THE SYNTHESIS OF SOME SECONDARY AMYL AND HEXYL HOMOLOGUES OF DINITRO ORTHO AND PARA CRESOLS

by

JOHN GILBERT MOFFATT

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Members of the Department
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ABSTRACT

Eight new dinitro-sec.-amyl and hexylphenols of unequivocal structure were synthesized and characterized by their piperidine, morpholine and cyclohexylamine salts.

The synthetic route followed involves the Fries rearrangement of phenyl acetate and phenyl propionate to give the easily separated isomers o- and p-hydroxyacetophenone and o- and p-hydroxypropiophenone. These compounds were then methylated to give the corresponding methoxyacetophenones and methoxypropiophenones. The methylated aryl-alkyl ketones were condensed through a Grignard reaction with various alkyl bromides to give tertiary alcohols which were dehydrated by the Dean and Stark method to the corresponding olefins and then hydrogenated to alkylanisoles. Demethylation was effected through the use of pyridine hydrobromide for the p-alkylphenols, or 47% hydriodic acid and phenol for the o-alkylphenols.

The alkyl phenols were then nitrated with fuming nitric acid in glacial acetic acid at -15°C., and the resulting dinitro-alkylphenols characterized as amine salts.

The phenols prepared were: 3-(o- and p-hydroxyphenyl)-pentane, 2-(o- and p-hydroxyphenyl)-hexane, 2-(o- and p-hydroxyphenyl)-3-methylpentane, 2-(o- and p-hydroxyphenyl)-4-methylpentane.

Of these, only 2-(p-methoxyphenyl)-3-methylpentane has been reported prepared by an unequivocal synthesis. All other phenols, their intermediates and derivatives, and their dinitro derivatives, are previously unreported except in odd cases through questionable condensation methods.

ACKNOWLEDGMENT

Sincerest thanks is extended to my Research Director, Mr. G.G.S. Dutton, for his ever ready assistance, interest, and friendship throughout the work on this project.

I should also like to express appreciation to the National Research Council and to the Standard Oil Company of British Columbia, for financial aid, and to the Sharples Chemical Company for samples of o-sec.-amylphenol, o-tert.-amylphenol, and p-sec.-amylphenol.

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I. INTRODUCTION.

The synthesis of a wide range of dinitro-o and p-alkylphenols has been undertaken in this laboratory during the past few years. Previously the alkylphenols prepared have all been those containing primary normal and isoalkyl groups. This thesis represents the first attempt to prepare phenols containing secondary alkyl groupings.

Previously isopropyl and sec.-butyl phenols of clearly defined structure have been prepared through various condensations of phenol with the appropriate alkyl halide, alcohol or olefin, but beyond this point isomerization occurs during condensation and the exact nature of the product is uncertain. We have, therefore, developed a synthesis for dinitro-o and p-alkylphenols in which each step can proceed in only one direction, giving as a final product a compound of unequivocal structure.

There are two distinct reasons for the preparation of these compounds. Firstly, it has long been known that 2:4-dinitrophenol and the dinitrocresols, especially dinitro-o-cresol or D.N.O.C., as it is known commercially, are potent insecticides and herbicides, their particular interest lying in their selective action which allows them to destroy undesirable weeds while leaving the main crop unharmed. Dutton and his co-workers at both Sir John Cass College, London, and the University of British Columbia[37], have extended this knowledge by preparing and testing twenty-two different dinitro-o and p-primary-alkylphenols where the alkyl group is either normal or iso and varies in length from ethyl to octyl, and also dinitro-o and p-tert.-butyl, and dinitro-p-tert.-amylphenols. These investigations have shown that maximum toxicity towards several test

organisms occurs at the o-ethyl or propyl homologues (see Figures 5 and 6) and that the other members of the series are less toxic. Chain branching appears to decrease toxicity as shown by those phenols containing tertiary and isoalkyl groups. Dinitro-o-sec.-butylphenol, however, shows anamolously high toxicity in comparison with all others tested, and this has led to the present study of other dinitro-sec.-alkylphenols.

2:4-dinitro-6-sec.-butylphenol has become well known as a herbicide and is marketed by Dow Chemicals under the trade name "Dow General". None of the other sec.-alkyl compounds have been tested and reported.

The second reason for this work involves the considerable industrial importance that alkylphenols and their derivatives have achieved during the last twenty years(36,146). Their chief use is as nondiscolouring antioxidants in the synthetic rubber and other industries(68), in which case it has been found that polyalkylphenols, especially those containing bulky tertiary groups ortho to the phenolic centre, are most efficient and desirable.

Other uses which alkylphenols have found are as intermediates in the production of synthetic resins, as polymerization inhibitors for gasoline, paints, and varnishes, as dye intermediates, as insecticides, as photographic developers (especially in the case of p-tert.-octylphenol), and as water-in-oil emulsion breakers. Some p-sec. and tert.-amyl and hexylphenols prepared through condensation methods have proved to be especially valuable in this latter class.

Various simple derivatives of alkylphenols have also found their place in industry. Hydrogenated alkylphenols with fairly long side chains are useful as perfume bases and modifiers in lubricating oils[11]. Their esters and ethers are used in plastics, paints, and waxes, and their sulphonates in detergents, emulsifying agents, textile finishing agents, and high pressure lubricants.

This rather long list shows the importance of alkylphenols to modern life, and when it is realized that nearly all these compounds are prepared through condensations giving mixtures of products, the exact structure of which are not conclusively known, it becomes obvious that once an extensive series of alkylphenols has been synthesized in such a way that their structures are definite, then the exact natures of these condensation products can be determined. A future project is planned at this university dealing with various phenol condensations, using the phenols prepared and characterized during the present study as reference compounds.

Nearly all the intermediates in the syntheses described are also previously unreported, and have been characterized as well as possible through physical constants, derivatives and analyses.

II. HISTORICAL.

1. The Development of Selective Herbicides.

Since man first took an economic interest in the cultivation of land, he has been faced with a retaliation by nature in the form of weeds which threaten his crops and cost him millions of dollars a year in damage and control measures. Through the years a great deal of work has gone into the development of various chemical agents which have the ability to combat the ever present weeds. Obviously, the most desirable compounds are those which may be applied to a cultivated field without damage to the desired crop, but at the same time destroying the unwanted weeds. Such compounds are described as "selective" herbicides, and many have been suggested from time to time.

The first true selective weed killer to be tested extensively was a dilute solution of copper sulphate which Bonnet discovered in 1896. By spraying a field of oats with this solution, Bonnet found that the oats were largely unharmed, but that yellow charlock, a very troublesome weed, was killed. The significance of this work did not seem to be realized, for very little work is reported along these lines for some years.

In 1911, however, Rabate(96) showed that as a general rule, spraying with dilute sulphuric acid would kill dicotyledenous weeds with very little injury to the desired crop. This agent was found to be efficient against a wide range of weeds, but it suffered from the obvious drawback of its corrosive action on equipment and the resulting difficulty in handling.

There was then another lapse of achievement for a number of years, broken in 1933 when Truffant and Pastac found that nitrophenols and cresols, particularly dinitro-o-cresol or D.N.O.C., as it became known, have very definite selective actions against various cereal crop weeds[9]. The toxic nature of phenols and nitrophenols against insect pests had long been known, and, as early as 1868, the use of soapy water and cresylic acid was reported in the Gardener's Monthly as being an efficient insecticide[116]. In 1892 a German company marketed the potassium salt of 3:5-dinitro-o-cresol as a stomach poison for the housefly and louse but this did not seem to have been accepted with much acclaim[133]. The compound itself had been known since 1866 and had found its chief use as a yellow dye which was even used in various foodstuffs until its toxic nature was discovered.

With the discovery that certain phenols and nitrophenols possessed selective properties towards weeds as well as insects, considerable interest in these compounds was aroused and initially centred on D.N.O.C. itself.

Until the middle 1930's, the vast majority of all herbicides and insecticides used were those based on various arsenic compounds, most commonly acid lead arsenate ($PbHAsO_4$) and arsenious oxide (As_2O_3). These agents had to be handled with great caution due to their toxicity towards mammals and certain trees and plants. The very significant discovery was made by Kagy in 1936 that inorganic salts of both D.N.O.C. and 2:4-dinitro-6-cyclohexylphenol were more toxic than the most efficient arsenic sprays marketed at the time[62]. The calcium salt of D.N.O.C. was on the average four times as potent against several test organisms.

With this discovery came a surge of research on the agricultural use of D.N.O.C. and dinitro-o-cyclohexylphenol. The results were promising and showed excellent control of both plant and insect pests using very dilute sprays or dusts. Cockchaffers were found to be controllable to an extent of 90% using sprays containing only 0.2-0.5% D.N.O.C.(86), while they were almost impervious to arsenic preparations(87). Very similar results were shown in the control of grasshoppers(33), blowfly(139), and coddling moth larvae(147). These compounds, however, have a tendency to damage foliage to a certain extent and so are not too suitable for use on fruit trees. Field crops, on the other hand, suffer very little damage and are highly suited to pest control with D.N.O.C. Fortunately, it has been found that while nitrophenols are highly toxic towards insects, they are not overly toxic to animals. Controlled experiments on rabbits and rats show that they are not appreciably irritating to the skin and that rats maintained on a diet containing 0.05% D.N.O.C., or related compounds, for six months, showed no ill effects(127). These compounds, however, have the undesirable property of staining everything they touch a vivid yellow or orange.

It is interesting to note that certain dinitrophenols, especially 2:4-dinitro-6-cyclohexylphenol, 2:4-dinitro-6-hexylphenol, and their dicyclohexylamine salts, can be used as "safeners" in arsenic sprays to minimize damage to trees and plants(30). The addition of from 0.5-6.0 oz. of the nitrophenol to 100 gallons of the parent spray, produces this effect.

The actual application of these compounds falls into two distinct classes - as sprays, and as dusts. There seems to be some evidence that sprays are most effective in cold weather, and dusts in hot weather, but both are used extensively. For sprays, it is generally found convenient to use the simple inorganic salts of the acidic dinitrophenols as a means of increasing their solubility. Unfortunately, the ammonium salt of D.N.O.C., which is the most toxic of the salts, also has a very limited solubility in water and so the somewhat less toxic sodium or potassium salts are usually preferred(45). The use of various amine salts appears to offer a solution to this problem since the ethylamine salt of D.N.O.C., has the toxicity of the ammonium salt, but is many times more soluble. The direct suspending of nitrophenols over some carrier such as redwood bark flour(41) or diatomaceous earth(8), gives good control of a wide range of insects and weeds, but since most of the dinitro-alkylphenols are liquids, this procedure is rather difficult. The solution here also seems to be the use of amine salts since these are well defined crystalline compounds and can easily be mixed homogeneously with the carrier.

A further advantage of the amine salts is their greatly reduced vapour pressure and volatility as compared with the parent nitrophenol. The toxicities seem to be comparable, but the toxic action of the amine salts persists long after that of the free nitrophenol(64). This factor of volatility must be carefully considered in testing any new herbicide since some of our most toxic agents are impractical due to high vapour pressure. Thus 4-bromoacetophenone, which is exceptionally toxic, is found to have completely disappeared within five days of application(131).

Moore and Graham[83] have studied the physical properties of efficient herbicides and insecticides by the addition of a non-toxic dye such as Trypan Blue and determination of the degree of penetration, and have concluded that, as a general rule, compounds with a viscosity greater than castor oil, or a volatility greater than xylene, are of little use. Those soluble in chloroform and other fat solvents have the highest penetrating power.

The principle of selective herbicides is admirably shown by a comparison of the actions of D.N.O.C. and of 2:4-dinitro-6-sec.-butylphenol. The latter proves to be over four times as toxic as D.N.O.C. towards mustard in peas, but only 0.55 times as toxic towards the peas, therefore, making it roughly eight times as selective in its action[9].

It must be remembered, however, that repeated use of one chemical agent will eventually sort out resistant strains within the weed population. In this way roadsides which have been repeatedly sprayed with oil which originally killed all the vegetation have appeared with new oil-resistant types of weed. Also, repeated use of 2:4-dichlorophenoxyacetic acid or 2:4D, has destroyed many dicotyledenous weeds but the resistant monocotyledenous varieties have increased in number. The only remedy for this is carefully arranged herbicide rotation.

There are many aspects of the action of herbicides and insecticides which are not yet fully understood, such as the reason why certain concentrations of growth regulating substances such as alpha-naphthylacetic acid, and certain substituted phenoxy and naphthoxyacetic acids, selectively destroy yellow charlock and do not affect cereal crops. This investigation

has been undertaken by Slade and Templeman[122,9] commencing in 1940 and promises to give us some interesting information. The concentrations and rates at which other agents are applied are also critical since for sprays that are absorbed into the plant and translocated to a critical area, the spray must not be too concentrated or the foliage will simply die where the droplets touch and the translocation will not occur. Thus, certain tests with nitroalkylphenols show greatest toxicity at low concentrations.

These facts clearly point out that weed and pest control is no longer in the hands of the ordinary farmer, but is the job of a trained specialist, if optimum results are to be obtained.

2. The Relationship of Structure to Toxicity.

It is always of interest to correlate the properties of a homologous series of compounds with the nature of the individual molecule. Toxicity tests on homologous and isomeric series of compounds possessing herbicidal or insecticidal properties provide an interesting experiment of this type and are certainly of economic importance in the development of the most efficient and practical agents for agricultural use. Quite a number of such correlative studies have been carried out since chemical interest in pest control has been aroused, and the most significant of these are described in this paper.

It was realized as early as 1865 by Lister that phenol is an effective germicidal agent, but a systematic study of other phenolic compounds does not seem to have been started until 1906 at which time Ehrlick found that polyhalogenated phenols have high toxicities towards

certain organisms[130]. Thus, pentabromophenol is five hundred times as toxic as phenol for the case tested. Strangely enough, following this discovery, there seems to be a lapse in the study of phenols which lasted for some fifteen years and did not become really active again until Johnson and Lane's work on alkylresorcinols[61].

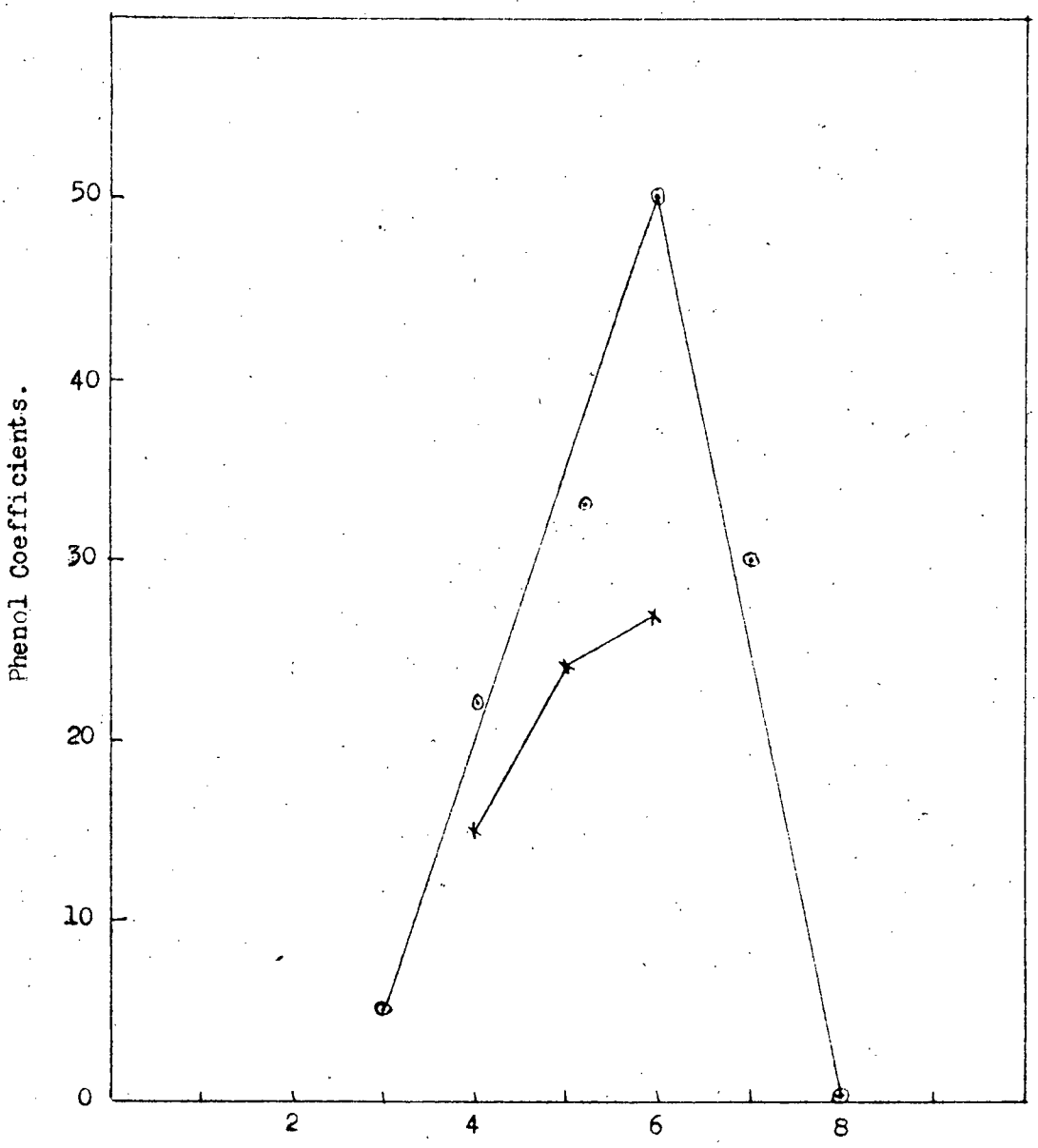
In the meantime a certain amount of work on the germicidal properties of alkyl alcohols and amines was undertaken by Morgan and Cooper[84]. Alcohols were found to be considerably less active than phenol and so it was concluded that the aromatic nucleus in some way gave the added toxicity. Chain branching was found to reduce the activity and thus n-butanol is more powerful than tert.-butanol with sec.-butanol holding an intermediate position. As will be shown later, this effect is usually also found in the alkylphenols. The alkylamines are better germicides than the alcohols, and their toxicity increases as the chain length becomes longer to a maximum value at n-heptylamine. While the aliphatic amines are stronger than the alcohols it is found that aniline is considerably weaker than phenol.

