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PHYSICAL AND CHEMICAL PROPERTIES
OF
PHENOLS AND PHENOL ETHERS USED IN MEDICINE

BY

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A Preliminary Paper Submitted in Partial Fulfilment
of the Requirements for the Degree of
Doctor of Philosophy
at the
UNIVERSITY OF WISCONSIN

1951

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INTRODUCTION

The main purpose in this paper has been to gather pertinent information regarding physical and chemical properties of phenols and phenol ethers used in medicine. Much time was spent to obtain the various physical constants not readily available. In most cases the original literature was consulted.

Phenols and phenol ethers constitute a very important class of drugs. They are also starting materials for many products such as dyes, plastics, and a great number of phenols have been identified with the active principles of natural products. Mono, di and tri phenols differ in their chemical behaviour and their effect on the living organisms. These functions may again be influenced by the introduction into the benzene ring of one or more alkyl and aryl groups of different structure by introduction of various numbers of halogen atoms, amido, nitro, aldehydic and carboxylis groups and by esterification and eterification of one or more hydroxylic groups ~~with~~ alkyl and aryl radicals of different configuration, Many of these compounds have been synthesized in search of new chemicals with definite characteristics.

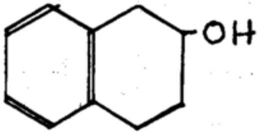
The manifestation of biological activity by a drug is a process which proceeds through various stages from the point of application of the drug to the final site of the chemical event which is the immediate cause of the observed effect. These stages may involve physiochemical phenomena such as passage through membranes, diffusion, transfer from aquous to lipid phases etc., of which some may be easy and rapid andothers critical and in the physiochemical semse rate-determining. Thus according to Hurst "the correlation of biological activity with simple drug distribution between heterogenous phases may be greatly extended if more specific factors, which influence molecular interaction in monolayers are taken into consideration."

Several biological effects are produced by compounds of diverse chemicalsstructure having low chemical reactivity, and these effects are produced by a mechanism which is primarily physical. Examples are seen in phenols and phenol ethers in their insecticidal, bacteriocial, and fungicidal properties. And in these instances although the concentrations necessary to produce the effect vary widely, the "activity" lies within a fairly narrow range which is a characteristic of the organisms. This is illustrated in the following table, which gives the bacteriocidal concentration and "activities" of various phenols.

Substances	Bactericidal Conc. Mol/lt	"Activity"
Phenol	0.097	0.11
o-cresol	0.039	0.17
Thymol	0.0022	0.38
Resorcinol	3.09	0.54

BETANAPHTHOL

$C_{10}H_8O$



Physical Properties - White to pale buff-colored shining leaflets or a white or yellowish crystalline powder. It has a faint, phenol-like odor and is stable in air, but darkens on exposure to sunlight.

Melting Point - 120° - 122°; sublimes readily when heated and is volatile with water or alcohol vapor.

Solubility -

t°	Gms. Betanapthol per 100 c.c. sat. soln.	
12.5°	0.044	(1)
25.1°	0.074	(2)
29.5°	0.0876	(3)

1 Gm. is soluble in about 80 c.c. of boiling water.

It is soluble in glycerine and in olive oil and is readily dissolved by solutions of alkali hydroxide.

100 c.c. 90% alcohol dissolves about 55 gm. of betanapthol at 15.5° (5)

100g. 95% formic acid dissolves 3.11 g. of betahapthol(15.5°)(6)

" Benzene dissolves 4.13 g. of betanapthol at 25° (7)

" CCl_4 " 0.442 " " (7)

Ionization Constant - 0.1×10^{-10} (8)

Chemical Properties -

(1) A cold saturated solution of betanapthol when

mixed with ammonia develops a faint, bluish flurorescence.

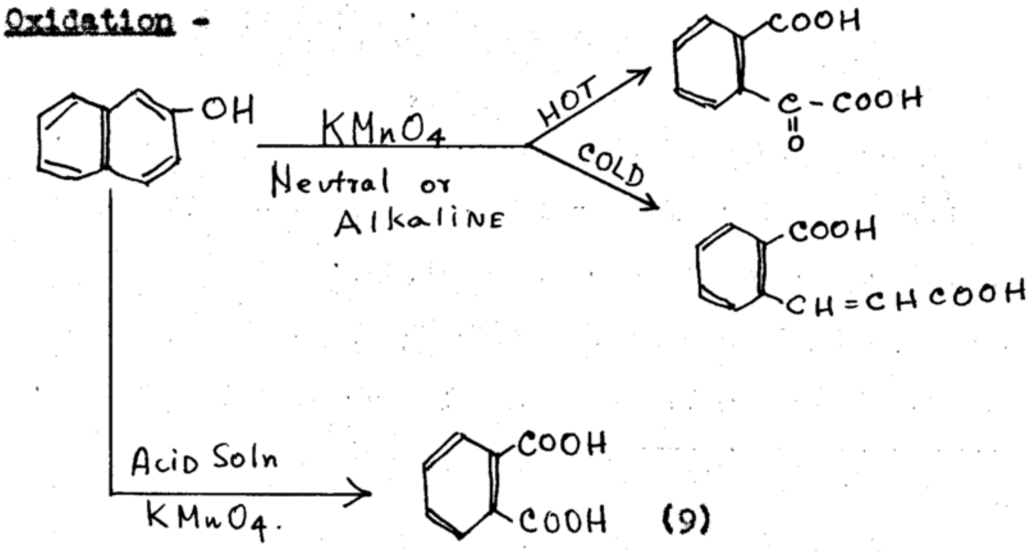
(2) When about 100 mg. of betanapthol are added to 5 c.c. of a solution of KOH (1 in 4) and then 1 c.c. of $CHCl_3$ and the mixture warmed gently, the water layer acquires a blue color which changes successively to green and brown.

(3) When $FeCl_3$ solution is added to a cold saturated solution of betanapthol a greenish color is produced and after some time whitish flakes separate which turn brown when heated.

Coefficient of Distribution - Coefficient of Distribution of betanapthol between water and chloroform at 25°

$$\frac{C_{H_2O}}{C_{CHCl_3}} = 0.0171 \qquad (4)$$

Oxidation -



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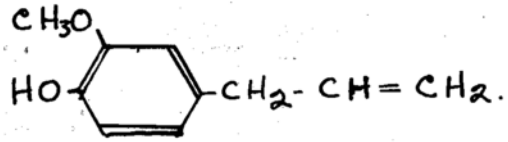
EUGENOL

$C_{10}H_{12}O_2$



Physical Properties - Eugenol is a colorless liquid widely distributed among plants and obtainable in practical amount from oil of cloves.

Boiling point -

Pressure	Boiling Point (1)
760 mm	252.66°
600	242.78
500	235.30
400	226.30
300	215.60
200	201.60
100	180.10
60	165.60
40	154.95
20	138.48
10	124.00
8	119.60
6	114.15
4	106.70

Freezing Point - 10.3° (2)

Density -

d_4^{25} - 1.0651 (2)

d_4^{20} - 1.0664 (3)

Solubility - Soluble in 5-6 vol. of 50% alcohol
" 2-3 " 60% "
" 1-2 " 70% " (4)

1 c.c. Eugenol dissolves in 4.27 c.c. of 50% alcohol at 25°

1 c.c. " " 5.22 c.c. " " 15°

1 c.c. Eugenol dissolves in 12.70 c.c. of 2% NaOH at 25°

% Conc. of Alcohol	c.c. of Eugenol soluble in 100 cc of alcohol at 22°-25° (5)
40	0.30
50	5.80
60	16.0

Critical temperature of a mixture of Eugenol & Glycerol - (6)

	Critical Solution Temp.	Wt % Glycerol in mixt.
Glycerol & Eugenol	166	14.0

Dielectric Constant - 10.337 at 20.2° (7)

Refractive Index - 1.540 to 1.542 at 20°

Ultra-Violet Absorption Data - Maximum absorption at 2809A

E = 1.41 at a conc. of 0.004 g. per 100 c.c. solution

Chemical Properties -

Identification - (1) Eugenol can be characterized by the preparation of several derivatives.

