THE RESOLUTION OF DENEIGNS
INTO
THEIR OPTICAL ANTIPODES

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by
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The work described in this thesis was carried out at the Battersea College of Technology under the supervision of Dr. J. Kenyon, F.R.A., to whom the author is indebted for his invaluable help and kindness throughout the course of the work.

To Dr. J. E. Salmon, the Head of the Chemistry Department, the author expresses his gratitude for his general interest.

4-Ethoxyphenol was reduced by means of the cold method and to its diphenolphenol, which was oxidized in the presence of a 50% nitric acid hot and the resulting diphenol-4-phenolic acid was hydrolysed by heating with water in presence of silica as catalyst.
ABSTRACT

Benzoins of the general formula, R-CC-CHOH-R', readily combine with phthalic anhydride in the presence of a tertiary base and the resultant esters form salts with alkaloids which are readily separable by fractional crystallisation into diastereoisomeric forms.

Decomposition of these alkaloidal salts with ice-cold dilute hydrochloric acid liberates optically active benzoins hydrogen phthalates; these, in turn, by hydrolysis with very dilute aqueous alcoholic sulphuric acid yield the optically pure benzoins.

4-Methoxybenzoins was prepared by condensation of benaldehyde with anisaldehyde in presence of potassium cyanide in aqueous ethanolic solution; 4-dimethylamino-benzaldehyde was similarly prepared by condensation of benzaldehyde with dimethylamino benzaldehyde. Both these benzoins were also prepared by the "reversion" procedure.

4-Methoxybenzoins was reduced by means of tin and hydrochloric acid to its desoxybenzoins, which was brominated in the presence of a 500 watt tungsten lamp and the resulting α-bromodesoxybenzoins was hydrolysed by heating with water in presence of dioxan as solvent.
Pivaloïn (hexamethylacetoïn) was obtained by the condensation of two molecular proportions of ethyl pivalate in the presence of sodium followed by hydrolysis. The pivalic acid was obtained by carbonation of tertiary butyl magnesium chloride.

Whereas optically active hydrogen phthalates of secondary alcohols are generally hydrolysed by means of alkali to obtain the active carbinols; basic hydrolysis of optically active hydrogen phthalates of benzoins gives racemic benzoins instantaneously. The hydrogen phthalates of benzoins were therefore hydrolysed by means of very dilute aqueous ethanolic sulphuric acid (Acid hydrolysis with acyl-oxygen fission).

Attempts to obtain fractionally crystallisable alkaloidal salts of 4'-methoxybenzoïn and pivaloïn hydrogen phthalates proved to be fruitless.
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CHAPTER I

Introduction to the Resolution of Alcohols

When dissymmetric compounds are prepared by synthetic methods, the usual result is a racemic modification; e.g., bromination of $n$-butyric acid results in the formation of dl-$\alpha$-bromobutyric acid.

\[ \text{EtCH}_2\text{COOH} \overset{\text{Br}_2}{\longrightarrow} \text{EtCHCOOH} \]

\[ \text{(1) H} \quad \text{H(2)} \]

n. butyric acid
Asymmetry is established with replacement of one of the two \( \alpha \)-hydrogen atoms by bromine, and a space model shows that there is exactly the same opportunity for replacement of the one as the other. The law of chance dictates the formation of equal amounts of the two possible products, and hence a \( \text{dl} \) -mixture results.

The process of separating a racemic modification into its optical isomers is known as resolution. A brief account of the underlying principles of various methods of resolution is given in this chapter.

(I) **Mechanical separation of Crystals:**

A solution of solid racemic substance under suitable conditions may deposit individual crystals which often exhibit enantiomorphism in external form by which the dextro and laevo forms may be separated by means of a pair of tweezers and a hand lens. It was in this manner that Pasteur (Ann. Chim. Phys., 1848, (3) 24, 442) separated the \( d \)-and \( l \) forms of sodium ammonium tartrate.

(2) **Preferential Crystallization due to Inoculation:**

Partial crystallization of one component may be induced
by inoculating a supersaturated solution with a crystal of that component (Gernez, Compt. rend.; 1866, 63, 843; Ann. 1867, 143, 387; and Ruff, Ber.; 1901, 34, 1362) or even with some other suitable material (Ostromissenski, Ber.; 1908, 41, 3035). In this case the second component remains in solution, at least temporarily, for lack of a suitable nucleus to initiate crystallization. The initial deposit is removed before crystallization of the other antipode is permitted to occur. The mother liquor may be induced to deposit the second antipode by suitable concentration and seeding. The two antipodes may be thus crystallized more or less alternatingly until the solution is exhausted.

(3) Biochemical Separation:

Certain bacteria and moulds, when they grow in a dilute solution of a racemic modification, destroy one optical isomer more rapidly than the other; e.g. Penicillium glaucum (a mould when grown in a solution of ammonium racemate, attacks the d-form in preference to the l-form (Pasteur, Compt. rend. 1857, 45, 1032; 1858, 46, 615; 1860, 51, 293). It is a queer fact of nature, not clearly understood, that certain organisms should manifest this preference for a right-hand or a left-hand molecule.
The microbiological method of separation is seldom of preparative value, particularly since one of the two forms, usually the more interesting natural one, is sacrificed. Also, the process must be conducted in very dilute solutions containing nutrient salts favourable to growth of the microorganisms, and recovery of the optically active product is often difficult and inefficient. The chief value of the method is in determining whether or not a given substance is resolvable. Whereas racemic acid is acted upon by Penicillium glaucum and gives a levorotatory solution, mesotartaric acid under the same conditions develops no optical activity, and this observation provides additional evidence that the meso acid is the internally compensated form.

Sec. Butyl carbimol, propylene glycol and various other lower secondary alcohols have been obtained in optically impure forms by microbiological methods (Le Bel, Compt. Rendus, 1879, 89,312; 1881, 92,532).

(4) **Selective Adsorption:**

Selective adsorption (Chromatography) on a suitable solid should provide a method of separating diastereoisomerides.
This was first achieved by Jamieson and Turner (J.C.S., 1942, 611) who suggested that diastereoisomerides should have different coefficients of adsorption on adsorbents devoid of stereo-orientation. It is shown that L-menthyl d and L-mandelates are adsorbed selectively on alumina. Prior to this, it had been shown that optically active solids could exhibit selective adsorptive action on enantiomerides. Henderson and Rule (Nature, 1931, 141, 247; J.C.S., 1939, 1568) separated dl-p-phenylene-bisimino camphor into its active forms by passing a dilute solution in petroleum ether through a column containing powdered d-lactose. Less complete separation of various racemic substances appears to have been achieved by using certain other sugars and d- or l-quartz powders as adsorbents (Chem. Abstr, 1936, 30, 926; Nature; 1938, 142, 162; Chem. Abstr; 1938, 32, 7411; 1939, 33, 7165) Prelog and Wieland resolved Tröger's base on d-lactose (Helv. Chim. Acta; 1944, 27, 1127).

(5) By means of Salt-formation:—

Resolution of inactive substance into its optically active components can be accomplished only in rare instances by crystallization and mechanical separation, as in the
classical experiment of Pasteur or by subsequently introduced modifications. Pasteur's contributions, however, included the discovery of a method of resolution that is practicable and capable of wide application. Either through scientific curiosity or because of an instinct for thorough investigation, the gifted experimentalist prepared and characterized very many salts derived from the combination of the tartaric acids with both inorganic and organic bases, including naturally occurring, optically active amine bases. The salts of d- and l-tartaric acid with metals, ammonia and aniline were identical in solubility and other physical properties; but Pasteur observed that with the salts derived from dissymmetric, optically active natural bases such as brucine, quinine, strychnine "all is changed in an instant. The solubility is no longer the same and the properties all differ as much as in the case of the most distantly related isomers". The reason is apparent from a consideration of an example. When a dl-acid is neutralized with a dextrorotatory (d') base, one of the two salts is composed of two right-handed parts (dd'), and the other is made up of right and left-handed parts (ld'). The two salts will
obviously differ in rotatory power and are in fact

diastereoisomers. (Gr. dia, apart). If the acidic and

\[
\text{Enantiomers} \left( \begin{array}{c}
\frac{d}{1} - \text{Acid} \\
\frac{1}{d} - \text{Acid}
\end{array} \right) + \text{d'} \text{ Base} \rightarrow \begin{array}{c}
\frac{dd'}{1d'} - \text{Salt}
\end{array}
\]

basic components are strongly rotatory, the \(dd'\) salt will
probably be dextrorotatory; the \(1d'\) salt is composed of

oppositely acting but unbalanced parts and may show either a
positive or negative rotation. In any case the two salts
have different rotatory powers, different melting points,
and, most important of all, different solubilities and they
are therefore separable by fractional crystallization, and
the course of separation can be followed by determination
of appropriate physical constants. Once one salt has been
secured pure, it can be treated with sodium hydroxide, the
resolving \(d'\) base recovered, and the optically active acid
liberated by acidification of the alkaline solution.

The salt formation method is one of the most widely
applicable of all the methods of resolution. Bases which are
used for the resolution of racemic acids are mainly alkaloids;
e.g. brucine, cinchonine, cinchonidine, quinine, quinidine,
strychnine, etc.
Acids which are used for the resolution of racemic bases are tartaric acid, camphor sulphonic acid bromocamphor sulphonic acid etc.

The method of salt formation has been extended to compounds other than acids and bases; e.g. racemic alcohols are converted into the acid ester derivatives by combination with phthalic anhydride or succinic anhydride.

The acid ester, consisting of equimolecular proportions of the $\alpha$ and $\beta$ forms may now be resolved by the method used for acids. This procedure has been widely applied by Kenyon and his collaborators in the resolution of a large number of different types of alcohols which are classified below:

(i) Purely aliphatic, e.g. Me.CH$_2$.Et (J.C.S. 1911, 32, 45)
(ii) Purely aromatic, e.g. Ph.CH$_2$.C$_6$H$_4$.Me (Z.Krist; 1928, 62, 62)
(iii) Hydroaromatic, e.g. $\text{H}_2\text{C} - \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COH}$ (J.C.S. 1926, 2332)

(iv) Heterocyclic, e.g. CH$_2$ - CH$_2$ - CH$_2$ - CH$_2$

(v) Mixed aliphatic-aromatic, e.g. Me.CH$_2$OH.CH$_7$

(J.C.S. 1941, 312)

(vi) Mixed alicyclic-aromatic, e.g. Ph.CH$_2$OH.C$_6$H$_{11}$ (J. Biol. Chem. 1927, 75, 587).

(vii) Mixed alicyclic-aliphatic, e.g. Me.CH$_2$OH.C$_6$H$_{11}$ (J.C.S. 1926, 184)

(viii) Unsaturated aliphatic, e.g. Me.CH$_2$OH.CH $\equiv$ CH$_2$ (J.C.S. 1925, 127, 1094)

(ix) Unsaturated aliphatic-aromatic, e.g. Ph.CH$_2$OH.CH $\equiv$ CH$_2$

(C.r. 1930, 236, II35)

The method of salt-formation of an acid ester is best illustrated by the resolution of octanol-2 by Pickard and Kenyon (J.C.S. 1907, 21, 2038).
Octanol - 2 Phthalic anhydride.

dl - Acid Phthalate.

Two salts separated.

NaOH → d and l - octanol - 2.
The method of salt formation of an acid ester of an alcohol has now been successfully applied to the resolution of some α-keto alcohols as described in this thesis.

With the exception of d,l-fructose, no externally compensated α-keto-alcohol, so far as is known, has been directly resolved into its optically active forms by any of the usual methods. Although Hopper and Wilson (J.C.S., 1928, 2483) resolved benzoin by condensing it with an optically active semicarbazide and subsequently hydrolysing the resulting semicarbazones with oxalic acid, the yield of d-and l-benzoin was very low and the method proved tiresome.

l-Benzoin has been synthesised in low yield by the action of phenylmagnesium bromide on l-mandelamide (McKenzie and Wren; J.C.S. 1909, 22, 309). The next year Wren synthesised d-benzoin by the action of phenylmagnesium bromide on d-mandelamide (J.C.S., 1909, 22, 1583).

α-Keto-alcohols (e.g. benzoin) are readily resolved by adopting the following procedure:
Preparation of (1) hydrogen phthalic ester of benzoin:

A hot solution of equimolecular proportions of phthalic anhydride and pyridine is cooled and stirred with the calculated amount of the \(\alpha\)-keto-alcohol for a few minutes. Triethylamine is then added in slightly more than the molecular proportion and again the mixture is intimately stirred for a few minutes until it becomes almost completely liquefied. The reaction mixture is triturated with an almost equal volume of acetone, the resulting solution diluted with water and sodium bicarbonate solution added to dissolve the hydrogen phthalic ester. Unreacted keto-alcohol is removed by filtration and the filtrate is added dropwise to the calculated amount of dilute hydrochloric acid in presence of crushed ice with continuous stirring to precipitate the hydrogen phthalate of the keto-alcohol in a finely divided condition. This is filtered, washed with water, dried on a porous plate and recrystallized. It was characterized by determining its equivalent by rapid titration with standard alkali.

Function of pyridine and triethylamine in hydrogen phthalate formation:

Gerward (J.C.S., 1940, 213) suggested that the function of pyridine when used as a catalyst in the reaction between
alcohols and acid chlorides is to assist proton removal from the hydroxyl group, rather than to cause ionic fission of the acid chloride. This view was supported by Kenyon and co-workers (Balf, Doughty, Kenyon and Poplett, J.C.S., 1942, 605) who found that p-methoxybenzhydryl, a compound very prone to react by alkyl-oxygen fission, is rapidly converted by acetyl chloride to p-methoxybenzhydryl chloride; in marked contrast the presence of pyridine causes the reaction to take an entirely different course and p-methoxybenzhydryl acetate is formed. Both these reactions give quantitative yields.

\[
\begin{align*}
\text{RO}+\text{HCl} & \rightarrow \text{ROH} + \text{Cl} \\
\text{Cl} & \rightarrow \text{AC}
\end{align*}
\]

It seems likely that a similar mechanism is involved when pyridine is used as a catalyst in the formation of an acid phthalic ester which involves alkoxy-hydrogen fission. Baker and Gaunt (J.C.S. 1949, 13) showed that the alternative mechanism involving hydrogen bonding between the base and the alcohol is also important and it seems probable that the reaction is complex and involves both mechanisms. They suggested that the amine catalyst and the alcohol rapidly form a complex in accordance with the general scheme.
\[
NR_3 + H_{3}OR' \quad \xrightarrow{\text{ran}} \quad NR_3 \cdot \cdot \cdot \cdot \cdot \cdot \cdot \cdot OR'.
\]

and both the free amino moles and the base-alcohol complex can function as catalysts for the reaction. Hydrogen bonding between the hydroxyl group and the N- of the base would result in an increased polarization and lengthening of the oxy-hydrogen bond, thus making the alkoxo-hydrogen fission mechanism easier. Since triethylamine \((K_B = 6.4 \times 10^{-4})\) is considerably stronger base than pyridine \((K_B = 2.4 \times 10^{-9})\) it would be expected that the hydrogen bonding between the hydroxyl group and N- of the base would be greater with triethylamine than with pyridine and thus the stronger base should be a more efficient catalyst. It has been actually found that benzoin combines with phthalic anhydride with excessive sluggishness in presence of pyridine, but that the reaction becomes more vigorous when triethylamine is added.

Kenyon et al (Dafle, Doughty, Kenyon and Peplett, J.C.S. 1942, 605) originally prepared \(\alpha\)-p-methoxybenzaldehyde hydrogen phthalate by heating a mixture of p-methoxybenzaldehyde, phthalic anhydride and pyridine at 55-60° for 4-5 hours.

It has now been found that the same reaction can be carried out by warming the mixture for 3 minutes and making combined use of pyridine and triethylamine. One advantage of pyridine over triethylamine is that phthalic anhydride dissolves in
hot pyridine and on cooling a hot solution of phthalic anhydride in pyridine, phthalic anhydride separates in a finely divided and reactive condition, while phthalic anhydride is insoluble in hot triethylamine. The advantage of triethylamine over pyridine is, as we have already seen, that triethylamine is a stronger base and hence a more efficient catalyst than pyridine. It is thus clear why a mixture of pyridine and triethylamine is more effective for the hydrogen phthalate formation of a carbonyl than either used separately.

It was found by Delfs, Koryon and Thain (J.C.S. 1931, 380), that di-(4-methoxyphenyl)-methanol is unreactive towards phthalic anhydride in the presence of pyridine alone but undergoes esterification on addition of triethylamine.

**Preparation of (+) and (−) hydrogen phthalates of benzoin:**

The purified (+) hydrogen phthalate of benzoin was combined with a suitable alkaloid (quinidine) in presence of an appropriate volume of solvent (methanol) so that one of the diastereoisomeric salts rapidly crystallized. The precipitated salt was recrystallized several times until optical purity was reached and then decomposed with dilute hydrochloric acid. On dilution with water, one of the optically active forms of the hydrogen phthalate was precipitated.
It was filtered, washed, dried and recrystallized. The other optical isomer of the hydrogen phthalate of the benzoin was similarly obtained by decomposition of the salt which remained in solution.

**Hydrolysis of (+) and (-) hydrogen phthalates of benzoin:**

In all the cases hitherto recorded of the resolution of alcohols by fractional crystallization of alkaloidal salts of their hydrogen phthalates the resultant optically active esters have been hydrolysed or saponified with aqueous or ethanolic caustic alkali to yield the optically pure alcohols.

The above procedure cannot be applied to the hydrolysis of hydrogen phthalates of benzoins since they as well as the liberated benzoins rapidly racemize through tautomerism:

\[
\begin{align*}
\text{(a)} & \quad \text{R}_1^\text{H} \quad \text{C}_\text{R}^\text{O} \quad \text{X} \quad \text{C}_\text{R}'^\text{O} \\
\text{(b)} & \quad \text{R}_1^\text{H} \quad \text{C}_\text{R}^\text{O} \quad \text{X} \quad \text{C}_\text{R}'^\text{O} \\
\text{(c)} & \quad \text{R}_1^\text{H} \quad \text{C}_\text{R}^\text{O} \quad \text{X} \quad \text{C}_\text{R}'^\text{O}
\end{align*}
\]

\[X = \text{OH in benzoin}\]

\[X = \text{C}_6\text{H}_4\text{C}^\text{O}_-\text{CO}_2\text{H} \quad \text{in hydrogen phthalate}\]

If the activated \(\alpha\)-hydrogen atom in (a) migrates in an equilibrium process to give an enol (b), the centre of
disacymetry is temporarily destroyed by the production of a double bond, and when the hydrogen migrates back to the carbon atom, the process can involve opening of either of the two linkages of the symmetrical double bond and hence can afford either the original configuration (a) or the opposite configuration (c); the chances being equal, a mixture of equal parts of (a) and (c) must result. Since all the transformations are reversible, formation of only a minute amount of enol would result in eventual racemization of the entire material. It has been observed that racemization occurs more rapidly with compounds having a carbonyl group adjacent to an asymmetric carbon carrying a hydrogen atom than with compounds in which this specific grouping is lacking. Thus, in contrast with acetic acid, PhCHOH.COCH₃, the C-methyl derivative atrolactic acid, Ph.C(Hc).CH.COCH₃, does not undergo racemization. These facts suggest that the α-hydrogen atom plays a part and then enolization is involved.

\[
\begin{align*}
\text{H} & \quad \text{C} - \text{C_O}^0 \\
\text{CH} & \quad \text{C} - \text{C_O}^0 \quad \text{CH}
\end{align*}
\]

It is thus evident that alkalis cannot be used to regenerate optically active benzoin from their hydrogen
phthalates. Hence some other method must be devised for their hydrolysis. It was eventually found that optically active hydrogen phthalates of benzoins could be hydrolysed without racemization by heating with very dilute aqueous ethanolic sulphuric acid at about 70° C.