In 1921, Johnson and Lane[61] started the first organized study of the relationship of toxicity to structure, by preparing the 4-n-alkylresorcinols from methyl to butyl and doing standardized toxicity tests. Their method of synthesis was the Nencki condensation of resorcinol with a fatty acid in the presence of zinc chloride to give an acylresorcinol, followed by a Clemmensen type reduction using zinc amalgam and hydrochloric acid. Their results showed that the toxicity steadily increased with the length of the alkyl side chain.

Five years later, Dohme, Cox, and Miller, extended this work by the preparation and testing of all the 4-n-alkylresorcinols up to n-octyl and also several isoalkyl derivatives. The results of their tests were very interesting and are shown in Figure 1. It can be seen that the toxicity, as measured by the phenol coefficient towards B. typhosus, rises to a maximum value for the 4-n-hexyl derivative and falls off for both higher and lower homologues, reaching a value of zero for the n-octyl and higher derivatives.

Figure 1.

Phenol Coefficients of 4-Alkylresorcinols to B. typhosus.



It is to be noted that the standard of efficiency used here and in many other studies is the phenol coefficient which is merely a comparison of the germicidal action of a compound to that of phenol as unity. Since the coefficient varies with the test organism and also with the temperature, care is to be taken in drawing comparisons, and several different tests are desirable. Thus, while the phenol coefficient of 4-n-alkylresorcinols is at a maximum at the hexyl homologue in tests against B. typhosus, the same compounds tested against Staph. aureus have progressively increasing coefficients as far as have been investigated(110).

Leonard(77) realized the significance of Dohme's work and showed that 4-n-hexylresorcinol possesses the properties of an ideal internal urinary antiseptic, a use which it still finds.

Dohme used the same synthetic method as Johnson and Lane, i.e., a Nencki condensation and Clemmensen reduction, but in 1931 Cox showed that the same compounds may be prepared in equally good yields by the condensation of the acid chlorides with resorcinol at 90°C. without any catalyst. This method is to be preferred in that it does not require the use of a large excess of acid which must be removed as in the Nencki condensation. Cox also showed that reduction of the acylresorcinols may also be effected using clean, mossy zinc and hydrochloric acid rather than zinc amalgam.

The next development was a study of the monoalkylresorcinol ethers by Klarmann et al(74). Once again the hexyl homologue showed maximum toxicity, with chain branching leading to lower values. The phenol coefficients seem approximately the same whether the alkyl group is attached to a carbon or to an oxygen atom. Dialkylresorcinols show an

increased toxicity when at least one of the alkyl groups is of greater than three carbon atoms[16], but no quantitative results are shown.

Of all the primary amines tested, cyclohexylamine is the most toxic, and by the addition of n-alkyl groups the toxicity is increased steadily as far as tests have been made[65]. It is interesting to note that in the case of cyclohexylamine, substitution in the ring reduces toxicity sharply as contrasted with most other types of compound tested.

Pyridine is not a particularly active fumigant, but alkylpyridines once more show considerable action[67]. Figure 2 shows the results of tests using 2-alkylpyridines against the red spider, and it can be seen that in this case the maximum does not occur at the hexyl derivative, but rather at the n-butyl homologue. The more difficultly obtained 4-alkylpyridines appear to be more toxic than their 2-alkyl isomers. For short side chains the iso compounds are less toxic, but for isohexyl and higher they are more toxic. The alkylpiperidines have not been carefully studied but appear to be slightly more efficient than the corresponding pyridines. Fused ring systems such as quinoline and acridine are among the most toxic insecticides known[66].

The studies of the greatest interest to the present work are those concerned with alkylphenols and nitrophenols and these will now be considered.

The alkylphenols themselves show a maximum phenol coefficient for n-amylphenol, there being very little difference between the ortho, meta and para isomers. The primary alkyl derivatives are more toxic than the secondary and tertiary isomers as shown in Figure 3 by the work of

Figure 2.

Toxicity of 2-n-alkylpyridines to Red Spider.

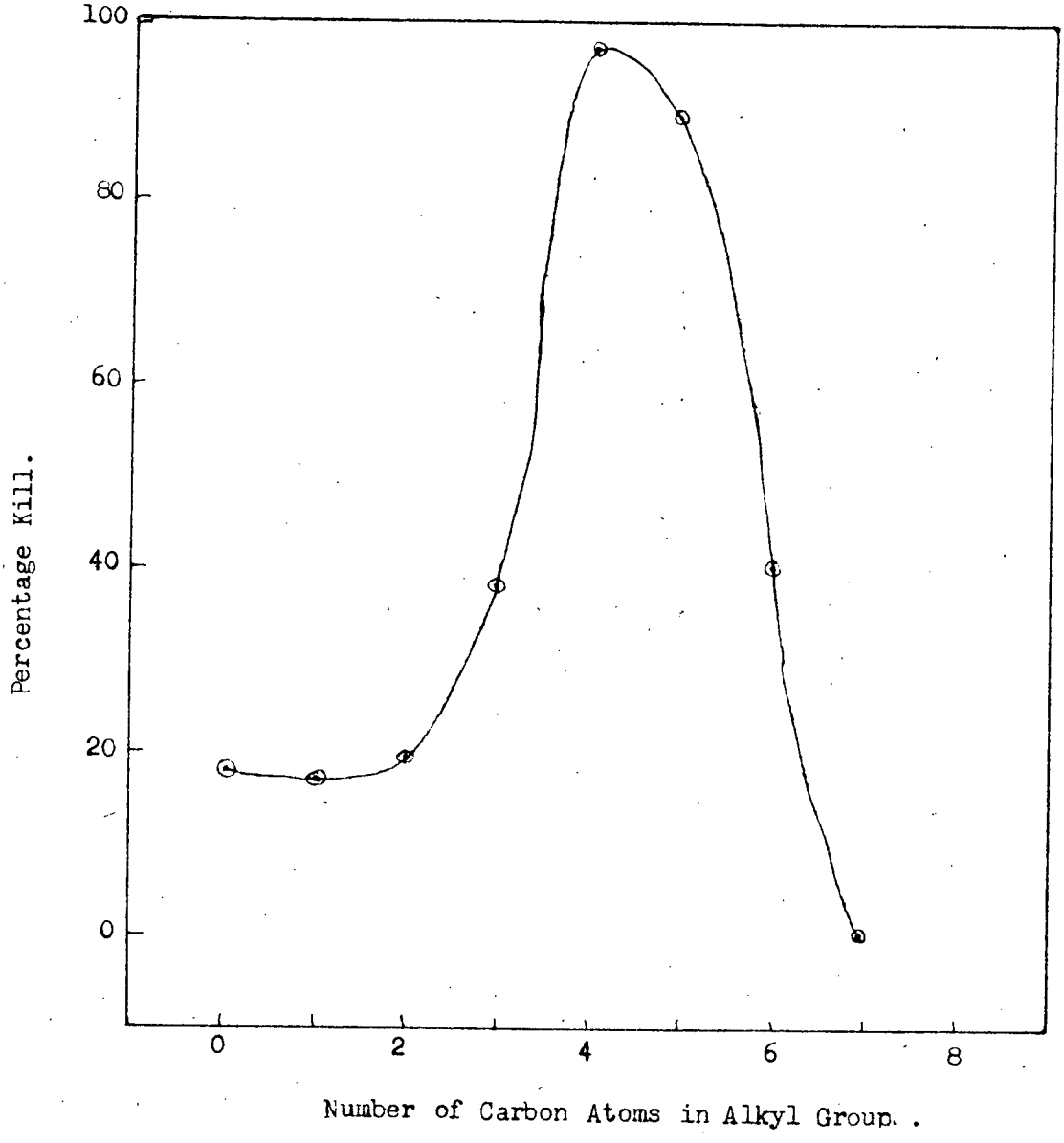
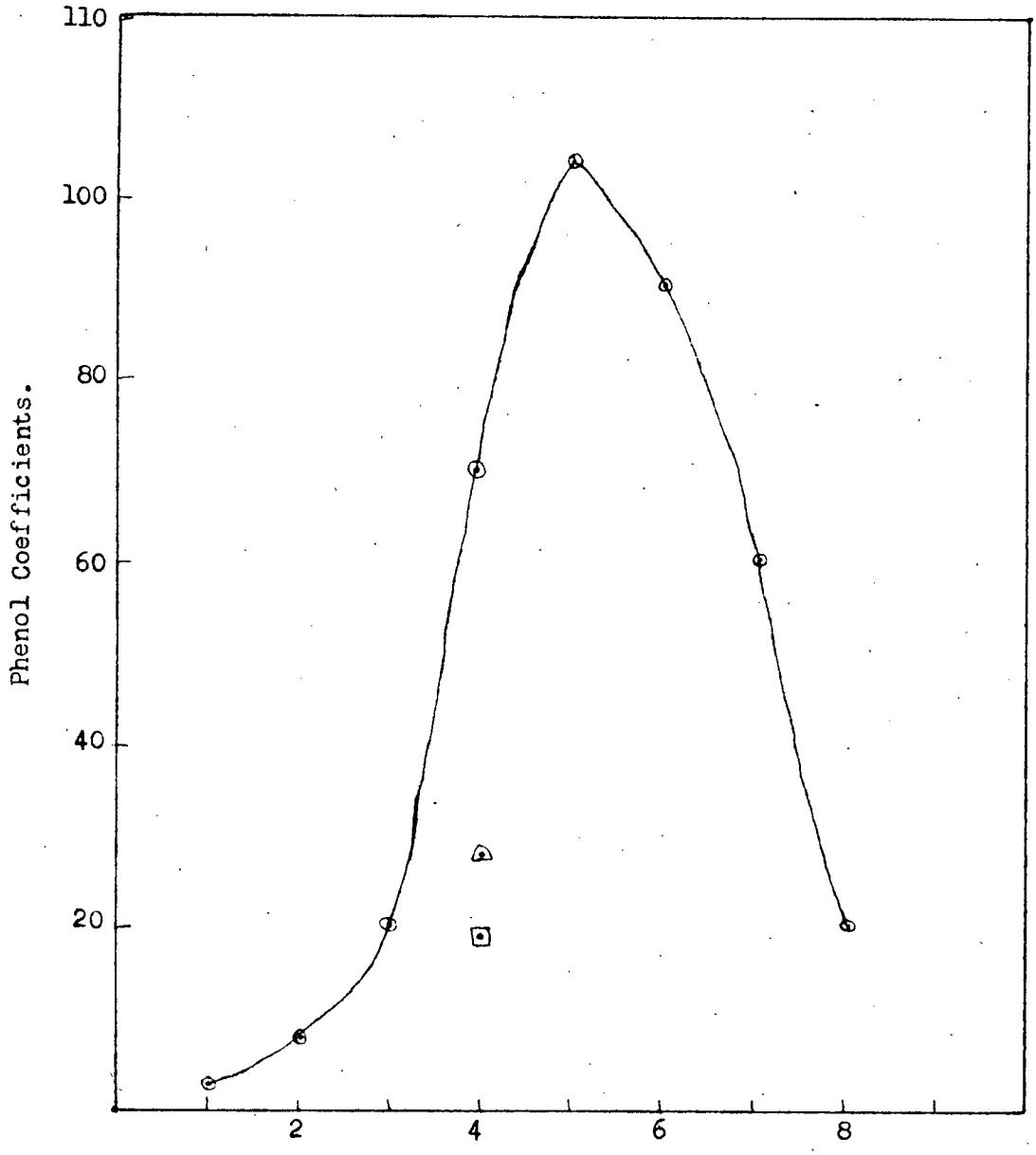


Figure 3.

Phenol Coefficients of p-Alkylphenols to B. typhosus.



Coulthard, Marshall and Pyman[26,103]. These workers have also shown the high toxicity of the amyl homologues of the four alkylcresols, and the 4-alkylguaiacols, all these compounds being prepared by one of the four following methods, followed by Clemmensen reduction:-

1. Nencki condensation of acid and phenol with zinc chloride.
2. Fries rearrangement of phenol esters with aluminum chloride.
3. Isomerization of phenol esters with zinc chloride.
4. Phenol-acid condensations using phosphorus oxychloride.

These studies show that the presence of a second alkyl group greatly increases the phenol coefficients of both alkylphenols and alkylresorcinols. Thus, the n-amylcresols show high values in the range 250-300.

The introduction of halogens into the alkylphenol nucleus causes increased toxicity, the 2-chloro-4-alkylphenols reaching their peak at the hexyl homologue and the isomers containing the halide para to the phenolic centre being more toxic yet. Fluorophenols, however, show no increased toxicity[75].

The introduction of nitro groups into the phenol nucleus is the point of chief interest in this study. Mazetti[81] has shown that nitrophenols have much higher phenol coefficients than phenol itself, with the p-nitro isomer, the most toxic of the mononitro derivatives being a hundred times more toxic than phenol[92].

The dinitrophenols are more potent yet, by a factor of about ten, and Tattersfield[133] was the first to show that the introduction of alkyl groups caused a sharp rise in toxicity. Thus dinitro-o-cresol was

found to be far superior to dinitrophenol. It appears that a nitro group para to the phenolic centre is necessary for maximum toxicity and thus the dinitro-o-alkylphenols are the compounds of chief interest rather than the p-alkyl series. The introduction of a third nitro group, however, reduces the toxicity to about that of the mononitro derivatives.

The first study of the toxic powers of 2:4-dinitro-6-n-alkylphenols was made by Kagy[63], and the results of his work against silkworm larvae are shown in Figure 4. Maximum toxicity is once more found between the hexyl and heptyl homologues.

All these compounds are powerful metabolic stimulants to man and D.N.O.C. has been used in slimming pills with some success. Fortunately, the order of toxicity of the dinitro-n-alkylphenols towards man is exactly opposite to that towards insects and this offers some added protection to the spray operator.

An extension of this work by Simon[117] against the fungus Tricoderma viride and the mustard Brassica alba is illustrated in Figures 5 and 6. In these cases the maximum toxicity is found with the compounds containing o-propyl and o-ethyl side chains respectively. In all cases the dinitro-o-alkylphenols are more toxic than their p-isomers, and the reduced toxicity accompanying iso and tertiary alkyl groups is admirably shown. The point of real interest is the anomolously high toxicity of 2:4-dinitro-o-sec.-butylphenol which would be expected to fall somewhere between the values for the primary and tertiary isomers.

It is this unexpectedly high toxicity which has prompted the present work involving other dinitro-sec.-alkylphenols and it will be very interesting to see whether or not the o-sec.-butyl homologue is unique in this property.

The only other reference that could be found dealing with toxicity tests on other sec.-alkylphenols merely showed that compounds that are presumably "di-sec.-hexyl" and "di-sec.-heptyl" resorcinols formed by resorcinol-alcohol condensations with zinc chloride, are extremely toxic and have coefficients of the order of 1000-1350[99].

For an excellent account of the toxic action of many series of polysubstituted phenols, the reader is referred to a review by Suter[130].

Figure 4.

Toxicity of 2:4-Dinitro-6-alkylphenols to Silk Worm Larvae.

