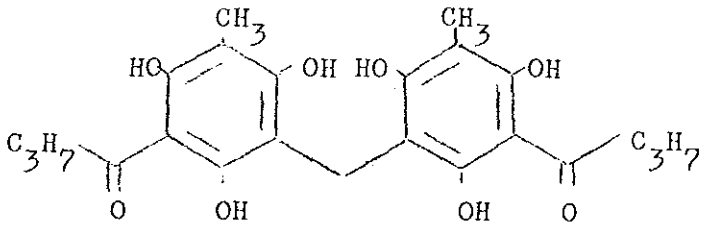


FIGURE : 8

e) Preparation of 5,5'-di-n-butyryl-2,4,6-2',4',6'-hexahydroxy-3,3'-dimethyl-diphenyl-methane (86)

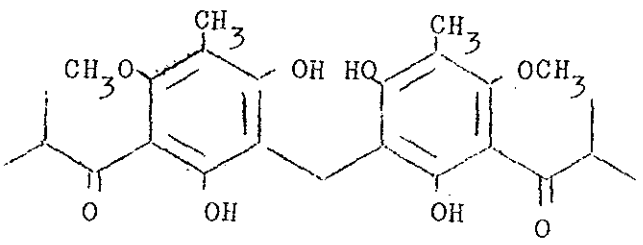


86

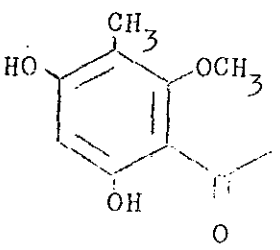
The condensation of aromatic rings with aldehydes or ketones is called hydroxyalkylation.[59] The reaction is not generally useful as a method for the preparation of alcohols. More often the alcohol intially produced reacts with another molecule of aromatic compound to give diarylation product.

The diarylation reaction is especially common with phenols. The reaction is normally carried out in alkaline solution on the phenolate ion.[76]

The condensation in alkaline solution was applied by Riedl[26] for the preparation of (102) from (103) and formaldehyde.



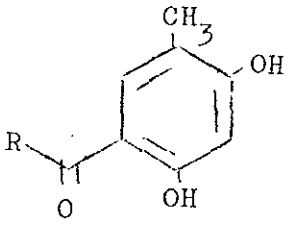
102



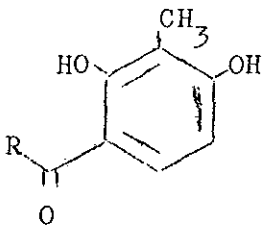
103

But an attempt to adopt this procedure for the condensation of 2,4,6-trihydroxy-3methylbutyrophenone (85) using 1% potassium hydroxide and 38% formaldehyde resulted in an oil, from which no product was isolated.

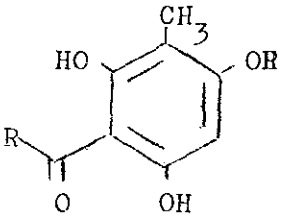
In 1951, a group lead by McCookin[29] reported the synthesis of symmetrical diphenylmethanes from ketones of the type (104), (105), (106), by the action of 40% aqueous formaldehyde and alcoholic sulfuric acid.



104

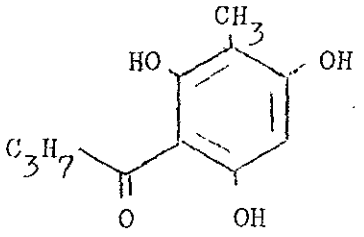


105

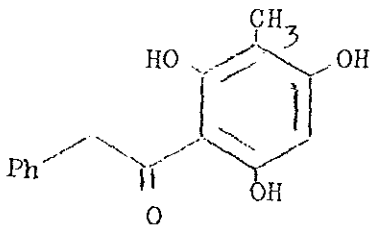


106

The group pointed out that, with the following ketones (107), (108), however, the use of aqueous formaldehyde gave products consisting mainly of oils with a little of the required diphenylmethanes, but when paraformaldehyde was employed excellent yields of the corresponding diphenylmethanes were obtained.

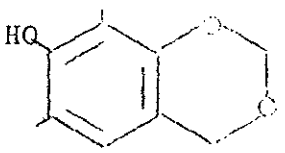


107



108

The group rationalized that the oil are mixtures of cyclic formals of the following type (109) which are known to be sometimes formed in the condensation of phenols and formaldehyde with acidic reagents.[31]



109

As formaldehyde is liberated very slowly from paraformaldehyde in acidic solutions, its concentration is small and thus the tendency for the intermediate hydroxybenzyl alcohols to give formals is reduced.

Following the procedure of McGookin[30] the condensation of (85) with paraformaldehyde was done and the product (86) was obtained in 60% yield. mp 212 - 213°C, lit 212°C, IR spectrum

(pellet, KBr): 3600 - 3200 (OH), 2900 (CH_3), 1640 (-C-) and NMR spectrum ($CDCl_3$, TMS) 1.0 ppm ($-CH_2-\underline{CH_3}$), 2.1 S ($Ar-\overset{O}{\overset{\|}{C}}-\underline{CH_3}$) 3.1 t ($-C-\underline{CH_2}-$), 3.43 ($Ar-CH_2-Ar$) confirmed the structure.

The overall yield of the 8 - step synthesis, starting from toluene, of the diphenylmethane (86) based on dissolving metal reduction is 2.7% and based on catalytic reduction is 4.3%.