Hydrolysis of Carboxylic Esters:-

We have seen that the resolution of racemic alcohols involves the hydrolysis of optically active phthalic esters in the last stage. The question immediately arises as to whether the alcohol suffers any loss of optical activity during this process of hydrolysis.

An answer is provided at once by re-combining the liberated optically active alcohol with phthalic anhydride and noting whether the rotatory power of the re-formed ester is identical with that of the original ester. If it is it follows that both the hydrolysis and re-esterification have occurred without loss of optical activity.

Many saturated secondary alcohols have been resolved via their hydrogen phthalic esters; and the optically active alcohols obtained by the hydrolysis of their hydrogen phthalates could be re-esterified to give the original hydrogen phthalates with sign and magnitude of rotation unchanged. When, however,
the (+) hydrogen phthalate of 1:3 dimethylallyl alcohol,
MeCHO = CH.CH2CHMe, is hydrolysed with aqueous sodium hydroxide
the rotatory power of the liberated alcohol varies with the
concentration of the alkaline solution \([\alpha]_D\) being high when
the concentration of sodium hydroxide is high [5N] and
progressively lower as the concentration is decreased so that
eventually racemization may be almost complete (Hills, Kenyon,

It thus appears likely that hydrolysis of carboxylic
esters may involve two different mechanisms, one should account
for the complete retention of optical activity whilst the
other should account for its loss.

Two mechanisms may be formulated:

\[
\begin{align*}
R' - CO & \xrightarrow{OH + H} :CH \\
(1)
\end{align*}
\]

\[
\begin{align*}
R' - CO & \xrightarrow{R + H^+} H \\
(2)
\end{align*}
\]

for which the useful terms (i) acyl-oxygen fission and (ii)
alcohol-oxygen fission were suggested by Day and Ingold.
Acyl-oxygen fission:

\[ R' - C\overset{\text{C}}{\text{O}} \text{OR} + \text{H}_2\text{O} \rightarrow \text{RCOOH} + \text{ROH} \]

In acyl-oxygen fission, the liberated alcohol derives its oxygen from the resolved ester and would be optically active since in the process of hydrolysis no bond attached to the asymmetric atom in ROH is broken.

Evidence that acyl-oxygen fission usually occurs:

Holmberg (Ber. 1912, 45, 2997) was the first to provide evidence of acyl-oxygen fission in carboxylic esters. He used a substituted alkyl group R, which was asymmetric at the point of union, and he assumed that, if R were to separate from this point in the course of reaction, then R would not retain its stereo-chemical configuration. In the example of 6-acetylmalic acid, R.CAC, where and R = \text{CH(CH\text{C}OH)CH}_2\text{C}O\text{CH}_2\text{CH}_2\text{C}O\text{CH}_3, he showed that the asymmetric group did fully retain its configuration during acid as well as alkaline hydrolysis and concluded that R did not separate.

\[ \text{AC} \rightarrow \text{CH} \text{CH}_2\text{C}O\text{CH}_3 \]

There is a loophole in this argument, namely, that if
R separated as R⁺ then it still might conceivably retain its configuration, owing to an intervention by one of the carboxylate ion-groups. The explanation given by Ingold and Hughes for retention of configuration in the unimolecular reaction is that the intermediate ion is a betaine, in which the electrostatic forces lead to retention of a pyramidal shape; the hydroxyl group then enters the position vacated by the O-acyetyl group, thus:

\[
\begin{align*}
&\text{O} - \text{C} = \text{O} \\
\text{H} - \text{C} - \text{O} &\quad \xrightarrow{\text{OAC}} \quad \begin{bmatrix}
\text{C} & = & \text{O} \\
\text{CH}_2 - \text{COOH}
\end{bmatrix} \\
&\quad \xrightarrow{\text{H}_2\text{O}} \\
&\quad \text{O} - \text{C} = \text{O} \\
\end{align*}
\]

In this connection it may be mentioned that \(\alpha\)-bromopropionate ion can be hydrolysed in an alkaline solution by a mechanism kinetically identifiable as bimolecular, \(\text{SN}_2\); and the produced lactic acid is formed, as it should be, with inversion.

However, Cowdrey, Hughes and Ingold (J.C.S., 1957, 1263) found that the \(\alpha\)-bromopropionate ion could also be hydrolysed under non-alkaline conditions, by the kinetically identified unimolecular mechanism, \(\text{SN}_1\); and then the lactic acid is formed.
with retention of original configuration. Schematically the process can be represented as:

\[
\begin{align*}
\text{O} - \text{C} &= \text{O} \\
\text{H} - \text{C} - \text{Br} &\rightarrow \text{H} - \text{C}^+ \\
\text{CH}_3 &\quad \text{CH}_3
\end{align*}
\]

\[
\begin{align*}
\text{O} - \text{C} &= \text{O} \\
\text{H} - \text{C} - \text{OH} &\rightarrow \text{H} - \text{C} - \text{CH}_3
\end{align*}
\]

Other noteworthy examples of the acyl-oxygen fission are as follows:

(1) Kevenson and Snellgrove J.C.S., 1925, 127, 1169) showed that

\(-\) \(\alpha\)-butylallyl hydrogen phthalate gave optically pure \((-\) carbinal on hydrolysis with aqueous sodium hydroxide. This was shown by reduction of the unsaturated \((-\) carbinal to \((+\) \(\alpha\)-butylethylcarbinal which possessed a rotatory power identical with that of the carbinal obtained by direct resolution. If hydrolysis had been accompanied by alkyl-oxygen fission, it is highly probable that the transient positively charged radical

\[
\text{Bu} - \overline{\text{CH}} - \overline{\text{CH}} - \overline{\text{CH}_2}
\]

would have resulted in some considerable loss of rotatory power and possibly also in some isomeric change to the inherently
optically inactive \( \gamma \)-\( \alpha \)-butylallyl alcohol.

(i) Kenyon and Snellgrove (loc. cit.) also showed that (-) \( \alpha \)-methylallyl hydrogen phthalate, on hydrolysis with aqueous sodium hydroxide, yields optically active (-) 1-methylallyl alcohol. This hydrolysis must have also proceeded by acyl-oxygen fission.

(iii) When the two isomeric esters, 1-methylallyl acetate and 3-methylallyl acetate were hydrolyzed with 0.5 N alkali (Prevost, Ann. Chim. 1928, 12, 147) or dilute acid (Ingold and Ingold, J.C.S., 1932, 756) each yielded its own alcohol unmixed with the other alcohol.

\[
\begin{align*}
\text{H}_2\text{C} & = \text{CH} - \text{CH} = \text{C} - \text{AC} \\
& \quad \text{Me, CH} = \text{CH} - \text{CH}_2 - \text{C} - \text{AC} \\
& \quad \downarrow - \text{Ac.OH} \\
& \quad \text{H} \quad \text{OH}
\end{align*}
\]

Acyl-oxygen fission.

Had the reactions involved allyl-oxygen fission, each ester would have yielded a mixture of the two alcohols, since both could give rise to the same mesomeric ion

\[
\begin{align*}
\text{Me} - \text{CH} = \text{CH} - \text{CH}_2
\end{align*}
\]
(iv) Norton and Quale (J.A.C.S., 1940, 62, 1170) showed that neopentyl esters, such as the acetate, undergo alkaline hydrolysis to give unrearranged neopentyl alcohol. Again, therefore, the reaction cannot involve a free carbonium ion. Furthermore steric hindrance by the neopentyl group would preclude the $B_{\alpha L}^2$ mechanism leaving the $B\alpha C2$ as the most probable alternative (Hughes, Quart. Rev., 1948, 2, 107)

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Me} - \text{C} - \text{CH}_2\text{O} & \quad \text{AC} \quad \rightarrow \quad \text{Me} - \text{C} - \text{CH}_2\text{OH} + \text{ACOH}
\end{align*}
\]

(v) All the above methods are limited by the necessity of choosing a special form of $R$, but the following method, first used in this problem by Polanyi and Szabo (Trans. Faraday, Soc., 1934, 30, 504) is completely general. They showed that the basic hydrolysis of $n$-amyl acetate in water enriched with $\text{C}^{18}$ yielded amyl alcohol of normal isotopic constitution so that the oxygen in the alcohol must have come from the ester. This result clearly requires acyl-oxygen fission.

\[
\begin{align*}
\text{R}' & \quad \text{CO} \quad | \quad \text{OR} \\
\text{KO}^{18} & \quad \text{H} \quad \rightarrow \quad \text{R CO CO}^{18} + \text{HOR}
\end{align*}
\]
(vi) Pett, Day and Ingold (J.C.S., 1938, 639) showed that when methyl hydrogen succinate was hydrolysed in an acid aqueous medium containing $\text{C}^{18}$, the liberated alcohol contained only the normal proportion of the isotope.

\[
\begin{align*}
\text{CH}_2\cdot\text{CO} & \quad \text{OCH}_3 \\
\text{H}_2\text{C}^{18}\text{H}_4 & \quad \rightarrow \quad \text{CH}_2\cdot\text{CO} \quad \text{O}^{18}\text{H} \\
\text{CH}_2\cdot\text{COOH} & \quad \rightarrow \quad \text{CH}_2\cdot\text{COOH} \\
\end{align*}
\]

(vii) Long and Friedman (J.A.C.S., 1950, 72, 3692) have given a similar demonstration for the alkaline hydrolysis of $\gamma$-butyrolactone.

\[
\begin{align*}
\text{CH}_2\cdot\text{CO} & \quad \text{O}^{18}\text{H} \\
\text{H} & \quad \rightarrow \quad \text{CH}_2\cdot\text{CO}^{18}\text{H} \\
\text{CH}_2\cdot\text{CH}_2 & \quad \rightarrow \quad \text{CH}_2\cdot\text{CH}_2\text{OH} \\
\end{align*}
\]

**Alkyl-oxygen fission:**

\[
\begin{align*}
\text{R}^+ \cdot \text{C}^{18} & \quad \rightarrow \quad \text{R}^+ \cdot \text{C}^{18}\text{H} + \text{ROH} \\
\end{align*}
\]

In alkyl-oxygen fission, the liberated alcohol derives
its oxygen from water and would be optically inactive even if it contained an asymmetric atom since in the process of hydrolysis one of the bonds attached to the asymmetric atom is broken and hence loss of optical activity would be expected owing to the radical $R$ assuming a planar configuration during the hydrolysis.

Recent work has shown that alkyl-oxygen fission occurs more commonly than has been realised when the group $R$ has electron releasing properties.

The first evidence bearing on alkyl-oxygen fission employed the criterion of optical activity and was furnished by Kenyon and his co-workers who encountered this form of reaction during their experiments on the preparation of optically active alcohols by hydrolysis of resolved hydrogen phthalates.

The occurrence of unimolecular alkyl-oxygen heterolysis during the hydrolysis of carboxylic esters was first observed in experiments on the resolution of some secondary allylic alcohols. $1:3$ Dimethylallyl alcohol, $\text{Me}_{1} \cdot \text{CH}=\text{CH} \cdot \text{CH}_{2} \cdot \text{Me}$, has been resolved through its hydrogen phthalic ester; saponification of the resolved ester in aqueous $5\%$ sodium hydroxide gave the almost optically pure alcohol, but with aqueous sodium carbonate or excess of dilute alkali highly
- 35 -

recomised alcohol was obtained. It seems, therefore, that
acyl-oxygen fission is mainly operative in concentrated
alkaline solution; but allyl-oxygen fission comes increasingly
into play as the alkaline solution becomes more dilute.
Since the postulated positively charged radical is symmetrical,

\[ (+) \]

\[ \text{Me, CH, CH, CH, Me} \]

the same racemic chemical individual is obtained, whether
the -OH group becomes attached to the 1 or the 3 carbon atom.
When, however, the molecule is not symmetrical as in
1-phenyl 3-methyl allyl alcohol, Me.CH = CH.CH2C = Ph, a second
possibility arises and Kenyon, Partridge and Phillips
(J.C.S., 1937, 207) have shown that when the hydrogen phthalate
of optically active 1-phenyl 3-methyl-allyl alcohol is
hydrolysed by dilute aqueous alkali, the highly recomised
isomeric 3-phenyl-1-methyl allyl alcohol is formed. Thus it
seems probable that the following mesomeric positive radical
becomes kinetically free at some stage of the reaction.

\[ (+) 1\text{-phenyl-3-methyl allyl hydrogen phthalate} \]

\[ \text{Me, C=OH, CH = CH, Ph} \]

\[ (\dagger) 3\text{-phenyl-1-methyl allyl alcohol} \]
3-phenyl methyl allyl alcohol is structurally more stable than 1-phenyl 3-methyl allyl alcohol and Kenyon, Partridge and Phillips (J.C.S. 1936, 85) have shown that when the optically active hydrogen phthalate of the former alcohol is hydrolysed by dilute aqueous alkali, almost optically inactive unisomerised alcohol is obtained.

However, when (+) 1-phenyl-3 methyl allyl hydrogen phthalate is hydrolysed with concentrated sodium hydroxide solution, optically active (+) 1-phenyl-3 methyl allyl alcohol is obtained.

The above results show that 1-phenyl-3 methyl allyl hydrogen phthalate undergoes allyl-oxygen fission in presence of dilute alkali and acyl-oxygen fission in presence of concentrated alkali.

The most marked examples of hydrolysis by allyl oxygen fission have, however, been found in the esters of the alcohols containing the anisyl radical e.g., phenyl anisyl alcohol or p-methoxybenzyl alcohol (Balfour, Kenyon, et al; J.C.S. 1942, 605).

From the foregoing discussion, it is evident that acyl-oxygen heterolysis or allyl-oxygen heterolysis in carboxylic esters depends upon the structure of the esters undergoing hydrolysis and also upon the nature and concentration of the hydrolysing agent. The object of the present
investigation was to discover experimental conditions for obtaining optically pure benzoins from their resolved hydrogen phthalic esters. It was found that these optically active esters, when heated with very dilute aqueous ethanolic sulphuric acid at 70°, slowly undergo hydrolysis without racemisation as is shown by the liberated benzoins yielding, on re-esterification, hydrogen phthalic esters of unchanged rotatory power. The unsubstituted benzoin thus obtained possessed a rotatory power which is in excellent agreement with that of (+) and (−) benzoins synthesised by McKenzie and Wen (loc. cit.). These observations lead to two important conclusions. In presence of very dilute aqueous ethanolic sulphuric acid (i) optically active hydrogen phthalic esters of benzoins undergo hydrolysis by acyl-oxygen fission (ii) neither benzoins nor their hydrogen phthalic esters undergo enolisation.

It has also been discovered that optically active benzoins do not racemise in presence of pyridine at room temperature; but that in marked contrast, the rotatory power of their hydrogen phthaliccs decrease rapidly at first and more slowly after some days in the same medium. These observations lead to the following conclusions:

Since optically active benzoins do not racemise in presence of pyridine at room temperature, it follows that they do not undergo enolisation under these conditions; whilst
the decrease in rotatory power of their hydrogen phthalates in the same medium can be attributed to two factors (i) interaction between the -COOH group of the hydrogen phthalate and pyridine (ii) the reactivity of the hydrogen on the carbon atom flanked between two negative groups -COOH (Carboxylic group) and -CO- (Carbonyl group) leads to enolisation in presence of pyridine, a weak base, and hence to racemisation. In this connection it might be recalled that Nopper and Wilson (loc. cit) also noted that a solution of d-homoin in freshly distilled pyridine showed no alteration in specific rotation on standing for a week in a quartz apparatus.
In the past, the name is usually replaced by
"phenyl" or "phenyl" or "diphenyl" ketones of the general
formula, Ar-CO.CH-CH-CH- Ar', and if the two nuclei are alike
the term is said to be symmetrical; if different,
unsymmetrical or mixed.

The term 'benzoic' is used to represent the molecule
containing two unsubstituted phenyl groups Ph.CO.CH-CH-Ph.
and substituents are indicated in the usual way, e. g.

\[
\text{Benzoic acid benzoin}
\]

In mixed benzoins, primes (') are used to indicate
substitution on the ring adjacent to the carbonyl carbon
atom, e. g.

\[
\text{4-chloro-4'-dimethylamino benzoin}
\]
In the past benzoins have also been named by replacing by
"oin" the suffix "ic" or "oic" of the carboxylic acid
(corresponding to the aldehyde from which the benzoin was
prepared, e. g.

\[
\begin{align*}
\text{MeO} \quad & \text{CO-CHOH} \quad \text{MeO} \\
\text{Anisoin} \\
\end{align*}
\]

\[
\begin{align*}
\text{CO-CHOH} \quad \text{OMe} \\
\text{Benzanisoin or Anisbenzoin} \\
\end{align*}
\]

This terminology does not serve to distinguish between
isomers. The letter "α" has been used to indicate the lower-
melting, less stable isomer, and "β" the higher-melting
more stable one.

Certain benzoins exist not only in the keto-form but
also in the enediol form Ar-C(OH):C(OH) Ar'. Cis and trans-forms
of certain enediols have been isolated. Enediols reduce
cupric acetate and Tollens reagent, whereas benzoins do not,
although the latter reduce Fehling's solution. The enediols
frequently ketonise spontaneously and readily when treated
with methanolic hydrochloric acid. They are easily oxidised
to the corresponding \( \alpha \)-diketones (benzils). The relatively stable enediols are found almost exclusively among those benzoins in which one or both aryl radicals have substituents in the two ortho-positions (2:6-and/or 2':6').

\[ \text{e.g. } 2:4:6:2':4':6'; \text{ hexamethylbenzoin. (R.C. Fuson, et al., J.A.C.S. 1939, } 61,975; 1940, 62,600, 2091, 2962; 1941, 63,1500, 1679, 2645, 2648; 1942, 64,2152; 1943, 65, 915; R.P. Barnes et al., J.A.C.S., 1938, 60,1549; 1940, 62,894; 1941, 63,867; 1942, 64,2258, 2260). \]

It would appear that the more extended conjugated system of the enediol is favoured by steric hindrance. In the kephalisation of unsymmetrical enediols, the hydroxyl group of the benzoin appears on the carbon atom \( \beta \) to the aryl group with the 2:4:6 substituents, e.g. \( \text{Ph.C(OH).C(OH).C}_6\text{H}_2\text{X}_3 \rightarrow \text{Ph.CHCO}.\text{CO. C}_6\text{H}_2\text{X}_3. \)

Unsymmetrical benzoins can exist in two structurally isomeric forms, \( \text{Ar.CO.CHCO}.\text{Ar}' \), and \( \text{Ar'.CO.CHCO}.\text{Ar} \). In general, one isomer is more stable than the other, and many of the less stable forms under suitable experimental conditions isomerise to the more stable forms. Not infrequently isomeric benzoins of this type yield identical derivatives, a shift from the less to the more stable isomer occurring during the reaction, e.g. an example of the formation of
4-methoxybenzoin hydrogen phthalate from 4'-methoxybenzoin by heating the reactants on a steam bath for forty minutes in presence of pyridine and triethylamine is given in this thesis.