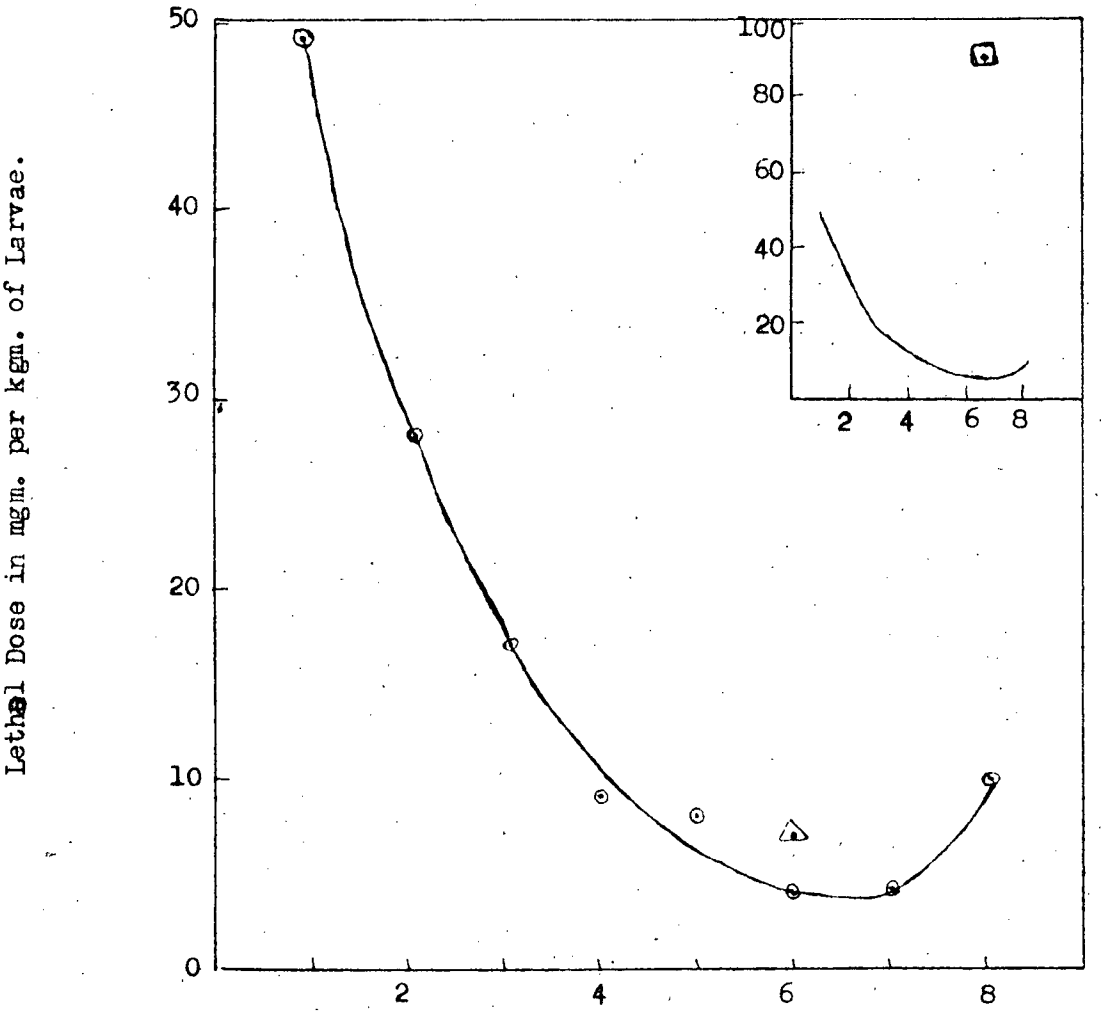
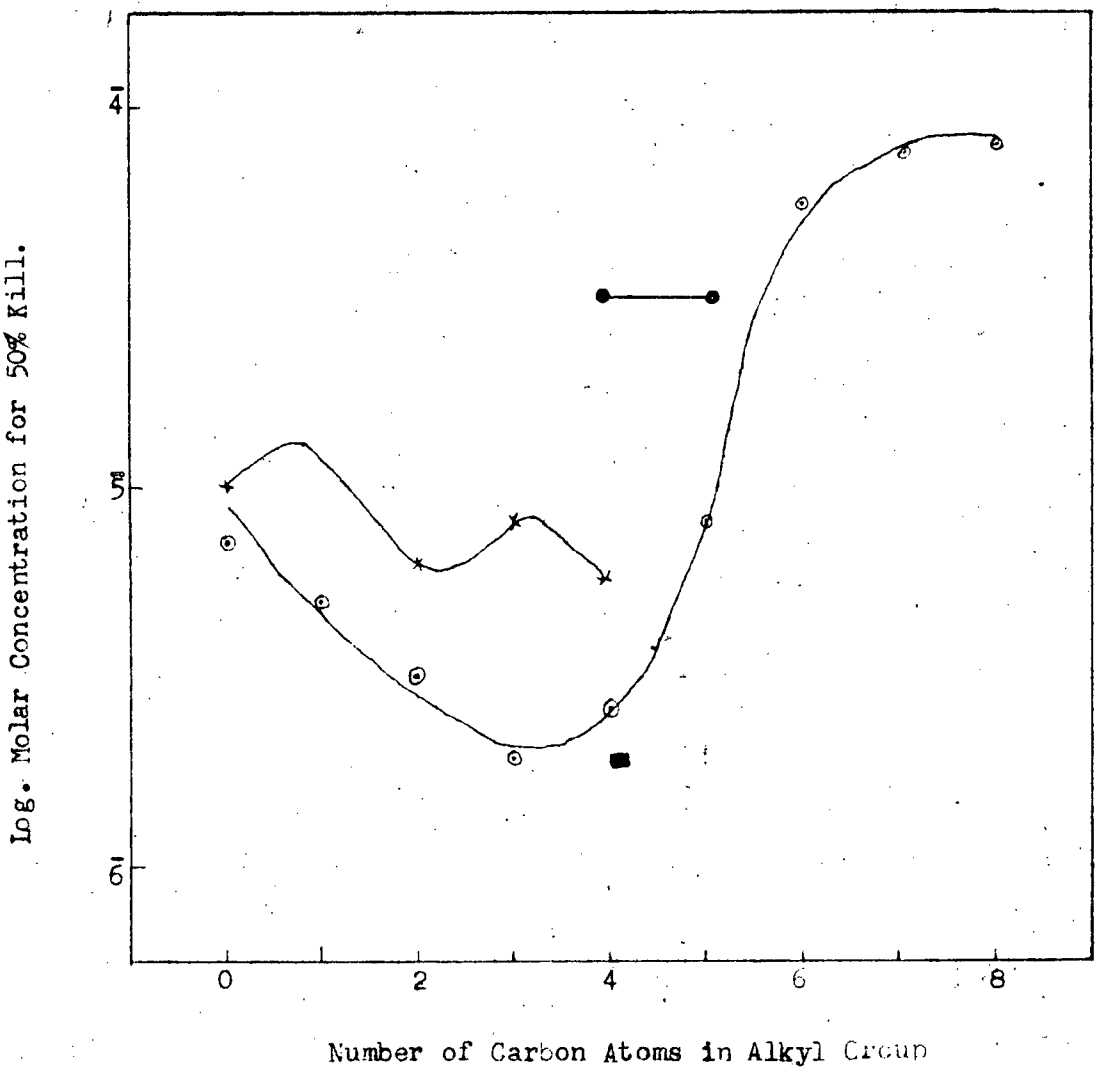


Figure 5.

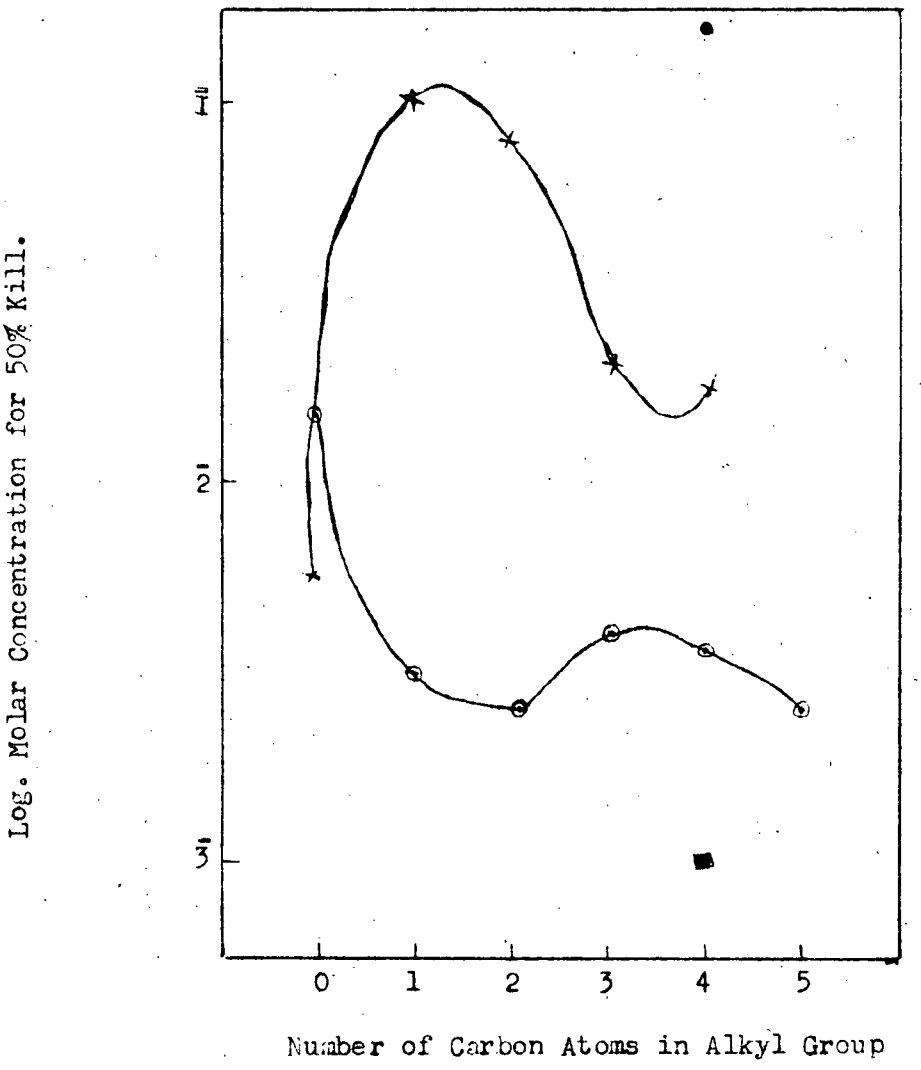
Toxicity of Dinitro-alkylphenols to Trichoderma viride.



⊙ = 2:4-dinitro-6-n-alkylphenols.
× = 2:6-dinitro-4-n-alkylphenols.
● = 2:6-dinitro-4-tert.-alkylphenols.
■ = 2:4-dinitro-6-sec.-alkylphenols.

Figure 6.

Toxicity of Dinitro-alkylphenols to Brassica alba.

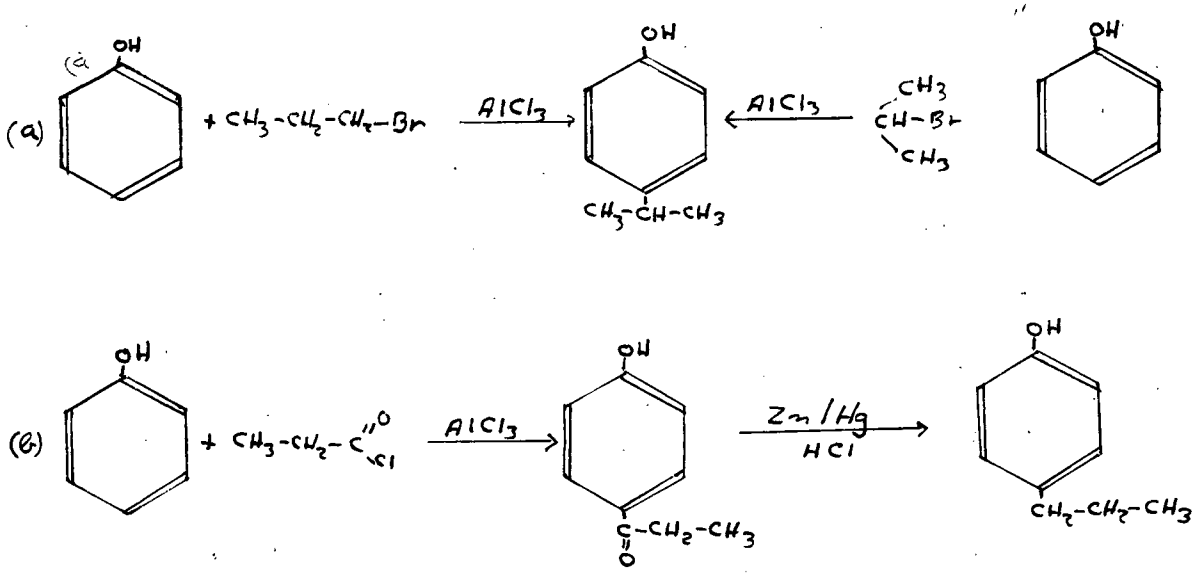


3. The Preparation of n- and iso-alkylphenols.

Primary alkylphenols have been prepared by quite a number of different methods. The more significant of these methods will be described in this section.

The problem confronting the chemist is either one of the introduction of an alkyl side chain into a phenolic nucleus, or of introducing a hydrozyl group into the nucleus of an alkyl benzene. The second case is somewhat trivial since it first requires the introduction of an alkyl group to benzene and this is essentially the same problem found in the first case. We shall then first of all consider the introduction of a side chain into the phenolic nucleus.

The first idea which meets the eye is a direct condensation of an alkyl halide, say, with phenol by a Friedel-Crafts type reaction(40,95). This possibility is immediately ruled out for two reasons. Firstly, the Friedel-Crafts reaction is known to give a mixture of isomerization products in nearly all cases using alkyl halides. Thus the alkylation of phenol, say, with both n-propyl bromide and isopropyl bromide, both give isopropylphenol. This isomerization effect will be discussed in greater detail in a later section of this thesis. The second disadvantage is that the Friedel-Crafts type condensation gives almost exclusively para substitution and thus a different method of approach is desirable for the synthesis of o-alkylphenols. The first difficulty may be surmounted by using the Friedel-Crafts ketone synthesis in which case an acid chloride is used instead of an alkyl halide, and the resulting aryl-alkyl ketone is reduced, usually by a Clemmensen type reduction.



Unfortunately, the para isomer once more predominates in most cases, but the structure of the resulting phenol is unambiguous. Ralston[98] has studied the acylation of phenol with acid chlorides and aluminum chloride, and claims that excess aluminum chloride favours para substitution while equimolecular amounts favour ortho substitution, presumably due to the directive influence of the aluminum complex that can form with both reactants and products. The use of low temperatures also increases the yield of ortho acylphenols.

One of the Clemmensen's earliest papers reports the use of his new reduction of aryl-alkyl ketones to produce p-ethyl and p-n-propyl-phenols obtained from a Friedel-Crafts reaction[21]. In 1931, Beranger[5] made a careful study of this method of synthesis and prepared all the para-primary acyl and alkyl derivatives of phenol and anisole from ethyl to heptyl. The anisoles were also demethylated to the corresponding

phenols by the use of gaseous hydrobromic acid in glacial acetic acid. Some years previous to this work, Skraup[120] had prepared and characterized the p-n-alkylanisoles from propyl to nonyl, by the Friedel-Crafts and Clemmensen reactions, as part of an investigation of the mechanism of the cracking process. On heating to 320°C. Skraup found that those compounds with an even number of carbons in the side chain split off the terminal methyl group while those with an odd number were stable. The anisoles were characterized as their sulphonamide derivatives.

This general method of synthesis has also been extended to the preparation of long chain o-alkylphenols such as o-dodecylphenol by both Friedel-Crafts condensation of fatty acid chlorides with anisole in nitrobenzene followed by Clemmensen reduction and demethylation using hydrobromic and glacial acetic acids, and by Nencki condensation of the fatty acid with phenol[91].

The use of different condensation catalysts such as anhydrous hydrofluoric acid[14] boron trifluoride, etc., for Friedel-Crafts type condensations, shows definite promise of reducing side reactions, isomerization and migration to a minimum, but need not be discussed here.

In 1908, Fries discovered that on heating phenol esters with anhydrous aluminum chloride, and hydrolysing the resulting complex, a mixture of isomeric ortho and para hydroxy alkylphenones are formed[6]. This reaction became known as the Fries Rearrangement and provides a very satisfactory route by which to obtain both ortho and para alkylphenols with none of the complications described above for the Friedel-Crafts method. By adjusting the temperature and the solvent used (if any), the

relative amounts of the two isomers may be altered to a considerable degree. It has been found in this laboratory that a temperature of 145-160°C. without solvent, gives roughly equimolecular amounts of the o- and p-hydroxyalkylphenones, which may be cleanly separated by fractionation since, due to chelation of the o-hydroxy ketones, their boiling points are reduced some sixty degrees below those of the para isomers. This chelation is also demonstrated in the steam volatility of the ortho isomers, and their much increased solubility in ligroin. The para isomers are also found to be solids and the ortho isomers liquids.

Varying the length of the alkyl group in the phenol esters does not appear to effect the para to ortho ratio of the rearrangement products in any consistant way, the ratio varying between 1-1.6 for phenol esters from phenyl caprylate to phenyl stearate(98). The use of nitrobenzene, as a solvent, favours the para isomer in a 3:1 ratio, while carbon disulphide only slightly favours the para isomer.

Experiments by Ralston(98), have shown that the hydroxy ketones themselves are stable to heating with two moles of aluminum chloride at 100°C. for six hours, and 90-98% of the unchanged hydroxy phenone may be recovered. If, however, three moles of aluminum chloride are used, decomposition results and only 35% of the reactants may be recovered. On the other hand, if only half a mole of aluminum chloride is used, the phenones are apt to condense with themselves. Thus, acetophenone heated with one-half a mole of aluminum chloride gives a 73% yield of dypnone(15).

$$2C_6H_5\cdot CO\cdot CH_3 \xrightarrow{AlCl3} C_6H_5\text{-}C(CH_3)\text{=}CH\text{-}CO\text{-}C_6H_5$$

With greater than one mole of aluminum chloride, however, this condensation does not take place.

These reactions are not apt to take place during a Fries rearrangement, but only illustrate the fact that the alkylphenones are stable structures and are not prone to isomerization, therefore giving rise to compounds of positive structure.

There have been quite a number of ways developed for the reduction of ketones to hydrocarbons, this being the reaction called for in order to convert the hydroxyalkylphenones to alkylphenols(60). A very early method consisted of heating the ketone with hydriodic acid and red phosphorus, and this was found to work in quite a few cases. Other workers had shown that zinc and sulphuric acid, or zinc alone, would work in certain cases and not in others. In 1898, Klages published the first of a series of papers on the use of sodium and ethanol in the reduction of aromatic ketones, but this method was also found to be unreliable for mixed aryl-alkyl ketones. Shortly later, Darzens(29) showed that this type of ketone could be reduced to the hydrocarbon by heating to 190°C. in the presence of hydrogen and a specially reduced nickel catalyst, and in 1942, Ipatieff(57) reopened this study and found that by using a copper oxide-aluminum oxide catalyst, a temperature of 100°C., and a hydrogen pressure of 120 atmospheres, alkylphenones were reduced to carbinols, but that at 150-180°C. the product was the corresponding alkyl benzene. The most efficient method for this type of reduction is, however, the Clemmensen reduction using zinc amalgam and hydrochloric acid(80,20). Clemmensen's early work did not involve aromatic ketones, and Voswinkel(141), in 1909,

was the first person to use this reaction for the reduction of hydroxy-alkylphenones to alkylphenols.