a) On treatment with Benzoyl chloride, eugenol forms a benzoate m. 69.5° according to Ikeda et al. (8)
Mc Kie (9) suggested a method of estimating the composition of mixtures of eugenol and iso-eugenol through the melting point curves of their benzoates, eutectic 25.5% iso-eugenol benzoate 56.5°

b) Phenyl urethane m. 97° (10)

c) Mercury derivative from mercuric acetate m. 95°-96°, hydrate m. 120.5°-121.5°. By shaking with dil HCl, eugenol is regenerated readily. (11)

d) Eugenol piperazine m,99°; this compound gives character-

-istic precipitate with alkaloids, thus it is useful in micro work. (12)

e) 2,4-Dinitro phenyl ether m. 114°-115° ; according to Bost & Nicholson. (13)

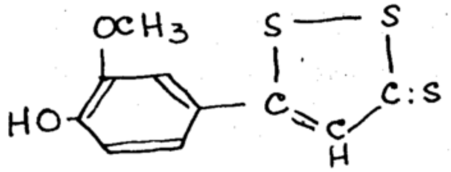
This compound is prepared by treating Eugenol in alkaline soltion with 2,4-dinitro chlorobenzene.

f) Dibromide m. 80°; tetrabromide m. 118°-119° as recorded by Gildmeister & Hoffmann. (4)

2. <u>Color Reactions</u> - In a cold saturated aqucus solution of $FeCl_3$, Eugenol gives a turbid, grayish yellow; in 2% alcoholic solution a blue color, which fades to gray-yellow in 15 minutes.

Bezssonoff's reagent gives a positive reaction (blue color) in a very small concentration according to Sabetay and Riechstoff. (14)

<u>Action of Sulfur on Eugenol</u> - Eugenol and iso-eugenol react with sulfur analogously to anethole yielding trithioeugenol m. 182°-183°, which is the point of instantaneous fusion. The structure -



Eugenol and maleic anhydride condenses a t 120°-140°, giving a product m. 245°-258°. (16)

On heating with KOH, eugenol is converted to iso-eugenol.

Stability and Discoloration - Eugenol is not entirely stable, particularly to strong alkali and acids; may cause discoloration.

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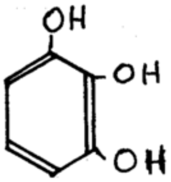
(C. A. - 42, 8174)

PYROGALLOL

$C_6H_6O_3$



Mol. wt.- 126.11

Melting Point - 133° - 134°

Boiling Point - 309°

Physical Properties - It forms colorless leaflets or needles of the specific gravity $1.453^{40°}$

Solubility - 62.0 g. of pyrogallol is soluble in 100 c.c. of saturated solution at 20°.

100 g. of pyrogallol is soluble in 100 g. of ethanol at 25°.

The primary and secondary dissociation constants of pyrogallol were detemmined by potentiometric titrations, with corrections being applied for interionic attractions with the help of Debye-Hucker theory.

K_1	K_2	
9.68×10^{-10}	2.30×10^{-12}	(1)

Chemical Properties - Its alkaline solutions turn rapidly brown when in contact with air, and its aquous solutions reduce the salts of rare metals, mercurous nitrate and $HgCl_2$. With $Pb(OAc)_2$ it forms a white, with Lead Subacetate a brownish-white precipatate.

It gives the following reactions as quoted from Rosenthaler (1923)

1. Diazobenzene sulfonic acid and alkali : intense brown
2. Millon's Reagent : Only after warming , yellow red.
3. Guareschi-Lustgarten reaction : no color

4. Berthelot-Lex reaction : in the cold, dark-purple, when heated, brown

5. Vanillin HCl reaction : in cold, marked red pink with a tint of purple when heated, a raspberry red.

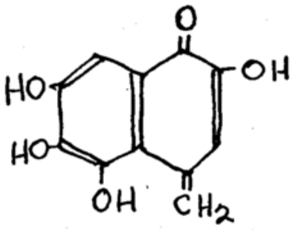
6. Formaldehyde-Sulfuric Acid reaction : red ring and upon shaking intense red turbid solution.

7. With iodopotassium iodide and NaOH, a temporary red Purple.

8. With formaldehyde and conc. HCl in the cold or with moderate warming, a ruby red.

9. If heated with ammonium oxalate, the residue (rufigallic ammonium) dissolves in water with red color. (2)

<u>Oxidation of Pyragallol</u> - Concentrated alkaline pyrogallol solution absorbs oxygen faster than hydrosulfite solutions, and much faster than ammoniacal Cu_2Cl_2 solutions. (3) Pyrogallol reduce NH_3-$AgNO_3$ vigorously. The reducing action is in proportion to the number of OH groups present. (4) Oxidative products of pyrogallol is purpurogallin. The structures for purpurogallin have been proposed ;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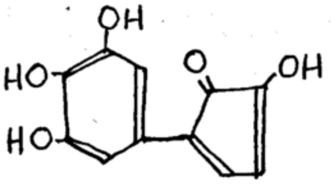
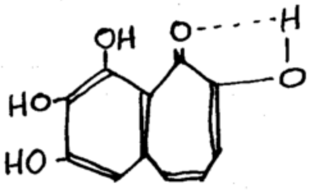

II


III

I - methylene-quinone structure due to Dean & Niernstein. (5)

II- a trihydroxy phenyl cyclopenta dienelone due to Willstatter and Heiss. (6)

III-J.A. Barltrop & J.S. Nicholson (7)

Hemin which possesses a strong catalase activity, does not promote oxidation of pyrogallol, whereas Hematin, with its about 10 times weaker catalase activity, distinctly promotes oxidation of pyrogallol. While Fe$(CN)_6^{\equiv}$ is entirely inactive, $Na_2(CN)_5NO$ has strong promoting effect on the oxidation of pyrogallol. (8)

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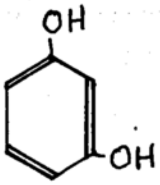
Resorcinol

$C6H_6O_2$



Mol. wt - 110.11

Physical Properties - It represents colorless rhombic crystals, of specific gfavity 1.272$^{15^\circ}$.

Melting Point - 110.7°

Boiling Point - 276.5°

Solubility - Solubility of resorcinol in different solvents- Determinations were made by synthetic method. Hydrogen was placed in sealed tubes in order to prevent oxidation. (1)

Results are in g. moles of $C_6H_4(OH)_2$ per 100 g. moles sat. sol.

t°	water	C_2H_5OH	acetone	CCl_4	$CHCL_3$	benzene
20	18.65	39.34	51.55	-	-	(0.15)
30	24.25	41.91	53.94	0.07	0.63	0.40
50	37.49	48.40	58.63	0.27	1.06	0.75
70	53.45	58.34	65.25	0.47	1.48	1.76
90	73.83	74.65	79.60	0.69	5.64	6.40
109.4	100.00	100.00	100.00	100.00	100.00	100.00

Solubility in Acetic Acid, in Nitrobenzene andin Urethane

t°	In Acetic Acid g./100g. HoAc	Nitrobenzene g./100g.$C_6H_5NO_2$	Urethane g./100g.Urethane
20	39.13	6.33	-
40	69.45	17.02	108.6
60	119.1	42.45	159.0

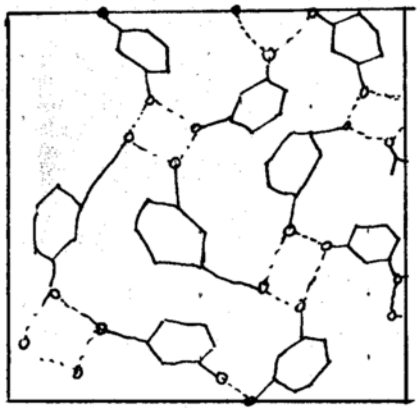
Latent Heat of Melting - The latent heat of melting was determined by the cooling method and the value obtained was 28.80 calories per gram. (3)

Dissociation Constant - Determinations were made by potentiometric titrations, with corrections being applied for interionic attractions with the help of Debye-Huckel Theory.

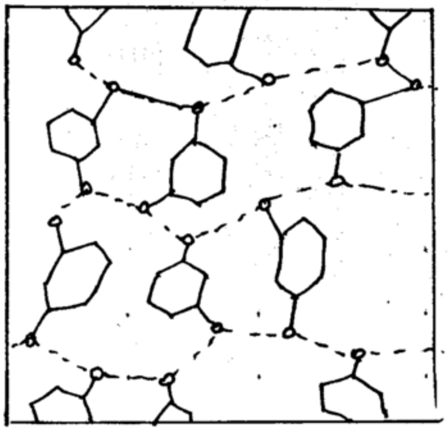
$$K_1 = 7.11 \times 10^{-10}$$

$$K_2 = 4.78 \times 10^{-12} \qquad (4)$$

The Structure of Crystalline Modifacations of resorcinol have been fully worked out and are shown in Figures I & II.