**Benzoin Condensation:** Treatment of aromatic aldehydes with an alkali cyanide, usually aqueous ethanolic solution, effects a dimerization known as the benzoin condensation. The reaction may be illustrated by the condensation of benzaldehyde itself to benzoin. (Organic Syntheses, Coll. Vol. I, 2nd Edition, 1941, p.94).

\[
\text{NaCN, aq. alcohol} \\
\text{2Ph CHO } \xrightarrow{\text{reflux 30 min.}} \text{Ph CHO CO Ph } (90 - 92\%)
\]

By the use of one mole of each of two different aromatic aldehydes, it is possible to prepare unsymmetrical or mixed benzoins.

\[
\text{Ar CHO} + \text{Ar' CHO} \rightarrow \text{Ar CHO CO Ar'}
\]

Discovery of the benzoin condensation resulted from the fortuitous circumstance that early workers purified crude 'oil' of bitter almonds by washing with aqueous alkali to extract acids, the crude material from amygdalin contained hydrogen cyanide, and the sodium cyanide produced in the alkali wash catalyzed formation of benzoin (Wöhler and Liebig, 1832). Cyanide ion is an indispensable catalyst and
probably participates as shown (Lepworth, J.C.S., 1903, 88, 995; 1904, 85, 1206)

\[
\begin{array}{c}
\text{Ph}-\text{C}=\text{H} + \text{CH}^- \rightarrow \text{Ph}-\text{C}=\text{H} + \text{Ph} \cdot \text{C} \rightarrow \text{Ph} \cdot \text{C} + \text{C} \cdot \text{Ph} \rightarrow \text{Ph} \cdot \text{C}-\text{C} \cdot \text{Ph} - \text{C} \\
0 \quad 0 \quad 0 \quad 0
\end{array}
\]

The details of the mechanism are given in Chapter Five.

In order that an aldehyde may form a symmetrical benzoin it must be able to act both as a donor and as an acceptor of the hydrogen atom. Two aldehydes, neither of which forms a symmetrical benzoin, may form a mixed benzoin if one aldehyde is an acceptor and the other a donor of the hydrogen atom, p-dimethylaminobenzaldehyde does not form a symmetrical benzoin, but condenses with other aldehydes, acting as the donor, to give mixed benzoins in which the dimethylaminophenyl group is attached to the carbonyl carbon atom. (Ar. above). Benzaldehyde, by contrast, readily forms symmetrical benzoin and in condensation with other aldehydes usually acts as the acceptor (Ar'. above) e. g.

\[
\begin{array}{c}
\text{Me}_3\text{N} \quad \text{CO} - \text{CH} = \text{N} - \text{CH} \\
\text{H} \quad \text{Ph} \quad \text{Ph}
\end{array}
\]

4-dimethylamino benzoin.
Similarly alkyl-, alkoxy-, amino- and halogen-benzaldehydes do not readily form symmetrical benzoins, but often readily give mixed benzoins. In a mixed benzin condensation a single unsymmetrical benzin is usually the only isolable product.

Evaporation of Benzoins:

(i) By the 'benzoin condensation' method as seen above
(Sieke, Ber., 1976, 2, 1769).

Ar.CHO + Ar'.CHO → Ar.CO.CHO.Ar'.

(ii) By the 'reversion procedure' (Buck & Ide, J. A.C.S., 1931, 53, 2556, 2784).

Benzoin tends to revert to benzaldehyde in the reaction mixture in which it is synthesised. This reversion has been used to synthesise unsymmetrical benzoins, usually in good yields, by the addition of an aldehyde or another benzoin to the reaction mixture in which a symmetrical or unsymmetrical benzoin has been formed.

Ar.CO.CH.CHO + 2 Ar'.CHO → Ar.CO.CH.CO.CH.OH + Ar'.CO.CH.CO.CH.OH.
Ar.CO.CH.CO.CH.OH + Ar'.CO.CH.CO.CH.OH → 2 Ar.CO.CH.CO.CH.OH.

(iii) By the Friedel-Crafts condensation of phenylglyoxal with aromatic hydrocarbons in the presence of aluminium chloride:

Ar.CO.CH.OH + Ar'.H → Ar.CO.CH.CO.CH.OH.
The benzosins prepared in this way have the carbonyl group adjacent to the aromatic residue of the glyoxal (R.C. Fuson et al. J.A.C.S., 1935, 57, 1803; 1936, 58, 1295; 1939, 61, 412). Two molecular equivalents of aluminium chloride are generally used together, with carbon disulphide or excess of the hydrocarbon reactant as solvent.

(iv) By the reaction of the mandelamides and mandelonitriles with arylmagnesium halides.

\[
\begin{align*}
\text{ArCHO} & \rightarrow \text{ArCHOH.CN} \xrightarrow{\text{H}_2\text{SO}_4-\text{H}_2\text{O}} \text{ArCHOH.CO.NH}_2 \xrightarrow{3\text{Ph.MgBr}} \\
\text{Ph} & \xrightarrow{\text{OMgBr}} \\
\text{ArCCH} & \xrightarrow{\text{NH}} \text{MgBr} \xrightarrow{\text{H}_2\text{O}} \text{ArCHOH.CO.PH} \\
(e.g. \text{Ar} = \text{C}_6\text{H}_4\cdot\text{NMe}_2-p)
\end{align*}
\]

Although the yields are 20-47%, both symmetrical and isomeric stable and less stable unsymmetrical benzosins can be prepared in this way. (McKenzie et al. J.C.S., 1908, 23, 309; 1928, 646; 1934, 412., Jenkins et al. J.A.C.S., 1930, 52, 4495, 5198; Bull Soc. Chim Fr., 1929, [IV], 45, 414; Ber; 1932, 65, 794; 1936, 62, 861, 876).

4-Dimethylaminomandelamide, obtained from 4-dimethylaminobenzaldehyde, reacts with three moles of phenylmagnesium bromide to give 4'-dimethylaminobenzoin (45% yield) the less stable isomer, whilst from mandelamide and 4-dimethylaminophenyl magnesium bromide, 4-dimethylaminobenzoin, the more stable
isomer is formed in 25% yield (Jenkins et al. loc. cit.).

(v) By the reduction of benzils, preferably with magnesium-magnesium iodide or bromide or catalytically.

\[
\text{Ar-CC-CC-Ar'} \rightarrow \text{Ar-C(OH)}: \text{C(OH)}: \text{Ar'} \\
\text{Ar'} \rightarrow \text{Ar-CO-CHOH-Ar'}
\]

The reaction is limited inasmuch as most benzils are accessible only through oxidation of the corresponding benzoins.

Catalytic reduction over platinum oxide proceeds in high yield. It is effective for hindered benzils, such as 2:4:6:2':4':6' hexamethyl benzil, when other reagents are ineffective. The cis and trans-enediols are formed from such benzils; they can be separated, and on treatment with piperidine acetate or with ethanolic hydrochloric acid they isomerise to the benzoins (R.C. Fuson et al. J.A.C.S., 1939, 61, 278; 1940, 62, 2091, 1941, 63, 2968).

(vi) By the reduction of the aromatic acids, their chlorides, esters and peroxides with magnesium-magnesium iodide in ether-benzene. (Gomberg & Bachmann, J.A.C.S., 1928, 50, 2762; Fuson et al., J.A.C.S., 1940, 62, 600, 2091, 2962; 1941, 63, 1500, 1679). With the acid or peroxide two steps are involved: the formation of the magnesium iodide salt and the reduction. With the acid chloride or ester the magnesium iodide derivative of the enediol forms directly and is hydrolysed to the benzoin.
2Ar· COCl —→ Ar.C(OMgI): C(OMgI).Ar. —→ Ar.CO·CHOH·Ar.

Acid chlorides give the best yields. Intermediate enediols have been isolated from the reduction of hindered acid chlorides.

This procedure can be applied when the aldehyde corresponding to the symmetrical benzoin desired is not available. No unsymmetrical benzoin has been prepared by this method.

(vii) By bromination of a desoxybenzoin, followed by subsequent hydrolysis of the α-bromo derivative formed.

Methods (i) and (ii) were used to prepare 4-methoxybenzoin and 4-dimethylamino benzoin; and method (vii) was used to prepare 4'-methoxybenzoin.

Before closing this Chapter, it may be mentioned that aliphatic analogs of benzoins are called acyloins, R—CO·CHOH·R. They cannot be prepared by a cyanide catalysed condensation of aliphatic aldehydes as the basic reagent promotes the more rapid aldol condensation, e.g.

\[
2\text{CH}_3\cdot\text{CHO} \quad \text{dil. aq. KCN} \quad 8^\circ\text{C for 2hr} \quad \text{CH}_3\cdot\text{CHOH} \cdot \text{CH}_2\cdot\text{CHO} \\
\text{0°C for 30hr.} \quad 40 - 50\% \\
\text{acetaldehyde} \quad \text{acetalaldol}
\]
They are customarily prepared by condensation of esters in an inert medium through the agency of metallic sodium; this acyloin condensation proceeds through the formation of the sodium salts of enediols, which are subsequently converted to acyloins by hydrolysis.

\[
\begin{align*}
2R.\text{COOR} + 4\text{Na} & \rightarrow R.\text{CO} + 2\text{NaOR} + 2\text{NaOH} \\
R.\text{CO} & \rightarrow \text{hydrolysis} \\
R.\text{CO} + 2\text{NaOH} & \rightarrow R.\text{CO} + 2\text{NaOH} + 2\text{H}_2\text{O}
\end{align*}
\]

The benzoin (Hexamethyl acetoin) was in this way prepared from pivalic acid ester (ethyl trimethyl acetate).

The benzoins, being readily prepared from aromatic aldehydes, constitute convenient intermediates for the preparation of many related compounds, including deoxybenzoins, benzils, hydrobenzoins, stilbene-diols and stilbenes.
CHAPTER IV

The Resolution of Benzoin

The hydrogen phthalic ester of benzoin was obtained in about 95.7% yield by making use of pyridine and triethylamine, the details of the method being given in the experimental section. After recrystallization from methylene chloride and light petroleum it had mp. 154° - 156°. It was separated from

The hydrogen phthalate could not be induced to form a crystalline salt with brucine, quinine, cinchonine, or cinchonidine. However, the crystalline quinidine salt of the (+) acid ester readily separated from methyl alcohol. It was recrystallised from acetone and methyl alcohol until optically pure and then decomposed with dilute hydrochloric acid to liberate the (+) hydrogen phthalate. The (+) acid ester was recrystallized from methylene chloride and light petroleum when it had mp. 132° - 133°.

The filtrate and washings from the less soluble quinidine salt of the (+) acid ester were concentrated and decomposed with dilute hydrochloric acid. The liberated optically impure (-) hydrogen phthalate, after two recrystallizations from methylene chloride and light petroleum yielded optically pure (-) hydrogen phthalate, mp. 132° - 133°.
Optically active benzoins (mp. $132^\circ - 133^\circ$) were obtained by hydrolysing the active hydrogen phthalates with very dilute aqueous ethanolic sulphuric acid at $70^\circ - 80^\circ$ for 120 hours. The (+) benzoin was obtained from the (+) hydrogen phthalate and the (-) benzoin was obtained from the (-) hydrogen phthalate.

When equal amounts of optically pure (+) and (-) hydrogen phthalates were mixed and allowed to separate from methylene chloride and light petroleum, the crystals had mp. $154^\circ - 155^\circ$, i.e., identical with that of the original (+) hydrogen phthalate. A solution of the resulting hydrogen phthalate in acetone had $[\alpha]_{D}^{25^\circ} = 0.0$.

Similarly when equal amounts of optically pure (+) and (-) benzoins were dissolved in ethanol and allowed to crystallize out, the crystalline benzoin obtained had mp. $133^\circ - 134^\circ$, i.e., the same as that of the original (+) benzoin and its solution in acetone had $[\alpha]_{D}^{25^\circ} = 0.0$.

The specific rotatory powers of the active hydrogen phthalates and active benzoins in acetone are given in Table I.
Specific rotatory powers of optically active benzoin and their hydrogen phthalates in acetone (I, I.)

**TABLE I**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Solvent</th>
<th>C</th>
<th>$[\alpha]^{25^\circ}$ - $26^\circ$</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+) Benzoin</td>
<td>Acetone</td>
<td>2.50</td>
<td>+ 118.4°</td>
</tr>
<tr>
<td>(-) Benzoin</td>
<td>Acetone</td>
<td>2.40</td>
<td>- 118.3°</td>
</tr>
<tr>
<td>(+) Acid ester</td>
<td>Acetone</td>
<td>2.54</td>
<td>+ 140.2°</td>
</tr>
<tr>
<td>(-) Acid ester</td>
<td>Acetone</td>
<td>2.50</td>
<td>- 140.0°</td>
</tr>
</tbody>
</table>

The close agreement in the values of the rotatory powers of the (+) and (-) hydrogen phthalates and of the (+) and (-) benzoin may be taken as an indication that optical purity has been achieved.

The optically active hydrogen phthalates had melting points lower than the mp. of the (+) hydrogen phthalate; but the mp. of the optically active benzoin was not much different from that of the (+) benzoin as shown below:
The specific rotatory powers of the (+) benzoin and its hydrogen phthalate in different solvents are recorded for light of different wave lengths. (Vide p. 92 and 90)

There are wide variations in rotatory powers in different solvents, viz., acetone, pyridine, chloroform etc., in the case of (+) benzoin. In the case of its (+) hydrogen phthalate, the values of specific rotatory powers in acetone at different wave lengths do not differ much from those in 99% ethanol; and the values of specific rotatory powers in chloroform at different wave lengths do not differ much from those in glacial acetic acid. The highest rotations are obtained in methylene chloride in case of the (+) hydrogen phthalate and in glacial acetic acid in the case of (+) benzoin.

"A Characteristic Diagram" for (+) benzoin has been constructed according to the method of Armstrong and Walker.
(Proc. Roy. Soc; 1913, A. 82, 383) and is given in the experimental section. A reference line with slope of unity is drawn and on it are plotted the various values of $[\alpha]$. The numbers representing the specific rotatory powers for other wave lengths $[\alpha]_{\lambda}$ were then plotted on the ordinates passing through the points previously located on the reference line. The points for the other values of $[\alpha]_{\lambda}$ were found to lie on straight lines of different slopes.

It may be pointed out that many reference books state that benzoin has mp. 137°C. This is surprising since over fifty years ago McKenzie and Wren (J. C.S., 1909, 22, 309) recorded that they were unable to raise the mp. of a specimen of Kahlbaum's benzoin above 132.5° - 133° even after six crystallizations from methyl alcohol.

The mp. of benzoin recorded in different text books is recorded below:


The benzoin used in the present experiments was a commercial sample of mp. 133° - 134° (uncorrected). The mp. remained unchanged after crystallization from ethanol.
CHAPTER V

The Preparation and Resolution of 4-Methoxybenzoin

Preparation of 4-Methoxybenzoin:

4-Methoxybenzoin was prepared by two methods:

(1) By the benzoin condensation. The method consists in heating under reflux one mole of benzaldehyde with one mole of anisaldehyde in aqueous ethanolic potassium cyanide solution for two hours. The reaction may be represented by the equation:

\[
\text{MeO} \cdot \text{C}_{6}\text{H}_{4} \cdot \text{CHO} + \text{ONC} \cdot \text{Ph} \rightarrow \text{MeO} \cdot \text{C}_{6}\text{H}_{4} \cdot \text{CO} \cdot \text{CNCH}_{2} \cdot \text{Ph}.
\]

Formally this reaction appears to take place by the addition of the hydrogen of one aldehyde group to the carbonyl of the other and the union of the carbon atoms. That the reaction is not simply an aldol-type condensation, however, is indicated by the fact that it is not catalyzed by ordinary bases but specifically by alkali cyanides.

Cyanide appears to be a specific catalyst for the benzoin condensation. The following mechanism was proposed by Lepworth (J. C. S. 1903, 82, 995; 1904, 85, 1206) and has been generally accepted.
Stabilized by mesomerism.
The reversibility of the reactions at each stage is indicated by the fact that when benzoin is heated with an aldehyde, \( \text{Ar}^+ - \text{CHO} \), in the presence of aqueous-ethanolic potassium cyanide, a mixed benzoin, \( \text{Ar}^+ \text{CHO} - \text{CN} - \text{Ar}^+ \) is also obtained (Duck and Heal, J.A.C.S.; 1931, 53, 2350; 1931, 53, 2724). The specific catalytic effect of the cyanide ion may be attributed to its two essential properties, (a) a strongly basic character, and (b) a \( \pi \) bond structure which renders the hydrogen atom, attached to the same carbon atom as the cyanide and phenyl group in the cyanhydrin (A), sufficiently acidic to be removed by another cyanide anion, thereby giving the mesomeric anion (B) required for condensation with a second mole of benzaldehyde.

\[
\begin{align*}
\text{MeO} \quad \text{C} & \quad \text{C} \equiv \text{N} \quad \text{MeO} \quad \text{C} & \quad \text{C} \equiv \text{N} \\
\text{OH} & \quad \text{OH} & \quad \text{OH}
\end{align*}
\]

(B)

\[
\begin{align*}
\text{MeO} \quad \text{C} & \quad \text{C} \equiv \text{N} \\
\text{OH}
\end{align*}
\]

Other common bases such as hydroxyl do not combine these two properties and this may explain their inability to act as catalysts for this type of condensation.
(11) By the Reversion Method:

4-methoxybenzonoin was also obtained by heating under reflux a solution of one mole of benzoin and two moles of 4-methoxybenzaldehyde in aqueous ethanolic potassium cyanide for two hours.

\[ 2 \text{MeO}_2C_6H_4\text{CHO} + \text{PhCOCl}_2\text{Ph} \rightarrow 2 \text{MeO}_2C_6H_4\text{COCl}_2\text{Ph} \]

Resolution of 4-methoxybenzonoin:

The (‡) hydrogen phthalic ester of 4-methoxybenzonoin was prepared in about 67% yield by making use of pyridine and triethylamine, after recrystallization from aqueous acetone and then from methylene chloride-light petroleum it had mp. 150° - 152°.

The crystalline quinidine salt of the (+) acid ester readily separated from a methanolic solution of the (‡) acid ester and quinidine. It was recrystallized from acetone and then decomposed with dilute hydrochloric acid. The liberated (+) hydrogen phthalate had mp. 36°, a value unchanged after recrystallization from methylene chloride and light petroleum.

The filtrate and washings from the less soluble
quinitine salt of the (+) acid ester were concentrated and
decomposed with dilute hydrochloric acid. The liberated
optically impure (-) hydrogen phthalate was so highly
soluble in common organic solvents like acetone, ethyl acetate,
chloroform, methylene chloride etc., that it was very
difficult to induce crystallization. The following method
was then finally used to obtain optically pure (-) hydrogen
phthalate of 4-methoxybenzoin. The optically impure (-)
acid ester was dissolved in methylene chloride and an equal
volume of cyclohexane was added. The solution was then
inoculated with (z) hydrogen phthalate. The separated (z)
hydrogen phthalate was removed by filtration and the filtrate
was evaporated to dryness in a vacuum desiccator. The solid
mass was dissolved in cold ethanol. A second crop of (z)
hydrogen phthalate separated and was removed by filtration.
The filtrate was diluted with water. The next day
the separated oily mass solidified, it was filtered and dried.
Its mp. was 80° - 90°. This solid mass, after being
recrystallized twice from ethanol, yielded optically pure
(-) hydrogen phthalate, mp. 80°.

The optically pure (+) 4-methoxybenzoin was obtained
by hydrolysing the (+) hydrogen phthalate of 4-methoxybenzoin
with very dilute aqueous ethanolic sulphuric acid at 70°
for 125 hours. The (-) 4-methoxybenzoin was similarly
obtained from (-) hydrogen phthalate.

When equal amounts of the optically pure (+) and (-) hydrogen phthalates of 4-methoxybenzoin were mixed and allowed to separate from methylene chloride and petroleum, the crystals had sp. 158° - 159°, i.e. identical with that of the original (±) hydrogen phthalate. A solution of this hydrogen phthalate in acetone had \([ \alpha ]^25^\circ_D \pm 0.0^\circ\).

Similarly when equal amounts of optically pure (+) and (-) 4-methoxybenzoins were dissolved in ethanol, and allowed to crystallize, the crystalline 4-methoxybenzoin obtained had sp. 100° - 109°, i.e. identical with that of the original (±) 4-methoxybenzoin. Its solution in acetone had \([ \alpha ]^25^\circ_D \pm 0.0^\circ\).