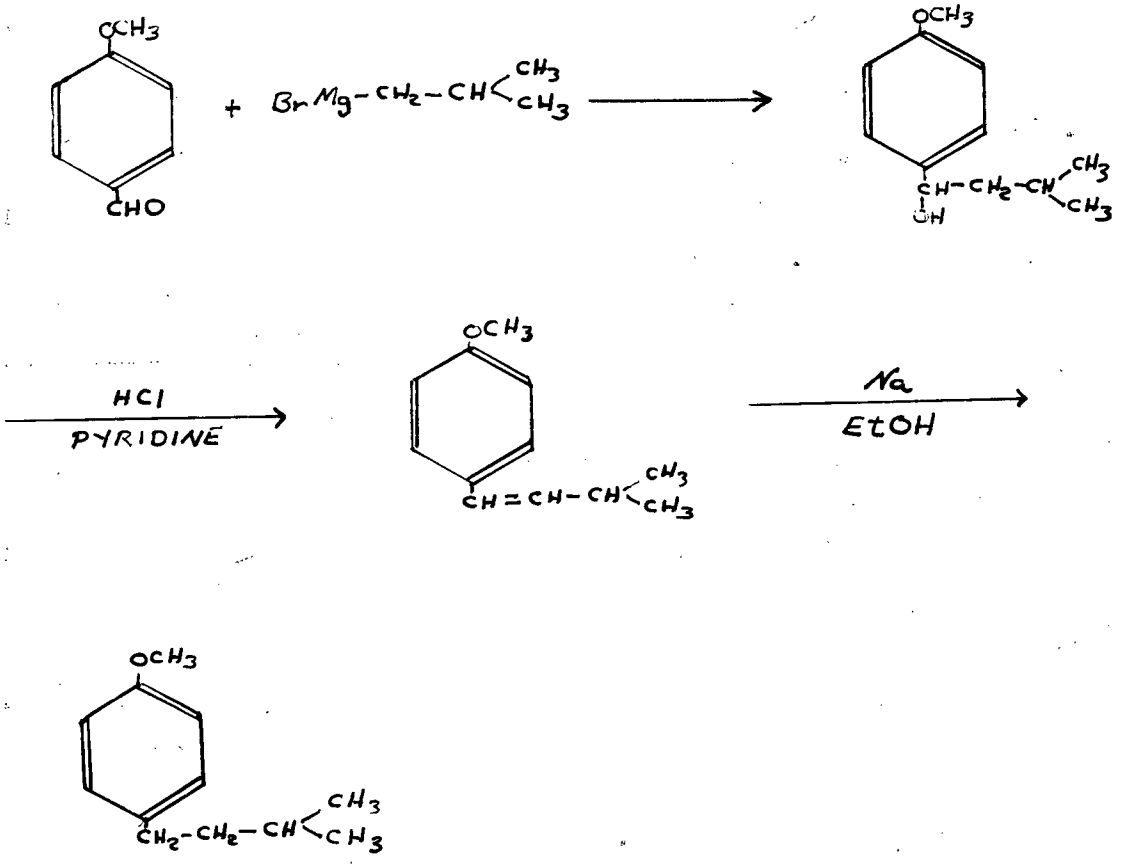
The Fries rearrangement followed by Clemmensen reduction was the method used in this laboratory for the preparation of eighteen normal and iso-alkylphenols with the side chain varying from ethyl to octyl[37]. The phenol esters were readily prepared from the corresponding acid chloride by refluxing with phenol, and fractionation.

This method of synthesis has also been used by Sandulesco and Girard[107] for the preparation of o- and p-acyl and alkylphenols with normal side chains from butyl to nonyl in an investigation of the hypnotic properties of these compounds. These workers showed that for the ortho series the reduction could be carried out by simply refluxing with equal volumes of glacial acetic acid and fuming hydrochloric acid. It may also be extended to the preparation of di and trialkylphenols by the Fries rearrangement by alkylphenol esters[113,39].

A third general method of synthesis involves the introduction of an alkyl side chain through a Grignard reaction between an alkyl halide and a methoxy benzaldehyde to give a secondary carbinol which may be dehydrated to an olefin, hydrogenated to an alkylanisole, and demethylated to an alkylphenol. This synthesis is very general and can be extended to the preparation of secondary alkylphenols by the use of the appropriate methoxy-alkylphenone. This is the method used in the experimental section of this paper and discussion will be withheld until the section on the synthesis of secondary alkylphenols.

The ortho and para isobutyl and isoamyl phenols have been prepared by Dutton by this method, and found to be identical with those by the Fries method(37).

The general method of this synthesis was originated by Klages in 1902 and was used by this worker to prepare various alkylanisoles, alkylphenatoles, and alkylbenzenes, with side chains varying from ethyl to heptyl(69,70,71,72,73). However, he never attempted demethylation of the anisoles to give the corresponding alkylphenols. A typical Klages synthesis is shown as follows:



The general plan of the series of reactions is the same as that used in this laboratory, but the procedures used in going from one step to the next have been altered. Thus, while Klages dehydrates his carbinol by first converting it to the chloride by treatment with concentrated hydrochloric acid and then dehydrohalogenates by refluxing with pyridine, it has been found more convenient to use the method of Dean and Stark(32) of refluxing the carbinol in an inert solvent such as toluene in the presence of a catalytic amount of iodine. Also, where Klages reduced his olefin to a saturated alkylanisole by treatment with metallic sodium and alcohol, the more recently developed catalytic methods of hydrogenation using Raney nickel as a catalyst have been found to be much easier, and infinitely more successful.

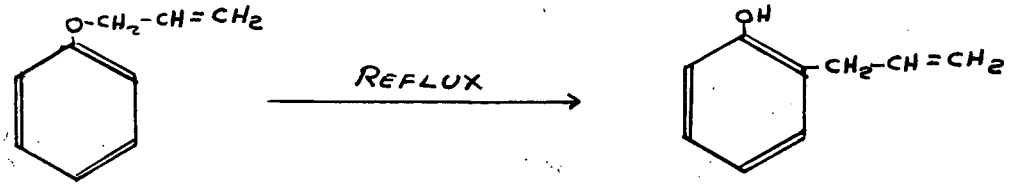
Another group of workers in France have also followed this synthesis for several steps in the synthesis of various unsaturated and saturated alkylanisoles as part of a very extensive programme of investigation of "affinity capacities and migration tendencies"(134). This group, under the direction of Tiffeneau, has produced a great deal of published material, but while they report many of the intermediates in the synthesis of the normal and iso-alkylphenols prepared in this laboratory, none of the secondary alkylphenols described in this paper are reported.

Davies, Dixon and Jones(31) have also used the Grignard method for the preparation of several unsaturated hexylbenzenes and anisoles, using the Klages method of dehydration.

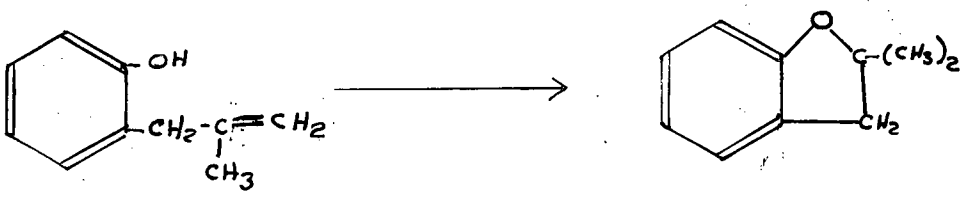
A more recent synthesis of alkylphenols by the Grignard method is reported by Alles[2] who, during work on the synthesis of cannabinol derivatives, prepared m-n-amylphenol by the action of nBuMgCl on m-MeO·C_6H_4·CHO to give 1-(m-methoxyphenyl)-pentanol-1 which was dehydrated by heating for one hour at 150°C. with potassium bisulphate, to give 1-(m-methoxyphenyl)-pentene-1. This compound was then hydrogenated to m-n-amylanisole using palladium oxide and hydrogen at 25°C., and then demethylated both by using 30% hydrobromic acid in glacial acetic acid, and by constant boiling hydriodic acid in glacial acetic acid. Alles also prepared m-n-amylphenol from m-methoxybenzyl chloride and n-butyl-magnesium chloride in rather poor yield. The compounds were identical, however, and were characterized by their 3:5-dinitrobenzoates, and, with difficulty, by analysis since they tended to explode on combustion.

These have been the three most important syntheses of normal and iso-alkylphenols, but there have also been several other methods of less general nature proposed which will be briefly described.

The first of these is the Claisen rearrangement of allylphenol ethers[18]. The commonest example of this reaction is in the rearrangement of the allyl ether of phenol, prepared by the action of allyl bromide on phenol in the presence of potassium carbonate. If this ether is refluxed for six hours it slowly rearranges to o-allylphenol which may then be reduced to o-propylphenol.



Ortho-isobutylphenol was first reported by the rearrangement of the methallyl ether of phenol prepared in a similar way to the allyl ether[4]. These rearrangements must be carefully controlled, however, or cyclization will take place to give substituted coumarans.



This cyclization can be smoothly accomplished by the addition of pyridine-hydrochloride[4], or hydrobromic acid in acetic acid[76,19]. The rearrangement always goes to the ortho position if it is open, and otherwise para.

The Claisen rearrangement is even more pronounced in the case of the allyl ethers of alkylphenols. During the alkylation of phenols with allyl halides, the solvent is the determining factor which determines whether O- or C-alkylation will result[17]. Alcohol promotes the formation of ethers, while non-dissociating solvents, such as benzene, favour C-alkylation.

Very limited use has been made of the Wurtz reaction to prepare alkyl phenols. Radcliffe[97] has obtained p-n-amylphenol in 25% yield by the action of butyl bromide on benzyl bromide in the presence of sodium wire, and, in somewhat better yield from bromobenzene and n-amyl bromide, followed by monosulphonation and alkali fusion. The usual side reaction makes the Wurtz reaction of little value when other methods are available.

Niederl and co-workers[88] in 1937 prepared a series of p-n-alkylphenols from ethyl to heptyl by condensation of equimolecular amounts of phenol and the appropriate aldehyde in glacial acetic acid at -5°C. in the presence of hydrochloric acid gas. A polymer resulted which, on distillation at atmospheric pressure, decomposed to give roughly 40% yields of the corresponding alkylphenols. The physical constants of these compounds, however, do not agree well with those obtained in this, and other, laboratories by other methods of synthesis. In general, it seems possible to prepare almost any desired alkylphenol by application of one of the Friedel-Crafts, Fries, or Grignard methods, and the latter two have been extensively studied in this laboratory.

4. The Preparation of Secondary Alkylphenols by Synthesis.

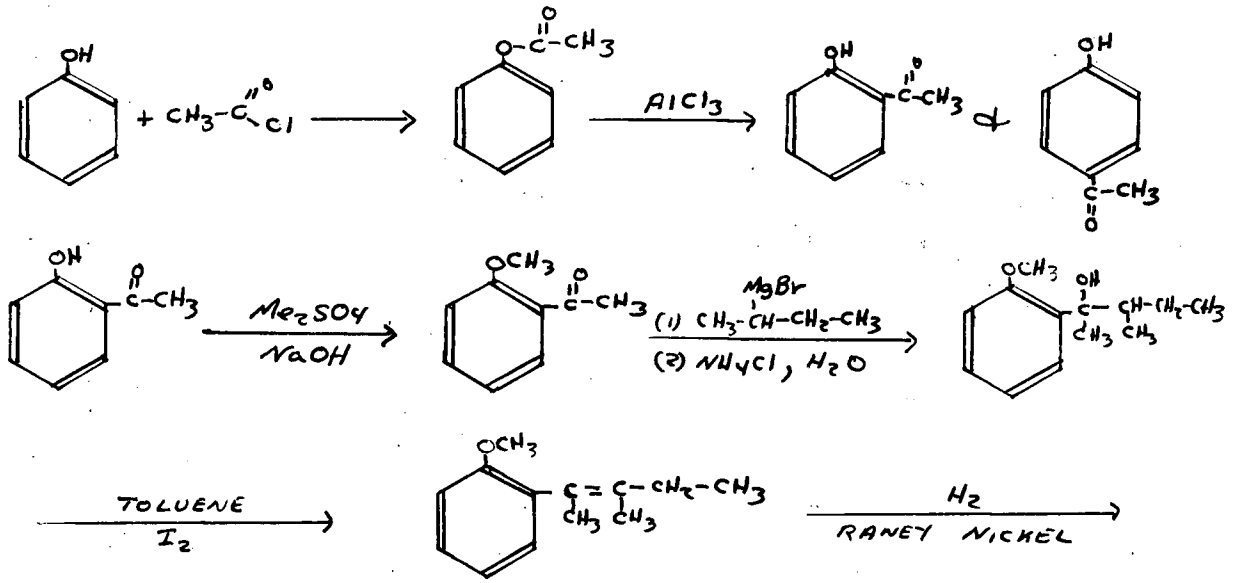
The methods described in the last section for the synthesis of primary alkylphenols are, in general, not applicable to the preparation of secondary alkylphenols. Condensations of the Friedel-Crafts type have been used rather extensively in the preparation of secondary and tertiary alkylphenols, but while these methods are adequate for the latter compounds, isomerizations occur almost inevitably during condensations of sec.-alkyl halides and alcohols, or olefins with phenol or its derivatives. The applications and limitations of condensation methods of this sort will be discussed separately in Section 5 of this paper. For the moment it is sufficient to say that secondary alkylphenols of an unequivocal structure cannot be generally prepared through condensation methods of the Friedel-Crafts type.

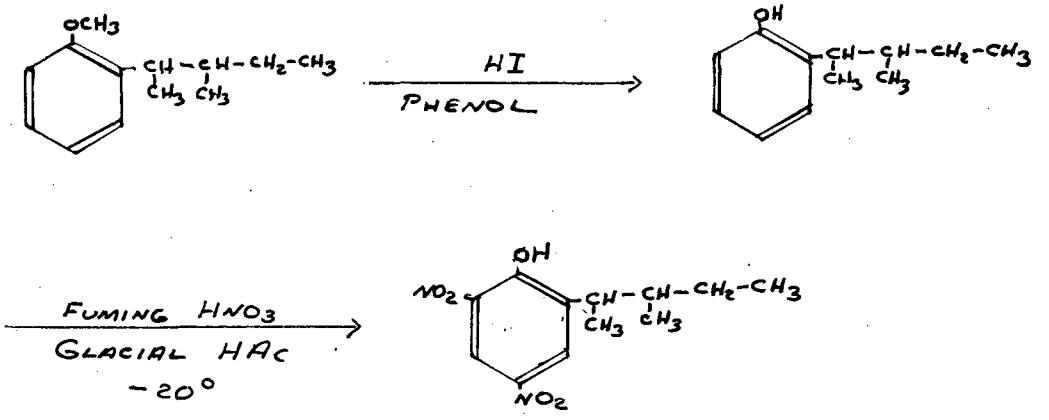
The Fries rearrangement method is obviously limited by its nature to the preparation of primary alkylphenols since it involves rearrangement to a phenone which can only be primary.

The Claisen rearrangement of γ-ethylallyl-phenyl ether has been reported to give a mixture of 3-(o-hydroxyphenyl)-pentene-1 and 2-(o-hydroxyphenyl)-pentene-3[51], but isomerization is inevitably encountered and the method seems most unsatisfactory.

The Grignard method, however, provides a highly specific and very general synthetic route by which almost any primary or secondary alkylphenol of unambiguous structure can be prepared by a correct choice of starting materials. It is this method that has been used for the preparation of the eight dinitro-sec.-alkylphenols described in this paper.

The complete synthesis may be summarized by the following example, namely, the preparation of 2-(2-hydroxy-3:5-dinitrophenyl)-3-methylpentane:





The synthesis is not a new one although the procedure has been developed in this laboratory from basic principles, and it has only been after an exhaustive literature survey that references have been found to workers who have carried it to completion by synthesis of secondary alkylphenols. Of the phenols described, only 2-(p-hydroxyphenyl)-3-methylpentane has been previously reported by an unequivocal synthesis, that being the Grignard method, and even in this case, no intermediates are listed(56).

As previously mentioned, the general method was first developed by Klages, and this worker has prepared both primary and some secondary alkylanisoles. Table XII shows a comparison of the physical constants of all compounds described in this paper that havebeen previously reported by reliable syntheses. Klages also prepared a series of primary and secondary alkylbenzenes with side chains ranging from ethyl to heptyl, by Grignard reactions between benzaldehyde or acetophenone and the appropriate alkylhalide(71,69). The only compounds which Klages has reported that duplicate those prepared for this paper were obtained by a Grignard reaction between ethyl anisate and ethyl magnesium iodide, the product

spontaneously dehydrating to 3-(p-methoxyphenyl)-pentene-2. Attempted reduction of this compound using sodium and ethanol proved very difficult, and after three attempts, the constants were still quite different from those obtained in this laboratory.

The next use of a Grignard method to produce a secondary alkylphenol was in connection with Smith and Ungnade's work on the structure of Vitamin E[124]. As part of a synthetic proof of structure, these workers prepared both 3-(o- and p-hydroxyphenyl)-hexane by Grignard reactions between o- and p-bromoanisole and hexanone-3. The resulting carbinols dehydrated spontaneously to the corresponding olefins which were hydrogenated, using a palladium catalyst, to the alkylanisoles. These compounds were demethylated by refluxing for two hours with hydriodic acid in glacial acetic acid. The phenols were characterized as their phenoxyacetic acid derivatives. 3-(p-Hydroxyphenyl)-hexane has been prepared by C.K. Harris at this university as part of an unpublished undergraduate research problem, and both this compound and its ortho isomer are soon to be reported in final form as part of the present study. There appears to be considerable deviations between the physical constants of some of the intermediates reported by Smith and those found in the undergraduate study previously mentioned. These constants are as follows:-

Compound	b.p.		n^{20}	
	Smith	Harris	Smith	Harris
3-(p-Methoxyphenyl)-hexene-2 (and 3)	125-30°/15	102-4°/0.5	1.5223	1.5302
3-(p-Methoxyphenyl)-hexane	125°/15	74-5°/0.4	1.4988	1.4997
3-(p-Hydroxyphenyl)-hexane	134-45°/14	116°/2.6	m.p.approx. 25°	m.p. = 47°

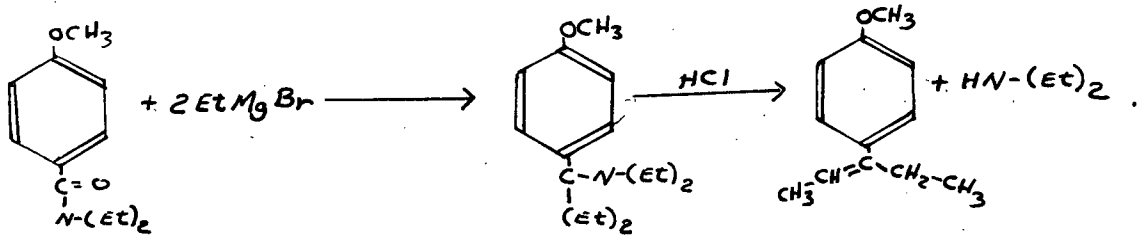
As part of a very lengthy study on Friedel-Crafts type condensations between various aromatic compounds and aliphatic alcohols, Huston[53], in 1945, reported the synthesis of 3-(p-hydroxyphenyl)-2-methylpentane and its intermediates as a proof of structure of the condensation product of phenol and 2-methyl-pentanol-4. His synthesis involved a Grignard reaction between ethylmagnesium bromide and p-methoxy-isobutyrophenone prepared by a Friedel-Crafts ketone synthesis. The resulting carbinol was found to spontaneously dehydrate to 3-(p-methoxyphenyl)-2-methyl-pentene-2 which was hydrogenated using a palladium catalyst, and demethylated by refluxing with 47% hydrobromic acid and phenol for four hours. This compound will also shortly be reported from this laboratory starting from p-methoxypropiophenone and isopropyl bromide.

