THE REDUCTION OF α-BROMOISOBUTYROPHENONE WITH ALUMINUM ISOPROPOXIDE

THE NITRATION OF p-CYMENE

A Thesis

by

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CLAIMS TO ORIGINAL RESEARCH
AND CONTRIBUTIONS TO KNOWLEDGE

1. The reduction of α-bromoisobutyrophenone with aluminum isopropoxide has been investigated thoroughly, and for the first time products have been isolated and identified which indicate extensive debromination and rearrangement as well as reduction of the parent substance.

2. As a result of the discovery of these products (a complex mixture of alcohols, ethers and hydroxy-ethers) the reducing action of aluminum isopropoxide has been proven to be much less straightforward than claimed by the original discoverers.

3. Additional support has been given to an intermediate oxide rearrangement mechanism postulated by Stevens et al. (3) for the reduction of α-bromopropiophenone.

4. The very nature of the products produced has necessitated a broadening of the original postulate to include other carbon-oxygen cleavages and group rearrangements.

SECTION I

THE REDUCTION OF α-BROMOISOBUTYROPHENONE WITH ALUMINUM ISOPROPOXIDE

Ph.D. Chemistry

Owen C. W. Allenby

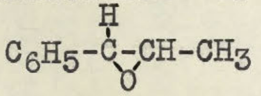
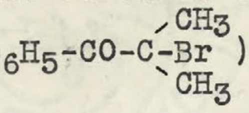
THE REDUCTION OF α-BROMOISOBUTYROPHENONE WITH ALUMINUM ISOPROPOXIDE

NITRATION OF p-CYMENE

From an investigation of the reduction of α-bromoisobutyrophenone with aluminum isopropoxide, products have been isolated which indicate extensive debromination and rearrangement as well as reduction of the parent substance. As a result, additional support has been given to an intermediate oxide rearrangement mechanism postulated by Stevens for the reduction of α-bromopropiophenone. The very nature of the products produced has necessitated a broadening of the original postulate to include other carbon-oxygen cleavages and group rearrangements.

The effect on the dinitration of cymene of wide variations of temperature, concentration and amounts of nitrating acids, addition and stirring times, as well as other factors, has been studied. The absolute and relative yields of the products dinitrocymene and dinitrotoluene were determined using a method of analysis dependent on the refractive index of the purified mixture. A method of separating the two compounds based on a solvent extraction with Skelly Solve B also was developed.

INTRODUCTION

In 1937, Lund (1) on applying aluminum isopropoxide to the reduction of compounds such as phenacyl bromide ($C_6H_5-CO-CH_2Br$), obtained excellent yields of the corresponding alcohols. On the theory that such α-halogenated compounds would lose HBr if a β-hydrogen also was available, Stevens et al. (2,3) carried out similar experiments on the reduction of α-bromopropiophenone ($C_6H_5-CO-CHBr-CH_3$). Results which were obtained seemed to indicate loss of halogen acid through an intermediate oxide  $C_6H_5-\overset{H}{C}\underset{O}{-}CH-CH_3$ and it was for the purpose of confirming this theory that the present research on the reduction of α-bromoisobutyrophenone ( $C_6H_5-CO-C\begin{matrix}CH_3\\ -Br\\ CH_3\end{matrix}$) was undertaken.*

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* Since published (4)

HISTORICAL

I ALUMINUM ALCOHOLATES AS REDUCING AGENTS

Introduction

All ordinary methods of transforming a carbonyl group into a hydroxyl, such as the addition of atomic, nascent or catalytic hydrogen or electrolytic reduction, suffer from the disadvantage that the reduction is not always limited to the carbonyl; on the other hand, if the compound contains for example $C = C$ links, halogens, nitro groups, etc., then the latter may also, even preferentially, be attacked. Again, the reduction of the carbonyl group might not stop at the carbinol stage but be carried right through to the paraffin. Such methods, too, may be long and tedious; in the method of reduction by hydrogen in the presence of platinum oxide - platinum black, the conditions for a satisfactory yield are highly specific, small variations in the proportions of the catalytic mixture or changes in its activity affecting the results in some cases very profoundly. Poisoning of the catalyst by the compound containing the carbonyl group is not uncommon, and constant reactivation is necessary. The use of metal combinations, although it can be applied fairly well to the reduction of aldehydes, often results in pinacol formation in the case of ketones. Complete reduction to the methylene group may also occur, as in the Clemmensen reaction. In common with alcohol alkali-metal alcoholate combinations, the method also often results in polymerization, condensation and aldol formation.