Specific rotatory powers of optically active 4-methoxybenzoins and their hydrogen phthalates in acetone are given in Table II.
TABLE II

Specific rotatory powers \([\alpha]\) of optically active 4 methoxybenzenoic and their hydrogen phthalates in acetone (1, 1).

<table>
<thead>
<tr>
<th>Substance</th>
<th>Solvent</th>
<th>(c)</th>
<th>([\alpha]^{25\circ\text{o}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+) 4-methoxybenzoic</td>
<td>Acetone</td>
<td>1.05</td>
<td>+ 72.0(^\circ)</td>
</tr>
<tr>
<td>(-) 4-methoxybenzoic</td>
<td>Acetone</td>
<td>1.10</td>
<td>- 71.8(^\circ)</td>
</tr>
<tr>
<td>(+) Acid ester</td>
<td>Acetone</td>
<td>2.55</td>
<td>+ 111.3(^\circ)</td>
</tr>
<tr>
<td>(-) Acid ester</td>
<td>Acetone</td>
<td>2.5</td>
<td>- 111.2(^\circ)</td>
</tr>
</tbody>
</table>

The close agreement in the values of the rotatory powers of the (+) and (-) hydrogen phthalates and of the (+) and (-) 4 methoxybenzoic may be taken as an indication that optical purity has been achieved.

The optically active hydrogen phthalates had melting points much lower than that of the (+) hydrogen phthalate; but the mp. of the optically active 4 methoxybenzoic was very near to the mp. of (+) 4 methoxybenzoic as shown below:
<table>
<thead>
<tr>
<th>Substance</th>
<th>Melting point</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-methoxybenzoin</td>
<td>101 - 102</td>
</tr>
<tr>
<td>4-methoxybenzoin hydrogen</td>
<td>101-102</td>
</tr>
<tr>
<td>4-methoxybenzoin hydrogen</td>
<td>105 - 109°</td>
</tr>
<tr>
<td>phthalate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>158 - 159°</td>
</tr>
</tbody>
</table>

The specific rotatory powers of the (+)
4-methoxybenzoin and its hydrogen phthalate in different
solvents are recorded for light of different wave lengths,
(vice p. 113 & 112)

There are wide variations in rotatory powers in different
solvents, *viz.* acetone, acetic acid, pyridine etc., in the
case of (+) 4-methoxybenzoin. In the case of its (+) hydrogen
phthalate, the values of specific rotatory powers in acetone
at different wavelengths are nearly the same as those in 95% ethanol;
and the values of specific rotatory powers in
glacial acetic acid at different wavelengths are nearly the
same as those in pyridine. The highest rotations were
obtained in methylene chloride in the case of the (+) hydrogen
phthalate and in glacial acetic acid in the case of the (+)
4-methoxybenzoin.

It is interesting to note that the specific rotatory
powers of (+) benzoin and its (+) hydrogen phthalate in
different solvents for light of different wavelengths show a
marked parallelism to the specific rotatory powers of (+)
4 methoxybenzoic acid and its (+) hydrogen phthalate in different solvents for light of different wavelengths.

A "Characteristic diagram" for (+) 4 methoxybenzoic acid has been constructed and is given in the experimental section.
CHAPTER VI

The Preparation and Resolution of 4-dimethylaminobenzoin.

Preparation of 4-dimethylaminobenzoin:

4-dimethylaminobenzoin was prepared by two methods:

(i) Benzoin Condensation Method:

One mole of benzaldehyde and one mole of 4-dimethylaminobenzaldehyde were condensed in the presence of aqueous ethanolic potassium cyanide solution.

\[ \text{Me}_2\text{N} \cdot \text{C}_6\text{H}_4 \cdot \text{CHO} + \text{CN} \cdot \text{Ph} \rightarrow \text{Me}_2\text{N} \cdot \text{C}_6\text{H}_4 \cdot \text{CO} \cdot \text{CHN} \cdot \text{Ph} \]

The resulting benzoin, after recrystallization from methylene chloride and petroleum, has mp. 158° – 159°.

(ii) Resolution Procedure:

One mole of benzoin is condensed with two moles of 4-dimethylaminobenzaldehyde in aqueous ethanolic potassium cyanide solution.

\[ 2\text{Me}_2\text{N} \cdot \text{C}_6\text{H}_4 \cdot \text{CHO} + \text{Ph} \cdot \text{CN} \cdot \text{CHN} \cdot \text{Ph} \rightarrow 2\text{Me}_2\text{N} \cdot \text{C}_6\text{H}_4 \cdot \text{CO} \cdot \text{CHN} \cdot \text{Ph} \]

The resulting benzoin after recrystallization from methylene chloride and petroleum has mp. 158° – 159°, in agreement with (i).
Due to the presence of the \( \text{N}_2\text{H}_2 \) group in 4-dimethylaminobenzoin, it was thought to be a strong base and hence it was expected that it would form salts with optically active acids, e.g., \( \text{d-tartaric acid} \) or \( \text{l-camphor sulphonic acid} \); but all the attempts to get the diastereoisomeric salts from different solvents unfortunately proved to be fruitless, each time uncombined 4-dimethylaminobenzoin was obtained. It is very surprising that 4-dimethylaminobenzoin does not give a stable salt even with a strong acid like hydrochloric acid as it does not dissolve in cold dilute hydrochloric acid. It dissolves in excess of hot dilute hydrochloric acid, but as the solution cools, the free 4-dimethylaminobenzoin separates, which has the same mp, as the original substance both alone and when the two are mixed, it seems that in solution it forms a loose salt with hydrochloric acid, which is easily hydrolysed by water, a view which received confirmation by the insolubility of the base in hot water alone.

It was then decided to resolve 4-dimethylaminobenzoin by the usual method and accordingly its hydrogen phthalic ester was prepared.

**Resolution of 4-dimethylaminobenzoin**

The hydrogen phthalic ester of 4-dimethylaminobenzoin was prepared by making use of pyridine alone as well as by
making combined use of pyridine and triethylamine. It is found that on using pyridine alone, the reactants have to be heated for a longer period and the yield of the hydrogen phthalic ester is less than when a combined use of pyridine and triethylamine is made.

The hydrogen phthalate, after recrystallization from methylene chloride and petroleum, has mp. 171° - 172°.

The crystalline quinidine salt of the (+) acid ester readily separated from a methanolic solution of the (±) acid ester and quinidine. It was recrystallized from acetone and methylalcohol until optically pure and then decomposed with dilute hydrochloric acid. The liberated (+) hydrogen phthalate was filtered, dried and recrystallized from acetone when it had mp. 167° - 168°.

The filtrate and washings from the less soluble quinidine salt of the (+) acid ester were concentrated and decomposed with dilute hydrochloric acid. The liberated optically impure (−) hydrogen phthalate was crystallized thrice from acetone when optically pure (−) hydrogen phthalate, mp. 167° - 168°, was obtained.

Optically active 4-dimethylaminobenzoins were obtained by hydrolysing their optically active acid phthalates with very dilute aqueous ethanolic sulphuric acid at 70° for 155 hours.
It is interesting to note that optically active 4-dimethylaminobenzoic show (+) rotatory power in some solvents and (-) rotatory power in some other solvents and also that they show (+) rotatory power in light of some wavelengths and (-) rotatory power in light of other wavelengths. Optically active dimethylaminobenzoic hydrocarbon phthalates do not show this unusual behaviour.

When equal amounts of optically pure (+) and (-) hydrogenphthalates of 4-dimethylaminobenzoic were mixed and allowed to crystallize from methylene chloride and petroleum, the crystals had mp. 171° - 172°, i.e. identical with that of the original (+) hydrogen phthalate. A solution of this hydrogen phthalate in acetone had $[\alpha]_{D}^{25} = 0.0$.

Similarly when equal amounts of optically pure 4-dimethylaminobenzoic obtained by hydrolysing (+) and (-) 4-dimethylaminobenzoic hydrogen phthalates were mixed and allowed to crystallize from methylene chloride and petroleum the crystals had mp. 158° - 160°, i.e. identical with that of the original (+) 4-dimethylaminobenzoic. A solution of this 4-dimethylaminobenzoic in acetone had $[\alpha]_{D}^{25} = 0.0$.

Specific rotatory powers of optically active 4-dimethylaminobenzoic hydrogen phthalates are of
4-dimethylaminobenzoins obtained from them by hydrolysis are given in Table III.

**TABLE III**

Specific rotatory powers of optically active 4-dimethylaminobenzoins and their hydrogen phthalates in acetone (1, 1).

<table>
<thead>
<tr>
<th>Substance</th>
<th>Solvent</th>
<th>g</th>
<th>[α]25° (25^\circ)</th>
<th>5893</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+) 4-dimethylamino-</td>
<td>Acetone</td>
<td>1.00</td>
<td>+ 94.0</td>
<td></td>
</tr>
<tr>
<td>benzoic hydrogen phthalate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(-) 4-dimethylamino-</td>
<td>Acetone</td>
<td>1.00</td>
<td>- 92.8</td>
<td></td>
</tr>
<tr>
<td>benzoic hydrogen phthalate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-dimethylamino benzoin obtained from (+)acid ester</td>
<td>Acetone</td>
<td>1.04</td>
<td>-22.6°</td>
<td></td>
</tr>
<tr>
<td>4-dimethylamino benzoin obtained from (-) acid ester</td>
<td>Acetone</td>
<td>1.06</td>
<td>+22.5°</td>
<td></td>
</tr>
</tbody>
</table>

The close agreement in the values of the rotatory powers of the (+) and (-) hydrogen phthalates and of the free benzoins obtained from them by hydrolysis renders it probable that optical purity has been achieved.

The optically active 4-dimethylaminobenzoic hydrogen
phthalates had melting points slightly lower than that of (I) hydrogen phthalate, but the melting points of the optically active 4-dimethylaminobenzoic obtained from them by acid hydrolysis were slightly higher than that of (I) 4-dimethylaminobenzoic, as shown below:

<table>
<thead>
<tr>
<th>Substance</th>
<th>Melting point</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-dimethylaminobenzoic</td>
<td>167 - 168°</td>
</tr>
<tr>
<td>4-dimethylaminobenzoic</td>
<td>167 - 168°</td>
</tr>
<tr>
<td>hydrogen phthalate</td>
<td>171 - 172°</td>
</tr>
</tbody>
</table>

The mp. of the optically active 4-dimethylaminobenzoic obtained from the optically active acid esters was 165° - 166°, while the mp. pf (I) 4-dimethylaminobenzoic was 160° - 161°, when recrystallized from methylene chloride and petrolatum, and 163° - 164°, when recrystallized from ethanol. The carbinol crystallizes in clusters of small needles from ethanol and in microscopic form from methylene chloride and petrolatum. When the carbinol with mp. 160° - 161° is mixed with the carbinol with mp. 163° - 164°, the mixed mp. is not lowered but ranges from 160 to 165°.

The specific rotatory powers of (+) 4-dimethylaminobenzoic hydrogen phthalate and of optically active 4-dimethylaminobenzoic obtained from (-) 4-dimethylaminobenzoic hydrogen phthalate by acid hydrolysis are recorded in different solvents for light of different wave lengths (Vide p. 124 & 126).
There are wide variations in rotatory powers in different solvents, viz: acetone, chloroform, methylene chloride, etc., in the case of (+) 4-dimethylaminobenzoin hydrogen phthalate. It is interesting to note that optically active 4-dimethylaminobenzoin hydrogen phthalate, shows (+) rotatory powers in acetone, pyridine, dioxan, ethyl acetate, chloroform and benzene, but shows (-) rotatory power in carbon disulphide in light of different wavelengths, whilst it shows (-) rotatory power for \( \lambda 5893 \) and (+) rotatory powers for \( \lambda 5461, \lambda 5086 \) and \( \lambda 4358 \) in methylene chloride; and it shows (-) rotatory powers for \( \lambda 5893, \lambda 5461, \lambda 5086 \) and (+) rotatory powers in \( \lambda 4358 \) in glacial acetic acid. Similarly the optically active 4-dimethylaminobenzoin, obtained from (+) 4-dimethylaminobenzoin hydrogen phthalate, shows the opposite optical behaviour.

"Characteristic diagrams" for (+) 4-dimethylaminobenzoin hydrogen phthalate and for optically active 4-dimethylaminobenzoin, obtained from (-) 4-dimethylaminobenzoin hydrogen phthalate have been constructed and are given in the experimental section.

(+) 4-dimethylaminobenzoin hydrogen phthalate has been obtained by fractional crystallization of its quinidine salt, whilst (-) 4-dimethylaminobenzoin hydrogen phthalate has been obtained by fractional crystallization of the optically impure
hydrogen phthalate obtained from the more soluble fractions of the alkaloidal salt. In the first case, the (+) 4-dimethylaminobenzoin hydrogen phthalate had \([\alpha]_{D}^{25\circ} + 94.0\); whilst in the second case, the (-) 4-dimethylaminobenzoin hydrogen phthalate had \([\alpha]_{D}^{25\circ} - 93.8\). In addition (+) 4-dimethylaminobenzoin hydrogen phthalate obtained by fractional crystallization of an impure sample, had \([\alpha]_{D}^{25\circ} + 93.7\). Since there is a close agreement in the values of the rotatory powers of the hydrogen phthalates obtained by two distinctly different procedures it seems exceedingly probable that optical purity has been reached by both procedures.
CHAPTER VII

Preparation and Attempted Resolution of 4'-Methoxybenzoin

4'-Methoxybenzoin (more stable form) can be converted to 4'-Methoxybenzoin (less stable form) by two methods:

**Method 1:**

4'-Methoxybenzoin gives the desoxy-compound related to the isomeric benzoin; the desoxy compound can be brominated to the bromo ketone, which can be hydrolysed to 4'-methoxybenzoin (Buck & Ido, J.A.C.S. 1932, 54, 3012; Jenkins, J.A.C.S. 1934, 56, 683, 1137; 1933, 55, 3048).

\[
\text{Ph.CO.CH}_2\text{CH}_2\text{C}_6\text{H}_4\text{O}_2\text{OH} \overset{\text{Sn}}{\longrightarrow} \text{Ph.CO.CH}_2\text{CH}_2\text{C}_6\text{H}_4\text{O}_2\text{OH}
\]

**4'-Methoxybenzoin**

\[
\text{Br}_2 \rightarrow \text{Ph.CO.CH}_2\text{CH}_2\text{C}_6\text{H}_4\text{O}_2\text{OH} \overset{\text{H}_2\text{O}}{\longrightarrow} \text{Ph.CO.CH}_2\text{CH}_2\text{C}_6\text{H}_4\text{O}_2\text{OH}
\]

**4'-Methoxybenzoin**

**Method 2:**

4'-Methoxybenzoin is converted to the oxime and then reduced catalytically to the corresponding amino carbinal. Oxidation of the amino carbinal with chromic acid gives the
amine ketone, which on treatment with nitrous acid gives 4'-methoxybenzoin. (Duck & Ide, J.A.C.S., 1930, 52, 4107; 1931, 52, 1912, 1933, 55, 4312; A. McKenzie et al., J.A.C.S. 1936, 58, 312; Ber., 1936, 69, 861, 870)

\[
\text{Ph.CHCH.CO.C}_6\text{H}_4\text{CHO} \rightarrow \text{Ph.CHCH.C}_6\text{H}_4\text{CH}_2\text{CHO} \quad \text{(101)}
\]

\[
\text{H}_2 \rightarrow \text{Ph.CHCH.C}_6\text{H}_4\text{CHO} \rightarrow \text{Ph.CHCH.C}_6\text{H}_4\text{CH}_2\text{CHO} \quad \text{(102)}
\]

\[
\text{H}_2\text{O}_2 \rightarrow \text{Ph.CO.CHCH.C}_6\text{H}_4\text{CHO} \quad \text{(103)}
\]

The first method was used to prepare 4'-methoxybenzoin.

It can be seen that it involves the following stages:

(a) Conversion of 4-methoxybenzoin into decybenzoine.

(b) Conversion of decybenzoine into bromo ketone.

(c) Conversion of bromo ketone into 4'-methoxybenzoin.

We now discuss these stages in turn:

(a) Conversion of 4-methoxybenzoin into decybenzoine.

It is known that symmetrical benzoins, when treated with certain metals and acids under suitable conditions yield decybenzoins (Zincke, Ann., 1861, 142, 180; and more recently by Duck and Jenkins, J.A.C.S., 1929, 51, 2163); the reaction
is usually explained by assuming a simple reduction of the alcoholic group \(-\text{CH}_2\) of the keto alcohol to the methylene group \(-\text{CH}_2-\) (Gattermann, "Practical Methods of Organic Chemistry", p. 306) according to the reaction:

\[
\text{R} \cdot \text{CHOH} \cdot \text{COR} + \frac{\text{H}_2}{\text{[acid]}} \rightarrow \text{R} \cdot \text{CH}_2 \cdot \text{CO} \cdot \text{R.}
\]

About thirty years ago, however, the reduction of two unsymmetrical benzenes p-dimethylaminobenzoin and p-dimethylamino-p-chlorobenzoin, by means of tin and concentrated hydrochloric acid was described (Jenkins, Buck & Digselow, J.A.C.S. 1930, 52, 4495; Jenkins ibid; 1931, 53, 3115) and in each case two isomeric ketones were obtained.

When 4-methoxybenzoin was reduced with tin and concentrated hydrochloric acid about 46% 4-methoxybenzyl phenyl ketone (mp. 97° - 98°) and 13% benzyl 4-methoxyphenyl ketone (mp. 65° - 66°) were obtained. Jenkins obtained the first isomer (mp. 96.5°, corr.) in about 47% yield and second isomer (mp. 77°) in very low yield (2%) by the same method (J.A.C.S., 1932, 54, 1155). It is surprising that by using the same method, Buck and Ide (J.A.C.S., 1931, 53, 1936) reported a yield of 67% of the first isomer (mp. 94°) and none of the second isomer.
The formation of the second isomer can be explained in the following way. In ethanolic solution an unsymmetrical benzoin enolizes in presence of concentrated hydrochloric acid and then on ketalisation can give either the original ketone or its isomer as follows:

\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
\text{R.CO.CHON.R' \rightleftharpoons R. C. = C - R' \rightleftharpoons R. CHON.CO.R'}
\end{align*}
\]

(1) \quad (II)

The reduction of the alcoholic group \(-\text{CHO}\) to the methylene group \(-\text{CH}_2-\) gives a mixture of two decamethanes from (i) and (ii) as already stated in the case of the reduction of symmetrical benzamines. Keto-enol tautomerism finds support from the fact that when ethanolic solution of optically active benzoin hydrogen phthalate is partially hydrolysed by heating with concentrated hydrochloric acid, the free benzoin and the unhydrolysed benzoin hydrogen phthalate are both obtained, in a highly racemised condition. It is well known that the racemisation is usually explained through the intermediate formation of an enediol as already stated in Chapter II. In this connection, it may be mentioned that it is now generally accepted that keto-enol tautomerism is catalysed by both acids and bases, and the rate of reaction is proportional
to the concentrations of the ketone and the catalyst. Hence there is every reason to believe that keto-enol tautomerism is rapidly established in presence of concentrated hydrochloric acid. When optically active benzoquin hydrogen phthalates are hydrolysed by heating with very dilute aqueous ethanolic sulphuric acid, the acidity of the solution is just sufficient to catalyse slowly the hydrolysis of the esters but is practically insufficient to effect enolisation.
(b) Conversion of the desoxybenzoin (p-carboxybenzyl phenyl ketone) into its bromo ketone:

The desoxybenzoin is readily brominated in presence of a source of light energy of sufficient intensity to give the bromo ketone as follows:

\[ \text{Ph.CO.CH}_2\text{C}_6\text{H}_4\text{OCH} \xrightarrow{\text{Br}_2} \text{Ph.CO.CHBBr.C}_6\text{H}_4\text{OCH} \]

(c) Hydrolysis of the bromo ketone to 4'-methoxybenzoin:

The bromo ketone is hydrolysed by heating with water in dioxan as medium to form 4'-methoxy benzoin. (mp. 90° - 91°).

\[ \text{Ph.CO.CHBBr.C}_6\text{H}_4\text{OCH} \xrightarrow{\text{H}_2\text{O}} \text{Ph.CO.CH}_2\text{C}_6\text{H}_4\text{OCH} \]

A certain amount of the isomeric 4 methoxy benzoin is also formed as the liberated hydrobromic acid effects condensation to a certain extent.

\[ \text{Ph.CO.CH}_2\text{C}_6\text{H}_4\text{OCH} \xrightarrow{\text{HBr}} \text{Ph.} \xrightarrow{\text{OH}} \text{C} = \text{C.} \xrightarrow{\text{OH}} \text{C}_6\text{H}_4\text{OCH} \]

4'-methoxybenzoin

According to Jenkins (*J.A.C.S.*, 1924, *66*, 683) the bromo ketone in absolute ethanol reacts with three equivalents of sodium ethoxide in absolute ethanol to form the corresponding
acetal which is easily hydrolysed by cold dilute hydrochloric acid to the corresponding benzoic. The following scheme illustrates the course of these reactions (Ward, J.C.S., 1929, 1541).

\[ \text{R'.C} = \text{O} \xrightarrow{\text{Br}_2} \text{R'.C} = \text{Br} \xrightarrow{\text{EtOH}} \text{R'.C} = \text{O} \]

Ward (loc. cit.) found that \( \alpha \)-chlorobenzyl phenyl ketone reacts with sodium ethylate to form the corresponding acetal, which readily undergoes hydrolysis in presence of dilute hydrochloric acid and forms benzoic.