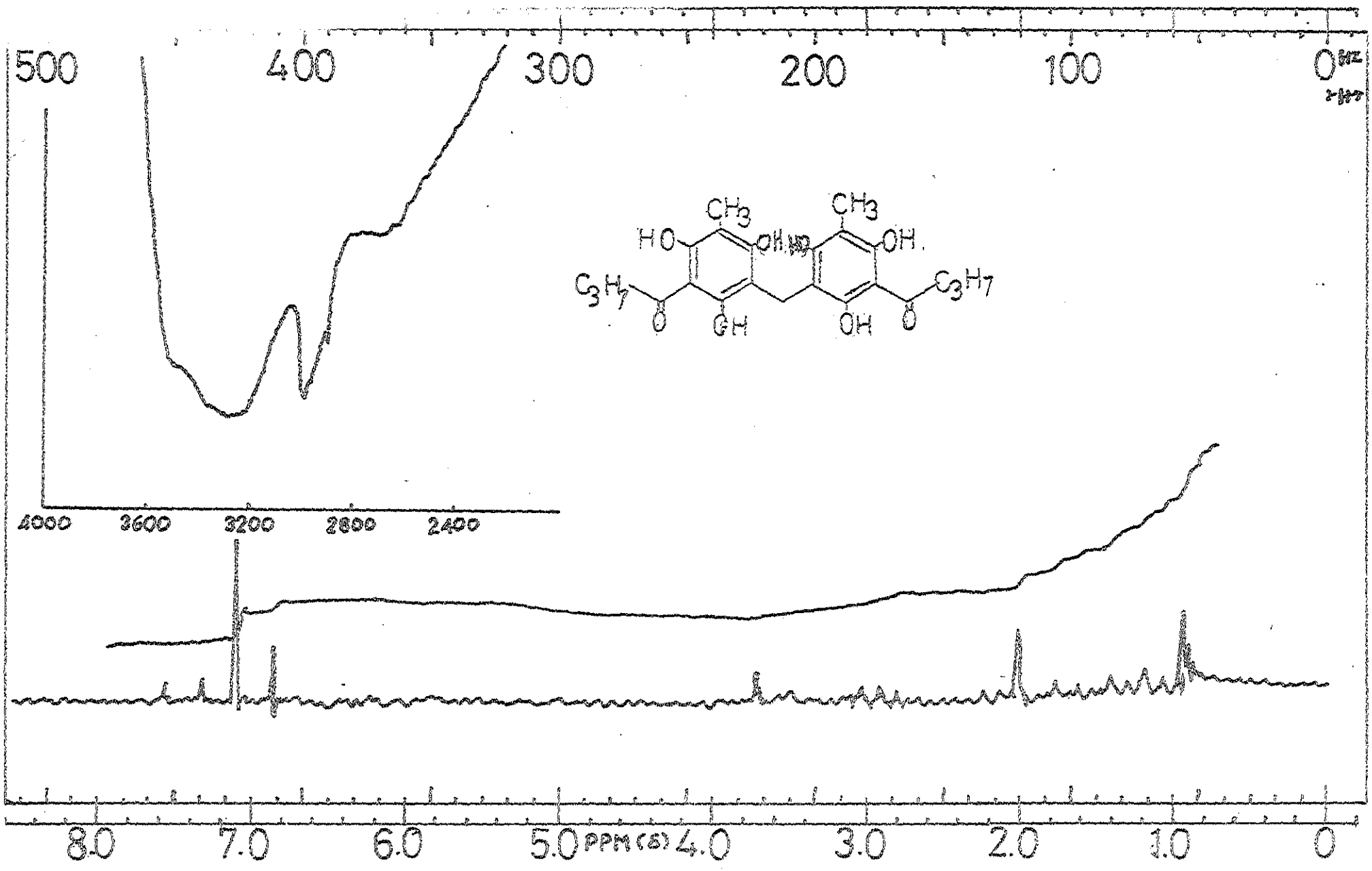

500
400
300
200
100
0
4000
3600
3200
2800
2400
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

FIGURE : 9

2. Attempted synthetic route to compound (92)

a) Nitration of m-xylene

The nitration of m-xylene proceeds more easily than that of toluene; owing to the facilitating effect of the alkyl groups in the ring.[44] Of the three isomers of xylene the most easily nitrated is m-xylene.

As in the nitration of toluene, the nitration of n-xylene was done following the procedure in Methoden der Organischen Chemie[46] in two steps. Nitration with 55.4% nitric and 98% sulfuric acid gave a mixture of nitroxylene and dinitro-xylene. Treatment of the mixture with fuming nitric acid and concentrated sulfuric acid directly gave trinitroxylene (88), with an overall yield of 76% mp 181 - 182°C lit 184°C. The higher yield in this case, is indicative of the fact that m-xylene is more reactive than toluene towards nitration.

b) Preparation of 1,3-dimethyl-2,4,6-triamino benzene (89)

Following the procedure of John Krueger, given for the reduction of S-trinitrobenzene and S-trinitrotoluene with modifications (89) was obtained in 57.2% yield mp 130 140°C, lit. 140 - 150°C IR spectrum (pellet, KBr), 3400 - 3450 (Ar - NH_2) 1600, 1500 cm^{-1} (aromatic), 1450, 1350 (CH_3) NMR spectrum ($CDCl_3$, TMS) 5.6, S (Ar - H) 3.36, b (Ar - NH_2), 1.9 S(Ar - CH_3)

Another synthetic method considered for the preparation of (89) was catalytic reduction. Some effort was made to study this reaction by changing the reaction time and Raney Nickel. Attempts using W_2, W_4 Raney Nickels prepared according to Augustine[51] and W_6 Raney Nickel prepared according to organic synthesis[52] and a reaction time ranging from 5 hrs to 48 hrs were unsuccessful. However using W_6 Raney Nickel prepared according to Augustine[51] and a reaction time of 48 hrs a crude product of the S-triamino-xylene (89) was obtained in 80% yield based on its hydrochloride salt.

c) Preparation of 1,3-dimethyl-2,4,6-trihydroxybenzene (15)

In common with the preparation of trihydroxy toluene (14) we found the preparation of 1,3-dimethyl-2,4,6-trihydroxybenzene (15) very difficult and some times not reproducible,

One problem noticed was the crystallization of S-trinitroxylene (88) which needs a large volume of benzene and chloroform, but we have found that, this can be avoided if the compound (88) is washed several times with water, which helps to remove traces of nitric and sulfuric acid which could oxidize the polyamines in the reduction step.

The synthesis of (89) was attempted following the direction of John Krueger[48] for the reduction of the S-trinitroxylene (88) and using the information given in Beilstein[23] for the hydrolysis of S-triaminoxylene (89). In one case when the reaction was done on the S-triamino-xylene (89) obtained by extraction with chloroform, refluxing the corresponding trihydrochloride salt in water under nitrogen atmosphere, and recrystalizing the product from benzene beautiful crystals of (15) were obtained but the yield was disappointing (7%).

Later when the reduction was done on triamino-xylene (89) obtained after removing the tin as its oxide, a better yield of (15) was obtained (17.5%).

Finally, a yield of 30% was achieved by reducing 2,4,6-trinitro-1,3-dimethyl benzene (88) with W_6 Raney Nickel[51,60] separating the triamino-compound (87) as its trihydrochloride salt from ethylacetate and refluxing it with water under nitrogen atmosphere for 24 hrs.

The last reaction tried for the preparation of this compound (15) was hydrolysis of diazonium salts[54] but gave no results.

The mp of the product (15) 161-163°C, lit 162-163°C, IR spectrum (pellet, KBr) 3300-3550 cm^{-1} (OH), 30,000 (Ar-H), 2950 (CH_3) 1630, 1510 (benzene ring), 1450, 1380 (CH_3 bending) NMR spectrum (DMSO-d_6, TMS), 1.8 (Ar-CH_3, 6H) 5.8 (Ar-H, 1H) 9.3 (Ar-OH) confirmed its identity.