α - Resorcinol



β - Resorcinol.

The low temperature, or α - form, shows a structure very similar to that of pentaerythritol, except that the converging -OH groups now form a spiral extending throughout tthe crystal, instead of the square which appears in the projection of the structure that has been drawn in Fig I.

The ordinary or α- form (Fig. I) like ice is a peculiarly open structure of low density (1.28) which is obviously maintained by the action of hydrogen bonds. On heating to about 74°, the structure begins to change. The molecules rearrange themselves to produce the more compact pattern shown in Fig. XI which has a considerable higher density (1.33). The change is a slow one, but evidently at this temperature a sufficient number of bonds become unstable to allow the crystals to achieve a lower van der waal's potential. The rearranged molecules are packed more closely and the reformed hydrogen bonds are of slightly greater length and exhibit considerable distortion of angle. (5)

Heats of Ionization - Heats of ionization was measured calorimetrically at 10°, 20°, 30° in approximately 0.05 M solutions. (6)

ΔC_p°	ΔH°	ΔS°	at 298.1° K
-38	159	-18.1	

<u>Chemical Properties</u> - Rosenthaler (1923) gives the following reactions for Resorcinol :

1. Resorcinol does not reduce alkaline solution of $CuSO_4$, but it reduces $AgNO_3$ solution at elevated temperature.
2. It forms no precipitate with bromine water, nor with Lead Acetate, but with basic Lead Acetate and with $Hg(NO_3)_2$.
3. Although its alkaline solutions are more stable when

3. (contd) in contact with air than those of catechol, they will gradually turn green in standing.

Oxidation of Resorcinol by means of H_2O_2 in the presence of tungstic acid sol :

Resorcinol is oxidized to CO_2, and maleic acid :-

$$C_6H_4(OH)_2 + H_2O_2 \longrightarrow C_4H_4O_2 + 2CO_2 + H_2O$$

The velocity of the reaction fits the equation :-

$$k = \frac{1}{t_2 - t_1} \ \mathrm{Log} \ \frac{P_{t_\alpha} - P_{t_1}}{P_{t_\alpha} - P_{t_2}}$$

Where P is the pressure of CO_2 at time t. (7)

Hydrogenation - Catalytic hydrogenation of resorcinol in NaOH and H_2O over Raney Ni hydrogenation catalyst at 50°/1000-1500 lbs for 10-12 hours gives 85-95% dihydroresorcinol. (8)

Catalytic reduction of resorcinol in Sodium acetate, Na-acetate-Acetic Acid, and water, the products are di-hydroresorcinol, resorcitol, and cyclo-hexanol. (9)

Auto Oxidation- The formation of 3,3'; 4,4'; 5,5'- hexahydroxy biphenyl from pyrogallol in $Ba(OH)_2$ solution (Harris - Ber. - 35, 2954 - 9 (1902) is explained by assuming that in an alkaline solution the pyrogallol ion losses its free negative charge by autooxidation, forming a radical (II), two of which combine at the free bond to give a compound from which I is formed by loss of H atoms from the 1-1' positions. By a similar process, resorcinol in alkaline solution should give 2-2'-dihydroxy biphenyl-4,4'-quinone (III).

Repeated recrystallizations of the mixture of products obtained from alkaline treatment of resorcinol gives a substance which corresponds fairly well to formula (III) except that the H is always too low. (10)

Color Reagents for the paper chromatography of Sugars :

The use of resorcinol and naptharesorcinol in addition to the usual ammoniacal $AgNO_3$ as a color reagent in the chromatographic determination of sugars permits possible identification of reducing as well as non-reducing sugars. (11)

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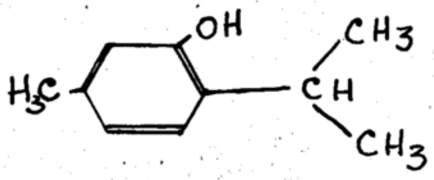
THYMOL

$C_{10}H_{14}O$



Mol. wt - 150.21

<u>Physical Properties</u> - Thymol forms transparant colorless monoclinic or hexagonal crystals. Its odor is reminiscent of thyme. Thymol crystals sink in water and therefore have a specific gravity above 1.0. Thymol can be undercooled considerably below its melting point without solidifying. (1)

Congealing Point - 49°-50° (2)

Melting Point - 50°-51.5° (2)

51° (3)

Boiling Point - 233.5° (Corrected) (4)

$b_{(749-752)}$ = 233°-234° (2)

Density - $d_{4}^{24.4}$ - 0.9689 (5)

d_{20}^{20} - 0.9757 (undercooled) (4)

d_{15}^{15} - 0.9790 (unercooled) (4)

Refractive Index - $n_{D}^{24.4}$ - 1.51893 (5)

n_{D}^{20} - 1.52269 (2)

Solubility - Solubility in water (7)

Temp.	Gm. Thymol/100g. sat. soln.
10	0.067
15	0.077
20	0.088
25	0.0995
30	0.112
35	0.126
37	0.132
40	0.141

100 g. para-cyme (b.p. 176°-176.5°) dissolves 113.85 g. thymol at 25°.

Thymol is only sparangly soluble in water (1:1200) and in glycerol (1:1000), better in paraffin oil (1:20) and readily soluble in alcohol, ether, chloroform, benzene or glacial acetic acid. It is soluble in volatile and fatty oils and volatile with steam.

Identification -
(1) Derivatives :
- a) Phenyl urethane m. 106°-107° (8)
- b) - napthyl urethane m. 160° (9)
- c) p-bromobenzene sulfonate m.103.5° (10)
- d) 3,5-dinitrobenzoate m. 103.2° (11)
- e) p-iodophenyl urethane m.175°-176° (12)
- f) By coupling with diazotized p-nitro aniline and subsequent chromatographic separation of the derived dyes it is possible to identify thymol in a mixture of several hydroxy benzenes. (13)

(2) Oxidation : Using K_2Cr2O_7 and H_2SO_4, Bargellini oxidized thymol or its nitroso and amino compounds to thymoquinone m. 44°-46°. (14)

Cohn and Richter (15) mentioned also the use of MnO_2 for the preparation of thymoquinone from thymol.

3. Color Reactions :

a) when fused with phthalic anhydride, thymol develops a strongly violet-red to red color, and in dilute alkaline solution an intense blue color (thymolphthalein).

b) when treated with $FeCl_3$, an alcoholic solution of thymol, contrary to carvacol does not show any color reaction, but when dissolved in H_2SO_4, thymol forms thymol sulfonic acid $C_6H_2(SO_3H).(CH_3).(C_3H_7).(OH)$ the latter, according to Gildemeister and Hoffmann, (16) producing a violet color with $FeCl_3$.

c) a very small crystal of thymol is dissolved in 1 c.c. glacial acetic acid, 6 drops of H_2SO_4 and 1 drop of HNO_3 added, the liquid shows a deep bluish-green color when viewed by reflected light.

d) 1 g. thymol heated in a test-tube in a water bath with 5 c.c. of a 10% NaOH solution : a clear colorless, or pale red solution is formed, which becomes darker on standing, without separation of oily drops. Upon the addition of a few drops of $CHCl_3$ to this solution and agitating the mixture, a violet color is produced.

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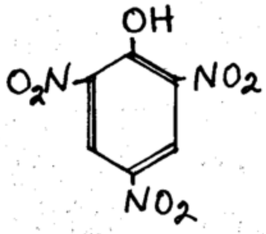
PICRIC ACID

$C_6H_3O_7N_3$



Mol. wt - 229.11

Physical Properties - It comes as yellow, rhombic crystals.