It may be mentioned here that Nuding and Schenker (Am., 1936, 92, 105, obtained 85% of benzoic methyl ether (m.p. 49°) by the action of sodium methoxide on \( \alpha \)-bromobenzyl phenyl ketone, a result which supports that obtained by the candidate but contradicts the results recorded by Jenkins and Ward.
That the compound now prepared by Jenkine's procedure was 4'-methoxybenzoin ethyl ether and not 4'-methoxybenzoin was suspected on the following grounds:

(i) It showed no indication of hydrogen phthalate formation.
(ii) It failed to react with 3:5 dinitrobenzoyl chloride.
(iii) It gave, on analysis, correct values for carbon and hydrogen as calculated for 4'-methoxybenzoin ethyl ether as shown in the experimental section.

**Attempted Resolution of 4'-methoxybenzoin:**

Equimolecular quantities of 4'-methoxybenzoin and pthalic anhydride were heated together in presence of pyridine and triethylamine for 40 minutes on a steam-bath, and then, after cooling and triturating with an equal volume of acetone, the reaction mixture was treated with dilute hydrochloric acid and excess of water was added when the hydrogen phthalic ester separated. It was filtered, dried and then recrystallised from methylene chloride and petroleum; it had mp. 157° - 158° alone and when mixed with an authentic specimen of 4-methoxybenzoin hydrogen phthalate. It would appear that heating, in presence of bases, converts 4'-methoxybenzoin into the more stable 4-methoxybenzoin which then reacts with pthalic anhydride.
This view was confirmed by showing that when authentic 4'-methoxybenzoin (mp. 90°-91°) was heated with pyridine and triethylamine on a steam-bath for 40 minutes and then liberated with dilute hydrochloric acid, the precipitated benzoin, after recrystallization from ethanol, had mp. 108°-109° alone and when mixed with authentic 4'-methoxybenzoin.

In this connection, it may be mentioned that the less stable 4'-methoxybenzoin, 4'-dimethylaminobenzoin and 4-chloro-4'-dimethylaminobenzoin are converted to their more stable isomerides, by treatment with ethanolic potassium hydroxide at room temperature for three days. (Jenkins, J.A.C.S., 1931, 53, 3115; 1933, 55, 3048; Luis, J.C.S., 1932, 2547).

It has been found that 4'-methoxybenzoin does not change to 4-methoxybenzoin on gentle warming with pyridine and triethylamine for 3-5 minutes. Accordingly, 4'-methoxybenzoin hydrogen phthalate was prepared from 4'-methoxybenzoin as follows:-

Phthalic anhydride was dissolved in boiling pyridine and the solution rapidly cooled to ensure small crystals. Calculated amounts of 4'-methoxybenzoin and triethylamine were added and the mixture gently warmed for 3-4 minutes. The resulting gummy mass was triturated with an equal volume of acetone and then treated with cold dilute hydrochloric acid followed by water when (1) 4'-methoxybenzoin hydrogen phthalate
separated. This, after recrystallisation from methylene chloride and petroleum, had m.p. 152° - 153°. When this acid ester was mixed with 4-methoxybenzoin hydrogen phthalate, (of m.p. 157° - 158°), the resulting mixture had m.p. 143° - 144°.

Non-formation of sulphone from 4'-methoxybenzoin:

It was found by Kenyon et al. (J.C.S., 1942, 607) that p-methoxybenzhydrol, a compound very prone to alkyl-oxygen fission, due to the presence of an electron repelling group (-OCH₃ group), readily forms a sulphone on treatment with sodium p-toluene sulphinate solution; in marked contrast, it was observed that 4'-methoxybenzoin, even though it contains an electron repelling group, showed no indication of sulphone formation with sodium p-toluene sulphinate solution.

Unfortunately all the attempts to obtain diastereoisomeric alkaloidal salts of 4'-methoxybenzoin hydrogen phthalate have so far been fruitless and hence no further work could be done. Nevertheless, during the preparation of 4'-methoxybenzoin and its hydrogen phthalate, some new results have been discovered, and new light thrown on the mechanism of the reactions.
CHAPTER VIII
Preparation and Attempted Resolution of Pivaloin (hexamethy lactone)

Preparation of Pivaloin:-

Starting from tert-butyl alcohol, pivaloin was prepared as follows:-

(1) Tert-butyl alcohol was converted to tert-butyl chloride by means of concentrated hydrochloric acid and tert-butyl magnesium chloride was carbonated and hydrolysed to give pivalic acid according to the method given in Organic Syntheses, Coll. Vol. I, p. 524. The reactions can be represented by the equations:

\[
\text{Me}_3\text{C}\cdot\text{MgCl} + \text{CO}_2 \rightarrow \text{Me}_3\text{C} - \text{C} = \text{O} \quad \text{OMgCl} \rightarrow \text{Me}_3\text{C} - \text{C} = \text{O} \quad \text{H}_2\text{O}
\]

Pivalic acid was then esterified in excellent yield by the following procedure.

A mixture of pivalic acid (1 mole) and ethyl alcohol (3 moles) was heated with methylene chloride (300 c.c.) and concentrated sulphuric acid (4.0 c.c.) under reflux for 16 hours and then allowed to cool. The solution of ethylpivalate in methylene chloride was separated, washed successively with water, sodium bicarbonate solution, water, dried over anhydrous calcium chloride and then fractionally
distilled to obtain ethylpivalate (B.P. 116°). This procedure is based on the method given in "Reactions of Organic Compounds" by Hickinbottom, 3rd Edition, 1957, p. 123 and first used by R.O. Clinton and S.C. Laskowski (J.A.C.S., 1948, 70, 3135), but the function of methylene chloride is not explained by the latter authors. The reason given by Hickinbottom is that the addition of a large excess of methylene chloride or some other liquid immiscible with water and sufficiently volatile to be separated by distillation from the ester helps the separation of the water formed during the esterification: however the candidate is inclined to believe that the presence of methylene chloride and concentrated sulphuric acid drives the reaction towards the formation of the ester by removing the resultant products (ester and water) from the field of reaction as the methylene chloride dissolves the ester and concentrated sulphuric acid absorbs the water formed.

Conversion of ethyl pivalate into pivaloin:

Ethyl pivalate undergoes bimolecular condensation in presence of sodium and on subsequent hydrolysis gives pivaloin (acyloin reaction)
Preparation of (+) Pivaloic hydrogen phthalate:

(+) Pivaloic hydrogen phthalate, prepared by heating equimolecular proportions of pivaloic and phthalic anhydride in presence of pyridine and triethylamine on steambath for 5 minutes, forms rhombic crystals, m.p. 130° – 131°. The details are given in the experimental section.

Attempts to obtain crystalline diastereoisomeric alkaloidal salts have unfortunately so far been fruitless and hence no further work could be done.
Phthalic anhydride (6.0 g) was dissolved in boiling dry pyridine (4 c.c.) and the solution rapidly cooled to ensure small crystals. Benzoin (8.4 g) was then added and the mixture well stirred for about 5-6 minutes. Triethylamine (4.8 c.c.) was then added and again the mixture was well stirred. The mixture becomes warm and mobile at first and then turned pasty after 3 minutes. The stirring was continued for 5-6 minutes after which the pasty mass was triturated with an almost equal volume of acetone and the resulting solution diluted with water. Sufficient sodium bicarbonate solution was then added to dissolve the hydrogen phthalate formed, and the solution filtered to remove small amounts of unreacted benzoin. The clear filtrate was added dropwise, with stirring, to the calculated amount of dilute hydrochloric acid mixed with ice. The precipitated hydrogen phthalate was removed by filtration, washed with ample water and dried on a porous plate. After drying, it weighed 14.0 g. and separated from methylene chloride and light petroleum (b.p. 40° - 60°)
in small clusters of microscopic needles, m.p. 154° - 156°.
Yield: 13.8 g. i.e. 95.7%.
0.3635 g. of the (+) hydrogen phthalate required
9.90 c.c. of 0.102N. NaOH, whence \( M, 360.\text{C}_{22}\text{H}_{16}\text{O}_{5} \) requires
\( M, 360. \)

(+) Hydrogen phthalic ester of Benzoin:

Quinidine (60.75 g) was warmed with methyl alcohol
(360 c.c.) and to the suspension the (+) hydrogen phthalate
of benzoin (67.5 g) was added. A clear solution was obtained
at first but the quinidine salt of the (+) hydrogen phthalate
(64.0 g) very rapidly separated. This crop, after
recrystallization from warm acetone (600 c.c.) and methyl
alcohol (5 c.c.) deposited the optically pure salt of the
(+) hydrogen phthalate in rosettes of needle shaped crystals
(63.4 g) m.p. 132° C. This salt suspended in about twice its
volume of acetone, was decomposed by addition of a small
excess of ice-cold dilute hydrochloric acid, and the
liberated (+) hydrogen phthalate precipitated by slow addition
of water. It was separated by filtration, washed with water,
dried and recrystallized from methylene chloride and light
petroleum (40° - 60°) from which it separates in bulky
clusters of short needles (32.7 g) m.p. 132° - 133° C.
Its rotatory powers are given in Table IV.

On rapid titration, using phenolphthalein as indicator, 0.349 g. of the (+) hydrogen phthalate required 9.70 c.c. of the 0.100N NaOH for neutralisation, whence $M,359.3$. $C_{22}H_{16}O_5$ requires $M,360$.

(-) Hydrogen Phthalic Ester of Benzoin:

The filtrate removed from the quinidine salt of the (+) hydrogen phthalate was decomposed with ice-cold dilute hydrochloric acid and the (-) hydrogen phthalate precipitated by addition of water. The (-) hydrogen phthalate was more soluble in methylene chloride than (+) hydrogen phthalate and hence the (-) hydrogen phthalate was obtained in optically pure condition in bulky clusters of short needles (32.95 g) melting at 132° - 133°C by fractional crystallization from methylene chloride and light petroleum (40° - 60°C). It had $[\alpha]_{25}^{D} = 140.00$ (1, 1; c, 2.50 in acetone).

On rapid titration, using phenolphthalein as indicator, 0.345 g. of the (-) hydrogen phthalate required 9.60 c.c. of 0.100N NaOH for neutralisation, whence $M,359.3$. $C_{22}H_{16}O_5$ required $M,360$. 
(+) Benzoin:

Optically pure (+) hydrogen phthalate of benzoin (7.2 g) was dissolved in 95% ethanol (200 c.c.) and I.N. H₂SO₄ (40 c.c.) added. The mixture was heated at 68° - 78° for 24 hours and then water (40 c.c.) added. The heating was continued for 100 hours more and then most of the alcohol was distilled off after adding water (160 c.c.). The solution was allowed to cool and some fragments of ice were added. Next day the precipitate was filtered, triturated with an almost equal volume of ethanol and then 5% NaHCO₃ solution added till slightly alkaline to methyl orange to dissolve any unhydrolysed hydrogen phthalate. The solution was thoroughly stirred, diluted, filtered after two hours and washed with sufficient water. The (+) benzoin thus obtained was partially dried and then recrystallized from 95% alcohol from which it separated in fine colourless needles (2.2 g), mp. 132° - 133°C. Yield: 51.9%. It had [α]²⁵° + 118.4° D (1, 1; C 2.50; in acetone) Wren (J.C.S. 1909, 95, 1583) records [α]¹¹° + 120.5° (1, 4; C 0.412; in acetone) and mp. 131-132.5° Hopper and Wilson (J.C.S. 1928, 2483) record [α]¹¹° + 118.3° D (1, 4; C 1.258; in acetone) and mp. 133-134°. Its rotatory
powers in different solvents at various wavelengths are given in Table V. (Found: C, 79.94; H, 5.64 calculated for C_{14}H_{12}O_2.
C, 79.23; H, 5.69%).

(−) Benzoin:

The optically pure (−) hydrogen phthalate (3.6 g) was hydrolysed in an exactly similar fashion. The liberated (−) benzoin separated from alcohol in fine colourless needles (1.06 g. i.e. 50% yield) mp. 132° - 133°. It had [α]_{D}^{25°} -118.3° (1, 1; C, 2.40 in acetone).

McKenzie and Wren (J.C.S. 1908, 23, 309) record mp. 131° - 132.5° and [α]_{D}^{10.5} -118.6° (1, 4; C, 0.9232 in acetone). Hopper and Wilson (loc. cit.) record mp. 133° - 134° and [α]_{D}^{11°} -118.5° (1, 4; C, 1.1467 in acetone).
Specific rotatory powers $[\alpha]_\lambda$, of (+) Hydrogen Phthalate of Benzoin at 25° - 26° (1,1).

**TABLE IV**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>C</th>
<th>$[\alpha]_{5893}$</th>
<th>$[\alpha]_{5461}$</th>
<th>$[\alpha]_{5086}$</th>
<th>$[\alpha]_{4358}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylene chloride.</td>
<td>2.50</td>
<td>+187°</td>
<td>+229.6°</td>
<td>+290°</td>
<td>+489.6°</td>
</tr>
<tr>
<td>Pyridine</td>
<td>2.00</td>
<td>176.5</td>
<td>213.5</td>
<td>272</td>
<td>460</td>
</tr>
<tr>
<td>Glacial acetic acid.</td>
<td>2.365</td>
<td>169</td>
<td>206</td>
<td>259</td>
<td>439</td>
</tr>
<tr>
<td>Chloroform</td>
<td>2.50</td>
<td>166</td>
<td>204</td>
<td>257</td>
<td>436</td>
</tr>
<tr>
<td>Acetone</td>
<td>2.54</td>
<td>140.2</td>
<td>175</td>
<td>216.6</td>
<td>375</td>
</tr>
<tr>
<td>99% Ethanol</td>
<td>2.52</td>
<td>140</td>
<td>172.6</td>
<td>215</td>
<td>370</td>
</tr>
</tbody>
</table>

The (+) benzoin hydrogen phthalate was too sparingly soluble in benzene and carbon disulphide to allow of accurate polarimetric determinations.
(1) Hydrogen Phthalate of Benzoin from its optical antipodes:

Optically pure (+) and (-) hydrogen phthalates of benzoin (0.15 g each, mp. 132° - 133°) were dissolved in methylene chloride and light petroleum added 40° - 60°. The solution deposited bulky clusters of short needles which had mp. 154° - 156°, and $[\alpha]^{25}_{D} = 0.0$° (l, 1; C, 2.50 in acetone)

(2) Benzoin from its optical antipodes:

Optically pure (+) and (-) benzoins (0.15 g each, mp. 132° - 133°) were dissolved in ethanol and allowed to crystallize; fine colourless needles separated, mp. 133° - 134° and $[\alpha]^{25}_{D} = 0.0$° (l, 1; C, 2.50 in acetone)
A solution of (+) Benzoin in freshly distilled pyridine suffered no loss in rotatory power even after keeping for 7 days at room temperature, while the rotatory power of a solution of (+) Benzoin hydrogen phthalate in pyridine gradually diminished on keeping as shown in Table VI. The rate of decrease was rapid at first and then gradually diminished with time.
Characteristic Diagram for Benzoin
Scheme for the Resolution of (±) Pyronen Phthalate of Benzoic:

\[ \text{(+)} \text{ Benzoic HNP} \quad \{67.59 \} \quad \{60.75\} \] in \( \text{HClOH} (360 \text{ c.c.}) \)

\[ \text{A (64.0 g)} \quad \text{mp. 131}^\circ \text{C} \]
\[ \text{Acetone (600 c.c.)} \quad \text{HClOH (5 c.c.)} \]

\[ \text{Decomposed with ice + dilute HCl.} \]

\[ \text{B (63.4 g)} \quad \text{mp. 132}^\circ \text{C} \]

\[ \text{Decomposed with ice + dilute HCl.} \]

\[ \text{(+)} \text{ HNP (32.7 g)} \quad \text{mp. 132}^\circ \text{C - 133}^\circ \text{C} \]
\[ \text{[\(\alpha\)]_{D}^{25^\circ} = 150^\circ} \]
\[ \text{(+)} \text{ HNP (1.2 g)} \quad \text{mp. 131}^\circ \text{C} \]
\[ \text{[\(\alpha\)]_{D}^{25^\circ} + 110^\circ} \]

\[ \text{(-)} \text{ HNP (33.5 g).} \]

Re crystallized twice from ethylene chloride and light petroleum (40-60°C) to get optically pure

\[ \text{(-)} \text{ HNP (32.95 g)} \quad \text{mp. 132}^\circ \text{C - 133}^\circ \text{C.} \]

\[ \text{[\(\alpha\)]_{D}^{25^\circ} = 140^\circ} \]

\[ \text{(+)} \text{ HNP; c, 2.50 in acetone) \quad \text{(1, 1; c, 2.50 in acetone) } \]
\[ \text{(-)} \text{ HNP; c, 2.50 in acetone) } \]
# TABLE VI

Loss in rotatory power of a solution of (+) benzoic hydrogen phthalate in freshly distilled pyridine at room temperature (25° - 26°) \( [\alpha]_{5893} \) (1, 1, C, 2, 00)

<table>
<thead>
<tr>
<th>TIME (hours)</th>
<th>( [\alpha]_{5893} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>176.5</td>
</tr>
<tr>
<td>25</td>
<td>152</td>
</tr>
<tr>
<td>35</td>
<td>136.5</td>
</tr>
<tr>
<td>50</td>
<td>107.5</td>
</tr>
<tr>
<td>122</td>
<td>64</td>
</tr>
<tr>
<td>170</td>
<td>46.5</td>
</tr>
<tr>
<td>216</td>
<td>36</td>
</tr>
<tr>
<td>298</td>
<td>27</td>
</tr>
<tr>
<td>319</td>
<td>24</td>
</tr>
<tr>
<td>325</td>
<td>22.5</td>
</tr>
<tr>
<td>333</td>
<td>19</td>
</tr>
<tr>
<td>484</td>
<td>17.5</td>
</tr>
<tr>
<td>529</td>
<td>16.5</td>
</tr>
<tr>
<td>638</td>
<td>15</td>
</tr>
</tbody>
</table>

The solution was too yellow after 648 hrs. to allow of further accurate polarimetric readings.
Benzil from (±) and (-) Benzoic

Instead of using the old nitric acid method, benzil was prepared from (±) and (-) benzoic by copper sulphate - pyridine method given in organic syntheses, VI, 6 (1926).