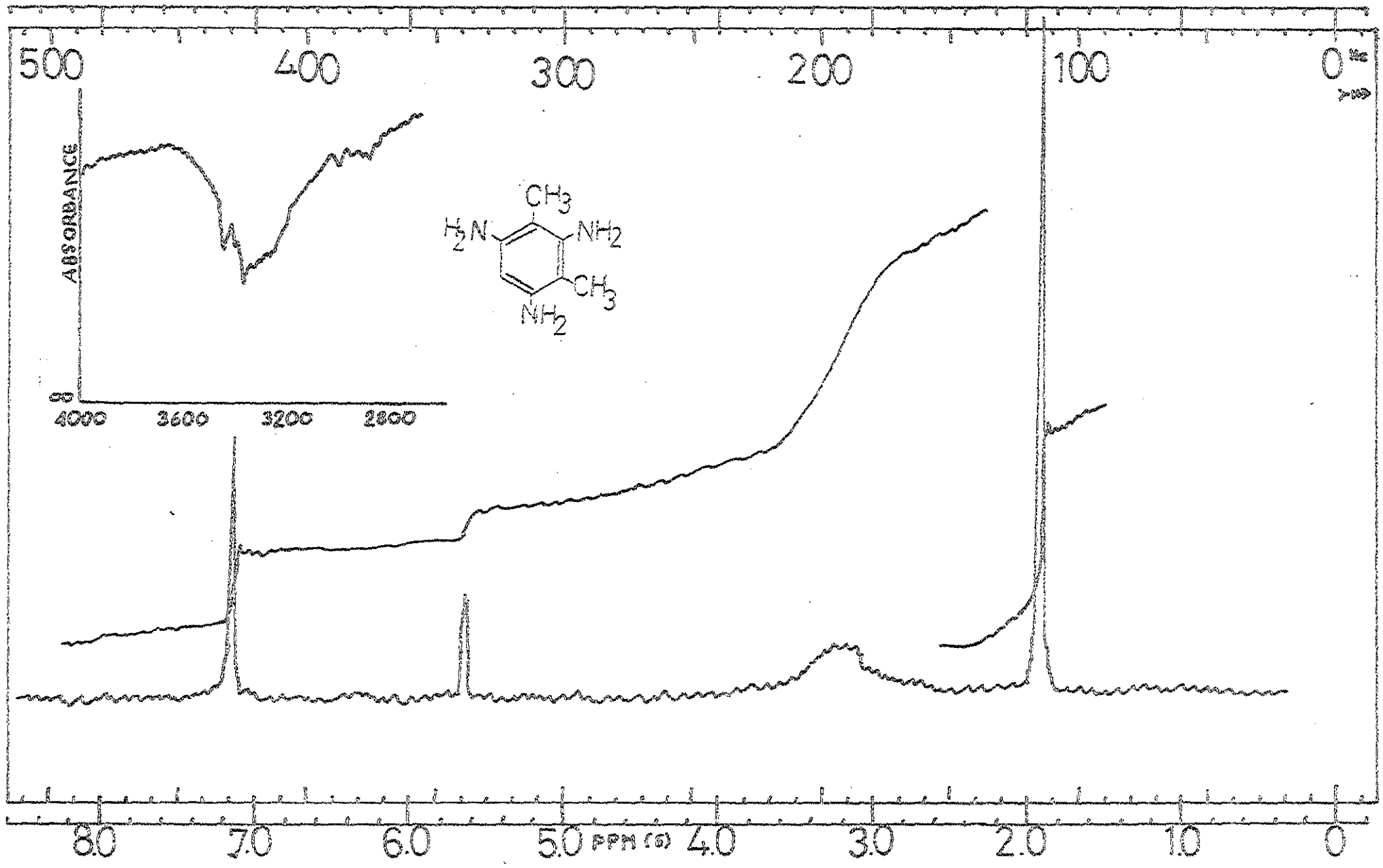

500
400
300
200
100
0
ABSORBANCE
4000
3600
3200
2800
CH3
H2N
NH2
CH3
NH2
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

FIGURE: 10

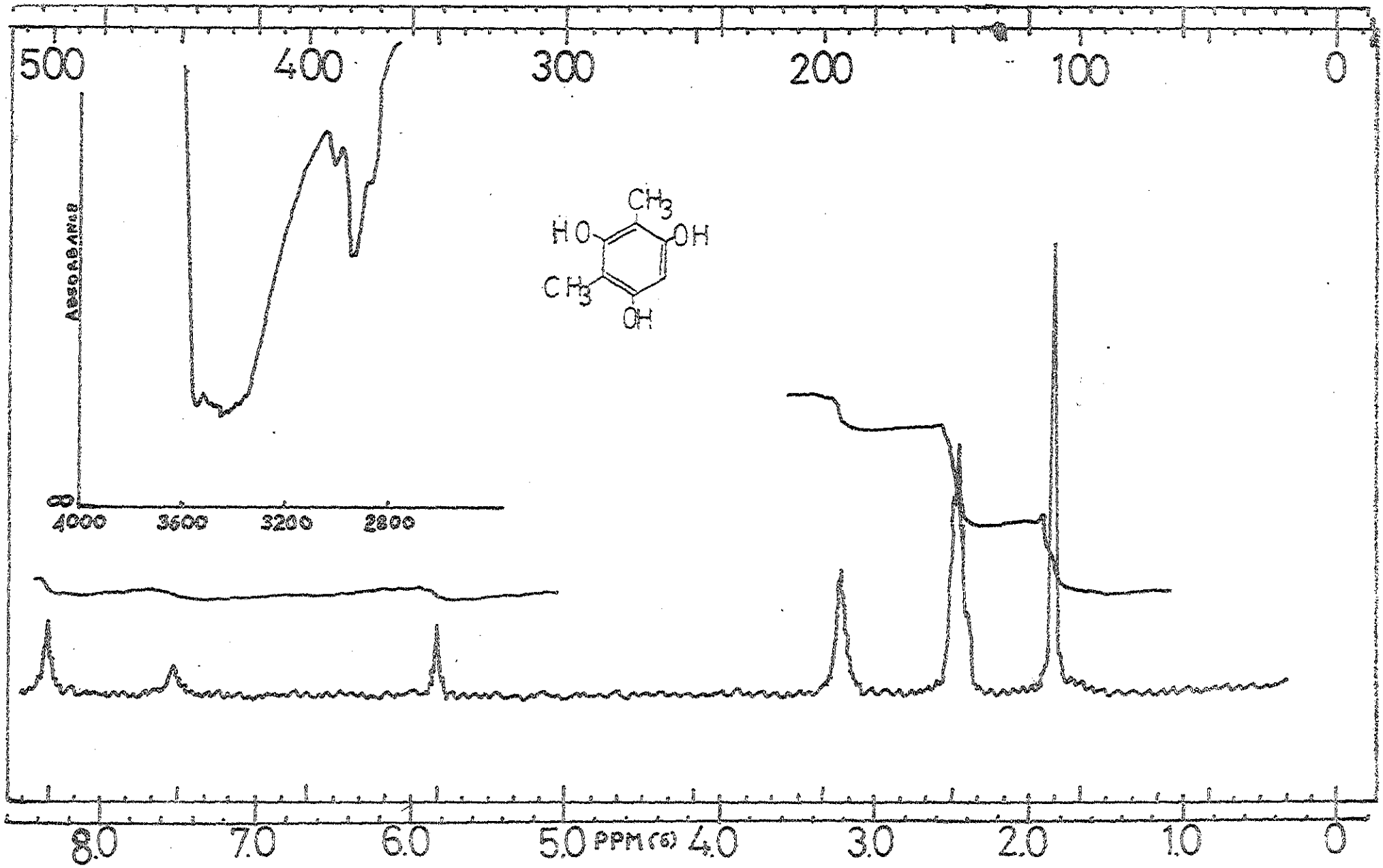
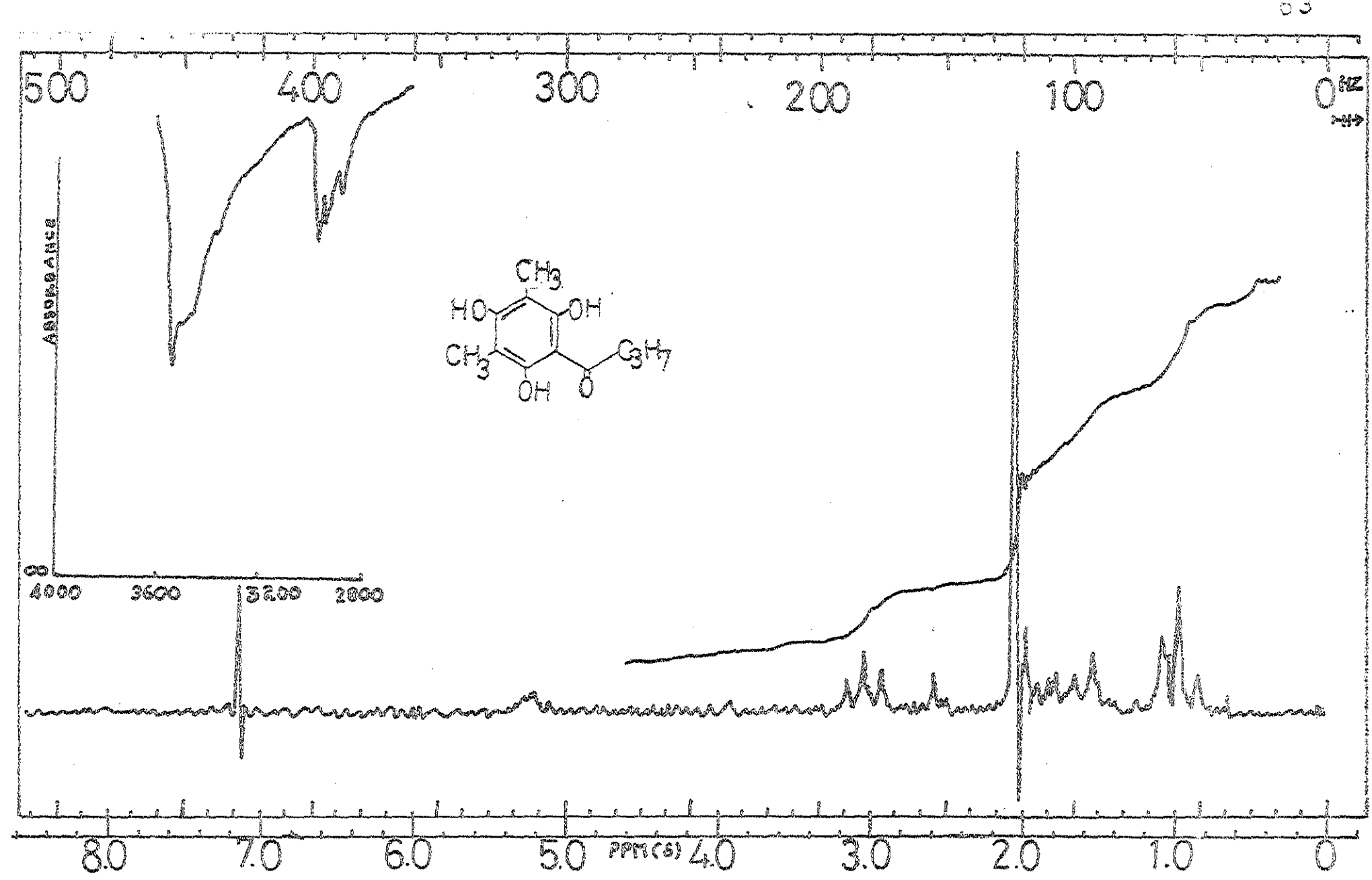