In a later paper, Huston has reported the synthesis of nine p-sec.-hexyl and heptylphenols starting from p-methoxyacetophenone and p-methoxy-propiophenone[56]. Unfortunately, no intermediates are listed and only boiling points and melting points of the alpha naphthylurethan derivatives of the phenols are given. Of these phenols, only 2-(p-hydroxyphenyl)-3-methylpentane duplicates the compounds reported in the experimental section of this paper, the constants being shown in Table XII.

One other use of this synthesis has been in the preparation of m-cyclohexylphenol from m-methoxybromobenzene and cyclohexanone[42] using catalytic hydrogenation and demethylation in 95% yield with hydrobromic and glacial acetic acids.

A rather difficult approach to the Grignard synthesis has been studied by Couturier[27] who reacted two moles of ethyl magnesium bromide with N,N-diethylanisamide to produce 3-(p-methoxyphenyl)-3-diethylamino-

pentane which was decomposed in dilute hydrochloric acid to give 3-(p-methoxyphenyl)-pentene-2 which he also obtained from ethyl anisate and ethyl magnesium bromide.



Experimentally it has been found in this laboratory that excellent yields of the phenol esters may be obtained by merely refluxing the appropriate acid chloride with phenol for an hour, washing the reaction mixture with dilute sodium hydroxide, and fractionation. For the case of phenyl propionate it is convenient to add thionyl chloride gradually to a slowly refluxing mixture of phenol and propionic acid, followed by fractionation(43,139). This is more satisfactory than first preparing the propionyl chloride since this compound boils at 80°C. and thionyl chloride at 77°C. Alternatively the chloride may be prepared by the action of phosphorus trichloride on propionic acid. It has been reported that the esterification of phenols proceeds in exceptionally high yields if ten grams of magnesium per mole of phenol is added to the reaction mixture(126).

The conditions required for optimum yields in the Fries rearrangement have previously been described, and it is sufficient to say that if, on addition of the phenol ester to anhydrous aluminum chloride preheated to 70°C., the temperature is allowed to rise to 145°C. and held at this point for a short while before cooling to room temperature and slow hydrolysis

with dilute hydrochloric acid and ice, that roughly equimolecular proportions of the ortho and para hydroxyalkylphenones result in an overall yield of 75-80%, the isomers being easily and cleanly separated by fractionation under reduced pressure.

Since the next step in the synthesis involves a Grignard reaction, it is necessary to protect the phenolic group as Grignard reagents are decomposed by acidic hydrogens. Methylation has been chosen as the means of accomplishing this masking since it provides a very stable group that will not decompose in either acidic or basic solutions under ordinary conditions. Methylation also provides an opportunity to follow the subsequent reactions by means of the simple and accurate Zeisel technique of methoxyl determination. All intermediates and derivatives reported in this paper have been analysed for methoxyl content and the method has been found to be most successful.

Use of the classical methylation procedure using dimethyl sulphate in alkaline solution has been found to be just as efficient and considerably less trouble than the more specialized methods using diazomethane or methyl iodine and silver oxide. Yields of 60-80% were obtained in most cases and it was found that recovery of much of the unreacted phenol could be made by alkaline extraction of the reaction mixture. It was found to be preferable to use potassium hydroxide rather than the more common sodium hydroxide during methylation due to the greater solubility of the potassium phenates in water.

It has been shown by Lewis and Treischmann[79] that the presence of alkali is necessary, and that no methylation occurs in neutral or acidic solutions, the amount of methylation being roughly of the same order as the ratio of alkali to phenol. With excess dimethyl sulphate it has been shown that only the first methyl group enters the reaction, but under forcing conditions treatment of one mole of phenol with 0.5 moles of dimethyl sulphate and 1.5 moles of sodium hydroxide, a 70% yield of anisole may be obtained.

The Grignard reaction is done by conventional methods using great care that all reagents and apparatus are scrupulously dry and that the reaction flask is kept under a slight pressure of dried nitrogen at all times. It has been found in this laboratory that the reaction mixture, after the addition of the carbonyl compound at -5°C., should be refluxed for from five to six hours in order to prevent contamination of the product with unreacted carbonyl. The use of two moles of Grignard reagent also opposes this contamination, and, if on completion of the reaction, the products shows the presence of a carbonyl group on testing with 2:4-dinitrophenyl-hydrazine, it should be carefully dried and treated with a further amount of Grignard reagent.

The tertiary carbinol formed by the Grignard reaction may be dehydrated by either of two ways. Firstly, it may be refluxed in an inert solvent such as toluene or xylene with a catalytic amount of iodine, the water which splits off being azeotropically distilled and collected in a Dean and Stark tube[32]. Alternatively, the dehydration may be effected by refluxing with ten percent sulphuric acid, or with sulphuric acid in

glacial acetic acid[76]. The former method is to be preferred whenever possible since the reaction may be followed to completion by merely measuring the amount of water split off, and also it avoids the use of a mineral acid which frequently causes polymerization of olefinic compounds. The Dean and Stark method was tried in all cases in the present work, but in several instances no water was collected and the compound was refluxed with sulphuric acid for two hours to ensure complete dehydration.

It is during this dehydration that the only possible isomerization might occur since in most cases it is possible for water to be split out in either of two directions, although one probably predominates. This problem will, however, be circumvented during the hydrogenation step to follow.

While alcohols such as $(CH_3)_3C{\cdot}CH_2OH$ containing fully substituted carbons adjacent to the carbinol group are known to undergo the Wagner-Meerwein rearrangement to a mixture of $(CH_3)_2C{=}CHCH_3$ and $CH_2{=}C(CH_3)CH_2CH_3$ on dehydration, there appears to be no evidence of rearrangement occurring in carbinols of the type produced in this work, and such a rearrangement would certainly seem energetically improbable.

The alkenes were characterized as their nitrosyl chloride derivatives which, unfortunately, proved to be quite unstable in most cases and had to be prepared immediately prior to analysis. This derivative was first developed by Tilden[135,47] for the characterization of terpenes, and it has been found that a nitrosyl chloride will not form from a terminal ethylenic bond in a carbon chain. Their formation may be represented as a direct addition of NOCl to the ethylenic bond and the derivatives were

originally formulated as nitroso compounds. It now appears that a further rearrangement takes place to give a colourless, oxime-like compound which occurs as a dimer.

Thus $R\text{-}CH_2\text{-}CH{=}C\text{-}(CH_3)_2 + NOCl \longrightarrow R\text{-}CH_2\text{-}\underset{N=O}{CH}\text{-}\underset{Cl}{C}\text{-}(CH_3)_2 \longrightarrow$

$$R\text{-}CH_2\text{-}\underset{N\text{-}OH}{C}{=}\underset{Cl}{C}\text{-}(CH_3)_2$$

Nitrosyl chlorides of olefins containing no hydrogens on the unsaturated carbons cannot isomerize in this way and are blue in colour.

The olefins were very easily reduced by pressure hydrogenation in the presence of Raney nickel. Almost quantitative yields were obtained in all cases and the alkylanisoles were characterized as their sulphonamide derivatives[144,50] by treatment with chlorosulphonic acid at -15°C. followed by the addition of ammonium hydroxide. The use of this derivative was first reported by Skraup[121] in 1924, but at this time the use of chlorosulphonic acid had not been developed and the derivative was prepared by treatment of the anisole with concentrated sulphuric acid, and conversion to the chloride by treatment with sodium or barium chloride, followed by addition to ammonium hydroxide.

The catalytic method of reduction is vastly superior to Klages method using sodium and alcohol which has been previously described.

The final step in the preparation of alkylphenols by the Grignard method is demethylation of the alkylanisoles, and this presented considerable difficulty in this laboratory before an efficient method was developed. The method most frequently mentioned in the literature consists of refluxing the anisole with 47% hydrobromic acid in glacial acetic acid[10,27] and this procedure has met with very varied success by different workers.

The addition of gaseous hydrogen bromide during the first few hours of the reaction seems to materially improve the yields[22]. The use of hydrobromic acid and phenol followed by steam distillation of the phenol has also been suggested[143], as have the use of various aluminum salts[27], quaternary ammonium salts and potassium hydroxide in ethanol at 200°C. In general, however, the methods involve the use of mineral acids, especially hydrogen halides, under temperature and usually pressure. The use of bound halides such aniline hydrochloride was then found to give fairly good results at 200°C., especially when the ether link was weakened by nuclear substituents. Anisole itself could not be demethylated in this way even on long heating. In 1941, however, Prey suggested the use of pyridine hydrochloride[94], and found that most simple ethers could be split in five hours at 200°C. The most important factor in this type of reaction is homogenization of the reaction mixture, and the addition of 5-15% of the total weight of glacial acetic acid was found to give optimum results. The presence of any water in the reaction is to be avoided since the reflux temperature of the mixture will be lowered, and as pyridine hydrochloride is quite hygroscopic, the use of non-delequescent pyridine hydrobromide has been developed in this laboratory. This compound is a stable salt which melts and boils without decomposition and may be stored easily. The use of 1.5 equivalents of pyridine hydrobromide to 1.0 equivalents of the alkylanisole plus 10% of the total weight of glacial acetic acid heated under reflux to 185-195°C. for five hours, provides a clean demethylation of para alkylanisoles in excellent yields. The yields for primary alkylanisoles are nearly quantitative while those for secondary alkylanisoles are roughly 70-90%.

This method, however, does not provide a means of demethylation for ortho-secondary alkylanisoles in greater than a few percent yield. In a search for a method for these compounds, the use of a macro scale Zeisel methoxyl determination type reaction was found to be adequate. The anisole was refluxed for three hours with an excess of constant boiling hydriodic acid and enough phenol to provide a homogeneous mixture. For the separation of the alkylphenol from the phenol solvent, use was made of the insolubility of higher sec.-alkylphenols in dilute sodium hydroxide, a phenomenon more frequently associated with polyalkylphenols[129]. Since the same reagents provide a quantitative estimation on a semimicro scale, it was assumed that the reaction was nearly quantitative and the free alkylphenol was purified by distillation under reduced pressure. Yields of 70-85% were obtained in this way.

All the alkylphenols were characterized as their 3:5-dinitrobenzoates prepared by the pyridine method[48] and purified by recrystallization from light petroleum ether. The use of alpha-naphthylisocyanate to give alpha-naphthylurethans also provides an adequate method of characterization[49].

In passing it is worth noting that alkylbenzenes may be converted to the corresponding p-alkylphenols either by sulphonation followed by fusion with moist potassium hydroxide[13], or by the use of a rather tedious synthesis developed by Reilly and Hickenbottom[105,102,104]. This method calls for mononitration of the alkylbenzene using either mixed sulphuric and nitric acids at -5°C. or fuming nitric and glacial acetic acids at -10°C., both of which give exclusively p-nitro-alkylbenzenes, followed by reduction to the amine with tin and hydrochloric acid.

The amine is then diazotized and the diazo compound decomposed to a phenol by boiling. This method has been used quite extensively by Huston as a "proof of structure" of alkylphenols prepared through condensation methods.

5. Secondary and Tertiary Alkylphenols by Condensation Methods.

While it can be seen that the preparation of secondary and tertiary alkylphenols by true synthetic methods has been quite limited, there has been rather a lot of work done on the preparation of these compounds through direct condensation reactions between phenol and various active alkyl compounds. Unfortunately, much of this work has been of a purely industrial nature, and as long as compounds possessing the desired properties were obtained, little work was done on determining the exact nature of these products and the mechanism of their production.

As previously mentioned, nearly all condensations of the Friedel-Crafts hydrocarbon synthesis type result in isomerization and a mixture of products. Huston has spent some thirty-five years studying condensations of this type and has written many papers on the subject, but still even he has to admit that the exact nature of the products cannot be accurately predicted, nor can a single, pure product be obtained in most cases(56).

In general, the aromatic nucleus may be condensed with an alcohol, a halide or an olefin, but in certain cases use may be made of ketones(138), aldehydes(88), sulphates(38), and other compounds with variable success.

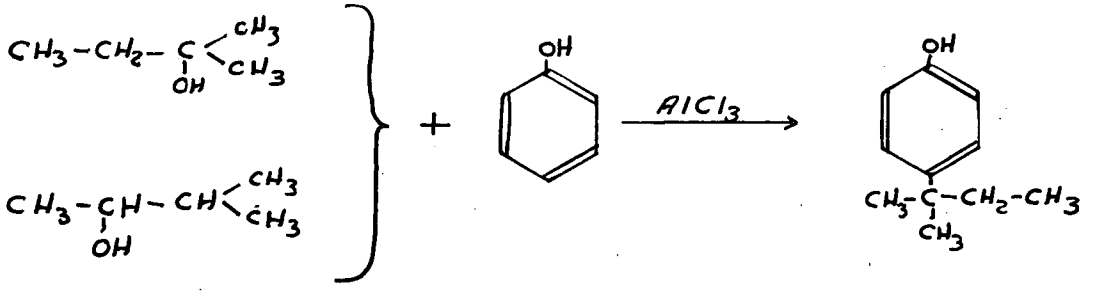
Sulphuric acid and anhydrous aluminum chloride are by far the most commonly used catalysts, but the use of many other agents including heteropolyacids such as phosphotungstic acid[120], perchloric acid[112], zinc phosphate[109], and others have been reported but need not be discussed further in a paper of this sort.

In general, the function of these catalysts may be exemplified by aluminum chloride which promotes condensation due to its electrophilic nature which allows it to capture electrons from an alkyl halide to leave a carbonium ion which may then condense with a point of high electron density in the aromatic nucleus.

It has been suggested by Skraup[120] that alkylations of this type proceed initially through the formation of O-alkyl derivatives which then rearrange in the presence of excess catalyst to the isomeric C-alkyl derivatives. By heating various phenol ethers with different catalysts, especially phosphotungstic acid, Skraup has shown that rearrangement of this type does occur, but this mechanism is not widely accepted today. There are, however, certain amounts of phenol ethers produced during alkylation, and these have been shown to isomerize to alkylphenols on treatment with aluminum chloride[125]. At low temperatures, ethers may be obtained as the sole reaction product of phenol alkylation using the more recently developed catalyst boron trifluoride[78], but at 40°C. there is no evidence of ether formation.

During his lengthy work on condensation reactions using aluminum chloride, Huston has shown that as a rule the condensation of phenol with primary alcohols gives, with difficulty, a mixture of primary and secondary

alkylphenols, those with secondary alcohols give a mixture of secondary and tertiary alkylphenols, and those with tertiary alcohols give mainly the corresponding p-tertiary alkylphenol[52,54]. These isomerizations may be looked upon as being due to migration of the carbonium ion charge to a position of maximum stability or to dehydration or dehydrohalogenation of the alcohol or halide in either of two directions. Almost inevitably if the functional group is adjacent to a chain branching, then the tertiary alkylphenol will result in great excess[53,55,56]. Thus both tert.-amyl alcohol and 2-methylbutanol-3 both gives p-tert.-amylphenol on condensation with phenol.



This phenomenon is explained by the great stability of tertiary carbonium ions.

The only secondary alcohols of those tested that do not isomerize were isopropyl, secondary butyl, and pinacoyl alcohols. Obviously the first two cannot give rise to more than one secondary carbonium ion without rearrangement of the carbon chain, and pinacoyl alcohol, (2:2-dimethylbutanol-3), because of the tertiary carbon atom adjacent to the carbinol group, also has but one choice.

Huston has attempted to prove the structures of his various reaction products by two different synthetic routes. Firstly he has used the Grignard synthesis to prepare ten different para secondary hexyl and heptyl phenols, only one of which duplicates those reported in this paper, and secondly he has alkylated benzene and introduced a para hydroxy group by mononitration, reduction and diazotization according to the method of Reilly[105]. This second method does not appear to offer very conclusive proof of structure, since isomerization is just as apt to occur during the benzene alkylation, but Huston claims to have identified these alkylbenzenes by molar refraction, parachor, density, and molecular volume determinations.

These same general tendencies have also been found by Read[100,101], using zinc chloride and hydrochloric acid, and in a much more indefinite way be several groups of Russian workers working with phenol and anisole [132,136,137,138]. These workers, however, often only refer to "sec.-amylphenol", etc., and in general their physical constants seem to be somewhat irregular and not to be trusted. For example, Tsukervanik and Nazarova[137] report o-ethylphenol as a solid melting at 137°C., this compound now being recognized as a liquid at room temperature. Their results for the preparation of tertiary alkylphenols, however, seem to agree favourably with others reported.

These Russian workers found the presence of considerable amounts of phenol ethers and dialkylphenols during aluminum chloride catalysed reactions and showed that these side reactions could be minimized by the use of excess catalyst. Their proposed mechanism of the alkylation reaction

is as follows:

$$ROH + AlCl_3 \longrightarrow AlCl_2(OR) + HCl$$

$$PhOH + AlCl_3 \longrightarrow PhOAlCl_2 + HCl$$

$$AlCl_2(OR) + PhOAlCl_2 \xrightarrow{HCl} PhOR + AlCl_3 + AlCl_2OH$$

$$2PhOR + AlCl_3 \longrightarrow RPhOR + PhOH$$

The alkylphenol is then obtained by the action of excess aluminum chloride in a manner not described.