A mixture of copper sulphate, (2.05 g) pyridine (2.0 g) and water (1 c.c.) was heated in a flask fitted with a reflux condenser on a steam-bath with stirring until solution was complete and then (±) benzoic (0.9 g) was added. Heating and stirring was continued for 2 hours. The reaction mixture became dark green in colour and the molten benzil formed the upper layer. After cooling, the copper sulphate - pyridine solution was decanted and the benzil washed with water and then heated with 2 c.c. of 10% hydrochloric acid. After cooling, the benzil was filtered, washed with water, dried and recrystallized from carbon tetrachloride; yellow needles, m.p. 94°- 95° (0.85 g. i.e. 75% yield). Its solution in acetone was optically inactive and it showed negative Fehling's test.

The method is based on the observation of E. Fischer (Ann. 1882, 211, 214 (foot-note) that benzoic reduces Fehling's solution in the cold. Recrystallized benzil obtained by copper sulphate - pyridine method gives negative Fehling's test; while that obtained by the nitric acid method
gives a positive Fehling's test. By the nitric acid oxidation it is difficult to obtain a product free from benzenoid. The yield by the nitric acid method is generally about 90-95%, whereas with the copper sulphate–pyridine method the yield falls to approximately 75-85%.

Pyridine is selected in the above method as it prevents the precipitation of cuprous oxide, is not so volatile as ammonia and acts as a partial solvent for the benzenoid.

Benzoil, similarly obtained from the (-) benzenoid, was optically inactive.

Experiments on the hydrolysis of the hydrogen phthalate of benzenoid:

Preliminary experiments were made to ascertain the mildest conditions under which benzenoid hydrogen phthalate would undergo hydrolysis at a reasonable rate. Details are as follows:

(1) (±) Hydrogen phthalate of benzoil (1.0 g) was warmed with 10 c.c. of 80% HNO₃ and on allowing the solution to stand for several days, it deposited crystals of unchanged hydrogen phthalate.

(1) (±) Hydrogen phthalate of benzoil (2.33 g) was dissolved in 25% alcohol (120 c.c.) and IN H₂SO₄ (10 c.c.) added. The solution was kept in a corked flask for one month. After one
month, the solution was made almost neutral to methyl orange by adding sodium bicarbonate solution dropwise. Most of the ethanol was distilled off. On allowing the solution to cool, it deposited clusters of fine needles which were triturated with an equal volume of ethanol and then sodium bicarbonate solution was added till alkaline. The clear solution deposited crystals of unchanged hydrogen phthalate after acidification with ice-cold dilute hydrochloric acid.

When the above experiment was repeated with optically active hydrogen phthalate, the recovered hydrogen phthalate possessed its original optical rotation. This shows that active hydrogen phthalate is not racemised in presence of dilute $\text{H}_2\text{SO}_4$.

(iii) (†) Hydrogen phthalate of benzoin (0.720 g) in 95% ethanol (30.0 c.c.) was taken in a 50 c.c. flask fitted with a water condenser and heated with 10 c.c. of 0.5N NaOH solution on a steambath for one hour. The solution was then diluted with water and the precipitated crystals were filtered after two hours, washed with water and dried. The crystals were identified as benzoin, mp. 133°-134° alone and when mixed with an authentic specimen.

The above experiment was then repeated with an optically active hydrogen phthalate of benzoin, but the recovered benzoin
was optically inactive in acetone solution.

It may be recalled at this stage that McKenzie and Wren (loc. cit.) noticed that 1-benzoic undergoes rapid racemisation in alcoholic alkaline solution through tautomeration to the enediol Ph. C \( \text{C(OH)} = C(\text{OH}) \text{ Ph.} 

(iv) \((\ddagger)\) Hydrogen phthalate \((1.5 \text{ g})\) in 25\% ethanol \((25.0 \text{ c.c.})\) was heated with oxalic acid \((15 \text{ g})\) in 15 c.c. water for two hours on a steam bath, but the hydrogen phthalate was not hydrolysed to any appreciable extent.

(v) It was found that \((\ddagger)\) hydrogen phthalate of benzoin was slowly hydrolysed by sodium bicarbonate solution at room temperature and rapidly on heating. On repeating this experiment with optically active hydrogen phthalate, it was found that the benzoin obtained was partially racemised when the hydrolysis was carried out at room temperature and highly racemised when the hydrolysis was allowed to occur at higher temperatures as shown below.

hydrolysis of \((+)\) benzoin hydrogen phthalate with 5\% sodium bicarbonate solution at room temperature:

\[(+)\text{ Benzoin hydrogen phthalate} \ (1.5 \text{ g}) \ 
\left[ \alpha \right]_{D}^{25\circ} + 136.0^\circ
\]

\((1,1; c, 2.5 \text{ in acetone})\) was dissolved in 5\% sodium bicarbonate solution \((25. \text{ c.c.})\) and the solution allowed to
stand at room temperature. After 112 hrs, 0.450 g of benzoin of $[\alpha]_{D}^{25^\circ} + 85.5^\circ$ (1, 2, 0, 4.0 in acetone) and mp. 118$^\circ$ - 121$^\circ$

had separated. After removing this the filtrate was allowed to stand for 4.8 hrs. when a second crop of benzoin (0.150 g) was obtained. It had $[\alpha]_{D}^{25^\circ} + 53^\circ$ (1, 1; 0, 1.5 in acetone) and mp. 115$^\circ$ - 130$^\circ$. After removing the second crop, the filtrate was allowed to stand for 76 hrs, then a third crop of benzoin (0.080 g) was obtained. It had $[\alpha]_{D}^{25^\circ} + 34^\circ$

(1, 1; 0, 0.8 in acetone) and mp. 125$^\circ$ - 132$^\circ$. After removing the third crop, the filtrate was allowed to stand for 76 hrs. when a fourth crop of benzoin (0.010 g) was obtained. The mother liquor was then heated for half an hour on steam bath but no more benzoin separated. This stepwise hydrolysis can be summarised as shown on the next page.
(+)-Benzoin hydrogen phthalate (1.5 g) \([\alpha]^{25}_D = 136.8^0\) 
(1, 1; C, 2.5 in acetone) + 25 c.c. 5N sodium bicarbonate solution at room temperature.

**After 112 hrs.**

Benzoin (1st crop, 0.450 g. 
mp. 1180 - 1210) 
\([\alpha]^{25}_D + 85.5^0(1,2; C, 4.00 in acetone)\)

**After 48 hrs.**

Benzoin (2nd crop, 0.180 g. 
mp. 1150 - 1300)  
\([\alpha]^{25}_D + 53^0(1,1; C, 1.50 in acetone)\)

**After 76 hrs.**

Benzoin (3rd crop, 0.080 g. 
mp. 1250 - 1320)  
\([\alpha]^{25}_D + 34 (1,1; C, 0.00 in acetone)\)

**After 76 hrs.**

Benzoin (0.010 g)  
mp. 1300 - 1320.  
Heated on steambath for half an hour, but no more benzoin separated.
Hydrolysis of (+)-Benzoin hydrogen phthalate with 5% sodium bicarbonate solution by heating on steam bath.

(+)-Benzoin hydrogen phthalate (1.0 g) \([\alpha]^{25}_D + 136.0^\circ\) (1,1, C, 2.5 in acetone) was dissolved in 17 c.c. 5% sodium bicarbonate solution and the solution was heated under reflux on a steam bath for 15 minutes, cooled under tap water and the separated benzoin (0.900 g; mp. 133\(^\circ\) - 125\(^\circ\)) was removed. It had \([\alpha]^{25}_D + 60^\circ (1,1, C, 1.00 \text{ in acetone}).\) After removing the first crop, the filtrate was again heated under reflux on the steam bath for 15 minutes, cooled and the separated benzoin (0.130 g, mp. 127\(^\circ\)-133\(^\circ\)) was removed. It had \([\alpha]^{25}_D + 37^\circ (1,1; C, 1.04 \text{ in acetone}).\) After removing the second crop, the filtrate was again heated under reflux on steam bath for 30 minutes, allowed to cool at room temperature for an hour and the separated benzoin (0.120 g, mp. 133-134\(^\circ\) alone and when mixed with an authentic sample of (+) benzoin) removed. It had \([\alpha]^{25}_D + 0.0 (1,1; C, 1.05 \text{ in acetone}).\) The mother liquor gave a negligible amount of benzoin on further heating. The stepwise hydrolysis can be summarised as shown on the next page.
(+) Bensoin hydrogen phthalate (1.0 g.) having \([\alpha]^{250}_D\) + 136.0° (1.1 C, 2.5 in acetone) + 17 c.c. 5% sodium bicarbonate solution.

Heated on steam bath for 15 minutes and then cooled.

\[
\text{Benzoin(0.290 g., mp. 123 - 125\(^\circ\))}
\]

\([\alpha]^{250}_D + 60^\circ (1,1; C, 1.00 \text{ in acetone})\]

Heated on steam bath for 15 minutes and then cooled.

\[
\text{Benzoin(0.130 g., mp. 127 - 133\(^\circ\))}
\]

\([\alpha]^{250}_D + 37^\circ (1,1; C, 1.00 \text{ in acetone})\]

Heated on steam bath for 30 minutes and cooled at room temp. for an hour.

\[
\text{(2) Benzoin(0.120 g., mp. 133 - 135\(^\circ\))}
\]

\([\alpha]^{250}_D + 0.0^\circ (1,1; C, 1.00 \text{ in acetone})\]

(gave negligible amount of benzoin on further heating).
(1) Hydrogen succinate of Benzoin

Succinic anhydride (4.0 g.) was dissolved in boiling dry pyridine (4 c.c.) and the solution rapidly cooled. Benzoin (8.4 g.) was then added and the mixture was well stirred for five minutes. Triethylamine (4.8 c.c.) was then added and again the mixture was well stirred for five minutes. The mixture became warm and mobile at first and then turned pasty after some time. The pasty mass was triturated with almost equal volume of acetone and diluted with water. Sufficient sodium bicarbonate solution was added to dissolve the hydrogen succinate formed and the solution was filtered to remove any unreacted benzoin. The filtrate was added dropwise with stirring to the calculated amount of dilute hydrochloric acid mixed with ice. The precipitated hydrogen succinate of benzoin was filtered, washed with ample water and then dried. After drying, it weighed 12.0 g., mp. 79°. It separated from carbon disulphide in small needles (11.9 g.) mp. 84° - 85°.

On rapid titration, using phenolphthalein as indicator 0.3056 g. of the (2) hydrogen succinate of benzoin required 9.2 c.c. of 0.10CN. Nalk solution for complete neutralisation, whence \( n = 311.7 \). \( C_{18}H_{16}O_5 \) requires \( n = 312 \).
Attempts to prepare alkaloidal salts of the hydrogen succinate and the hydrogen phthalate of benzoin:

(1) The solution of (I) hydrogen succinate of benzoin (0.624 g.) and cinchonidine (0.566 g.) in acetone did not give any crystalline salt even after allowing the solution to stand for several days and by trying with various solvents like benzene, ethyl acetate, methyl alcohol etc.

(II) The solution of (II) hydrogen succinate (0.624 g.) and cinchonine (0.566 g.) in acetone gave a gummy mass after three days and showed no signs of crystal formation on trying with various solvents.

(iii) Attempts to get a crystalline quinine salt from the solution of hydrogen succinate (0.624 g.) and quinine (0.643 g.) in acetone after several days proved to be fruitless.

(iv) The above experiment was repeated with 0.643 g. of quinidine, but the same negative result was obtained.

(v) Attempts to obtain a crystalline brucine salt from the solution of the hydrogen succinate (0.624 g.) and brucine (0.783 g.) in acetone were also unsuccessful.

(vi) Attempts were also made to obtain crystalline brucine, quinine, cinchonine and cinchonidine salts of the (I) hydrogen phthalate of benzoin as described above, but they also proved to be fruitless.
CHAPTER X:

Preparation and Resolution of 4-methoxy benzoin

(A) By the Benzoin Condensation:

To a solution of potassium cyanide (50 g.) in water (300 c.c.) in a two-litre flask fitted with a reflux condenser was added 4-methoxy benzaldehyde (272 g.) benzaldehyde (212 g.) and 95% ethanol (700 c.c.). The mixture formed a homogeneous solution at the boiling temperature and was refluxed for two hours. Steam was then passed through the solution until all the ethanol and nearly all the unchanged aldehydes were removed. The condensed water was decanted from the oily residue which solidified after keeping in a refrigerator for several days. The solid was pressed as free as possible from oily material on a suction funnel, washed with cold ethanol and dried. In this way about 252 g. (52% yield) of crude product was obtained. The crude material was recrystallized from hot ethanol giving pure 4-methoxy benzoin in rosettes of long needles, mp. 108°-109° (124 g. 25% yield).

(B) By the "Reversion" Procedure:

To a solution of benzoin (mp. 133°-134°, 21.2 g) and
4-methoxy benzaldehyde (27.2 g, 2 mols) in hot 95% ethanol (100 c.c.) in a 250 c.c. flask was added a solution of potassium cyanide (13 g.) in water (25 c.c.). The mixture was heated under reflux for two hours, during which time, water (15 c.c.) was added to keep most of the potassium cyanide in solution. Steam was then passed through the solution until all the ethanol and nearly all the aldehydes were removed. The condensed water was then decanted from the oily product which solidified after keeping in a refrigerator for several days. The solid was pressed as free as possible from the oily product on a suction funnel, washed with cold ethanol and dried (24 g; 49.5% yield). The crude product was recrystallized from hot ethanol giving pure 4-methoxy benzoin in rosettes of long needles mp. 108° - 109° (11.3 g, 24% yield).

The ethanol washings from the above experiments yielded some more (5.0 g) 4-methoxy benzoin on refluxing with more potassium cyanide solution and on keeping the resulting solution in a refrigerator for several days.

Equal amounts of pure 4-methoxy benzoin prepared by the benzoin condensation and by the reversal procedure were intimately mixed; the resulting mixture had mp. 108° - 109°. The mp. of 4-methoxy benzoin as recorded in "Organic Reactions" IV, 280, is 106°.
(1) Hydrogen phthalic Ester of 4-methoxy benzoin:

Phthalic anhydride (37.0 g.) was dissolved in boiling dry pyridine (20 c.c.) and the solution rapidly cooled to ensure small crystals. Triethylamine (25 c.c.) and 4-methoxybenzoin (60.5 g.) were added and the mixture heated for about 20 minutes on a water bath. The reaction mixture was then allowed to cool and then triturated with an almost equal volume of acetone. The resulting solution was diluted with water. Sufficient sodium bicarbonate solution was then added to dissolve the hydrogen phthalate formed and the solution filtered to remove small amount of unreacted 4-methoxy benzoin. The clear filtrate was added dropwise, with stirring, to the calculated amount of dilute hydrochloric acid mixed with ice. The precipitated hydrogen phthalate was removed by filtration, washed with ample water and dried on a porous plate. After drying, it weighed 95.0 g. and separated from acetone in large colourless rhombic crystals, mp. 158°-159°, yield 35.0 g. The second crop which separated from aqueous acetone in yellowish microscopic rhombs yielded 52.0 g. of colourless hydrogen phthalate (mp. 158-159) after recrystallization from methylene chloride and light petroleum (bp. 40°- 60°) Total yield: 87.0 g. i.e. 89.2%.
0.390 g. of the (+) hydrogen phthalate required 9.8 c.c. of 0.102 N. NaOH; whence M, 390.2. C₂₃H₄₈O₆ requires M, 390.0.

(+) Hydrogen phthalic Ester of 4 methoxy benzoin:

Quinidine (32.4 g.) was warmed with methyl alcohol (150 c.c.) and to the suspension (+) hydrogen phthalate of 4 methoxy benzoin (38.6) dissolved in methyl alcohol (100 c.c.) added. A clear solution was obtained at first but the quinidine salt of the (+) hydrogen phthalate (40.8 g.) very rapidly separated. This crop, after recrystallization from warm acetone (100 c.c.) and methyl alcohol (10 c.c.) deposited the optically pure salt of the (+) hydrogen phthalate in clusters of small microscopic needles (total yield: 32.0 g.) mp. 119-120. This salt suspended in about twice its volume of acetone, was decomposed by addition of a small excess of ice-cold dilute hydrochloric acid, and the liberated (+) hydrogen phthalate precipitated by slow addition of water. It was separated by filtration, washed with water, dried and recrystallized from methylene chloride and petroleum in clusters of short needles (15.9 g.) mp. 88°C. The melting point and optical rotation were unchanged after recrystallization. Its rotatory powers are given in Table VII.

On rapid titration, using phenolphthalein as indicator
0.398 g. of the (+) hydrogen phthalate required 10.20 c.c.
of 0.100 N. NaOH for neutralisation, whence M, 390.2.
C$_{23}$H$_{18}$O$_6$ requires M, 390.0.

(–) Hydrogen phthalic Ester of 4 methoxy benzoin:–

The filtrate, removed from the quinidine salt of the
(+)-hydrogen phthalate, was decomposed with ice-cold dilute
hydrochloric acid and the (–)-hydrogen phthalate precipitated
by addition of water. The slightly impure (–)-hydrogen
phthalate was so highly soluble in common organic solvents
like acetone, ethyl acetate, chloroform, methylene chloride
etc., that it was very difficult to crystallize it from these
solvents. Hence it was obtained in an optically pure form
by a method given in Section 1, p. 59. It had [α]$_{D}^{25}$ = 111.2
(1, 1; C, 2.50 in acetone).

On rapid titration, using phenolphthalein as indicator
0.406 g. of the (–)-hydrogen phthalate required 10.40 c.c. of
0.100 N. NaOH for neutralization, whence M, 390.3.
C$_{23}$H$_{18}$O$_6$ requires M, 390.0.

(+) 4 methoxy benzoin:–

Optically pure (+)-hydrogen phthalate of 4-methoxy
benzoin (7.8 g.) was dissolved in 95% ethanol (200 c.c.) and
1 N. H$_2$SO$_4$ (40 c.c.) added. The mixture was heated at about
70°C for 125 hours and then most of the alcohol was distilled off after adding water (200 c.c.) in portions. The solution was then allowed to cool and some fragments of ice added.

Next day the precipitated mass was removed, triturated with an almost equal volume of ethanol and then ice-cold dilute NaHCO₃ solution added till slightly alkaline to methyl orange to dissolve any unhydrolysed hydrogen phthalate. The solution was thoroughly stirred, diluted, filtered after two hours and the precipitate washed thoroughly with water. The (+) 4 methoxy benzoin thus obtained was partially dried and then recrystallized from 95% ethanol from which it separated in colourless prisms (2.4 g.) mp. 102°-103°. Yield: 49.6%. It had $[\alpha]_{D}^{25^\circ} + 72$ (1.1; C, 1.00 in acetone).

Its rotatory powers in different solvents for light of different wavelengths are given in Table VIII.

(-) 4 methoxy benzoin:

The optically pure (-) hydrogen phthalate of 4 methoxy benzoin (3.9 g.) was hydrolysed in an exactly similar manner. The liberated (-) 4 methoxy benzoin separated from alcohol in colourless prisms (1.1 g.), mp. 102°-103° 49% yield. It had $[\alpha]_{D}^{25^\circ} -71.8^\circ$ (1.1; C, 1.00 in acetone).