500
400
300
200
100
0
ABSORBANCE
4000
3600
3200
2800
HO
CH3
OH
CH3
OH
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

FIGURE : 11

d) Preparation of 2,4,6-trihydroxy-3,5-dimethyl-butyrophenone (90)

The Friedl-Crafts method, following the procedure given for the acylation of phloroglucinol (13) by isobutyronitrile[67] resulted in a gumy product which could not be crystalized. From the IR and NMR spectra of this crude product, O-acylation was suspected but no further effort was made to characterize it.

The Hoesch's method, following literature procedure's[60,58] gave the product (90) in 38.5% mp 138-140°C, lit 140°C, IR spectrum (pellet, KBr) 3300-3600 cm^{-1} (OH), 2950 cm^{-1} (CH_3), 164 (-C-) 1580, 1480 cm^{-1} (Aromatic), 1450, 1380 cm^{-1} (CH_3) NMR spectrum: 5.2 (OH), 3.0 t (-C-$\underline{CH_2}$-CH_2-CH_3,2H) 2.0, S (Ar-$\underline{CH_3}$, 6H), 1.6, M (-C-CH_2-CH_2-CH_3) 1.0, t(-C-CH_2-CH_2-$\underline{CH_3}$).


500
400
300
200
100
0
HZ
ABSORBANCE
4000
3600
3200
2800
CH3
HO
OH
CH3
C3H7
OH
O
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

e) Condensation of 2,4,6-trihydroxy-3,5-dimethyl butyrophenene (90)

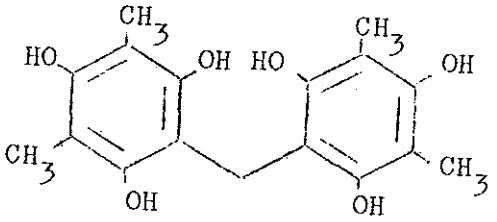
This reaction was attempted by adapting the procedure of McGookin[30] given for the condensation of butyromethyl phloroglucinol (85), at room temperature for 96 hrs under reflux for 120 hrs, but in both cases only the starting material was isolated.

H. Schnell and H. Krimm[76] working on the condensation of Aromatic hydroxy compounds and Oxo compounds reported that the condensation of aromatic hydroxy compounds proceeds with elimination of water and unless this water is bound, or otherwise removed, the condensation stops after low conversion. The reaction is catalyzed by acid condensing agents such as hydrogen chloride, hydrogen bromide, hydrogen fluoride sulfuric acid and mixtures of sulfuric and hydro-chloric acid. The group also stated that ketones give better yields of well defined condensation products than aldehydes do. According to this group the preferred acid condensing agents are hydrogen chloride concentrated hydrochloric acid and sulfuric acid having a maximum concentration of 70%. The most efficient would be sulfuric acid but its use is precluded by the fact that it causes sulfonation of the aromatic hydroxy compounds and diarylmethane derivatives. The 70% sulfuric acid is less efficient than concentrated and the latter less than hydrogen chloride.

In view of the above fact, the condensation of (90) with formaldehyde was attempted using dry HCl gas as catalyst and methanol as solvent. The reaction gave a red product which does not melt and was suspected to be a polymer.

The next attempt was made using 1% potassium hydroxide and aqueous formaldehyde following the procedure of Riedl,[26] but only an orange oil was obtained from which no solid product was isolated by crystallization.

The last attempt was made, according to T.Meikle et al.[32] using sodium ethoxide as a base. This reaction gave a solid product, that starts melting at 250°C, which corresponds to the melting point of (110) (mp 260°C) the formation of which is possible in a basic medium.



110

3. Attempted synthetic route towards compound (93)

Following the procedure of Riedl[68] the unsymmetrical condensation of (85) and (90) using 1% KOH and aqueous formaldehyde (38%) was attempted, giving rise to a red gumy product, showing two spots on TLC ($CHCl_3$/EtOH: 9:1). Preparative TLC (selica gel 2 mm plate, CH_2Cl_2/cyclohexane/EtOH/:14:4:1) was not successful. An attempt made to separate the mixture by silica gel column chromatography by gradient elution ($CHCl_3$, EtOH) gave only a very small solid fraction which was supposed to be the symmetrically condensed product (86) by TLC.