Specific Gravity - 1.763^{20°

Melting Point - 121.8

Solubility - in water

t°	Gm./100 g. water	
9	0.979	(1)
50	2.328	
20	0.0515	(2)
20	0.0568	(3)
25	0.0487	(4)
25	0.0533	(5)

in CH_3OH (absolute) (6)

0	13.8
14	16.3
25	21.1

in C_2H_5OH (6)

Gms. C_2H_5OH per 100 g. aq. solvent	Gms. $C_6H_2OH(NO_2)_3$ per 100g. solvent at		
	0°	25°	50°
90	8.1	12.3	21.1
100	4.5	8.0	14.8

Solubilities (Contd) -

In aquous solution of Organic Compounds. (7)

Solvent aquous 1.0 g. mole solution of	Gms, $C_6H_2OH(NO_2)_3$/100 c/c. aquous solvent
Glycerol	1.119
Mannitol	1.063
Chloral Hydrate	1.597
Glucose	1.035
Sucrose	1.161

Adsorption - Adsorption of picric acid by "Carbo-medicinalis" Merck from 0.01 M solution in binary mixture of water, ethyl alcohol, acetone, di-ethyl ether, nitro benzene, toluene, benzene and carbon tetrachloride was determined at 25°. Solubility and adsorption curves are antibatic except in acetone solution. In acetone, the adsorption maxima is at 4500 A, behaviour in this solvent being anomalous. (8)

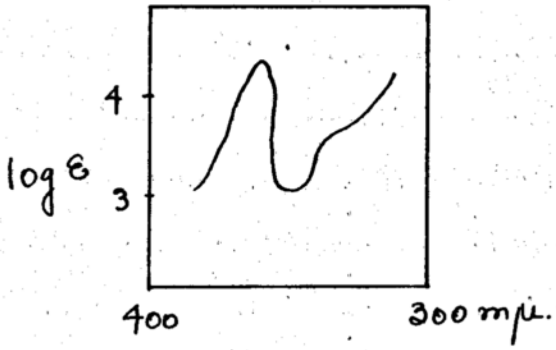
The adsorption of picric acid from aquous solution by SiO_2 gel at 25° is a continuous process, and the data satisfy the Langmuir Equation. (9)

Heat of Combustion - The isothermal heat of combustion in calories at 17° at constant volume is 2695.6 calories. (10)

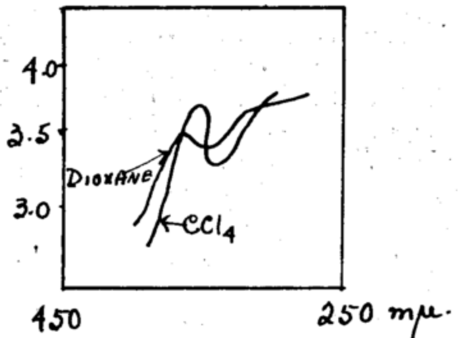
Dissociation Constant - The dissociation constant in n-butyl alcohol at 25° is 6.23×10^{-5} (11)

Crystal Structure - Picric Acid is orthorhombic, space group C_{20}^{5}. The unit cell contains 8 formula nets and has the dimensions ;: a = 9.25 ; b = 19.08 ; c = 9.68 A.u. The structure is built up of unsymmetrical pairs of $C_6H_2OH(NO_2)_3$ groups with 4 of these pairs in the unit cell. (12)

Absorption Curve - Absorption curve of Picric acid in alcohol solution (13)



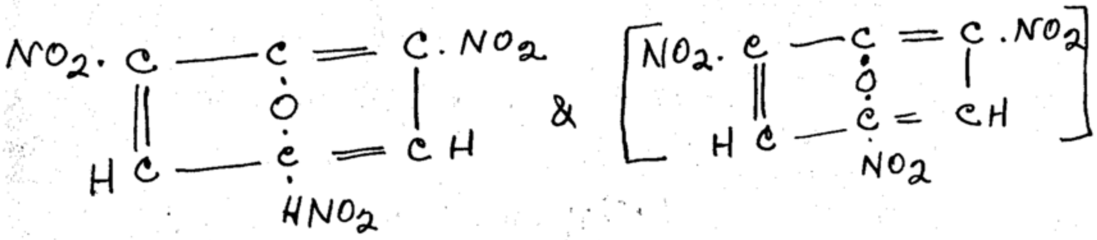
Absorption curve of Picric acid in dioxan soln. (14)



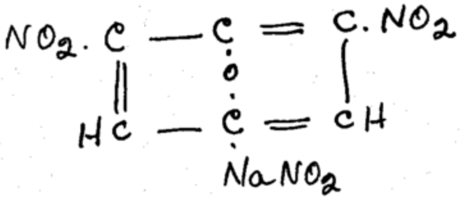
Variation of Physico-chemical properties of picric acid -

In addition to the yellow, colorless (in very acid media) and red (as picrate in very alkaline media) form of picric acid, a greenish yellow form is obtained at very high pH. From considerations of the U-V spectra of the various forms at various concentrations and pH values, the ratio of absorption (x 2400/ x 2600 & pH 1-13) solubility at varying pH, and electric transport it is concluded that there are 7 forms of the acid :

$$\left.\begin{array}{l} C_6H_2(NO_2)_3OH_2Cl \\ \left[C_6H_2(NO_2)_3.OH_2\right]^+ \\ \& \ C_6H_2(NO_2)_3OH \end{array}\right\} \text{COLORLESS}$$



Yellow



& $C_6H_2(NO_2)_3ONa$.

Yellow- GREEN.

Kinetics of the oxidation of Picric acid by $KMnO_4$ - Picric acid is completely oxidized to HNO_3nand CO_2, permanganate ions being reduced to MnO_2. The reaction is bimolecular over fairly wide range of conditions, the cinstant being independent of the concentration of H and only very slightly affected by the addition of electrolytes.

$$3\,C_6H_2(NO_2)_3OH + 28\,MnO_4^- + 19\,H^+ \longrightarrow 18\,CO_2 + 9\,NO_3^- + 28\,MnO_2 + 42\,H_2O. \quad (16)$$

Photochemical decomposition : An alkaline solution of picric acid (pH greater than 13) exposed to light develops a red-brown tint, slowly in diffused light rapidly in sunlight and still more rapidly closed to a Hg-lamp, followed in the last case by a violet tint and then decoloration. Chemical analysis shows the formation of picramic and isopurpuric acids, HNO_2, NH_3, and HCN. (17)

The activation energy for the oxidation of picric acid is 12.2 Kg-calories per gram.

Ammonium salt of picric acid : For making a phlegmatized and substantially shock-proof NH_4-salt of picric acid, a reaction medium is formd by dissolving ammonia gas in a viscous petroleum jelly or viscous lubrication oil having no substantial solvent effect upon the NH_4-salt and having a high b.p. and the resulting reaction medium is brought into contact with the acid in the solid state, and the reaction medium is then incompletely removed. (19)

Electrolytic Reduction : A $SnCl_2$ carrier catalyst was emplyed in the electrolytic reduction of picric acid to tri-amino phenol. (20)

Conductometric Titration : Conductometric titrations of picric acid was made at 25° in acetone-water mixture with 0.1 N alcoholic NaOH. Bright Pt-electrodes and a bridge input of 3000cycles were used. The acetone-water mixture was varied from 30% to 90% acetone. (21)

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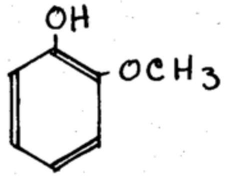
Guaicol

$C_7H_8O_2$



Mol. wt - 124.13

Physical Properties - It forms prisims of the specific gravity $1.140 \frac{15^\circ}{15^\circ}$. The critical solution temperature of mixtures of guaicol and citronellal is about 18°. (1)

Melting Point - 32°

28.3° (2)

Boiling Point - 205°

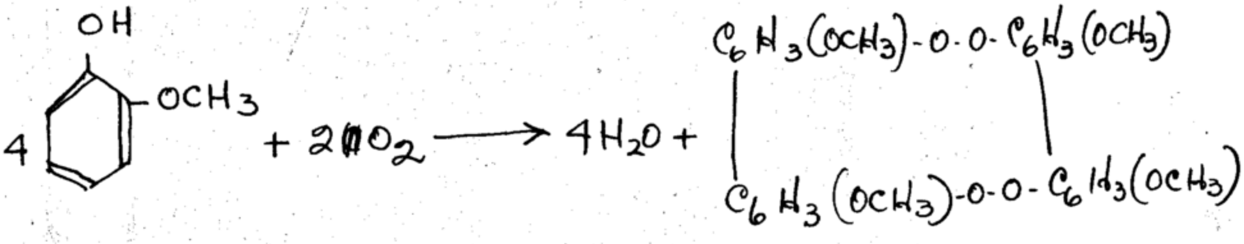
Solubility - Guaicol is soluble in water to the extent of 1.7%. It is very soluble in alcohol and ether. (2)

Chemical Properties - According to Rosenthaler (1923) guaiacol can be identified by its picrate which forms orange-yellow needles m. 86°.