McKenzie and Kelman who synthesized 4-methoxybenzoin by the interaction of (+) mandelonitrile with anisylmagnesium bromide,
(J.C.S., 1934, 412) record mp. 102.5°-103.5° and \([\alpha]^{200}_{5461}\) -76.5° (1, 2; C, 1.0005 in acetone), \([\alpha]^{200}_{5461}\) -90° (1,2; C, 1.0055 in ethanol). The values obtained by the candidate for \(\mathcal{H}_{\text{g}}\) green light were as follows: - \([\alpha]^{250}_{5461}\) - 83° (1,1; C, 1.00 in acetone) \([\alpha]^{250}_{5461}\) - 99° (1, 1; C, 1.00 in ethanol).
**TABLE VII**

Specific rotatory powers of (+) Hydrogen Phthalate of 4-methoxybenzoin \( \alpha \) at 25 - 260

<table>
<thead>
<tr>
<th>Solvent</th>
<th>( \alpha )</th>
<th>5893</th>
<th>5461</th>
<th>5006</th>
<th>4358</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylene chloride</td>
<td>2.54</td>
<td>+152(^\circ)</td>
<td>+150.3(^\circ)</td>
<td>+222.4(^\circ)</td>
<td>+347.3(^\circ)</td>
</tr>
<tr>
<td>Pyridine</td>
<td>2.45</td>
<td>+137.1(^\circ)</td>
<td>+164.1(^\circ)</td>
<td>+200 (^\circ)</td>
<td>+320 (^\circ)</td>
</tr>
<tr>
<td>Glacial acetic acid</td>
<td>2.50</td>
<td>+136 (^\circ)</td>
<td>+164 (^\circ)</td>
<td>+199.6 (^\circ)</td>
<td>+318 (^\circ)</td>
</tr>
<tr>
<td>Chloroform</td>
<td>2.54</td>
<td>+132.0 (^\circ)</td>
<td>+159.9 (^\circ)</td>
<td>+192.2 (^\circ)</td>
<td>+309.3 (^\circ)</td>
</tr>
<tr>
<td>Acetone</td>
<td>2.55</td>
<td>+111.8 (^\circ)</td>
<td>+139.6 (^\circ)</td>
<td>+163.1 (^\circ)</td>
<td>+275.0 (^\circ)</td>
</tr>
<tr>
<td>99% Alcohol (Ethanol)</td>
<td>2.51</td>
<td>+110.4 (^\circ)</td>
<td>+137.4 (^\circ)</td>
<td>+162.9 (^\circ)</td>
<td>+273.0 (^\circ)</td>
</tr>
</tbody>
</table>

The (+) hydrogen phthalate of 4-methoxy benzoin was too sparingly soluble in benzene and carbon disulphide to allow of accurate polarimetric determination.
### TABLE VIII

Specific Rotatory Powers $[\alpha]_{\lambda}$ of (+) 4-methoxy benzoin at 250° - 260°

<table>
<thead>
<tr>
<th>Solvent</th>
<th>0</th>
<th>$[\alpha]_{5893}$</th>
<th>$[\alpha]_{5461}$</th>
<th>$[\alpha]_{5000}$</th>
<th>$[\alpha]_{4358}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glacial acetic acid</td>
<td>1.00</td>
<td>+173°</td>
<td>+200°</td>
<td>+300°</td>
<td>+520°</td>
</tr>
<tr>
<td>Methylene chloride</td>
<td>1.00</td>
<td>+136</td>
<td>+163</td>
<td>+235</td>
<td>+392</td>
</tr>
<tr>
<td>Chloroform</td>
<td>1.00</td>
<td>+124</td>
<td>+150</td>
<td>+216</td>
<td>+350</td>
</tr>
<tr>
<td>Absolute alcohol</td>
<td>1.00</td>
<td>+80</td>
<td>+101</td>
<td>+142</td>
<td>+217</td>
</tr>
<tr>
<td>Acetone</td>
<td>1.00</td>
<td>+72</td>
<td>+85</td>
<td>+120</td>
<td>+168</td>
</tr>
<tr>
<td>Pyridine</td>
<td>1.00</td>
<td>+60</td>
<td>+72</td>
<td>+100</td>
<td>+136</td>
</tr>
</tbody>
</table>

A solution of (+) 4-methoxy benzoin in freshly distilled pyridine suffered no loss in rotatory power after keeping for 7 days at room temperature but its hydrogen phthalate in the same solvent gradually suffered loss in rotatory power.
Characteristic Diagram for
4-methoxy benzoin
The rotatory power of a solution of the (+) Hydrogen Pthalate of 4-methoxy-benzoic in pyridine gradually diminished on keeping as shown in Table IX. The sample had \( \alpha_{5893}^{25^\circ} = 137.1^\circ \) (1, 1; 1, 2, 4, 9) in the beginning.

<table>
<thead>
<tr>
<th>Time (hrs.)</th>
<th>( \alpha_{5893}^{25^\circ} )</th>
<th>Time (hrs.)</th>
<th>( \alpha_{5893}^{25^\circ} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>137.1^\circ</td>
<td>424</td>
<td>56.72^\circ</td>
</tr>
<tr>
<td>1, 25</td>
<td>134.7^\circ</td>
<td>473</td>
<td>48.16^\circ</td>
</tr>
<tr>
<td>15, 25</td>
<td>129.0^\circ</td>
<td>500</td>
<td>46.13^\circ</td>
</tr>
<tr>
<td>23, 25</td>
<td>127.0^\circ</td>
<td>520</td>
<td>44.42^\circ</td>
</tr>
<tr>
<td>44</td>
<td>119.2^\circ</td>
<td>600</td>
<td>32.99^\circ</td>
</tr>
<tr>
<td>119</td>
<td>100.0^\circ</td>
<td>630</td>
<td>28.77^\circ</td>
</tr>
<tr>
<td>183</td>
<td>85.7^\circ</td>
<td>707</td>
<td>33.47^\circ</td>
</tr>
<tr>
<td>210</td>
<td>60.41^\circ</td>
<td>1000</td>
<td>23.57^\circ</td>
</tr>
<tr>
<td>254</td>
<td>72.61^\circ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>326</td>
<td>63.66^\circ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>356</td>
<td>59.99^\circ</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The solution was too yellow after 1000 hours to allow of further accurate polarimetric readings.
(†) Hydrogen phthalate of 4 methoxy benzoin from its optical antipodes.

Optically pure (+) and (−) hydrogen phthalates of 4 methoxy benzoin (0.159 each, mp. 63°0) were dissolved in methylene chloride and a few drops of light petroleum added. The solution deposited crystals in the form of small needles, which had mp. 155° – 157° and $[\alpha]_{D}^{25^0} = 0.0^0 (1, 1; C, 2.50$ in acetone).

(†) 4 methoxy benzoin from its optical antipodes:

Optically pure (+) and (−) 4 methoxy benzoin (0.1 g each, mp. 103° – 105°) were dissolved in ethanol. The solution deposited fine colourless needles, mp. 106° and $[\alpha]_{D}^{25^0} = 0.0^0 (1, 1; C, 1.20$ in acetone.)
Scheme for the Resolution of (†) Hydrogen Phthalate of 4-methoxybenzoin

---

**Extraction of (+) Hydrogen Phthalate of 4-methoxybenzoin**

(+) 4-methoxybenzoin

HPh (32.0 g.) in MeOH (250 c.c.)

Quinidine

HPh (32.4 g.)

---

1. **A** (40.3 g.)
   
   m.p. 110 - 120°

   Filt. ice + dil HCl.

   Acetone (100 c.c.)

   HPh (10 c.c.)

   m.p. 137 - 147°

   and

   2. **A** (32.0 g.)
   
   m.p. 119 - 120°

   Filt.

   [α]₂⁵° = -72.8°

   (1; C, 2.5 in acetone after purification as described on p. 59) m.p. 68°

   and

   3. **B** (2.4 g.)
   
   m.p. 119 - 120°

   Filt. dec.

   [α]₂⁵° = 1.0°

   (1; C, 2.5 in acetone)

   D

   and

   4. **B** (2.1 g.)
   
   m.p. 150°

   (+) HPh 15.99 g., m.p. 200°, [α]₂⁵° = 111.6° D

   (1,1; C, 2.55 in acetone)

   E

---

Crystals

D' tartrate (dil. HCl)

(+1) HPh 1.09 g., m.p. 200°, [α]₂⁵° = +111.6° D

(1,1; C, 2.50 in acetone)
Preparation and Resolution of 4-dimethylaminobenzoin:

Preparation of 4-dimethylamino benzoin:

(1) Benzoin Condensation Method:

A solution of 4-dimethylaminobenzaldehyde (150 g., 1 mole) and benzaldehyde (106 g., 1 mole) in 95% ethanol (400 c.c.) was heated under reflux for two and a half hours after mixing with a solution of potassium cyanide (55 g.) in water (225 c.c.) 4-dimethylaminobenzoin which separated in fine needles as the solution cooled, was filtered, washed with small portions of ethanol and then refluxed for half an hour with ethanol (600 c.c.) when some of the benzoin dissolved.

The separated 4-dimethylaminobenzoin was filtered after two hours and after drying it had mp. 163° - 164°, (yield 105 g., 41.2%). The benzoin which dissolved in ethanol separated in fine needles and, it also had mp. 163° - 164°, when 4-dimethylaminobenzoin is crystallized from methylene chloride and light petroleum, it separates in microscopic crystalline form and has mp. 158° - 159°. When the carbinal which separates from methylene chloride and petroleum (mp. 158° - 159°) is mixed with the one which separates from ethanol (mp. 163° - 164°), the mp. of the mixture is not
lowered, but range from 160° to 163°. This shows that the
carbinol which separates from ethanal is not chemically
different from the one which separates from methylene chloride
and petroleum. This was confirmed by the fact that both
specimens of the carbinol gave the hydrogen phthalate which had
after recrystallization from methylene chloride and petroleum
the same m.p. (171° - 172°) and gave optically active hydrogen
phthalates with the same m.p. (167° - 168°) and rotatory power.
They are probably dimorphic.

(11) **Preparation Procedure:**

A solution of 4-dimethylaminobenzaldehyde (25.0 g., N/6)
and benzoin (17.7 g., N/12) in 95% ethanol (70 c.c.) was
heated under reflux for two and a half hours in presence of
a solution of potassium cyanide (10 g.) in water (4.0 c.c.).
4-dimethylaminobenzoin separated in fine needles as the
solution cooled. After recrystallization as above, the yield
of pure 4-dimethylaminobenzoin was 14.0 g. (33%) m.p. 150°-159°
(after recrystallization from methylene chloride and petroleum)

(‡) **Hydrogen phthalic ester of 4-dimethylaminobenzoin:**

Phthalic anhydride (37.0 g.) was dissolved in boiling
dry pyridine (20 c.c.) and the solution rapidly cooled to ensure
small crystals. Triethylamine (25.0 c.c.) and
4-dimethylaminobenzoin (65.75 g.) were added and the mixture
heated for about 20 minutes on a steam bath. The viscous
reaction mixture was allowed to cool, triturated with an
equal volume of acetone and diluted with water. Sufficient
sodium bicarbonate solution (5%) was added to dissolve the
hydrogen phthalate formed and the solution filtered to remove
any unreacted 4-dimethylaminobenzoin. The clear filtrate was
added dropwise, with stirring, to the calculated amount of
ice-cold dilute hydrochloric acid. The precipitated hydrogen
phthalate was removed by filtration, washed with ample water,
dried on a porous plate and boiled with methylene chloride
(250 c.c.) for 15 minutes, when only a part of the hydrogen
phthalate dissolved. The hydrogen phthalate was filtered
after two hours and after drying it had mp. 171 - 172°.
(Yield: 36.9 g, 95.2%). It can also be crystallized from
aqueous acetone in fine needles, mp. 171 - 172°.

0.403 g. of the (2) hydrogen phthalate required
9.8 c.c. of 0.102 N. HCl; whence M, 403.4, C₂₁H₂₄O₅ requires
M, 403.2.

(+) Hydrogen phthalic ester of 4-dimethylaminobenzoin—

Quinidine (64.66 g) was heated with methyl alcohol
(300 c.c.) and to the suspension (2) hydrogen phthalate of
4-dimethylaminobenzoin (80.64 g) dissolved in methyl alcohol
(150 c.c.) added. A clear solution was obtained at first
but the quinidine salt of the (+) hydrogen phthalate very rapidly separated. This crop (76.5 g.) after recrystallization from warm acetone (350 c.c.) and methanol (30 c.c.) deposited the optically pure salt of the (+) hydrogen phthalate in clusters of small needles, mp. 116 - 117°, total yield: 65.2 g.

This salt, suspended in about twice its volume of acetone, was decomposed by addition of a small excess of ice-cold dilute hydrochloric acid, and the liberated (+) hydrogen phthalate precipitated by slow addition of water. It was separated by filtration, washed with water, dried and recrystallized from aqueous acetone in clusters of short needles (24.2 g.) mp. 167 - 168°. Its rotatory powers are given in Table I.

On rapid titration, using phenolphthalein as indicator 0.425 g. of the (+) hydrogen phthalate required 10.3 c.c. of 0.102 N. NaOH for neutralization, whence H, 4.94.6.

C₂H₄₂O₄N₂ requires H, 4.03.2

(-) Hydrogen phthalic ester of L-dimethylaminobenzenamine

The filtrate removed from the quinidine salt of the (+) hydrogen phthalate, was decomposed with ice-cold dilute hydrochloric acid and the (-) hydrogen phthalate precipitated by addition of water. It was filtered and dried, yield 39.1 g. mp. 154 - 155°. After two recrystallizations from aqueous acetone, the optically pure (-) hydrogen phthalate (yield: 24.8 g.) was obtained mp. 167 - 169°.
On rapid titration, using phenolphthalein as indicator, 0.408 g. of the (-) hydrogen phthalate required 10.1 c.c. of 0.102 N. NaOH for neutralization, whence M, 405.4. C_{24}H_{21}NO_{5} requires M, 403.2.

Optically active 4-dimethylaminobenzoin obtained from (+)

Optically pure (+) 4-dimethylaminobenzoin hydrogen phthalate (9.5 g.) was dissolved in 95% ethanol (240 c.c.) and IN. H_{2}SO_{4} (50 c.c.) added. The mixture was heated at about 70°C for 136 hours after which about 120 c.c. ethanol was removed under reduced pressure. After dilution with an equal volume of ice-cold water, the precipitated material was filtered, dissolved in acetone and the solution mixed with ice-cold dilute sodium bicarbonate solution until slightly alkaline. The solution was then diluted with a large excess of ice-cold water and the precipitated optically active 4-dimethylaminobenzoin filtered after two hours. It was again dissolved in acetone and the yellow coloured solution of decolourised twice with animal charcoal and the optically active 4-dimethylaminobenzoin precipitated from it by addition of water. It was filtered and crystallized first from aqueous acetone and then from acetone: fine needles, mp. 165° - 166°. Yield 2.5 g. (41.3%). It had [\alpha]_{D}^{25°} = 22.6°
(1, 1; C, 1.04 in acetone).

Optically pure 4-dimethylaminobenzoic acid was similarly obtained from optically pure (-) 4-dimethylaminobenzoic acid hydrogen phthalate. It also had mp. 165°-166° and $[\alpha]_{D}^{25°} + 22.5$ D (L, 1; C, 1.06 in acetone). Its rotatory powers in different solvents for light of different wavelengths are given in Table XI.
TABLE X

Specific Rotatory Powers of (+) 4-dimethylaminobenzoin hydrogen phthalate, \([\alpha]_\lambda\) at 250 - 260°

<table>
<thead>
<tr>
<th>Solvent</th>
<th>C</th>
<th>([\alpha]_{5893})</th>
<th>([\alpha]_{5461})</th>
<th>([\alpha]_{5086})</th>
<th>([\alpha]_{4358})</th>
</tr>
</thead>
</table>
| Methylenec
chloride | 1.02 | 127.0              | 155°                | 175°                | 235°                |
| Glacial
acetic acid | 1.10 | 115                 | 141                 | 156                 | 212                 |
| Chloroform    | 1.08 | 106                 | 131                 | 143                 | 196                 |
| Pyridine      | 1.04 | 104.0               | 127                 | 143                 | 190                 |
| Acetone       | 1.05 | +94.0               | +114                | +130                | +167                |

The (+) hydrogen phthalate of 4-dimethylamino benzoin was too sparingly soluble in ethanol (99%) to allow of accurate polarimetric determinations.

The 'characteristic diagram' for the (+) hydrogen phthalate is given on p. 125.
Chromatogram diagram for
\( \alpha \)-D-glucopyranose hydrogen phthalate.
TABLE XI

Specific Rotatory Power of optically pure 4-diethylamino-
benzoin obtained from optically pure (-) 4-diethylamino-
benzoin hydrogen phthalate, $[\alpha]_\lambda$ at 25° - 26° (1, 1).

<table>
<thead>
<tr>
<th>Solvent</th>
<th>C</th>
<th>$[\alpha]_2$</th>
<th>$[\alpha]_4$</th>
<th>$[\alpha]_{10}$</th>
<th>$[\alpha]_{20}$</th>
<th>$[\alpha]_{30}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td>1.04</td>
<td>+39.93</td>
<td>+36.61</td>
<td>+32.86</td>
<td>+30.06</td>
<td>+29.06</td>
</tr>
<tr>
<td>Pyridine</td>
<td>1.09</td>
<td>+25.0</td>
<td>+43.75</td>
<td>+63.75</td>
<td>+281</td>
<td></td>
</tr>
<tr>
<td>Acetone</td>
<td>1.06</td>
<td>+22.5</td>
<td>+37.5</td>
<td>+56.0</td>
<td>+256.25</td>
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<tr>
<td>Chloroform</td>
<td>1.08</td>
<td>+12.0</td>
<td>+31.25</td>
<td>+43.75</td>
<td>+233.75</td>
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</tr>
<tr>
<td>Dioxan</td>
<td>0.96</td>
<td>+10.0</td>
<td>+23.75</td>
<td>+37.5</td>
<td>+217.0</td>
<td></td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>0.95</td>
<td>+7.5</td>
<td>+17.5</td>
<td>+30.25</td>
<td>+206.25</td>
<td></td>
</tr>
<tr>
<td>Methylene chloride</td>
<td>0.94</td>
<td>-3.75</td>
<td>+15</td>
<td>+30</td>
<td>+251.25</td>
<td></td>
</tr>
<tr>
<td>Glacial acetic acid</td>
<td>1.05</td>
<td>-59.0</td>
<td>-57.5</td>
<td>-60.0</td>
<td>+27.5</td>
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<tr>
<td>Carboniculphide</td>
<td>1.07</td>
<td>-139.0</td>
<td>-148.75</td>
<td>-169.0</td>
<td>-44.75</td>
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</table>
A solution of optically active 4-dimethylamino-
benzoin in freshly distilled pyridine suffered no loss in rotatory power after keeping for 10 days at room temperature, but the rotatory power of a solution of optically active 4-dimethylaminobenzoin hydrogen phthalate gradually diminished on keeping, as shown in Table XII.

The characteristic diagram for optically active 4-dimethylaminobenzoin obtained from the (-) hydrogen phthalate is given on p. 128.
Characteristic Diagram for 4-dimethylaminobenzoin
(obtained by hydrolysis of 4-dimethylaminobenzoin
hydrogen phthalate)

(i) Benzene
(ii) Chloroform
(iii) Methylene chloride
(iv) Glacial acetic acid
(v) Carbon disulphide
TABLE XII

Loss in rotatory power of a solution of (+) 4-dimethylamino-
benzoin hydrogen phthalate in freshly distilled pyridine

\[ [\alpha]^{25-260}_{5893} \] (1, 1; C; 1.05 in pyridine)

<table>
<thead>
<tr>
<th>Time (hrs.)</th>
<th>([\alpha]^{25-260}_{5893})</th>
<th>Time (hrs.)</th>
<th>([\alpha]^{25-260}_{5893})</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>+104°</td>
<td>426</td>
<td>+40°</td>
</tr>
<tr>
<td>24</td>
<td>101</td>
<td>472</td>
<td>32</td>
</tr>
<tr>
<td>93</td>
<td>88</td>
<td>522</td>
<td>30</td>
</tr>
<tr>
<td>140</td>
<td>81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>186</td>
<td>77</td>
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</tr>
<tr>
<td>207</td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>251</td>
<td>63</td>
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<td></td>
</tr>
<tr>
<td>331</td>
<td>52</td>
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<td></td>
</tr>
<tr>
<td>375</td>
<td>46</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The solution was too yellow after 522 hours to allow of further accurate polarimetric readings.
Optically pure (+) and (-) hydrogen phthalates of 4-dimethylaminobenzoin (0.15 g. each, m.p. 167 - 168°) were dissolved in acetone and a few drops of water added. The solution deposited crystals of (†) 4-dimethylaminobenzoin hydrogen phthalate in the form of small needles, m.p. 171 - 172° and [α]D 25° + 0.6° (1.1; C, 1.10 in acetone).