By the action of pentanol-2 on phenol, Tsukervanik reports 3-(p-hydroxyphenyl)-pentane as a crystalline solid of melting point 86°C., accompanied by both o- and p-(2-hydroxyphenyl)-pentane.

In this laboratory 3-(p-hydroxyphenyl)-pentane was found to melt at 72°C., and a purified commercial sample of 2-(o-hydroxyphenyl)-pentane was found to have a refractive index of 1.5154 compared to the value of 1.519 reported.

In a later paper Tsukervanik reports the preparation of 3-(p-hyroxyphenyl)-pentane from diethyl ketone and phenol with a melting point of 79°C., and a twenty degree boiling range, along with another "p-secondary amylphenol" which must be 2-(p-hydroxyphenyl)-pentane, this time with a refractive index of 1.5215 at 20°C.

These statistics are meant merely to point out the difficulties which have been found in attempting to isolate pure compounds by condensation methods.

The use of aluminum chloride as the condensation catalyst causes less isomerization than does sulphuric acid[59] the effect being most felt in the case of halide condensations. While using olefins and sulphuric

acid, the isomerization is caused by initial addition to the ethylenic bond followed by removal of sulphuric acid, thus:

$$(CH_3)_2\text{-}CH_2\text{-}CH{=}CH_2{+}H_2SO_4 \rightleftharpoons (CH_3)_2\text{-}CH\text{-}\underset{OSO_3H}{CH}\text{-}CH_3$$

$$\upharpoonleft\downharpoonright$$

$$(CH_3)_2\text{-}\underset{OSO_3H}{C}\text{-}CH_2\text{-}CH_3 \rightleftharpoons H_2SO_4{+}(CH_3)_2\text{-}C{=}CH\text{-}CH_3$$

The use of anhydrous hydrofluoric acid(14,118,119) as a condensation catalyst shows considerable promise in reducing side reactions to a minimum, but only rather limited use has been made of this reagent for phenol condensations other than those leading to p-tert.-butylphenol. Boron trifluoride(78,148) and some other fluorine containing compounds(128) also appear to be effective in producing high yields and pure products.

It is to be noted that substitution is almost invariably in the para position and only by blocking this position can ortho substitution be induced. A very elegant synthesis of o-tert.-butylphenol was introduced by Hart(46) in 1949 involving the condensation of p-bromophenol with isobutylene followed by removal of the halogen by treatment with Raney Ni-Al alloy inaqueus alkali according to the method of Papa(90). Dinitro-o-tert.-butylphenol has also been prepared by condensation of isobutylene with p-nitrophenol followed by nitration(58).

From this account it can be seen that apart from the preparation of p-tert.-alkylphenols, condensation methods do not provide a very reliable synthetic route to alkylphenols of unambiguous structure, but at the same time it is felt that for most commercial purposes at the present time, the condensation processes provide satisfactory products, and that with the development of definitely known reference substances,

such as those prepared in this laboratory, the quality of these compounds may be materially improved.

6. The Preparation and Characterization of Dinitro-alkylphenols.

Phenols, being activated ring systems, are very easily nitrated using dilute nitric acid to give both o- and p-nitrophenols. In order to introduce a second nitro group, it is necessary to use slightly more severed conditions and on applying these procedures to alkylphenols, care must be exercised to prevent oxidation of the side chain which is quite susceptible to attack by oxidizing agents, such as nitric acid. To counteract this oxidation, there have been two general methods developed for the dinitration of alkylphenols.

The first of these involves an initial sulphonation using concentrated sulphuric acid followed by conversion of the sulphonic groups to nitro groups by the action of concentrated nitric acid (density 1.36) initially at -10°C. Unfortunately, this procedure(93), while giving quite good yields, requires rather a long reaction time to give optimum results.

The second method makesuse of the powerful nitrating agent fuming nitric acid (density 1.50) at a low temperature using glacial acetic acid as a solvent. The phenol dissolved in glacial acetic acid is slowly dropped, with constant stirring, into a mixture of fuming nitric acid and glacial acetic acid, the reaction mixture being maintained at a temperature of -20°C. throughout the addition. The mixture is then allowed to come to room temperature during two to three hours and is poured over crushed ice. The resulting oil or solid is extracted in chloroform, carefully washed free of excess acid, dried and distilled under high vacuum.

Both procedures have been used in this laboratory and both give roughly the same yields on the order of 60-80%. However, the second method requires much less time to complete and is somewhat easier, therefore making it the preferred procedure, and the one used in the experimental section of this paper.

Great care must be taken in seeing that the crude nitrophenol is washed free of excess nitric acid since, if any remains, decomposition will result on distillation.

A somewhat similar procedure has been used by Baroni[3] in the dinitration of various simply alkylphenols. This involves the use of concentrated nitric acid (density 1.45) in a large excess of chloroform at 15°C. and is reported to give excellent yields.

A rather interesting method of nitration is by the use of nitrous vapours evolved from a mixture of arsenious oxide and nitric acid[82]. The choice of solvent is very important in this reaction and determines whether mono or dinitration will result. The use of glacial acetic acid favours dinitration while light petroleum ether gives mononitration.

By the use of concentrated nitric acid (density 1.36) in glacial acetic acid at -20°C., mononitration results and this is the method most frequently used in the conversion of alkylbenzenes to alkylphenols by nitration, reduction and diazotization.

While phenols and alkylphenols are easily characterized as benzoates, urethans, p-toluenesulphonates, etc., these reagents are nearly useless when applied to the more acidic dinitrophenols. The use of various amine salts of dinitrophenols have been suggested as suitable derivatives for

these compounds, and at the same time are of interest because of their insecticidal and herbicidal nature and their ability to render dinitrophenols water soluble. Almost any amine may be used provided its bacisity is sufficient to enable salt formation, and a wide variety has been suggested including diethylamine[25], benzylamine[1] and various diamines[23,123].

All the dinitrophenols prepared in this laboratory have been characterized as their piperidine, morpholine and cyclohexylamine salts all of which are easily purified red, orange, or yellow crystalline compounds ranging in melting point from 120-234°C. for those tested to date. These salts are especially valuable as derivatives since isomeric compounds differ widely in their melting points. For example, the piperidine salts of 2-(2-hydroxy-3:5-dinitrophenyl)-pentane and 3-(2-hydroxy-3:5-dinitrophenyl)-pentane melt at 141°C. and 173°C. respectively. This characteristic seems to be quite general and isomeric compounds may be easily identified as their amine salts. The salts are sharp melting and relatively pure after one recrystallization from benzene-petroleum ether,

The experimental section of this paper describes in detail the conditions found to be optimum in all the steps involved in the synthesis of dinitro-sec.-amyl and hexylphenols.

III EXPERIMENTAL.

NOTE: All temperatures are uncorrected and in degrees Centigrade. Melting points are determined using an electrically heated copper block fitted with a cased thermometer, the sample being placed in a sealed glass tube within the block.

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1. Preparation of Phenyl Acetate.

a. Sodium Phenate - Acetic Anhydride Method[141].

Phenol (230 gms., 2.4 moles) was dissolved in sodium hydroxide solution (1600 mls. of 10%) contained in a three liter, wide necked bottle. Crushed ice (1750 gms.) was added, followed by acetic anhydride (325 gms., 3.2 moles). The bottle was stoppered and shaken vigorously for five minutes. Carbon tetrachloride (150 mls.) was added and the lower layer separated, washed with saturated sodium bicarbonate until effervescence stopped, and dried over magnesium sulphate. The carbon tetrachloride was removed by distillation and the phenyl acetate collected from 193-200°. The ester was redistilled at atmospheric pressure, giving a colourless liquid of b.p. 193-4°, $n^{20} = 1.5037$. Literature gives b.p. = 195-6°, $n^{20} = 1.5038$. The yields obtained on three runs were 80%, 90% and 90%.

b. Phenol - Acetyl Chloride Method.

Phenol (385 gms., 4.1 moles) was placed in a one liter ground glass flask fitted with a dropping funnel and reflux condenser. Acetyl chloride (314 gms., 4.0 moles) was added slowly through the dropping funnel at such a rate as to keep the evolution of hydrogen chloride under control. The mixture was refluxed gently for thirty minutes and distilled through a

twelve inch Vigreaux column as a colourless liquid boiling at 192-4°, n^{20} = 1.5037. Literature gives b.p.= 195-6°, n^{20}= 1.5038. Yield= 93%.

Because of its good yield and simplicity, the phenol-acetyl chloride method is to be preferred.

2. Preparation of Phenyl Propionate(141).

Phenol (300 gms., 3.2 moles) and propionic acid (264 gms., 3.5 moles) were placed in a one liter ground glass flask fitted with a dropping funnel and reflux condenser. Thionyl chloride (398 gms., 3.5 moles) was slowly added through the dropping funnel at such a rate as to keep the evolution of hydrogen chloride and sulphur dioxide under control. The mixture was refluxed for one hour to drive off these volatile gases, and distilled, the crude ester being collected from 203-212°. It was then redistilled through a twelve inch Vigreaux column to give phenyl propionate as a colourless liquid of b.p.= 206-8°, n^{21}= 1.5010. Literature gives b.p.= 211°, n^{20}= 1.5011. The yields on two runs were 75% and 76%.

3. Preparation of o- and p-Hydroxyacetophenone.

Finely powdered anhydrous aluminum chloride (540 gms., 4.0 moles) was warmed up to 70° in a two liter, two necked flask. Phenyl acetate (360 gms., 2.7 moles) was added very slowly with constant stirring. During this addition the temperature rose to 120° and the mixture became an orange-red glass. The mixture was heated to 140° for forty-five minutes and then cooled to room temperature. The flask was fitted with a reflux condenser and placed in an ice bath. Ice cold hydrochloric acid (1500 mls. of 6N) was added very slowly with swirling. On hydrolysis a dark red oil formed as an upper layer and was separated by decantation.

The residual solid material and acid was refluxed for thirty minutes and the oil once more removed. This procedure was continued until no solid material remained. The red oil was washed with dilute hydrochloric acid (200 mls. of 6N) and twice with water (200 mls.). The water was removed under water suction and the residual mixture fractionated under vacuum using a Bruel receiver and passing steam through the condenser while the solid p-hydroxyacetophenone fraction was collected. o-Hydroxyacetophenone was obtained in 41% yield as a colourless liquid of b.p. = 75°/2.4 mm., n^{21} = 1.5588. Literature gives b.p. = 96°/10 mm., n^{21} = 1.558. Semicarbazone m.p. = 215-6°, 2:4-dinitrophenylhydrazone m.p. = 212-3°. Literature gives semicarbazone m.p. = 209-10°, 2:4-dinitrophenylhydrazone m.p. = 211°. p-Hydroxyacetophenone was obtained in 39% yield as a red solid of b.p. = 160°/4 mm., a sample of which on recrystallization from ethanol melted at 106-7°. Literature gives b.p. = 148°/3.0 mm., m.p. = 109°. Semicarbazone m.p. = 203-4°, 2:4-dinitrophenylhydrazone m.p. = 258-60°. Literature gives semicarbazone m.p. = 198°, 2:4-dinitrophenylhydrazone m.p. = 261°.

The percentage yields of a series of duplicate runs are given in Appendix I.

4. Preparation of o- and p-Hydroxypropiophenone.

Anhydrous aluminum chloride (555 gms., 4.1 moles) was placed in a two liter, two necked flask and warmed to 70°. Phenyl propionate (400 gms., 2.7 moles) was added with constant stirring and the mixture heated to 140° for one hour, then cooled to room temperature and hydrolysed by the slow addition of concentrated hydrochloric acid (750 mls.) and water (250 mls.) as described in the Fries rearrangement of phenyl acetate.

Hot water (500 mls.) was added to the mixture to dissolve all the aluminum chloride, the pinkish p-hydroxypropiophenone removed by filtration and dried. The o-hydroxypropiophenone appeared as a black oil in the filtrate and was separated. Both fractions were dried under water suction and fractionated under vacuum using a Bruel receiver. o-Hydroxypropiophenone was thus obtained in 44% yield as a colourless oil boiling at 79°/.8 mm., n^{22}= 1.5498, semicarbazone m.p.= 214-5°. Literature gives b.p.= 115°/15 mm., n^{22}= 1.548, semicarbazone m.p.= 213°. p-Hydroxypropiophenone was obtained in 22% yield as a light pink solid of b.p.= 181°/5 mm., which on recrystallization from ethanol gave colourless plates melting at 147-8°. Semicarbazone m.p.= 167-8°. Literature gives b.p.= 191°/10 mm., m.p.= 148°, semicarbazone m.p.=168°.

5. Methylation of the Hydroxy-Aceto- and Propiophenones.

p-Hydroxyacetophenone (50 gms., 0.37 moles) was dissolved in a solution of potassium hydroxide (40 gms.) in water (250 mls.) contained in a 500 ml., three necked ground glass flask fitted with a dropping funnel and a very efficient mechanical stirrer. The flask was cooled in an ice back to 0° and dimethyl sulphate (90 gms., 0.71 moles) added through the dropping funnel over a period of twenty minutes. The ice bath was then removed and the flask warmed to about 50° for two hours with constant, vigorous stirring throughout. More potassium hydroxide was added, if necessary, to keep the solution basic. The mixture was allowed to settle and the oily upper layer separated. A further portion of dimethyl sulphate (10 gms.) and sufficient potassium hydroxide, to ensure basicity, was added to the residual liquid and stirring continued

for half an hour. This procedure was continued until no more oily layer formed. The combined upper layers were washed with 10% potassium hydroxide until no cloudiness resulted on acidification of the washings, then with water, the oil dried under water suction and distilled under vacuum. In all cases, considerable unreacted hydroxy alkylphenone was recovered on acidification of the remaining basic solution.

p-Methoxyacetophenone was obtained on distillation as a colourless liquid of b.p. = 97°/0.7 mm., which solidified on standing to give large colourless plates of m.p. = 36-7°. Semicarbazone m.p. = 198-9°. Literature gives b.p. = 145°/14 mm., m.p. = 38-9°, semicarbazone m.p. = 197°. The results of seven duplicate runs are recorded in Appendix II.

o-Methoxyacetophenone was obtained as a colourless liquid of b.p. = 85°/0.7 mm., $n^{20} = 1.5390$, semicarbazone m.p. = 184-5°. Literature gives b.p. = 131°/18 mm., $n^{23.5} = 1.538$, semicarbazone m.p. = 182-3°. The results of nine methylations of o-hydroxyacetophenone are recorded in Appendix II.

p-Methoxypropiophenone resulted in 56% yield as a colourless liquid of b.p. = 97°/0.4 mm., $n^{20} = 1.5460$, semicarbazone m.p. = 177°. Literature gives b.p. = 145°/14 mm., $n^{15} = 1.5477$, semicarbazone m.p. = 172-3°,177°. An almost quantitative recovery of unreacted starting material was achieved.

o-Methoxypropiophenone was obtained in 72% yield as a colourless liquid of b.p. = 86°/0.4 mm., $n^{20} = 1.5320$, semicarbazone m.p. = 156°. Literature gives b.p. = 137°/16.5 mm., semicarbazone m.p. = 154°.

6. Preparation of Isobutyl Bromide(140).

Isobutyl alcohol (277.5 gms.) and red phosphorus (25.6 gms.) were placed in a one liter ground glass flask fitted with a dropping funnel and reflux condenser. Bromine (315 gms.) was slowly added through the

dropping funnel while the flask was gently warmed. On completion of the addition the mixture was refluxed for one hour, the reflux condenser removed and the majority of the bromide distilled off. Water (100 mls.) was added to the residue and distillation continued until no more heavy oil appeared in the distillate. The lower layer was separated, washed twice with equal volumes of concentrated hydrochloric acid, water, 10% sodium carbonate, water, and dried over calcium chloride. The bromide was then distilled and collected as a heavy, very pale yellow liquid boiling at 90-92°, and having $n^{25} = 1.4330$. Literature gives b.p. = 91°, $n^{20} = 1.436$. Yields of 44% and 49% were obtained in two preparations.

7. Preparation of Alkyl-Methoxyphenyl Carbinols.
(e.g. 3-(p-Methoxyphenyl)-pentanol-3)

Magnesium turnings (24.3 gms., 1 mole) were placed in a scrupulously dried one liter, three necked, ground glass flask fitted with an efficient, mercury sealed stirrer, pressure equalizing dropping funnel, and reflux condenser. The whole apparatus was fitted so as to allow it to be kept under a slight pressure of nitrogen dried by bubbling it through concentrated sulphuric acid. Anhydrous, sodium dried ether (180 mls.) was added to the flask, and ethyl bromide (109 gms., 1 mole) dissolved in anhydrous ether (250 mls.) placed in the dropping funnel. Nitrogen was passed through the apparatus for ten minutes to displace all air, and the flow regulated so as to keep a slight pressure of nitrogen throughout the remaining procedure. The stirrer was started and the ethyl bromide and ether added very slowly. A reaction started after the addition of a few mls. The remaining bromide was added over forty-five minutes, the black mixture refluxed for one hour and then cooled to -5° in an ice-rock salt

bath. With the temperature kept at about 0°, p-methoxypropiophenone (82 gms., 0.5 mls.) dissolved in anhydrous ether (70 mls.) was added through the dropping funnel during forty-five minutes. The mixture was then refluxed for five or six hours during which time it turned grey and became full of suspended solid material. The mixture was then added very slowly and with constant stirring to a saturated solution (1 liter) of ammonium chloride and cracked ice. When the layers cleared the ether layer was separated, washed with water, and dried over magnesium sulphate. The ether was removed under reduced pressure and a small amount of the remaining 3-(p-methoxyphenyl)-pentanol-3 distilled under mercury diffusion in order to attempt to obtain physical constants without spontaneous dehydration. B.p.= 67°/0.005 mm., n^{25}= 1.5278, yield = 88%. Calculated for $C_{12}H_{18}O_2$:MeO,15.81%. Found: MeO, 15.93, 16.09%.