Identification -

a) alcoholic solution of Guaiacol + $FeCl_3 \longrightarrow$ a blue color
b) Guaiacol + bromine water ⟶ brown precipitate
c) " + diazobenzene sulfonic acid + alkali ⟶ light brown color + HCl ⟶ red brown
d) " + formaldehyde + $H_2SO_4 \longrightarrow$ violet ring
e) " + Vanillin. HCl ⟶ pink red color heat intense violet tint
f) " + Guareschi-Lustgarten reagent → ruby-red color
g) " + Berthlot-Lex reagent ⟶ green color

According to Bertrand (3) Guaiacol is oxidized in presence of lacase to a red compound tetraguaiacoquinohe according to the following equation :-



TetRA GUAICOQUINONE

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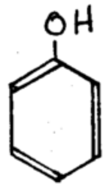
PHENOL

C_6H_6O



Mol. wt - 94.11

Physical Properties - It represents colorless needles which have a sweetish pungent taste.

Specific Gravity - 1.071^{25°

Melting Point - 40.85° (1)
41.00° (2)
42.6° (3)

Solubility - There exists a mutual solubility of phenol and water.

Mutual Solubility of Phenol & Water. (4)

No.	Temp. C°	Phenol Phase		Water Phase	
		Wt. % of Phenol	Density	Wt % of Phenol	Density
1	20	72.16	1.0541	8.36	1.0018
2	25	71.28	1.0469	8.66	1.0045
3	30	69.90	1.0429	9.22	1.0039
4	36	67.63	1.0405	9.91	0.9974
5	54.83	59.22	-	-	-
6	57.30	-	-	14.87	-
7	59.20	55.76	-	-	-
8	62.55	51.87	-	-	-
9	62.74	-	-	19.35	-
10	65.24	44.09	-	-	-
11	65.79	-	-	27.77	-
12	66.01	-	-	29.13	-
13	65.79	-	-	30.21	-
14	65.90	-	-	31.35	-
15	65.84	-	-	32.23	-
16	65.86	-	-	32.79	-
117	65.84	34.23	-	-	-

The consulate temperature has been found to be 65.85° 0.15°, other values reported in the literature - 65.8° (5); 66.06° (6); 66.09° (7)

Distribution of Phenol between Water & Benzene at 25° (8) -

Gm. Mols. Phenol per lt Water (layer) A	 Benzene (layer) B	$\frac{C_A}{C_B}$
0.00202	0.00466	0.433
0.00565	0.01324	0.427
0.00797	0.01859	0.429
0.01094	0.02528	0.433
0.01440	0.03428	0.420

Density - Density at 40° accurately determined :- 1.0586 (9)

Densities, Relative Densities, and Surface Tension of phenol-benzene mixtures have been determined for various concentrations of phenol at 25° C (10)

Phenol-Benzene Mixtures

Mol. Fraction Phenol	Density 25°	Rel. Viscosity	Abs. Viscosity x 10^3	Surface Tension (Dynes)
0.083	0.89112	1.145	6.592	27.375
0.279	0.9313	1.801	10.370	28.440
0.522	0.9794	3.212	18.494	30.302
0.658	1.0065	4.833	27.828	32.220
0.762	1.0271	6.923	39.36	33.866

Hydrolysis Constant - $k = \frac{C_{acid} \times C_{base}}{C_{salt}}$

$= 4.5 \times 10^{-4}$ (15°) (11)

Ionization Constant - 1.3×10^{-10} (12)
1.27×10^{-10} (13)

Oxidation-Reduction Potential - at 25°

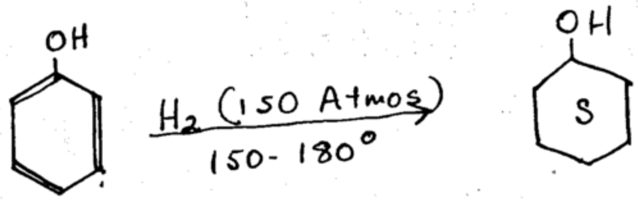
$E_c(v) - 1.089$ (14)

Free Energy F - The free energy F of phenol vapor is given by - $-15{,}130 \quad 24.95\ T \ \mathrm{Log}\ T - 0.0194\ T^2 - 106.62\ T$ (15)

Vapor Pressure - The vapor pressure rises from 0.053 mm of Hg at 0° to 0.63 at 30.3° (16)

Different forms of Phenol - Examination of the spectrum between wave-lengths 2370 and 2760 A of solutions of phenol at ph 2 - 12 indicates 3 forms of phenol : A (pH 1-7) a hemiquinone, B (pH 7-9) alifiable phenol and C (pH above 9) salified phenol. (17)

Lowering of Viscosity - Like Camphor, and menthol phenol lower the viscosity of oils in which it is dissolved to an extent that varies directly with the concentration of phenol. (18)
Reduction and Hydrogenation - Pd and $SrCO_3$ (2%) is an excellent catalyst for pressure hydrogenation in dioxane at elevated temperature.



PHENOL

CYCLO-HEXANOL

Phenol hydrogenates under 200 atmosphene pressure of hydrogen over pure pelleted MoS_2 as catalyst. Yield 62% Cyclohexanol at 300°, 100% at 400°.

A British Patent (20) describes reaction between phenol vapor and a reducing gas as H_2 at high temperature (750°) for producing Benzene.

Oxidation of Phenol -

Phenol $\xrightarrow{\text{Acetic Acid}}$ Muconic Acid p-quinone (21)

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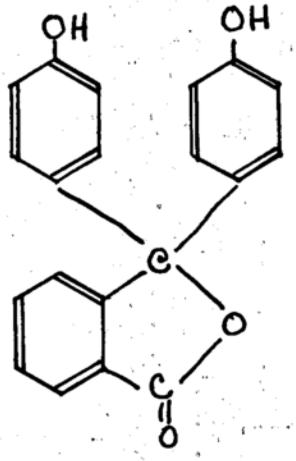
Phenolpthalein

$C_{20}H_{14}O_4$



Mol. wt - 318.10

Melting Point - 235° - 237° (1)
261° (Handbook of Chemistry & Physics)

Analysis of 104 lots of domestic U.S.P. phenolpthalein sold by the two principal manufacturers of this drug since 1937 showed an average m. 261.2° - 261.9°. (6)

Physical Properties -

Solubility -	100 g.	of water	dissolves	0.0175 g.	at 20°	(2)
	100 g.	"	"	0.04 g.	at 20°-25°	(3)
	100 g.	Pyridine	"	796 g.	at 20°-25°	(4)
	100 g.	Ethyl alcohol	"	20.91 g.	at 15°-20°	(5)
	100 g.	Methyl alcohol	"	14.18 g.	at " "	"
	100 g.	Acetone	"	26.39 g.	" "	"
	100 g.	Pet. Ether	"	0.017 g.	at 25°	"

Careful solubility determinations were made at 25° 0.3° (6)

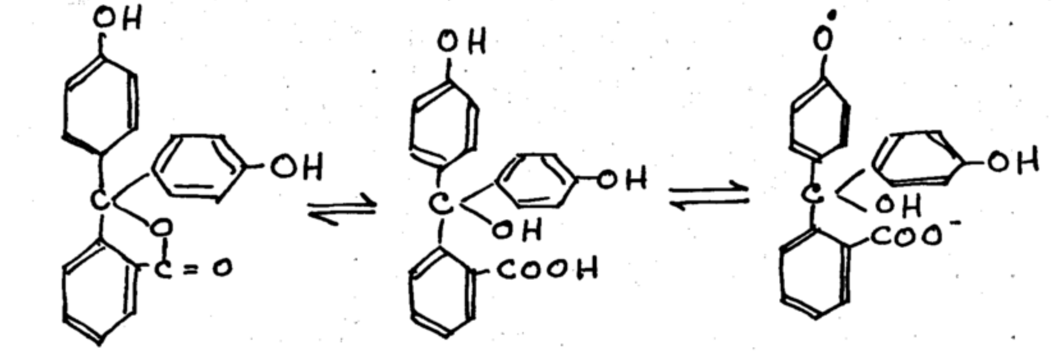
Solvent	Grade	Solubility/100g. solvent
Water	dist.	0.0002
Glycerine	U.S.P. XII	0.053