In the past five years, aluminum isopropoxide has come into prominence as a reducing agent, and from all indications it seems to be ideal for the conversion of aldehydes and ketones into the corresponding alcohols. Unlike most alcoholates, it is not a strong condensing agent (in the strict classical sense of the term), it attacks only the carbonyl group (perhaps the nitroso group as well) and this group in many cases is quantitatively reduced to the carbinol when the reduction is properly carried out. Many hitherto unknown alcohols (especially those containing halogens, nitro groups, $C = C$ bonds, etc.) are easily prepared and many known ones obtained in better yields. The process presents no difficulty and the starting materials - aluminum and isopropyl alcohol - are cheap. The nature of the reaction is such that reduction beyond the alcoholic stage occurs but very infrequently and then only in certain specialized cases; resinification, condensation and similar side reactions do not take place in appreciable amounts.

Theory of their reducing action

Aluminum alcoholates had originally been conceived by Tischtschenko (5) as an improvement on the use of alkali alcoholates as catalysts in the Claisen reaction (the preparation of esters by dismutation of the corresponding aldehydes with or without the use of an inert solvent) (6).

$$2R\text{-}CHO \xrightleftharpoons{Al(OR)_3} R\text{-}CH_2O - CO\text{-}R$$

Formerly the reaction was strictly limited in its application, functioning almost exclusively for aromatic aldehydes; this new development by Tischtschenko widened its use considerably and generalized it to include a large number of both aliphatic and aromatic aldehydes.

In 1925, Meerwein and Schmidt (7) (and independently Ponndorf (8) and Verley (9)) by operating in the presence of an oxidizable alcohol, converted these alcoholates into reducing agents which, for specificity of action, wideness of application and yield of pure products, have yet to be surpassed. Most of their preliminary information was obtained from the use of aluminum ethoxide and other primary alcoholates. In the reaction of these compounds with other oxidizable materials, it was shown that no free hydrogen was evolved, and any unsaturated C = C links, nitro groups, α-halogens, etc. were safe from attack. In the presence of some free ROH, all types of aldehydes at moderate temperatures readily gave 80-90% yields of the corresponding alcohols.

The course of the reaction can be shown in a simplified manner as follows:

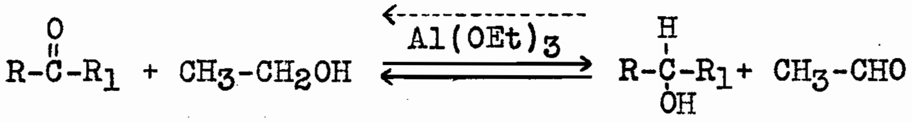
$$R\text{-}CHO + CH_3\text{-}CH_2OH \xrightleftharpoons{Al(OEt)_3} R\text{-}CH_2OH + CH_3\text{-}CHO$$

The final equilibrium depends upon the relative reducing powers of the two alcohols CH_3-CH_2OH and R-CH_2OH (other factors being constant). For example, if CH_3-CH_2OH

is a more powerful reducing agent than R-CH_2OH, then it will produce the latter by reduction of its aldehyde. It is convenient to speak of this tendency in terms of oxidation - reduction potentials because the effectiveness of any alcohol as a reducing agent can be predicted, qualitatively at least, by the oxidation - reduction potential of the corresponding aldehyde or ketone. In any system involving two such carbonyl groups, the one with the higher potential will be found in the larger concentration after equilibrium has been established. This means that in order for the reaction above to go favorably to the right, the oxidation - reduction potential of the acetaldehyde should be greater than that for R-CHO. Starting with equimolecular amounts of R-CHO and CH_3-CH_2OH, if the potentials of R-CHO and CH_3-CHO are the same, then after equilibrium has been established, there will be equivalent amounts of each alcohol and aldehyde present, i.e. the yield of R-CH_2OH would be 50%.

This argument, of course, is based on the assumption that an equilibrium is established without the application of any external influences. If, on the other hand, the acetaldehyde were to be distilled off as it was produced, then the equilibrium would shift to the right with a more favorable production of R-CH_2OH. This is taken advantage of in the reduction of aldehydes with aluminum ethoxide, and accounts in a large measure for the good yields which are obtained.