This procedure was applied to obtain eight different tertiary carbinols, physical constants and analyses of which are shown in Table I.

8. Dehydration of the Carbinols.
(e.g. The Preparation of 3-(p-Methoxyphenyl)-pentene-2)

Crude 3-p-methoxyphenyl-pentanol-3 (92.5 gms.) obtained directly from the Grignard reaction was placed in a 500 ml., ground glass flask fitted with a reflux condenser and Dean and Stark tube. Toluene (150 mls.) and a very small crystal of iodine were added and the mixture refluxed for several hours until no more water was collected. Very close to the theoretical volume of water was collected in the Dean and Stark tube. The toluene was then removed under reduced pressure and the remaining alkene vacuum distilled. 3-(p-Methoxyphenyl)-pentene-2 was obtained as a colourless, somewhat oily liquid of b.p.= 58°/0.03, n^{25}= 1.5310. Calculated for

$C_{12}H_{18}O$:MeO,17.61%. Found: MeO, 17.52, 17.55%. Nitrosyl chloride m.p. = 76°(d.). Calculated for $C_{12}H_{16}O_2NCl$:MeO, 12.84; N, 5.80%. Found: N,

This method was used to prepare eight alkenes, physical constants and analyses of which are recorded in Tables II and III.

The nitrosyl chloride derivatives[135,47] were prepared by adding dropwise a mixture of glacial acetic acid (2 mls.) and concentrated hydrochloric acid (2 mls.) to the alkene (2 mls.) dissolved in glacial acetic acid (2 mls.) and isoamyl nitrite (3.3 mls.) contained in a small Erlenmeyer flask chilled to -5° in an ice-hydrochloric acid bath. The mixture was stirred constantly during the addition which took thirty minutes. The mixture was green and eventually threw out of solution a white solid which was filtered off and washed repeatedly with methyl alcohol. It was then dried in a vacuum dessicator and melting points, analyses, etc., done immediately since the nitrosyl chlorides were frequently found to be unstable.

9. Hydrogenation of the Alkenes.
(e.g. The Preparation of 3-(p-Methoxyphenyl)-pentane).

3-(p-Methoxyphenyl)-pentene-2 (63 gms., 0.36 moles) was placed in the glass liner of the hydrogenator along with Raney nickel (approx. 2 gms.) and ethanol (10 mls.). The liner was placed in the bomb and hydrogen introduced to a pressure of 750 p.s.i. The bomb was then shaken at 50° until no further pressure drop occurred (approx. one hour). The Raney nickel was then filtered off, washed with ethanol, and the ethanol removed under reduced pressure. The alkane was then vacuum distilled, giving 3-(p-methoxyphenyl)-pentane in 90% yield as a colourless oil of b.p. =

56°/0.02, n^{25} = 1.5030. Calculated for $C_{12}H_{18}O$:MeO, 17.41%. Found: MeO, 17.40,17.47. Sulphonamide m.p. = 107°. Calculated for $C_{12}H_{19}O_3NS$:MeO, 12.11; N,5.49%. Found:MeO,12.28; N, 5.52%.

Eight alkanes were prepared in this way and their physical constants are reported in Tables IV and V.

The sulphonamide derivative[145] was prepared by dissolving the phenol ether (1 gm.) in chloroform (5 mls.) contained in a 25 ml., Erlenmeyer flask. Chlorosulphonic acid (7 mls.) was added dropwise to the mixture kept at -15° in an ice-hydrochloric acid bath. The mixture, which turned red and became somewhat viscous, was then added slowly to crushed ice (30 gms.). The chloroform layer was separated, the chloroform evaporated under reduced pressure, the residue added to concentrated ammonium hydoxide (10 mls.) and boiled for fifteen minutes. Water (50-100 mls.) was added, the solid filtered off and recrystallized from petroleum ether.

10. Demethylation of the Alkylanisoles.

(a) The Preparation of Pyridine Hydrobromide.

Pyridine (80 gms., 1 mole) was placed in a 500 ml., 3 necked ground glass flask fitted with a reflux condenser and dropping funnel. Hydrobromic acid (47%, 192 gms., 1.2 moles) was slowly added through the dropping funnel and the mixture refluxed for thirty minutes.

The reflux condenser was replaced by a distilling head and the water and excess hydrobromic acid distilled off up to 130°. The residue was poured into a large mortar while still hot, allowed to cool, and ground up. Pyridine hydrobromide was obtained a slightly pink solid or, on

recrystallization from ethanol, as white crystals of m.p.= 214-5°. Literature m.p.= 213°. Yields of 91%, 94% and 96% were obtained in three preparations.

(b) The Preparation of 3-(p-Hydroxyphenyl)-pentane.

3-(p-Methoxyphenyl)-pentane (45.5 gms., 0.25 moles) was placed in a 100 ml., ground glass flask fitted with a reflux condenser. Pyridine hydrobromide (53.5 gms., 0.325 moles) and glacial acetic acid (9.8 gms., 10% of total weight) were added and the mixture refluxed at 190-200° overnight, the temperature being controlled by a Variac and a thermometer hung down the reflux condenser with its bulb in the liquid. The mixture was cooled, water (50 mls.) added and the mixture extracted with ether. The ether extracts were washed twice with 10% sodium bicarbonate, and the phenol extracted several times with 10% potassium hydroxide. The alkaline solution was then acidified with hydrochloric acid at which point the phenol appeared as an oil which was extracted in ether, dried over magnesium sulphate, the ether removed under reduced pressure, and the phenol vacuum distilled. 3-(p-Hydroxyphenyl)pentane was obtained in 68% yield as a colourless oil boiling at 83°/0.3 mm., which solidified on cooling to a white solid of m.p.= 71-2°. Calculated for $C_{11}H_{16}O$:C, 80.44; H, 9.82%. Found: C, 80.26; H, 9.44%. 3:5-Dinitrobenzoate m.p.= 92-3°. Calculated for $C_{18}H_{18}N_2O_6$:N, 7.82%. Found:N,7.92%.

(c) The Preparation of 2-(o-Hydroxyphenyl)-4-methylpentane.

(i) Using pyridine hydrobromide.

2-(o-Methoxyphenyl-4-methylpentane (37.6 gms.) was refluxed with pyridine hydrobromide (41 gms.), and glacial acetic acid (7.9 gms.) as

previously described. On extraction with 10% potassium hydroxide and acidification, only approximately 0.5 gms., of a brown oil was liberated. The demethylation was considered to be a failure and the residual organic phase was dried and distilled to recover 30 gms. of the unreacted phenol ether.

(ii) Using hydriodic acid and phenol.

2-(o-Methoxyphenyl)-4-methylpentane (35.5 gms.) was refluxed for three hours with a mixture of 40% hydriodic acid (175 gms.), and phenol (175 gms.). At the end of this time the reaction mixture was cooled to room temperature, dissolved in ether, and extracted repeatedly with 5% sodium hydroxide until acifidication of the extracts gave almost no clouding of the solution. The ether solution was then washed with water, dried over magnesium sulphate and distilled under reduced pressure, giving a 76% yield of 2-(o-hydroxyphenyl)-4-methylpentane as a colourless viscous liquid of b.p. = 59°/0.03 mm., $n^{25} = 1.5077$. Calculated for $C_{12}H_{18}O$: C,80.85; H,10.18; MeO. 0.0%. Found: C, 81.05; H, 10.17; OCH_3, 0.30%.

The product was only very sparingly soluble in dilute sodium hydroxide. This method of demethylation was used for all the ortho alkylphenols reported.

II. Nitration of the Alkylphenols.
(e.g. The Preparation of 3-(4-Hydroxy-3:5-dinitrophenyl)-pentane).

3-(p-Hydroxyphenyl)-pentane (24 gms.) was mixed with glacial acetic acid (60 mls.) and added dropwise, with constant mechanical stirring, to a mixture of yellow fuming nitric (density 1.50, 40 mls.) and glacial acetic acids(75 mls.) contained in a stainless steel beaker and cooled to -20° in an acetone-dry ice bath. The temperature was kept at -20°

throughout the addition which took forty-five minutes. On addition of the phenol the mixture became a dark red colour. The beaker was removed from the cooling bath and allowed to come slowly to room temperature. It was then allowed to stand for two hours and poured onto crushed ice (200 gms.) whereupon a red oil sank to the bottom. The ice was allowed to melt slowly and the mixture extracted three times with 100 ml. portions of chloroform. The chloroform extracts were then carefully washed with warm water until neutral to congo red indicator paper. This usually required about ten washings. The solution was then dried over anhydrous magnesium sulphate, the solvent removed under reduced pressure, and the remaining red liquid distilled under high vacuum, to give a 75% yield of 3-(4-hydroxy-3:5-dinitrophenyl)-pentane as a viscous amber coloured liquid of b.p. = 149°/ 0.03 mm., $n^{25} = 1.5664$.

This technique was used in the preparation of ten dinitrophenols, physical constants of which are listed in Table VIII.

12. Preparation of Amine Salts of Dinitro-alkylphenols. (e.g. The Preparation of the piperidine salt of 3-(4-hydroxy-3:5-dinitrophenyl)-pentane.

3-(4-hydroxy-3:5-dinitrophenyl)-pentane (1 ml.) was dissolved in benzene (5 mls.) contained in a small Erlenmeyer flask. Piperidine (1 ml.) was added to this mixture which immediately turned red, and the solution was boiled for a few minutes on a hot plate. On cooling and addition of low boiling petroleum ether (b.p. = 30-60°) a solid mass of orange crystals was deposited which was filtered and recrystallized twice from a benzene-petroleum ether (b.p. 65-100°) solvent pair. The product was easily purified in this way giving small orange plates melting at 213o.

Calculated for $C_{16}H_{25}N_3O_5$: N, 12.38%. Found: N, 12.36%.

Piperidine, morpholine and cyclohexylamine salts of the eight dinitroalkylphenols were prepared in this way and their melting points and analyses are recorded in Tables IX, X and XI.

TABLE 1.

PHYSICAL CONSTANTS OF CARBINOLS

Compound	b.p.	n^{25}	% Methoxyl		% Yield*
			Found	Calculated	
2-(p-Methoxyphenyl)-hexanol-2	68°/0.005	1.5285	14.92, 14.82	14.90	85
2-(p-Methoxyphenyl)-4-methylpentanol-2	63°/0.005	1.5128	15.06, 15.11	14.90	84
2-(p-Methoxyphenyl)-3-methylpentanol-2	Dehydrated spontaneously.			14.90	81
3-(p-Methoxyphenyl)-pentanol-3	87°/0.005	1.5278	16.09, 15.93	15.81	88
2-(o-Methoxyphenyl)-hexanol-2	79°/0.005	1.5095	14.78, 14.77	14.90	79
2-(o-Methoxyphenyl)-4-methylpentanol-2	68°/0.005	1.5260	15.20, 15.26	14.90	85
2-(o-Methoxyphenyl)-3-methylpentanol-3**	73°/0.005	1.5170	16.18, 16.14	14.90	84
3-(o-Methoxyphenyl)-pentanol-3	76°/0.005	1.5160	15.96, 15.90	15.81	95

* Based on amount of water split off during dehydration whenever possible.

** Apparently dehydrated spontaneously on distillation. Methoxyl determinations high in most cases indicating partial dehydration.

TABLE II.

PHYSICAL CONSTANTS OF ALKENES.

Compound	b.p.	n^{25}	% Methoxyl	
			Found	Calculated
2-(p-Methoxyphenyl)-hexene-2	70°/0.01	1.5329	16.15, 16.25	16.31
2-(p-Methoxyphenyl)-4-methylpentene-2	68°/0.04	1.5290	16.22, 16.26	16.31
2-(p-Methoxyphenyl)-3-methylpentene-2	63°/0.04	1.5260	(17.45, 17.45) (17.45, 17.40)	16.31
3-(p-Methoxyphenyl)-pentene-2	58°/0.03	1.5310	17.52, 17.55	17.61
2-(o-Methoxyphenyl)-hexene-2	64°/0.04	1.5199	16.34	16.31
2-(o-Methoxyphenyl)-4-methylpentene-2	59°/0.01	1.5134	16.16, 16.21	16.31
2-(o-Methoxyphenyl)-3-methylpentane-2	57°/0.04	1.5170	16.60, 16.53	16.31
3-(o-Methoxyphenyl)-pentene-2	70°/0.03	1.5220	17.54, 17.52	17.61

TABLE III.

NITROSYL CHLORIDES OF ALKENES.

Compound	m.p. of nitrosyl chloride	% Nitrogen	
		Found	Calculated
2-(p-Methoxyphenyl)-hexene-2	86	5.48	5.48
2-(p-Methoxyphenyl)-4-methylpentene-2	104	5.53	5.48
2-(p-Methoxyphenyl)-3-methylpentene-2	-	-	5.48
3-(p-Methoxyphenyl)pentene-2	79	5.83	5.80
2-(o-Methoxyphenyl)-hexene-2	103	5.45	5.48
2-(o-Methoxyphenyl)-4-methylpentene-2	-	-	5.48
2-(o-Methoxyphenyl)-3-methylpentene-2	-	-	5.48
3-(o-Methoxyphenyl)-pentene-2	97	5.81	5.80

TABLE IV.

PHYSICAL CONSTANTS OF ALKANES.

Compound	b.p.	n^{25}	% Methoxyl		% Yield
			Found	Calculated	
2-(p-Methoxyphenyl)-hexane	60°/0.03	1.5012	16.26, 16.30	16.14	100
2-(p-Methoxyphenyl)-4-methylpentane	54°/0.04	1.4930	16,28, 16.16	16.14	80
2-(p-Methoxyphenyl)-3-methylpentane	60°/0.03	1.5060	(16.88, 16.90) (16.89, 16.92)	16.14	87
3-(p-Methoxyphenyl)-pentane	56°/0.02	1.5030	17.40, 17.47	17.41	90
2-(o-Methoxyphenyl)-hexane	59°/0.02	1.5045	15.96, 16.01	16.14	91
2-(o-Methoxyphenyl)-4-methylpentane	54°/0.04	1.4951	15.99, 16.15	16.14	94
2-(o-Methoxyphenyl)-3-methylpentane	52°/0.01	1.5070	16.22, 16.25	16.14	96
3-(o-Methoxyphenyl)-pentane	50°/0.01	1.5010	17.20, 17.24	17.41	93

TABLE V.

SULPHONAMIDES OF ALKANES.

Compound	m.p. of sulphonamide	% Methoxyl		% Nitrogen	
		Found	Calculated	Found	Calculated
2-(p-Methoxyphenyl)-hexane	79	11.59	11.44	5.18	5.16
2-(p-Methoxyphenyl)-4-methylpentane	92	11.43	11.44	5.10	5.16
2-(p-Methoxyphenyl)-3-methylpentane	100	11.44, 11.48	11.44	5.16	5.16
3-(p-Methoxyphenyl)-pentane	107	12.28	12.11	5.52	5.49
2-(o-Methoxyphenyl)-hexane	-	-	11.44		5.16
2-(o-Methoxyphenyl)-4-methylpentane	103	11.47, 11.51	11.44	5.13	5.16
2-(o-Methoxyphenyl)-3-methylpentane	-	-	11.44		5.16
3-(o-Methoxyphenyl)-pentane	71 crude	-	12.11		5.49

TABLE VI.

PHYSICAL CONSTANTS OF ALKYLPHENOLS.

Compound	b.p.	m.p.	n^{25}	% Carbon*		% Hydrogen*		% Yield
				Found	Calculated	Found	Calculated	
2-(p-Hydroxyphenyl)-hexane	80°/0.05	-	1.5110	80.37	80.85	9.93	10.18	68
2-(p-Hydroxyphenyl)-4-methylpentane	80°/0.1	-	1.5082	80.69	80.85	10.21	10.18	89
2-(p-Hydroxyphenyl)-3-methylpentane	87°/0.09	-	1.5210	80.60	80.85	10.01	10.18	56
3-(p-Hydroxyphenyl)-pentane	83°/0.3	72°	-	80.26	80.44	9.44	9.82	68
2-(o-Hydroxyphenyl)-hexane	60°/0.01	-	1.5160	80.99	80.85	10.12	10.18	81
2-(o-Hydroxyphenyl)-4-methylpentane	59°/0.03	-	1.5077	80.38	80.85	10.17	10.18	76
2-(o-Hydroxyphenyl)-3-methylpentane	53°/0.02	-	1.5074	81.05	80.85	10.00	10.18	81
3-(o-Hydroxyphenyl)-pentane	61°/0.1	64°	-	79.93	80.44	9.78	9.82	71
2-(o-Hydroxyphenyl)-pentane	68°/0.05	-	1.5154)	Commercial Samples.				
2-(o-Hydroxyphenyl)-2-methylbutane.	65°/0.03		1.5208)					

* Carbon and hydrogen analyses by Drs. Weiler and Strauss, Oxford.

TABLE VII.

3:5-DINITROBENZOATES OF ALKYLPHENOLS.

Compound	m.p. of 3:5-dinitro-benzoate	% Nitrogen	
		Found	Calculated
2-(p-Hydroxyphenyl)-hexane	92	7.66	7.53
2-(p-Hydroxyphenyl)-4-methylpentane	93	7.57	7.53
2-(p-Hydroxyphenyl)-3-methylpentane	103	7.64	7.53
3-(p-Hydroxyphenyl)-pentane	92	7.92	7.82
2-(o-Hydroxyphenyl)-hexane	94	7.60	7.53
2-(o-Hydroxyphenyl)-4-methylpentane	95	7.49	7.53
2-(o-Hydroxyphenyl)-3-methylpentane	94	7.57	7.53
3-(o-Hydroxyphenyl)-pentane	87	7.67	7.82
2-(o-Hydroxyphenyl)-2-methylbutane*	154	7.92	7.82
2-(o-Hydroxyphenyl)-pentane**	96	7.75	7.82

* Sharples o-tert.-amylphenol.

** Sharples o-sec.-amylphenol.

TABLE VIII.

PHYSICAL CONSTANTS OF DINITRO-ALKYLPHENOLS.