Solvent	Grade	Solubility/100 g. Solvent
Ethanol	U.S.P XII(92.4%)	10.37
Ether	Pure, distilled several times over Na.	0.48
Methanol	Anhydrous	9.17
Acetone	b.p. 55.5°-55.8°	28.01
Pyridine	Anhydrous	152.29

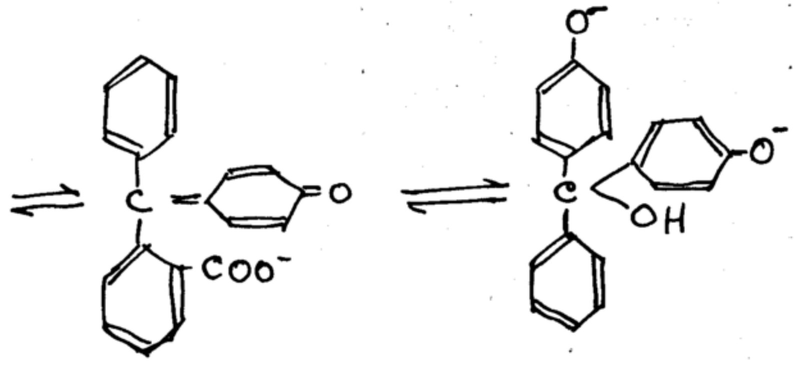
Ultra-Violet Absorption - Absorption curves are given for pH 10.2. Maximum absorption is at about wave-length 450mu (7)

Dissociation Constant - 2x 10^{-10} ; pK_a - 9.7 (1)

Polarographic Behaviour of Phenolpthalein - Phenolpthalein in solution can exist in different forms, which are in equilibrium. Representing the various forms by the classical formulas we have -



I. LACTONE II. COLORLESS III. COLORLESS



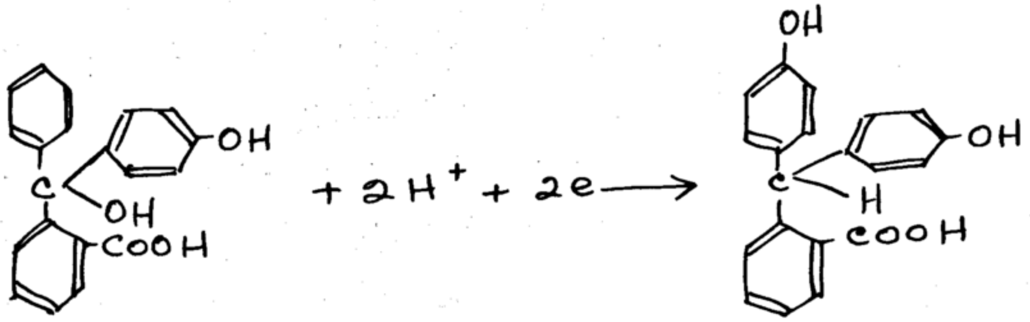
IV. RED V. CARBINOL. - COLORLESS.

At a pH 8 and smaller than 8 practically all of the phenolpthalein is present in the lactone form I. It is estimated that the conc. of II is less than 0.01% of thant of I. For reasons mentioned below that form II is reducible at the dropping electrode, but form I is not, at least at potentials more positive than that at which the wave of the supporting electrolyte used appears. Both forms II & III give a single reduction wave. The red form IV gives a two step reduction, both waves of equal height. The colorless carbinol form V formed in strongly alkaline medium does not give a reduction wave, at least not at potentials more positive than that at which the Na-wave appears. When a strongly alkaline solution of phenolpthalein is permitted to stand the color fades and a corresponding reduction of the diffusion current is observed.

In the region of pH between 0 and about 10 the half wave potential varies according to

$$\pi_{1/2} = -0.54 - 0.046\,\mathrm{pH}.$$

The reduction which is irreversible can be represented by the equation :



The reduction of form III can be represented by a similar equation as that of form II.

The reduction of the red form IV, however, occurs in two steps. The sûm of the two diffusion currents is equal to that of the sihgle wave observed at lower pH. The polarographic reduction of phenolpthalein to phenolpthalin is accompanied by a transfer of 2e.

In the presence of a phosphate buffer of a pH of 7 the diffusion current decreases abnormally when the ethanol conc. is increased. In 60% ethanol the "apparent" diffusion current becomes extremely small at 25°. It is concluded that the lactone form of phenolpthalein is not reduced, but its hydrated form is . At alcohol conc. of 25% or less the rate of hydration at the surface of the electrode is so large that a normal diffusion current is observed. At high alcohol conc. the "apparent diffusion current" becomes entirely rate and not diffusion controlled. Experiments carried out at various temperatures substantiate this interpretation.

In 25% ethanol in the presence of a buffer of pH 7.0 the diffusion current remains constant in a potential range between -1.0 and -1.2 volt; it decreases slightly between -1.2 and -1.4 volt and then drops suddenly to attain a small minimum value at a potential of about -1.6 volt. Experimental evidence has been given substantially the interpretation that the occurance of the minimum is to be attributed to a decrese rate of transformation of the lactone form into the reducible hydrated form at the surface of the dropping mercury electrode.

(8)

Activated Phenolpthalein - Phenolpthalein is dissolved in benzyl alcohol and then the greater part of the solvent is removed.

Kinetics and Equilibria of the carbinol formation of Phenolpthalein - The kinetics of the reaction of phenolpthalein with OH^- to produce a colorless carbinol have been investigated spectrophotometrically at 25° for NaOH solution (0.006 to 0.02 M) with and without the addition of NaCl.

Precise values of the transmittances of phenolpthalein solution at 550 mu have been obtained by extrapolating to zero time. The extinction coefficient is independent of the conc. of alkali showing that no perciptible secondary salt effect at these conc.

The limiting slope of the log K_1 (forward rate constant) vs. the square root of ionic strength, u establishes that carbinol formation involves the reaction of a doubly charged negative phenolpthalein ion with a OH^-.

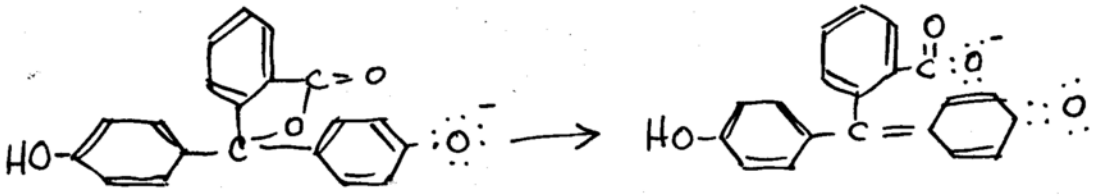
$$R^{=} + OH^{-} \longrightarrow ROH^{\equiv}$$

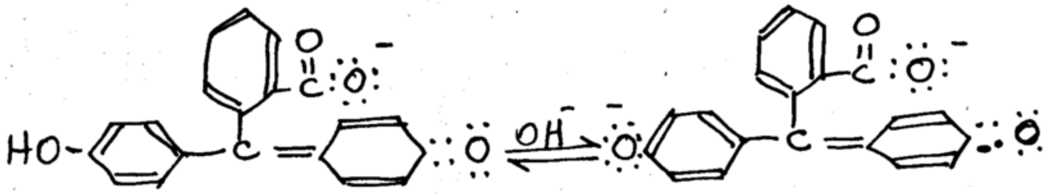
The limiting slope of log K (Equilibrium Constant) vs. u is one-half that predicted for the simple formulation

$$R^{=} + OH^{-} \longrightarrow ROH^{\equiv}$$

An interpretation consistent with established electrostatic principles is obtained on the assumption that the carbinol is partially hydrolysed, viz,

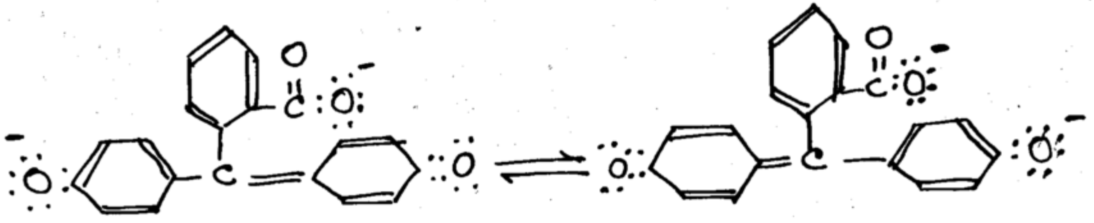
$$ROH^{\equiv} + H_2O \longrightarrow RHOH^{=} + OH^{-}$$





(9)

The part of the compound containing the two phenolic groups is now symmetrical and resonance is possible. The resonance forms are given below :



Permanent fading of alkaline Phenolpthalein solution - Permanent or irreversible fading of alkaline phenolpthalein solutions was found to be caused by air oxidation. The products of this oxidation are 2-(4'- hydroxy benzoyl) benzoic acid and phthalic acid.