Following the observation of H. Schnill and H. Krimm[61] that dry HCl gas is the most efficient catalyst for condensation of phenols with formaldehyde, condensation of (85) and (90) was tried, by bubbling dry HCl in CH_3OH and adding (85) gradually over 3 hrs. The red precipitate separated (M-A) indicated four components (TLC) the result of TLC comparison of 2,4,6-trihydroxy-toluene (14), 1,3-dimethyl-2,4,6-trihydroxy dimethyl phloroglucinol (15), the symmetrically coupled product (86) and the red mixture (M - A) is summerized below.

Compounds	R_f on TLC ($CHCl_3$/EtOH:9:1)	Color with fast blue salt
14	0.299	Violet
15	0.36	Orange red
85	0.45	Brown
90	0.59	Pale yellow
86	0.68	Pale brown
M-A		
1	0.48	Pale brown
2	0.56	Brown
3	0.61	Orange
4	0.71	Pink, which fades on standing

Table 1. TLC: Comparison of (14), (15), (85), (90), (86), M-A

Finally, following the procedure of McGrookin,[30] the condensation of (85) (0.35 g), and (90) (0.25 g) with paraformaldehyde in methanol, using H_2SO_4 as catalyst, and adding (85), which is more reactive, gradually over 20 hrs gave a solid product (0.30 g) mp 150 - 160°C. Evaporation of the solvent from the mother liquor gave a solid (0.25 g) mp 110 - 120°C which is mainly (90) (TLC, $CHCl_3$/EtOH:9:1).

Recrystallization of the solid from Ethanol gave 0.20 gm of solid mp 210 - 213°C (fraction-1), which is proved to be (86) by TLC (Silica, $CHCl_3$/EtOH:9:1), IR and mp lit 212 - 213°C. Evaporation of the EtOH gave 0.1 gm of another solid (fraction-2) mp 197 - 199°C after crystallization from CH_3OH, but having almost the same IR, NMR and UV spectra as that of (86). TLC using different solvent systems also does not show any significant R_f differences. Thus we concluded the absence of the unsymmetrically coupled compound (94) in the product.

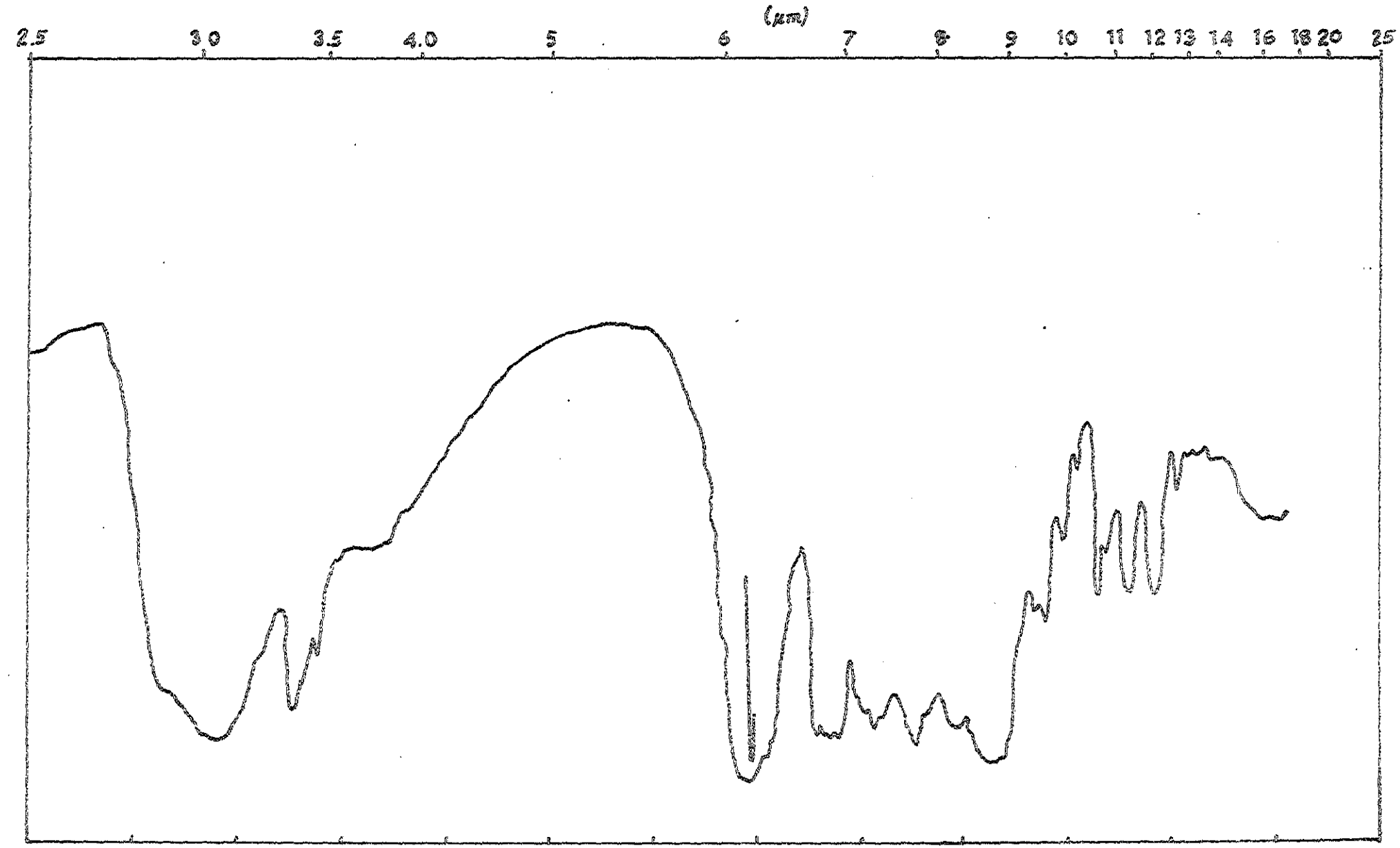

(μm)
2.5
3.0
3.5
4.0
5
6
7
8
9
10
11
12
13
14
16
18
20
25
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400
(CM⁻¹)