Compound	b.p.	n^{25}	% Yield
2-(4-Hydroxy-3:5-dinitrophenyl)-hexane	160°/0.02	1.5574	71
2-(4-Hydroxy-3:5-dinitrophenyl)-4-methylpentane	147°/0.01	1.5562	74
2-(4-Hydroxy-3:5-dinitrophenyl)-3-methylpentane	157°/0.03	1.5648	60
3-(4-Hydroxy-3:5-dinitrophenyl)-pentane	149°/0.03	1.5664	75
2-(2-Hydroxy-3:5-dinitrophenyl)-hexane	145°/0.05	1.5636	66
2-(2-Hydroxy-3:5-dinitrophenyl)-4-methylpentane	142°/0.04	1.5589	63
3-(2-Hydroxy-3:5-dinitrophenyl)-pentane	138°/0.007	1.5668	55
2-(2-Hydroxy-3:5-dinitrophenyl)-3-methylpentane	137°/0.05	1.5520	62
2-(2-Hydroxy-3:5-dinitrophenyl)-2-methylbutane*	158°/0.3	(m.p.=53°) 1.5770	58
2-(2-Hydroxy-3:5-dinitrophenyl)-pentane*	132°/0.03	1.5698	63

* Phenol obtained from Sharples Chemical Company.

TABLE IX.

PIPERIDINE SALTS OF DINITRO-ALKYLPHENOLS.

Salt of	M.P.	% Nitrogen	
		Found	Calculated
2-(4-Hydroxy-3:5-dinitrophenyl)-hexane	150	11.84	11.89
2-(4-Hydroxy-3:5-dinitrophenyl)-4-methylpentane	186	11.87	11.89
2-(4-Hydroxy-3:5-dinitrophenyl)-3-methylpentane	160	11.80	11.89
3-(4-Hydroxy-3:5-dinitrophenyl)-pentane	213	12.36	12.38
2-(2-Hydroxy-3:5-dinitrophenyl)-hexane	-	-	-
2-(2-Hydroxy-3:5-dinitrophenyl)-4-methylpentane	136	11.83	11.89
2-(2-Hydroxy-3:5-dinitrophenyl)-3-methylpentane	187	11.89	11.89
3-(2-Hydroxy-3:5-dinitrophenyl)-pentane	173	12.33	12.38
2-(2-Hydroxy-3:5-dinitrophenyl)-2-methylbutane	164	12.29	12.38
2-(2-Hydroxy-3:5-dinitrophenyl)-pentane	141	12.22	12.38

TABLE X.

MORPHOLINE SALTS OF DINITRO-ALKYLPHENOLS.

Salt of	m.p.	% Nitrogen	
		Found	Calculated
2-(4-Hydroxy-3;5-dinitrophenyl)-hexane	145	11.73	11.83
2-(4-Hydroxy-3;5-dinitrophenyl)-4-methylpentane	168	11.75	11.83
2-(4-Hydroxy-3;5-dinitrophenyl)-3-methylpentane	113	12.15	11.83
3-(4-Hydroxy-3;5-dinitrophenyl)-pentane	185	12.17	12.31
2-(2-Hydroxy-3;5-dinitrophenyl)-hexane	133	12.81	11.83
2-(2-Hydroxy-3;5-dinitrophenyl)-4-methylpentane	144	11.78	11.83
2-(2-Hydroxy-3;5-dinitrophenyl)-3-methylpentane	-	-	11.83
3-(2-Hydroxy-3;5-dinitrophenyl)-pentane	157	11.84	12.31
2-(2-Hydroxy-3;5-dinitrophenyl)-2-methylbutane	154	11.84	12.31
2-(2-Hydroxy-3;5-dinitrophenyl)-pentane	147	12.22	12.31

TABLE XI.

CYCLOHEXYLAMINE SALTS OF DINITRO-AIKYLPHENOLS.

Salt of	m.p.	% Nitrogen	
		Found	Calculated
2-(4-Hydroxy-3:5-dinitrophenyl)-hexane	138	11.32	11.44
2-(4-Hydroxy-3:5-dinitrophenyl)-4-methylpentane	165	11.34	11.44
2-(4-Hydroxy-3:5-dinitrophenyl)-3-methylpentane	163	11.36	11.44
3-(4-Hydroxy-3:5-dinitrophenyl)-pentane	217	11.77	11.89
2-(2-Hydroxy-3:5-dinitrophenyl)-hexane	173	11.48	11.44
2-(2-Hydroxy-3:5-dinitrophenyl)-4-methylpentane	193	11.37	11.44
2-(2-Hydroxy-3:5-dinitrophenyl)-3-methylpentane	207	11.42	11.44
3-(2-Hydroxy-3:5-dinitrophenyl)-pentane	192	11.80	11.89
2-(2-Hydroxy-3:5-dinitrophenyl)-2-methylbutane	205	11.74	11.89
2-(2-Hydroxy-3:5-dinitrophenyl)-pentane	190	11.84	11.89

TABLE XII.

COMPOUNDS PREVIOUSLY REPORTED IN THE LITERATURE.

Compound	Ref.	Method	b.p.		Refractive Index	
			lit.	thesis	n^{21} lit.	n^{25} thesis
3-(p-Methoxyphenyl)-pentanol-3	27	p-MeO·C_6H_4COOEt + EtMgBr	120°/3	87°/0.005	-	1.5278
3-(p-Methoxyphenyl)-pentene-2	27	p-MeO·C_6H_4·CO·N(Et)$_2$ + EtMgBr	117°/8	58°/0.03	-	1.5310
3-(p-Methoxyphenyl)-pentene-2	72	p-MeO·C_6H_4·COOEt + EtMgI	129°/17	58°/0.03	1.5395	1.5310
3-(p-Methoxyphenyl)-pentane	72	Above olefin + Na/EtOH	-	56°/0.02	1.5276	1.5030
2-(p-Hydroxyphenyl)-3-methylpentane	56	p-MeO·C_6H_4·CO·CH_3 + 2° BuMgBr	120°/3	87°/0.09	-	1.5210
3-(p-Hydroxyphenyl)-pentane	56	Condensation	108-17°/2	83°/0.03	-	m.p.=72°
2-(p-Hydroxyphenyl)-hexane	56	Condensation	110°/2	80°/0.05	-	1.5110
2-(p-Hydroxyphenyl)-3-methylpentane	56	Condensation	120°/3	87°/0.09	-	1.5210
2-(p-Hydroxyphenyl)-4-methylpentane	56	Condensation	109°/2	80°/0.1	-	1.5082

IV. DISCUSSION OF RESULTS.

The Grignard method of synthesis of both ortho and para secondary alkylphenols described in this paper appears to provide the only complete synthesis of these compounds in such a way that their structures are unequivocal. By a judicious choice of the correct starting materials, almost any desired phenol may be prepared. The only limitations which might be imposed are those due to steric effects during more complicated Grignard reactions, and possibly steric hindrance preventing the formation of the ortho isomer during the Fries Rearrangement of highly branched phenol esters.

It was originally thought in this laboratory that a Grignard reaction between tert.-butylmagnesium chloride and the methoxyacetophenones in the syntheses of 2-(o- and p-hydroxyphenyl)-3:3-dimethylbutane would be a failure due to the rather limited ability of tertiary Grignard reagents to react without reduction. Huston and Kaye[56] have, however, reported the synthesis of the para isomer of this phenol by the Grignard method, and therefore it appears that even tertiary halides may be used in certain cases. An alternative synthesis of these phenols is planned in this labloratory starting with a Fries Rearrangement of phenyl pivalate (phenyl trimethylacetate) to give o- and p-hydroxyphenyl-tertiary butyl ketone which may then be methylated and treated in the usual way with methyl magnesium iodide. It will be interesting to see whether the ortho hydroxy ketone may be obtained in spite of steric hindrance.

Yet another route to these phenols was considered but found to be impractical. This involved a Grignard reaction between o- and p-bromo-

anisole and pivaldehyde (trimethylacetaldehyde), but the aldehyde could not be obtained in sufficiently large yields and proved to be most unstable, being oxidized in air to pivalic acid. The method of synthesis attempted was that using an anomalous Grignard reaction between tert.-butyl magnesium chloride and methyl formate at -50°C. as suggested by Whitmore[144].

The phenol esters were very easily prepared in high yields and in the case of phenyl acetate it was found to be more efficient to use acetyl chloride rather than acetic anhydride and sodium hydroxide as suggested by Vogel[141]. Phenyl propionate was best prepared by refluxing a mixture of phenol, propionic acid, and thionyl chloride rather than attempting to isolate propionyl chloride first.

It is to be noted that almost equimolecular amounts of the ortho and para isomers were obtained by the Fries Rearrangement of phenyl acetate under the reported conditions. By increasing the temperature of reaction, the ortho isomer is obtained in larger amounts, presumably due to the greater stability of this compound due to chelation. The low yield (22%) of p-hydroxypropiophenone obtained by the Fries Rearrangement of phenyl propionate is unfortunate since a quite pure crude product was obtained in almost 50% yield. However, during distillation of this compound trouble was encountered with the laboratory plumbing and the distillation had to be stopped and started several times, resulting in some decomposition and a large pot residue.

The methylation procedure described seems to be quite satisfactory and very easily executed. It appears that excessive caution in cooling the reaction mixture during addition of the dimethyl sulphate is

unnecessary provided the addition is made slowly and the temperature kept under control. The use of potassium hydroxide in salt formation of the phenol is to be preferred over sodium hydroxide due to the much greater solubility of the potassium salt and the resulting smaller volume of reaction mixture which may be more efficiently stirred. Very efficient mechanical stirring was found to be necessary if good yields are to be obtained. The methylation of a 100 gram batch of p-hydroxy-acetophenone rather than the usual 50 grams was found to give only a 50% yield, some 20-30% lower than those obtained with the small batch. This is presumably due to the less efficient stirring possible with the larger volume of reaction mixture.

The use of red phosphorus and bromine in the preparation of primary alkyl bromides from the corresponding alcohols appears to give only 45-50% yields compared with that of 90% reported by Vogel[140]. These yields, however, are for the twice distilled product, a crude yield at 71% being obtained.

The Grignard reactions were carried out using the usual precautions with regard to dry equipment and freshly distilled reagents, the reaction mixture being kept constantly under a slight pressure of dried nitrogen throughout the reaction. In all cases a reaction started almost immediately on the addition of the halide to clean magnesium turnings and in no case was it found necessary to resort to seeding the mixture with iodine or methyl iodide. The lengthy five hour refluxing has been found to effectively eliminate the presence of unreacted ketone which has a tendency to codistil with the reaction product. The use of two moles

of Grignard reagent also favours complete reaction. Once again, very efficient, mechanical stirring is required, especially during the addition of the ketone at -5°C. at which point a solid material is sometimes thrown out of solution. The hydrolysis is best carried out using a very mildly acidic agent such as ammonium chloride rather than a mineral acid which would promote dehydration of the unstable tertiary carbinols. Even using ammonium chloride, 2-(p-methoxyphenyl)-3-methylpentanol-2 was found to dehydrate spontaneously, and the slightly high methoxyl content of nearly all the other carbinols indicates partial hydrolysis during dehydration or during distillation under high vacuum. The crude carbinols were dehydrated directly by the Dean and Stark method and only a small portion was distilled to obtain constants.

Alpha-naphthylurethan derivatives were attempted, but in no case was any product other than dinaphthylurea (m.p. 296°C.) obtained. Alpha-naphthylisocyanate is, in general, a much more satisfactory reagent than phenylisocyanate due to its much greater stability towards water. Urethans are the only standard derivatives which have been used for tertiary alcohols, but only very few cases have been reported and in general they are considered to be of use for only primary and secondary alcohols. Ordinary alcohol derivatives, such as benzoates, p-toluenesulphonates, etc., cannot be prepared for tertiary alcohols since they require acidic reagents which cause dehydration to occur.

In the few cases where no water was collected during Dean and Stark dehydration, it was necessary to reflux the carbinol with 10% sulphuric acid to ensure complete dehydration. This measure was, however, avoided

if at all possible, since sulphuric acid is known to induce polymerization of olefins, and, indeed, when it was used a considerable high boiling residue was left which undoubtedly consisted of polymeric material. Once again the problem of preparing a derivative was encountered, but the use of nitrosyl chlorides seems to have provided an answer. These compounds do not seem capable of recrystallization without a large loss occurring and since the nitrosyl chlorides are frequently only obtained in very small yield, it has been found more convenient to merely wash the derivatives repeatedly with absolute methanol to remove any impurities. In this way the nitrosyl chlorides were obtained as finely divided white powders which started to darken in colour within twenty-four hours and eventually became black tars. Because of this instability (which seems to be absent in the nitrosyl chlorides of lower primary alkylanisoles), the derivatives were prepared immediately prior to analysis and dried under vacuum at room temperature.

Hydrogenation of the alkenes was very easily accomplished using a pressure hydrogenator and a Raney nickel catalyst at 50°C. No refinements in this procedure are desirable or necessary, high yields and standards of purity being obtained consistently.

Sulphonamides provide a satisfactory, but sometimes difficult to obtain, derivative for alkylanisoles, the procedure using chlorosulphonic acid being infinitely more successful than that using sulphuric acid and barium chloride previously described. Only oils could be obtained from two of the eight anisoles prepared, and in most other cases the yield of purified sulphonamide was small.

The problems related to demethylation of the alkylanisoles have been described earlier in this paper. The use of pyridine hydrobromide appears to be suitable for the para series, but not for the ortho series. The use of constant boiling hydriodic acid and phenol certainly provides demethylation in quite good yields, and while the reaction is probably quantitative, considerable losses are bound to occur during separation of the alkylphenol from the solvent on the basis of the smaller solubility of the o-alkylphenol in sodium hydroxide. Considerable thought has been devoted to finding another solvent, but all seem to have a disadvantage. Glacial acetic acid would be ideal but does not appear to work, even on long refluxing. Hydrobromic acid and phenol, and hydrobromic acid and acetic acid have both been attempted at this university, but with only moderate success. Hydriodic acid and acetic acid suffers from the added drawback that some decomposition to free iodine occurs and the alkylphenol is difficult to isolate free from the colour of iodine. Further investigation of the use of 47% hydrobromic acid glacial acetic acid plus gaseous hydrogen bromide might provide satisfactory results. Pyridine hydriodide suffers in the same way as the hydrochloride in being hygroscopic and carrying water of hydration with it.

Nitrations are best carried out using the fuming nitric-glacial acetic acid method which gives yields of 55-75% in all cases tested. The use of a longer period of standing after the addition of the phenol to the acid, might increase the yields somewhat but was not considered to be worth the extra time required. It is interesting to note that the percentage yield varies according to the amount of reactants, being highest when a

large batch of phenol is nitrated. This is presumably due to the relatively smaller amount of dinitrophenol lost during extraction of the excess nitric acid with water. Usually the dinitrophenol was obtained as the sole reaction product but in a few cases a very small amount of a yellow solid was obtained boiling at a lower temperature. This was apparently a mononitro derivative but only 0.5-1.0 grams were ever obtained.

Salt formation of the dinitrophenols proved very easy except for two piperidine and one morpholine salts which could only be obtained as viscous oils on repeated attempts. The cyclohexylamine salts were all easily obtained. All the amine salts were readily recrystallized from a mixture of petroleum ether, benzene, and ethanol as required in the individual cases.

Nitration and salt formation of a sample of "o-sec.-amylphenol" obtained from the Sharples Chemical Company proved this compound to be different from 3-(o-hydroxyphenyl)-pentane prepared in this laboratory, and thus it is to be assumed that it was 2-(o-hydroxyphenyl)-pentane. This compound is being prepared in this laboratory and will be described shortly.

No explanation can be given for the anomalous methoxyl analyses shown for 2-(p-methoxyphenyl)-3-methylpentene-2 and 2-(p-methoxyphenyl)-3-methylpentane, both of which showed reproducable determinations respectively 1.1 and 0.8% higher than the theoretical. Carbon and hydrogen analysis of the resulting phenol indicates a relatively pure compound, both being within 0.2% of the theoretical values. Analyses of the derivatives of these compounds are very close to the theoretical.

It is hoped that the experimental results obtained in this study will find some use in the dual purpose for which they were intended - both as selective herbicides or insecticides and as reference compounds in further studies of phenol condensations to be undertaken at this university. The results of toxicity tests being undertaken at Oxford university under the direction of Professor G.E. Blackman are eagerly awaited and will be reported at a later date.

APPENDIX I.

YIELDS IN THE FRIES REARRANGEMENT OF PHENYL ACETATE.

Run No.	% Yield o-Hydroxy-acetophenone	% Yield p-Hydroxy-acetophenone	Overall Yield
1	28	35	63
2	33	36	69
3	33	38	71
4	41	39	80

APPENDIX II.

RESULTS OF METHYLATIONS OF p-HYDROXYACETOPHENONE.

Run No.	Percentage Yield[c]	B.P.
1[a]	50	134°/5.0 mm.
2	60	114°/3.0 mm.
3	73	108°/2.5 mm.
4[b]	50	100°/0.9 mm.
5[b]	48	98°/0.9 mm.
6	78	97°/0.7 mm.
7	75	96°/0.7 mm.

(a) Sodium hydroxide used instead of potassium hydroxide. Phenol found difficult to dissolve.

(b) Double quantities used and stirring not as efficient due to larger volume.

(c) Yields are based on reactants and do not take into account recovered unreacted material.

APPENDIX III.

RESULTS OF METHYLATIONS OF o-HYDROXYACETOPHENONE.

Run No.	Percentage Yield	B.P.	n^{20}
1	36	88°/1.0 mm.	1.5390
2	47	82°/0.4 mm.	1.5390
3	65	85°/0.5 mm.	1.5391
4	60	86°/0.8 mm.	1.5388
5	65	85°/0.7 mm.	1.5391
6	69	81°/0.6 mm.	1.5391
7	46	89°/1.2 mm.	1.5391
8	64	82°/0.7 mm.	1.5390
9[a]	40	82°/0.7 mm.	1.5390

(a) Methylation of crude, recovered o-hydroxyacetophenone.

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