It was found that phenolpthalein on oxidation by H_2O_2 produced, besides phtahalic acid, hydroquinene. (11)

Colloidal Phenolpthalein - Colloidal phenolpthalein in solid form is prepared by adding 2.15 g. phenolpthalein dissolved in N NaOH to 5.0 g. gelatin dissolved in 50 c.c. distilled water. A stream of CO_2 gas is passed over the surface of the mixture until the color is completely discharged. Citric Acid is then added until the pH of 5.5 is attained. The resulting mixture is spread thin on glass plates and dried at room temperature. Colloidal phenolpthalein gives a pink color with $NaHCO_3$ solution (pH 8), is more soluble than crystalline phenolpthalein at the H-ion concentration prevailing in the human body, has a bitter taste, may pass through the stomach, and is somewhat more active in producing bowel evacuation than isthe crystalline form. (12)

Colloidal phenolpthalein is considerable more soluble and at a lower pH, being capable of producing the pink Na-phenolpthalein with $NaHCO_3$ solution of pH 8.0 - 8.2. The solubility of alcohol increases with increase in strength of alcoholic water mixtures up to that of U.S.P. official alcohol. It is slightly less soluble in absolute alcohol. The liquids of the aliphatic series are in general better solvents for phenolpthalein than those of the aromatic series, the exceptions being CCl_4 and the petroleum products which are very poor solvents. Phenolpthalein is poorly dissolved by oil with the exception of caster oil which can dissolve as much as 0.5% of phenolpthalein. (13)

Chemical Properties -

Action of Bromine on phenolpthalein - The action of bromine upon Phenolpthalein varies greatly with conditions. In the absence of a special solvent, such as EtOH, $CHCl_3$, etc, the tetra bromo derivative is not formed. The reaction is accompanied by the loss of 5 mols of Br, 4 mols reacting by substitution and 1 by addition. The reaction product is brownish yellow, on heating there results a brown residue and as a sublimate $Br_3C_6H_2OH$; for every mole of phenolpthalein brominated 1 mole of $Br_3C_6H_2OH$ splits off. (14)

Ammonium salt of Phenolpthalein - Phenolpthalein dissolves in liquid NH_3 giving an intensely purple solution, the color of which shows no tendency to fade. When NH_3 is removed a red residue is obtained. As pumping is continued, the color fades to a bright pink which seems permanent. Prolonged evacuation finally brings the compound very close to absorb moisture from the air, a property which dry phenolpthalein does not have. Analysis for N showed that none was present. Heating discharged the color and the compound melts at the m. of phenolpthalein.

(15)

Anhydrous ammonia was passed into a mixture of methyl ethyl ketone and phenolpthalein until the latter dissolved. On evaporating spontaneouly in a disiccator over H_2SO_4, white crystals were obtained.

Formula given - $C_{20}H_{14}O_4 \cdot NH_4OH$ (16)

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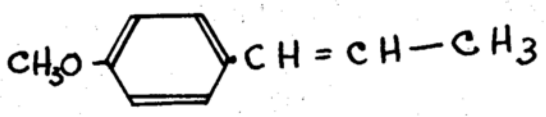
ANETHOLE

$C_{10}H_{12}O$



p-propenylanisole or p-methoxy propenyl benzene

Mol. wt - 148.20

Physical Properties - Anethole is a white crystalline mass of intensely sweet odor and taste, characteristic of anisi seed. It melts to a colorless, highly refractive liquid.

Congealing Point - 21°-22° (1), (2)

21.3° (3), (4)

Melting Point - 22.5°-23° (1)

22.32° (5)

Boiling Point - 232°-234° (4)

Boiling Point$_{751}$ 23 233°-234° (1)

Density$_{25°}$ - 0.986 (6) ; 0.984-0.986 (1)

$_{11.5°}$ - 0.999 (7)

Refractive Index $n_D^{25°}$ - 1.559-1.561 (1)

$n_D^{18°}$ - 1.56149 (6)

$n_D^{11.5°}$ - 1.5624 (7)

Solubility - Soluble in 2-3 volumes of 90% alcohol (1)

333.3 g. of Anethole will dissolved in 1 lt of 90% alcohol at room temperature. (8)

Anethole is almost insoluble in water, but miscible in all proportions with organic solvents.

Absorption Spectra -

Maxima	max	Minima	min	Inflection	inf
258	20350	228	2520	290	2280

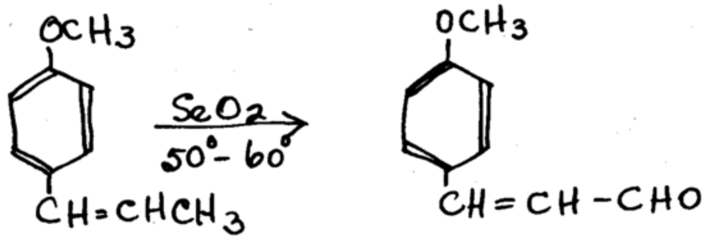
(Solvent - Alcohol 95%)

Double bond in conjugation with the benzene ring produces a very characteristic spectrum, by which this type of compound may be differentiated from saturated derivatives, and from unsaturated compounds without double bond in conjugation. (9)

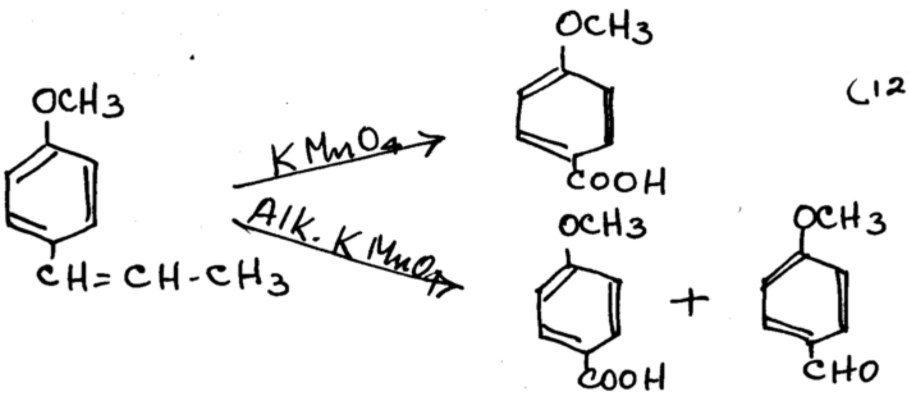
Absorption Maxima of the polymer - Polyanethole

mu		E_{max}		max		
Ist	2nd	Ist	2nd	Ist	2nd	
278	284	10.11	8.65	1500	1280	(10)

Chemical Properties -

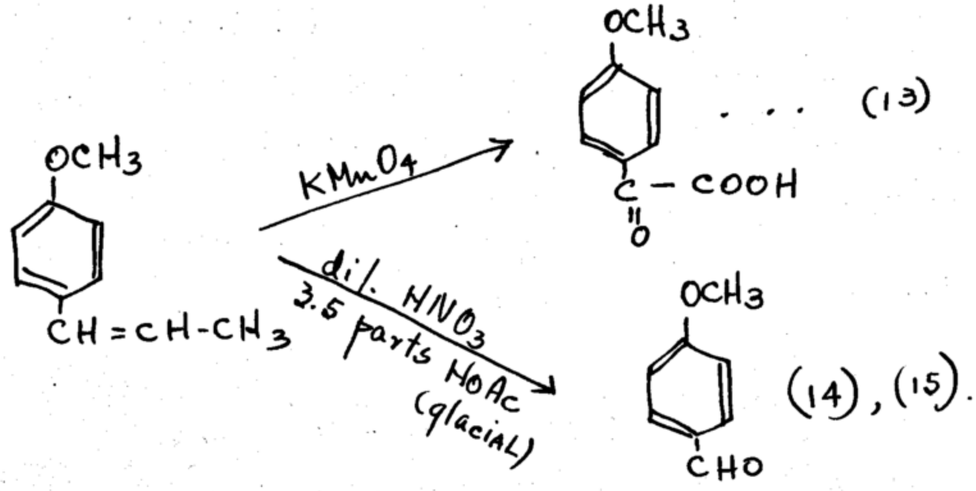


(11)