Optically pure 4-dimethylaminobenzoin (0.15 g. each, m.p. 165 - 166°), obtained from optically pure (+) 4-dimethylaminobenzoin hydrogen phthalate and (-) 4-dimethylaminobenzoin hydrogen phthalate were dissolved in acetone. The solution deposited crystals of (†) 4-dimethylaminobenzoin in the form of small needles, m.p. 163 - 164° and [α]D 25° - 26° + 0.0° (1.1; C, 1.06 in acetone).
Scheme for the Resolution of (†) Hydrogen Phthalate of 4-dimethylaminobenzoin:

(†) 4-dimethylaminobenzoin hydrogen phthalate (80.64 g.) and quinidine (64.88 g.)

in MeOH (450 c.c.)

Filt. ice + dil. hydrochloric acid.

A (76.5 g.) m.p. 113-116°

Acetone (350 c.c.) MeOH (30 c.c.)

(−) hydrogen phthalate (39.1 g.) m.p. 164-165° and [α]25° = 52°

B (63.2 g.) m.p. 116-117° Filt.

B' (2.0 g.) m.p. 116-117°

After two recrystallisations from aqueous acetone, yield: 34.3 g., m.p. 167°-168° and [α]25° = 93.8°

ice + (1; 1; C, 1.08 in acetone)

dil. hydrochloric acid.

(+)-hydrogen phthalate, m.p. 161°-164° [α]25°-26° + 51° (1; 1; C, 1.04 in acetone)

After two recrystallisations from aqueous acetone, m.p. 167-168°; [α]25° + 93.7° (1; 1; C, 1.02 in acetone)

ice + dil. hydrochloric acid

(+)-hydrogen phthalate, after recrystallisation from aqueous acetone, m.p. 167-168°; yield: 34.2 g. [α]25° + 94.0° (1; 1; C, 1.00 in acetone).
CHAPTER XII

Preparation and Attempted Resolution of 4'-methoxybenzoin.

Preparation of 4'-methoxybenzoin:

4'-methoxybenzoin was first prepared by Steadinger's method (Ber. 1913, 46, 3530, 3533) from benzaldehyde and anisaldehyde and then converted into 4'-methoxybenzoin stepwise as follows:

(a) Conversion of 4'-methoxybenzoin into p-methoxybenzyl phenyl ketone (desokeybenzoin):

\[
\text{Ph.CH}_2\text{CO.C}_6\text{H}_4\text{ONE} \xrightarrow{\text{Sn}} \text{Ph.CO.C}_6\text{H}_2\text{C}_6\text{H}_4\text{ONE}
\]

A mixture of 4'-methoxybenzoin (96.8 g.), granulated tin (62 g.), hydrated copper sulphate (1.9 g.), ethanol (450 c.c.) and concentrated hydrochloric acid (250 c.c.) was heated under reflux for 7 hours on the steam bath and then filtered. After standing overnight, the solution deposited crystalline material which was separated by filtration, washed with small portions of methanol, and recrystallised from methanol in colourless plates, m.p. 97° - 98°, yield: 41.6 g. (46%).
The filtrate, after removing p-methoxybenzyl phenyl ketone, was diluted with water and the precipitated material was crystallised twice from methanol when p-methoxyphenyl benzyl ketone (11.7 g., 13%) was obtained in needle-shaped crystals m.p. 65° - 66°.

Methanol proved a better solvent than ethanol for the recrystallisation of p-methoxybenzyl phenyl ketone as well as of p.methoxyphenyl benzyl ketone.

(b) Conversion of p-methoxybenzyl phenyl ketone into the bromo-derivative:

\[
\text{Ph.CO.CH}_2\cdot \text{C}_6\text{H}_4\cdot \text{OME} \xrightarrow{\text{Br}_2} \text{Ph.CO.CHBr. C}_6\text{H}_4\cdot \text{OME}
\]

A solution of the desoxybenzoin (45.2 g., 0.2 mole) in warm carbon tetrachloride (400 c.c.) was prepared in a three necked flask fitted with a mechanical stirrer, a dropping funnel and an air condenser. The flask was exposed to a 500 watt tungsten lamp and 400 c.c. of a solution containing 8.0 g. bromine per 100 c.c. of carbon tetrachloride was slowly added with stirring. Under these conditions the reaction was quite rapid; hydrogen bromide was liberated and the bromine colour quickly disappeared. The major portion of the solvent was distilled off under reduced pressure and as the solution cooled the crystals rapidly began to
separate in fine needles on scratching the sides of the flask. The crystalline material was separated, washed with small portions of carbon tetrachloride and dried.

Yield: 50.6 g. (83%) and m.p. 93° - 94°. Jenkins (loc. cit.) reports 84% yield and m.p. 93° - 94°.

(c) Hydrolysis of the bromo ketone to 4'-methoxybenzoin:

\[
\text{Ph.CO.CHBr. C}_6\text{H}_4\cdot\text{CH} = \text{H}_2\text{O} \rightarrow \text{Ph.CO.CH} = \text{H}_4\cdot\text{OME.}
\]

The bromoketone (45.8 g.) was dissolved in dioxan (225 c.c.) and heated with water (225 c.c.) on a water bath at 85° for 1.5 hours and then the solution was diluted with excess of ice cold water. The separated solid was removed by filtration, washed with water and dried; wt. 39.8 g; m.p. 85° - 87°. The filtrate on acidification with dilute nitric acid and treatment with silver nitrate gave a copious precipitate of pale yellow silver bromide.

The hydrolysed product was recrystallised from ethanol when pure 4'-methoxybenzoin separated in matted long needles, yield: 30.9 g. (85%), m.p. 90° - 91°. The m.p. remained unchanged after further recrystallisation. The filtrate was
diluted with water and the precipitated solid after two 
recrystallisations from ethanol, gave pure 4'-methoxybenzoin, 
3.4 g., m.p. 108° - 109° alone, and when mixed with an 
authentic specimen of 4'-methoxybenzoin.

Asahina and Terasaka (J. Pharm. Soc. Japan, 1923, 
12, 219) and Julian and Passler (J. A. C. S., 1932, 54, 4756) 
record 89° as the m.p. of 4'-methoxybenzoin.

(±) 4'-Methoxybenzoin hydrogen phthalate:—

Phthalic anhydride (7.4 g.) was dissolved in boiling 
dry pyridine (4.0 c.c.) and the solution rapidly cooled 
to ensure small crystals. Triethylamine (5.0 c.c.) and 
4'-methoxybenzoin (12.1 g.) were added and the mixture 
gently warmed for 3-4 minutes. The resulting gummy mass was 
triturated with an equal volume of acetone and then treated 
with cold dilute hydrochloric acid until acidic followed by 
addition of water. When (±) 4'-methoxybenzoin hydrogen 
phthalate separated. This, after recrystallisation from 
methylene chloride and petroleum, had m.p. 152° - 153°. 
Yield: 18.4 g. (94.9%). When this was mixed with 
4'-methoxybenzoin hydrogen phthalate (m.p. 157° - 158°), the 
resulting mixture had m.p. 143° - 144°.
On rapid titration using phenolphthalein as indicator 0.405 g. of the (†) 4'-methoxyhydrogen phthalate, required 10.2 c.c. of 0.102 N. NaOH, whence \( M \), \( \text{C}_{25}\text{H}_{18}\text{O}_6 \) requires \( M \), 330.0.

Attempts to prepare diastereoisomeric alkaloidal salts of \( 4'\)-methoxybenzoin hydrogen phthalate:

(i) A mixture of (†) 4'-methoxybenzoin hydrogen phthalate (0.780 g.) and quinine (0.650 g.) was dissolved in acetone and the solution allowed to stand for several days. The gummy mass was obtained which showed no sign of crystal formation on trying with various solvents like methanol, ethylacetate, benzene etc.

(ii) The solution of (†) hydrogen phthalate of \( 4'\)-methoxybenzoin (0.780 g.) and cinchonidine (0.590 g.) in acetone did not give any crystalline salt after allowing the solution to stand for several days and trying with various other solvents.

(iii) A suspension of (†) 4'-methoxybenzoin hydrogen phthalate (0.780 g.) and strychnine (0.790 g.) in acetone was heated with a few drops of chloroform and the clear solution allowed to stand for several days, when strychnine separated, m.p. 289° - 291° alone and when mixed with an authentic specimen of strychnine.
(iv) Attempts to obtain crystalline brucine, cinchonine, quinine and morphine salts of the (2) 4'-methoxybenzoin hydrogen phthalate as described above also proved to be fruitless.

Preparation of 4'-methoxybenzoin ethyl ether—

p-methoxy - α-bromobenzyl phenyl ketone (30.5 g.) was dissolved in 150 c.c. warm absolute ethanol and sodium (7.0 g. three equivalents) dissolved in absolute ethanol (150 c.c.) added to it. The solution was allowed to stand until sodium bromide was completely precipitated. (about half an hour). It was acidified with dilute hydrochloric acid when a yellow oil separated which gradually solidified. This solid material was separated, washed with water, dried and crystallised from ethanol when 4'-methoxybenzoin ethyl ether separated in prismatic needles, m.p. 72"-73°. Yield: 25.2 g. (93.3%) Found: C, 75.5; H, 6.63; C_{17}H_{18}O_{3} requires C, 75.5; H, 6.7%.

Conversion of 4'-methoxybenzoin into 4'-methoxybenzoin——

4'-methoxybenzoin (6.0 g.) was heated with pyridine (2.0 c.c.) and triethylamine (2.5 c.c.) on a steambath for 45 minutes and then treated with dilute hydrochloric acid. The precipitated mass was separated, washed with water and
then recrystallised from ethanol when 4'-methoxybenzoin separated in fine needles, m.p. 108°-109°.

NOTE: It was found that 4'-methoxybenzoin remains unchanged when the heating period is limited to five minutes.

Formation of 4'-methoxybenzoin hydrogen phthalate from

A mixture of 4'-methoxybenzoin (6.0 g.), pyridine (2.0 c.c.) and triethylamine (2.5 c.c.) was heated on a steambath for 45 minutes and the resulting gummy mass triturated with an equal volume of acetone. The solution was treated with dilute hydrochloric acid when (†) 4'-methoxybenzoin hydrogen phthalate separated in a semi-solid condition. The semi-solid mass was separated, washed with water, dissolved in methylene chloride; the solution was dried over anhydrous calcium chloride and then on adding petroleum (†) 4'-methoxybenzoin hydrogen phthalate separated in small needles, m.p. 157°-158°. When this was mixed with an authentic specimen of 4'-methoxybenzoin hydrogen phthalate, the resulting mixture had m.p. 157°-158°.

Non-formation of sulphone from 4'-methoxybenzoin:

(i) Equimolecular proportions of 4'-methoxybenzoin and sodium p-toluene sulphinate were dissolved in 40% formic
acid by warming; after 10 minutes unchanged 4'-methoxybensoin separated in long needles, m.p. 90° - 91° alone and when mixed with an authentic specimen.

(ii) Equimolecular proportions of 4'-methoxybensoin and sodium p-toluenesulphinate were dissolved in glacial acetic acid and the solution allowed to stand for 10 days. The separated crystals were filtered, washed with water and dried. The m.p. (90° - 91°) corresponded with that of 4'-methoxybensoin. When this was mixed with an authentic specimen of 4'-methoxybensoin (m.p. 90° - 91°) the resulting mixture had m.p. 90° - 91°.
CHAPTER XIII

Preparation and Attempted Resolution of Pivaloin (hexamethylcyclooctan)

Preparation of Pivaloin:

Starting from tert-butyl alcohol, pivaloin was prepared by the following steps:

(i) Preparation of tert-butyl chloride:

A mixture of tert-butyl alcohol (74 g., 1 mole) was shaken with concentrated hydrochloric acid (275 c.c., 3 moles) in a separatory funnel and allowed to stand for 15-20 minutes. The upper layer was then drawn off, washed successively with 5% sodium bicarbonate solution and water till neutral to litmus paper, shaken thoroughly with anhydrous calcium chloride (10 g.) and then transferred to a distillation flask. The fraction distilling at 49.5°-52° was collected. Yield: 75.5 g. (81%).

(ii) Preparation of pivalic acid:

In a 3-1-three necked flask fitted with a mercury sealed mechanical stirrer, a 250 separatory funnel and an efficient reflux condenser was placed 61 g. (2.5 atoms) of magnesium turnings. The magnesium was covered with 200 c.c. of anhydrous ether. About 5 c.c. of tert. butylchlorode and a crystal of iodine were added to initiate the reaction.
Stirring was begun and a solution of 227 g. (2.5 moles) of tert-butyl chloride in 1000 c.c. of anhydrous ether was dropped slowly on the magnesium turnings during 8 to 9 hours.

The reaction mixture was cooled in an ice and salt mixture and then gradually and cautiously added to excess of solid carbon dioxide. When the unused dry ice had evaporated, ordinary ice and 25% hydrochloric acid were added to liberate pivalic acid and to dissolve basic magnesium salt: the ether layer was separated, washed with water, dried over anhydrous calcium chloride, fractionally distilled and the fraction boiling at 164°-165° collected and allowed to cool when pivalic acid (m.p. 34°-35°) solidified. Yield: 143 g. (56%).

(iii) Preparation of ethyl pivalate:

A mixture of pivalic acid (102 g., 1 Mole) and absolute ethyl alcohol (138 g., 3 moles) was heated with methylene chloride (300 c.c.) and concentrated sulphuric acid (4.0 c.c.) under reflux for 16 hours. The solution of ethyl pivalate in methylene chloride was separated, washed successively with water, 5% sodium bicarbonate solution, water, dried over anhydrous calcium chloride and fractionally distilled to obtain ethylpivalate (E.P. 118°). Yield: 124 g. (95.4%).
(iv) Preparation of Pivalolm:

Clean metallic sodium (25.0 g., 1 gram atom) and xylene (50 c.c.) were placed in a 1-litre three necked flask fitted with an efficient reflux condenser, a mechanical stirrer and a dropping funnel. The sodium was finely powdered by heating the flask until the sodium melted and then stirring vigorously as the melted sodium cooled. The cooled xylene was decanted and the powdered sodium washed with dry ether. About 300 c.c. of dry ether was added.

The stirrer was restarted and ethyl pivalate (65 g., ½ mole) in dry ether (100 c.c.) was added dropwise. Stirring was continued until there was no further reaction and practically all the sodium had been converted into a voluminous yellowish solid.

The reaction flask was then surrounded by an ice-bath and a cooled solution of concentrated sulphuric acid (52 g., 30 c.c.) in water (100 c.c.) was added slowly with vigorous stirring. The stirrer was then removed and the flask was allowed to stand in the ice-bath until the lower layer of hydrated sodium sulphate had solidified. The ethereal solution of pivalolm was then separated, washed with sodium carbonate solution, dried over anhydrous potassium carbonate, concentrated to a small bulk (50 c.c.) and light
petroleum (25 c.c.) added when pivaloin separated in clusters of small needles, m.p. 80° - 81°; yield: 34.0 g. (39.5%).

Preparation of (†) Pivaloin hydrogen phthalate:—

A hot solution of phthalic anhydride (14.8 g.) in pyridine (0.9 c.c.) was allowed to cool and then pivaloin (17.2 g.) and triethylamine (10.0 c.c.) were added and the mixture heated for 5 minutes on a steambath. The resulting gummy mass was triturated with an equal volume of acetone and acidified with cold dilute hydrochloric acid followed by addition of water when (†) pivaloin hydrogen phthalate was precipitated. It was separated, washed with water, dried and recrystallised from methylene chloride and petroleum when (†) pivaloin hydrogen phthalate separated in rhombic crystals, m.p. 130° - 131°. Yield: 30.2 g. (94.4%).

On rapid titration, using phenolphthalein as indicator 0.326 g. of the (†) pivaloin hydrogen phthalate, required 10.0 c.c. of 0.102 N. NaOH for neutralisation, whence M, 319.6. C_{10}H_{12}O_5 requires M, 320.0.

Attempts to prepare diastereoisomeric alkaloidal salts of pivaloin hydrogen phthalate:—

(i) A solution of (†) Pivaloin hydrogen phthalate (0.640 g.) and quinidine (0.648 g.) in acetone did not give any crystalline
salt even after allowing the solution to stand for several days and by trituration with various solvents.

(ii) Strychnine (0.790 g.) was heated with methanol (20 c.c.) and a solution of (D) pivaloin hydrogen phthalate (0.440 g.) in acetone added to it. Suspended impurities were removed by filtration and the filtrate allowed to stand for several days. The racemate (strychnine (D) HPh) separated after 15 days; this was filtered, dried, washed with small portions of acetone and decomposed with dilute hydrochloric acid when (D) pivaloin hydrogen phthalate precipitated, m.p. 130° - 131° alone and when mixed with an authentic sample of (D) pivaloin hydrogen phthalate. The filtrate, after removing the insoluble salt, also gave (D) pivaloin hydrogen phthalate on decomposition with dilute hydrochloric acid.

(iii) Attempts to obtain crystalline brucine, quinine, cinchonine, cinchonidine, and morphine salts of pivaloin hydrogen phthalate also proved to be unsuccessful.
Purification of Solvents and Reagents:

ETHYL:— Commercial ether was allowed to stand over anhydrous calcium chloride for a day, distilled on a water bath and fraction, b.p. 33° – 36°, collected and freshly drawn sodium wire introduced in it.

ETHANOL:— Commercial 99% ethanol was used for the determination of the rotatory power of all the samples of hydrogen phthalates and of carbinites. Commercial 99% ethanol was used as a reagent for synthetic work.

CARBONIC SULPHIDE:— Was dried over calcium chloride, distilled and the fraction, b.p. 46 – 47° collected.

ETHANOL:— Was dried over anhydrous copper sulphate and the fraction, b.p. 65° collected.

ACETONE:— Was dried over calcium chloride and the fraction, b.p. 50° collected.

BENZENE:— Was dried over calcium chloride, distilled and the fraction, b.p. 60 – 81° collected and freshly drawn sodium wire introduced in it.

CHLOROFORM:— Analar chloroform was used for optical observations.

PYRIDINE:— Was refluxed with potassium hydroxide, distilled and the fraction, b.p. 117 – 118° collected and stored over potassium hydroxide pellets.

TRICYCLETAMINE:— Was kept over potassium hydroxide pellets.
DIOXAN: Commercial dioxan (250 c.c.) concentrated hydrochloric acid (4 c.c.) and water (25 c.c.) was refluxed for 10 hours whilst a slow stream of nitrogen was bubbled through the solution to remove the acetaldehyde. The cold solution was treated with potassium hydroxide pellets with shaking until some remain undissolved, and the aqueous layer was run off; most of the residual water was removed by keeping the dioxan over fresh potassium hydroxide pellets for 24 hours. It was then refluxed over excess of sodium until the reaction ceased and the sodium remained bright (6 hours). It was then distilled from sodium and the fraction, b.p. 101°, collected and stored out of contact with air.


FRACTION II: Purified as above and the fraction, b.p. 124 – 135°/12 mm, collected.

FRACTION III: Was dried over calcium chloride, fractionated and the fraction b.p. 40 – 41° collected.
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