FIGURE : 13

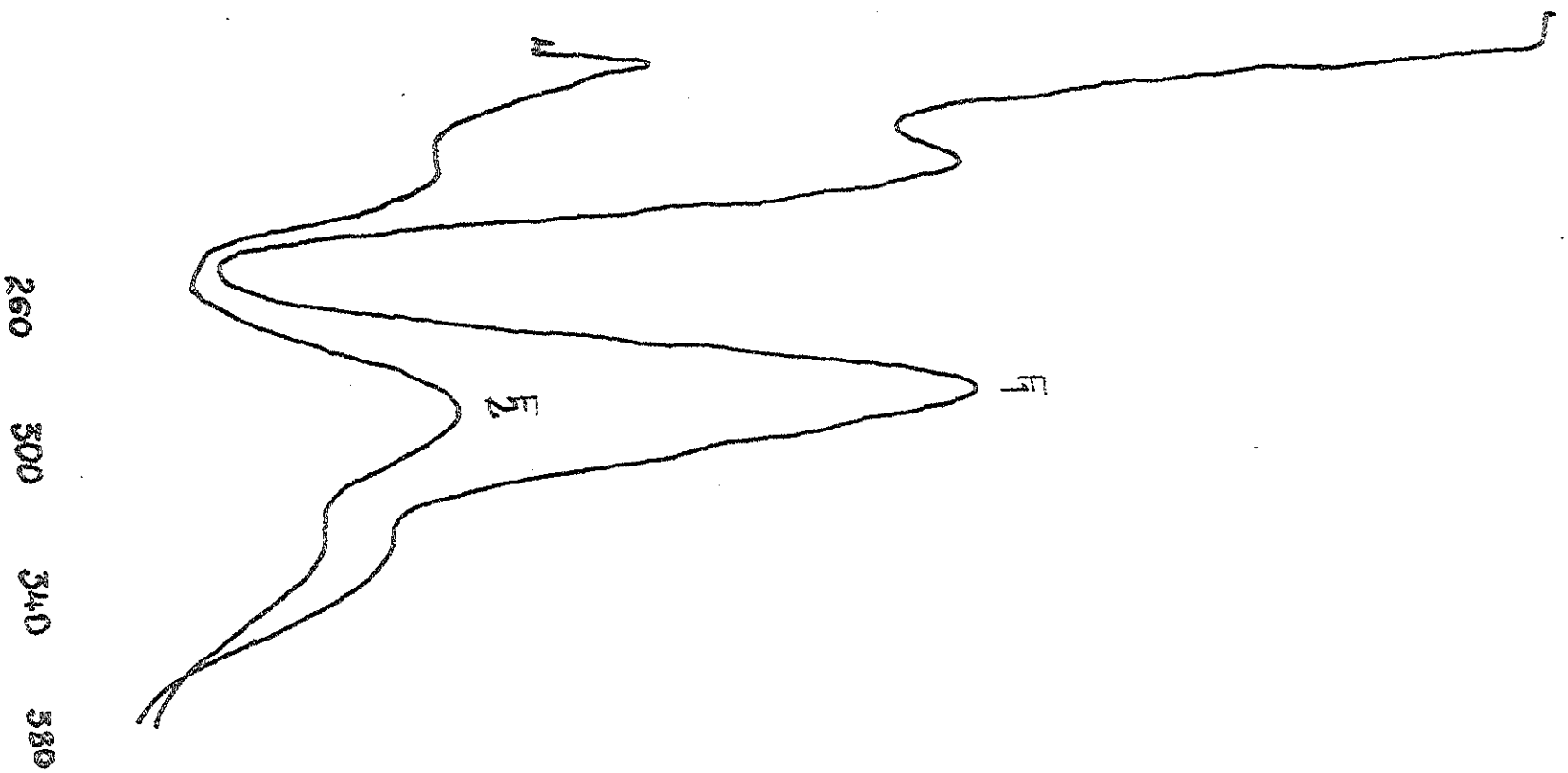


FIGURE : 14

4, Synthetic route towards compound (95)

a) Acylation of phloroglucinol (13)

Following literature procedure[58] the product (94) was obtained in 20% yield mp 180 - 182°C, lit 180 - 181°C.

b) Condensation of butyrophloroglucinol (94)

Riedl's procedure was applied for the condensation of (94) with formaldehyde in alkaline solution, but gave a product which does not melt upto 250°C.

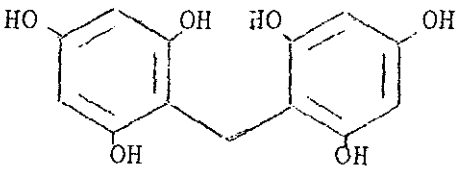
The reaction was then done using sulfuric acid as catalyst, following the procedure of McGookin[30] and the product mixture was followed by TLC (Silica, OH_2CL_2/ cyclohexane/ EtOH:7:2:1). Two spots were indicated. Recrystallization from EtOH gave two fractions, the first fraction melts at 240 - 242°C and the second fraction melts at 180 - 184°C which is probably the starting material. Fraction - 1 is supposed to be (95).

5. Model studies

a) Condensation of phloroglucinol (13)

Condensation of phloroglucinol with formaldehyde in the presence of 15% hydrochloric acid, according to literature procedures[63] gave 2,4,6,2',4',6'-hexahydroxy diphenyl methane (111) mp 224 - 230°C, lit 225°C, NMR indicating the bridge protons

(Ar - CH_2 - Ar) at 3.6 ppm in 7.5% yield

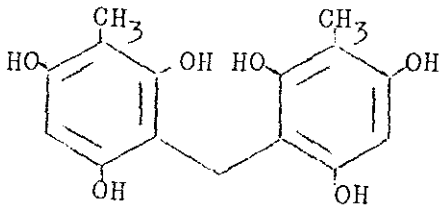


111

b) Condensation of methyl phloroglucinol (14)

The condensation of (14) with aqueous for maldehyde in the presence of dilute H_2SO_4[64] gave the product (112) mp 230 - 235°C lit 230°C, NMR indicating the bridge protons

(Ar - CH_2 - Ar) at 3.8 ppm in 42% yield.

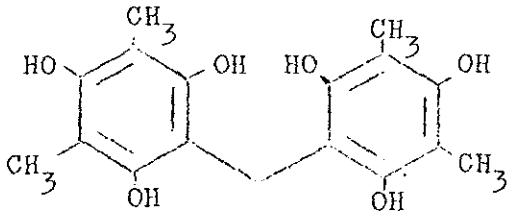


112

c) Condensation of dimethylphloroglucinol (15)

This reaction was tried according to McGookin,[30] using H_2SO_4 as catalyst, but only a red solid which does not melt upto 300°C was obtained; which is suspected to be the sulphonated product.

However condensation of (15) with formaldehyde, using concentrated HCl as catalyst the corresponding product (113) was obtained in 84.0% yield. mp 259 - 260°C lit. 250°C, NMR ($CDCl_3$, TMS) indicates the bridge protons (Ar - CH_2 - Ar) at 3.8 ppm.



113

As is indicated, the yield of the product is higher for dimethylphloroglucinol (15) than for methylphloroglucinol (14) which in turn is higher than that of phloroglucinol (13) which could be accounted by the increased reactivity and limited poly-condensation as the aromatic sites are occupied by more methyl groups.

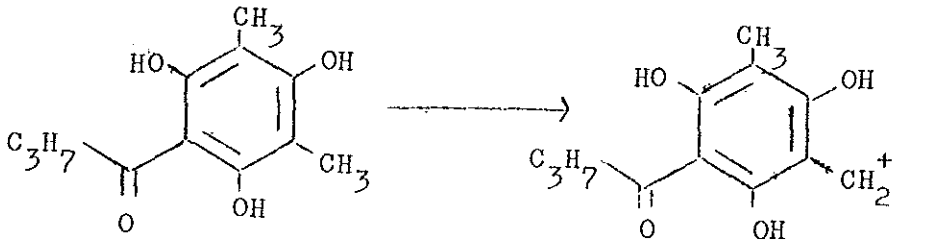
d) Future Plan

Our studies on the unsymmetrical condensation of butyromethylphloroglucinol and butyrodimethylphloroglucinol using formaldehyde or paraformaldehyde has revealed that the reaction is difficult. The attempts made using H_2SO_4 as catalyst gave the starting material in all cases. The studies made using HCl gas as catalyst gave a mixture showing 4 spots on TLC and the reaction done using KOH (1%) as catalyst showed two spots on TLC. Therefore it is worth to repeat the above two reactions and put some effort to separate the mixtures.