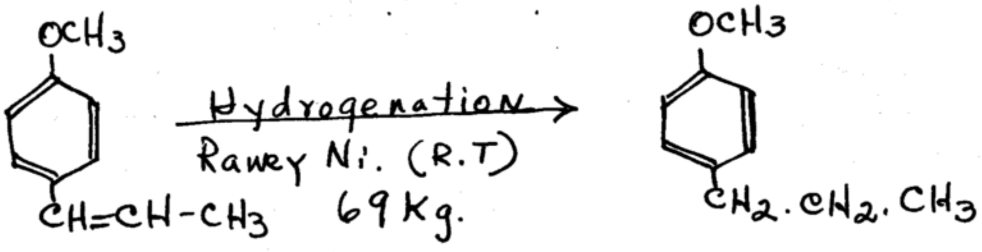
(12)

(12)



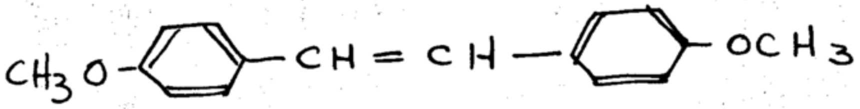
Studying the oxidation of Anethole with molecular oxygen at 150°, Schulz and Treibs (28) obtained acetaldehyde, carbon dioxide, anisic acid, and acetic acid, free and esterified.

Hydrogenation -



Effect of Heat and Light - Under the influence of light and air, or heat, anethole loses its ability to crystallize, assuming simultaneously a viscid, consistency, a yellow color, and a somewhat bitter, disagreeable taste. This is accompanied by an increase in the specific gravity above 1 and a better solubility in alcohol.

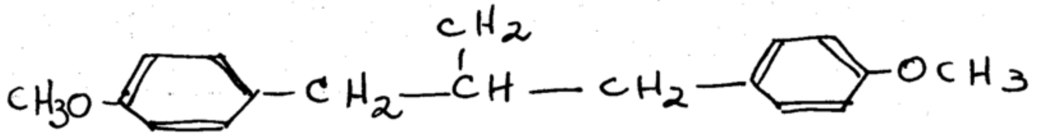
It is doubtful whether this change is caused, according to de Varda (16), by polymerization of anithole or, according to Hoering andGralert (17) by oxidation to anisaldehyde, anisic acid, and other products of oxidation among them 4,4'-dimethoxy stilbene, the so called "protoanethole" (Beilstein,(18)



4,4'-dimethoxy stilbene (Protoanethole)

It is quite possible that Protoanethole does not form directly from anethole but from anisaldehyde as an intermediary product of the reaction.

Campbell (19) found that on heating in the absence of air, anethole undergoes fission and dimerization resulting in the formation of 1,3 - di-p-methoxy phenyl 1-2- methyl propane.

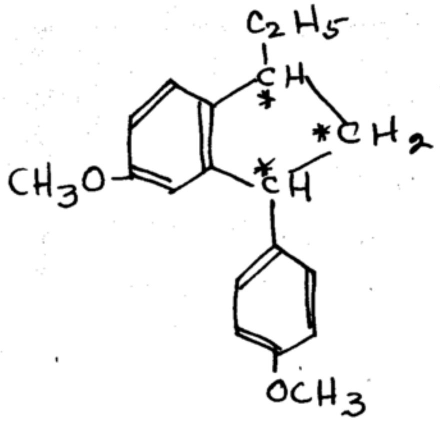


1,3-di-p-methoxy phenyl-2- methyl propane

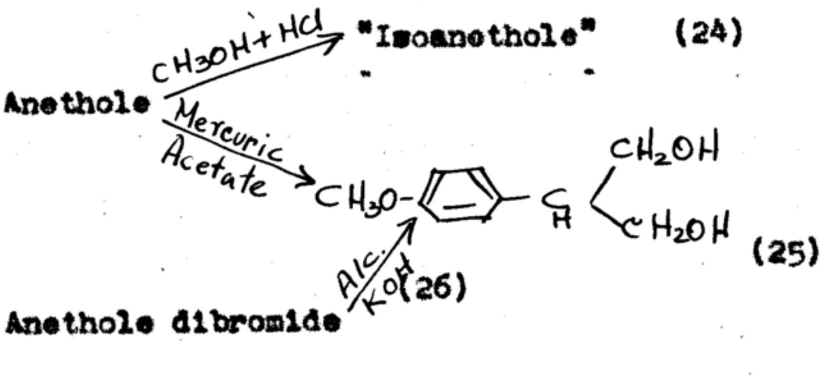
The following data are from New York Laboratories of Fritzche Brothers Inc., and illustrates the effect of light and air upon physical properties of Anethole.

	Original Anethole	Exposed to light & air	Exposed to air in dark
Sp. Gravity 25°	0.986	1.114	1.080
Solubility	1.5 to 2 vol. and more of 90% alcohol	Miscible with 80% alcohol	0.5 vol. 80% alcohol & more
Acid No.	0	1.4	1.4
Aldehyde Content as Anisaldehyde	0.7%	25.0%	17.6%

Under the influence of acid reagent anethole forms various polymers. Orndorff, Terrasse and Morton (20) treated anethole with $ZnCl_2$, while Puxeddu (21) used $FeCl_3$ in ether and obtained a dimeric 'metanethole' or 'dianethole' m.p. 132°-133°, the structure of which was studied by Baker and Enderby (22). They believe that "metanethole" must be one of the four possible racemic forms of the following structures which contains 3 dissimilar asymmetric carbon atoms, and is 6-methoxy-1-p-methoxy phenyl - 2-methyl 3-ethyl hydrindene -



Staudinger and Brunner (23) prepared a hemicolloid polyanethole "anisoin" by shaking anethole with small amounts of conc. H_2SO_4 or H_3PO_4 or with $SnCl_4$ in benzene solution.



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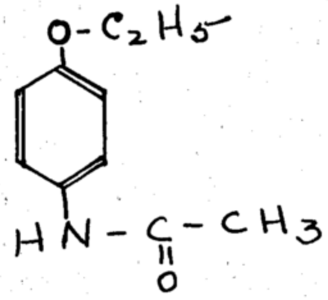
ACETOPHENETIDIN

(Phenacetin)

$C_{10}H_{13}O_2N$



Mol. wt - 179.21

Physical Properties - Acetophenetidin occurs as white, glistening crystals, usually in scales, or as a fine, white, crystalline powder. It is odorless, and is stable in air.

Melting Point - 134°-136°

Solubility -

Solvent	Temperature	Solubility	
Water	14°	0.054	(1)
Alcohol (abs).	20-25°	18.80	(2)
Quinoline	"	7.83	(2)

Solubility in aqueous alcohol at 25° (3)

Wt % C_2H_5OH in solvent	Gms. Phenacetin/100g. saturated soln.	Wt.% C_2H_5OH in solvent	Gm. Phenacetin /100 g. Sat.Sol.
0 (Water)	0.0766	60	4.55
20	0.28	80	7.63
40	1.50	100	6.64

Solubilities in miscellaneous solvents -

(Figures in parenthesis are sp. gravity of sat. solution)

Solvent	Temperature	Gms. Phenacetin per 100 gms. sat. soln.
Acetone	30-31°	10.68

Solubilities in miscellaneous solvents - (Contd.)

(Figures in parenthesis are sp. gravity of sat. solution)

Solvent	Temperature	Gms. Phenacetin per 100 gms. sat. soln.
Amyl Acetate	30-31°	2.42 (0.819)
Acetic Acid(99.5%)	21.5°	13.65 (1.064)
Aniline	30-31°	9.46 (1.025)
Benzaldehyde	30-31°	8.44 (1.063)
Benzene	30-31°	0.65 (0.873)
Chloroform	25°	4.76
Ether	25°	1.56
Toluene	25°	0.30 (0.863)
Xylene	32.5°	1.25 (0.847)

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