Furthermore, one can try the condensation reaction on the selectively methylated phloroglucinol (31). Due to the fact that the methylation reduces the reactivity of butyromethylphloroglucinol, the symmetrical condensation may be suppressed thereby making the unsymmetrical condensation possible. As mentioned earlier the selective methylation could be accomplished by first protecting the more reactive 'OH' sites by benzyl groups, followed by methylation using dimethyl sulfate and eventual hydrogenolysis using pd/c.

It also seems legitimate, to look for other procedures, preferably those closer to biosynthetic pathways, for the coupling reaction. In fact it is known that arylmethanes could be converted to the corresponding benzyl cations by using super acids[79,80] or oxidizing agents like Ce^{+4} or lead tetraacetate in the absence of

stronger nucleophiles than the aromatic ring. The generated benzyl cations could serve as an intermediate for the condensation reaction. In light of this we recommend the following scheme for the synthesis of kosotoxin (1).



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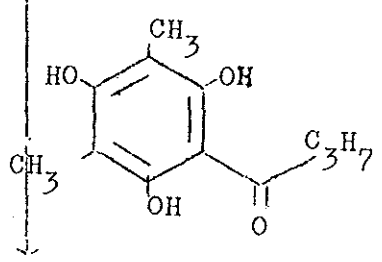

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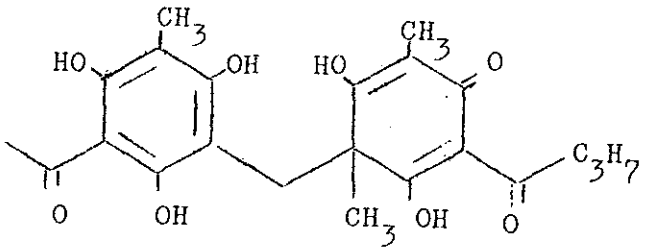

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6. Conclusion

In the course of this work several kosotoxin (1) intermediates were synthesized and especially the preparation of the unstable compounds namely 2,4,6-triaminotoluene (84) 2,4,6-trihydroxy toluene (14) and 2,4,6-trihydroxy xylene (15) has been circumvented. In addition various methods for the synthesis of kosotoxin (1) intermediates were compared and the best methods recommended.

Furthermore the key problem in the synthesis of kosotoxin (1) is identified to be the unsymmetrical condensation of (85) and (90). As expected the condensation of (90), has proved to be difficult and is unlikely, presumably because of the presence of the methyl groups at the condensation sites, which could create some steric crowding. However in view of the fact that kosotoxin (1) is a naturally occuring compound, its synthesis could be possible if reaction conditions which reverse the rottlerone change[31] are selected.

In a nutshell a substantial contribution has been made to the challanging synthesis of kosotoxin which could help future endeavours to realize its synthesis.

IV. EXPERIMENTAL

1. General

Organic solvents were dried over anhydrous sodium sulfate and molecular sieve. All melting points were determined by unimelt Thomas Hoover apparatus and are uncorrected. IR spectra of pellets were taken on Perkin Elmer, model 727 B in frared spectrophotometers NMR spectra were taken on varian T 60 spectrophotometer ($CDCl_3$, DMSO-d_6, TMS); UV spectrum was taken on Perkin Elmer, model 555, UV-Vis-spectrophotometer.

2. Methods for the preparation of compounds

2.1 Preparation of fuming nitric acid

Fuming nitric acid was prepared according to reference 46.

2.2 Preparation of trinitrotoluene (83)

The procedure given in Metholen der Organischenchen Chemie.[46] was followed.

2.3 Catalytic reduction of trinitrotoluene (83)

An ethylacetate solution of trinitrotoluene (83) was shaken with hydrogen at about 37 lb/in ^{2} initial pressure and Raney Nickel catalyst (W_6) (15% of the weight of the nitrocompound[66]) for 48 hrs. At the end of the reduction, the solution was filtered and concentrated HCl was added to isolate the triamino compound as its hydrochloride salt.

2.4 Preparation of Rancy Nickel

W_2, W_4, W_6 were prepared according to Augustine.[51]

2.5 Dissolving metal reduction of trinitrotoluene (83)

Trinitrotoluene (12 gms) and granulated tin (40 gms) were added to concentrated hydrochloric acid (130 mls) at 60 - 75°C. The reaction was allowed to proceed for one hour at the said temperature. Unreacted tin was filtered and the filterate was chilled, then treated with concentrated hydrochloric acid (100 mls). The tin double salt which precipitated was filtered off and was added to 20% sodium carbonate (135 mls) carefully, and sucked dry with chloroform. Drying over sodium sulfate and evaporation of the chloroform gave the triamino compound (84).

2.6 Preparation of 2,4,6-trihydroxy toluene (14)

2,4,6-trinitrotoluene (12 gm) and granulated tin (40 gm) were added to concentrated hydrochloric acid (130 mls) at 60 - 75°C. The reaction was allowed to proceed for 1 hr at the said temperature. Unreacted tin was filtered off and the filterate was chilled, then treated with concentrated hydrochloric acid (100 mls). The double salt which precipitated was filtered off and was treated with 20% sodium carbonate solution (135 mls). The tin oxide was filtered off, under nitrogen atmosphere, and concentrated hydrochloric acid was added to the filterate until the solution is acidic. Then the solution was refluxed for

30 hrs under nitrogen atmosphere. After 30 hrs, the solution was saturated with ammonium chloride and the product (14) was extracted 10 times with 150 mls of ether. Drying of the ether over sodium sulfate and evaporation of the ether gave 2,4,6-trihydroxytoluene (14).

2.7 Acylation of 2,4,6-trihydroxytoluene (14)

A solution of anhydrous phloroglucinol (0.006 mole) in dry ether (25 mls) was shaken with pulverized fused zinc chloride (0.4 gm). To this was added n-propyl cyanide (0.01 mole) and a steady stream of dry, ether saturated HCl gas was passed through the mixture at $0^{o}C$. The reaction was continued for 10 hrs and was kept in a fridge for 5 days. Then the supernatant liquid was decanted, and the oil was taken up in water (25 mls) and washed twice with ether (50 mls). The aqueous layer was concentrated to about one half of its volume by heating, after being neutralized with dilute amonia solution. Upon cooling long silky needles separated which after recrystallization from hot water gave colorless needles of (85).

2.8 Purification of the reagents for the above reaction

All the reagents were carefully dried Methylphloroglucinol (14) was dried in a dessicator over calcium chloride, under vacuum for 2 days. Ether was distilled from sodium and received over molecular sieve, butyronitrile was distilled from P_2O_5 and

received over molecular sieve, and zinc chloride was dried by fusion.

2.9 Condensation of Butromethyl phloroglucinol (85)

A mixture of 2,4,6-trihydroxy-3-methyl-n-butyrophenone (0.5 gm) in methanol (7 ml) and water (2 ml) paraformaldehyde (0.15 gm) and concentrated sulfuring acid (10 drops) was agitated for 24 hrs. The precipitate consisted of 5,5'-di-n-butyryl-2,4, 6,2',4',6'-hexahydroxy-3,3'-dimethyldiphenylmethane, forming pale yellow needles from alcohol.

2.10 Preparation of trinitroxylene (88)

Trinitroxylene (88) was prepared following the procedure of methoden der organischen chemie.[46]

2.11 Preparation of triamino-m-xylene (89)

2.11a Catalytic reduction

The procedure given for the reduction of S-trinitrotoluene (83) was followed,[49] that is using W_6 Raney Nickel as catalyst, Ethyl acetate as solvent and a reaction time of 48 hrs.

2.11b Dissolving metal reduction

Trinitroxylene (13 gm) and granulated tin (40 gm) were added to concentrated hydrochloric acid (130 ml) at 60 - 75°C. The reaction was allowed to proceed for 2 hrs at the said temperature. Unreacted tin was filtered off and the filterate was chilled, to which was bubbled HCl gas for 3 hrs. The tin double salt which precipitated was filtered off and was treated with 20% sodium carbonate solution and sucked dry with powdered sodium carbonate. Then the amine was extracted with chloroform. Drying over sodium sulfate and evaporation of the chloroform gave tri-amino-m-xylene (89).

2.12 Preparation of trihydroxy-m-xylene (15)

a) Dry HCl was bubbled to the cold chloroform extract obtained in the preparation triamino-m-xylene (89) and the hydrochloride precipitated was separated by filteration. To this 450 mls of distilled water was added and refluxed for 24 hrs under nitrogen atmosphere. The aqueous solution was saturated with ammonium chloride and trihydroxy-m-xylene was extracted 15 times with 150 mls of ether. The ether was distilled off, after drying over Na_2SO_4, and the residue was boild two times with benzene. Cooling gave beautiful yellowish crystals of (15).

a) Trinito-m-xylene (13 gm) and granulated tin (40 gm) were added to concd. hydrochloric acid (130 ml) at 60 - 75°C. The reaction was allowed to proceed for 2 hrs at the said temperature. Unreacted tin was filtered off and the filterate was chilled, to which was bubbled HCl gas for 3 hrs. The double salt which precipitated was filtered off and was treated with 20% sodium carbonate solution 175 ml). The tin oxide was filtered off and concentrated hydrochloric acid was added to the filterate until the solution is acidic. Water was added to a volume of 500 ml and refluxed for 24 hrs under nitrogen atmosphere. The aqueous solution was saturated with ammonium chloride and trihydroxy-m-xylene (15) was extracted 10 times with 150 ml of ether. Drying of the ether extract over sodium sulfate, and distilling of the solvent gave the compound (15).

2.13 Acylation of trihydroxy-mxylene (15)

2.14 Attempted acylation of trihydroxy-m-xylene by isobutyryl chloride according to Friedl-Crafts method.

The procedure given by Vogel[67] for the acylation of phloroglucinol (13) by isobutyronitrile was followed.

2.15 Purification of reagents for the above reaction

Dimethylphloroglucinol (15) was dried in a dessicator over calcium chloride and under vacuum for 2 days. Carbon disulfide[68]

was shaken with mercury, then with cold saturated solution of mercuric chloride followed by cold, saturated solution of potassium permanganate and the solution was distilled from P_2O_5, nitrobenzene was dried over anhydrous $CaCl_2$ and distilled under vacuum.

2.16 Preparation of isobutyryl chloride

The preparation of isobutyryl chloride from isobutyric acid was done following Vogel's procedure.[71]

2.17 Purification of $SOCl_2$

The commercial thionyl chloride was first fractionated in all glass apparatus from quinoline in order to remove acid impurities ($SOCl_2$: quinoline = 5:1). The receiver was protected from the entrance of moisture by guard tube filled with calcium chloride. The distillate was refractionated as before from boilded lin seed oil (b.P. 76 - 78°C) (50 g $SOCl_2$ to 20 ml of oil).

2.18 Acylation of trihydroxy-m-xylene (15) by Hoesch's method[60,58]

The procedure followed is the same as the procedure given for the acylation of methyl phloroglucinol. The purification of the reagents and solvents was also done in the same way.

2.19 Attempted condensation of 2,4,6-trihydroxy-3,5-dimethylbutyrophenone (90)

a) Sulfuric acid as a catalyst

The procedure of McGookin given for the condensation of butyromethyl phloroglucinol was followed.[30]

b) Dry HCl gas as catalyst

Butyrodimethylphloroglucinol (0.55 gm), paraformaldehyde (0.15 gm), methanol (9 ml) was agitated to which was bubbled dry HCl gas, for 6 hrs. The red precipitate was separated by filteration.

c) KOH as catalyst[62]

Butyrodimethylphloroglucinol (1.34 ml) 1% KOH (35 ml), 38% formalin (0.07 ml) was stirred at $0^{o}C$ for 2 hrs. The mixture was acidified with hydrochloric acid (2%). Evaporation of the ether extract, after drying with Na_2SO_4 gave an oil.

d) Sodium ethoxide as catalyst[32]

A mixture of butyrodimethylphloroglucinol (0.25 gm), paraformaldehyde (0.05 gm), Na (0.1 gm), EtOH (10 ml) was agitated for 2 hrs. The precipitate formed was separated by filteration.

2.2 Attempted condensation of (85) and (90)

a) KOH as catalyst[62]

Butyrodimethylphloroglucinol (90) dissolved in 1% KOH (12 ml) was taken in an erlemyor flask to which was added Butyromethyl-

phloroglucinol (85) dissolved in 1% KOH, gradually over 1 hr. The solution was acidified with hydrochloric acid (2N). Evaporation of the ether extract dried over sodium sulfate, gave a red gumy product.

b) HCl gas as catalyst[76]

Butyrodimethylphloroglucinol (90) (0.35 gm) was dissolved in 4 ml of methanol in a small buchner flask to which was added paraformaldehyde (0.15 gm), and while bubbling HCl gas, Butyromethylphloroglucinol (0.25 gm) dissolved in methanol was added gradually over 5 hrs. The precipitate showed 4 components by TLC ($CHCl_3$/EtOH, 9:1).

c) H_2SO_4 as catalyst

Here the procedure given for the condensation of butyromethylphloroglucinol (85) was followed.[30]

2.21 Acylation of phloroglucinol (13)

The Hoesch method was employed following the procedure of Howells and Little.[58]

2.22 Condensation of butyrophloroglucinol (94)

a) Attempted condensation in basic medium[62]

Butyrophloroglucinol (2.68 ml) was dissolved in 1% KOH (30 mls) and was mixed with 38% formalin (0.10 ml). After letting it stand for 30 minutes the solution was acidified with 2N HCl. without regards to the resulting precipitate, was

exhaustively (10 x 15) extracted with ether. The ether concentrated in vacuum.

b) Condensation using H_2SO_4 as catalyst

The procedure given for the condensation of butyromethylphloroglucinol was followed.[30]

2.23 Condensation of phloroglucinol (13)

Phloroglucinol (2 mole) and aqueous formaldehyde (1 mole) in the presence of hydrochloric acid (15%) was stirred for 1 hr. The product separated by filteration is suspended in water and extracted with ether. The residue after removing the ether was taken up with ethyl acetate and separated into three fractions with benzene. The second fraction was methylene-bis phloroglucinol (111).

2.24 Condensation of methylphloroglucinol (64)

Methylphloroglucinol (2 mole) and 38% formaldehyde (1 mole) in the presence of dilute sulfuric acid was stirred for 1 hr. The precipitate separated was pecrystallized from alcohol to give the product (112).

2.25 Condensation of dimethylphloroglucinol (15)

Dimethylphloroglucinol (2 mole) and aqueous formaldehyde (1 mole) in the presence of concentrated hydrochloric acid was stirred for 1 hr. Recrystallization of the product separated by filteration from 25% alcohol, gave needles of (113).

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