Ketones have even higher oxidation - reduction potentials than aldehydes: the value for acetaldehyde is about 1.9V, that for acetone about 2.2V, when measured with a dropping mercury electrode (10). This would indicate that by the substitution of a secondary alcoholate such as aluminum isopropoxide for the aluminum ethoxide (with ensuing production of acetone rather than acetaldehyde) better reduction of the R-CHO would occur. This has been found experimentally to be the case. Ordinarily it is difficult to reduce ketones with aluminum ethoxide because the equilibrium is unfavorable for R-CHOH-R_1 formation even with removal of the acetaldehyde:



$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}R_1 + CH_3\text{-}CH_2OH \xrightleftharpoons{\overset{\longleftarrow}{Al(OEt)_3}} R\text{-}\underset{OH}{\overset{H}{C}}\text{-}R_1 + CH_3\text{-}CHO$$

The higher potential of the R-CO-R_1 displaces the reaction to the left; the formation of a ketone such as CH_3-CO-CH_3 on the right would, however, lower or even reverse the oxidation - reduction potential difference.

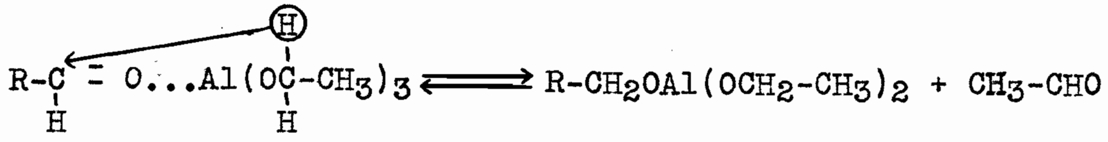
From the oxidation - reduction potentials of various ketones determined by equilibration against fluorenone (11), it is possible to arrange the corresponding alcoholates (theoretically at least) in the order of their relative utility as reducing agents. From the values available, the alcoholates of diisopropylcarbinol should be the best, followed in descending order by di-n-butyl, di-n-propyl, di-i-butyl, diethyl, methylethyl and dimethylcarbinol. Conditioned by sources of supply, relative rates at which equilibrium is attained and ease of formation of the alcoholate, there is, however, no reason to believe that aluminum isopropoxide can be replaced by a more effective alcoholate. According to Adkins (12), of the alcoholates prepared from methyl, ethyl, propyl, isopropyl, butyl or isobutyl alcohol, aluminum isopropoxide is the most easily made.

Reduction mechanisms

A mechanism for the reduction of aldehydes and ketones was proposed by Meerwein in his original paper of 1925 which (with a few further elaborations in 1936 (13)) has been accepted until quite recently. He assumed first of all that it was the alcoholate itself which was the effective agent in the reduction. A preliminary molecular compound formation with the carbonyl group of the aldehyde or ketone seemed to be indicated because of the halochromic appearance of the reduction mixture and from the previously known facts about complexes of Grignard reagents with alcohols, ketones, ethers, esters and so on. (To simplify illustration, aluminum ethoxide will be employed.)

$$R\text{-}CHO + Al(OCH_2\text{-}CH_3)_3 \rightleftharpoons R\text{-}CHO...Al(OCH_2\text{-}CH_3)_3$$

According to Meerwein, it can be assumed that by the secondary valence combination of the carbonyl group with the alcoholate, there is an increase in the primary valence character of the carbon of the carbonyl group which results in an internal rearrangement of the complex. This involves removal of a hydrogen from one of the $OCH_2\text{-}CH_3$ radicles of the alcoholate to the carbon mentioned:



$$R\text{-}\underset{H}{C}=O\ldots Al(O\underset{H}{\overset{\textcircled{H}}{C}}\text{-}CH_3)_3 \rightleftharpoons R\text{-}CH_2OAl(OCH_2\text{-}CH_3)_2 + CH_3\text{-}CHO$$

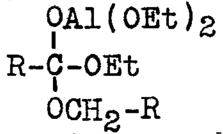
It is clear that alcoholates of secondary alcohols should be better reducing agents than primary alcoholates because the mobility of the hydrogen concerned is greater for the former than the latter. Tertiary alcoholates naturally do not act as reducing agents since no hydrogen is available. Meerwein assumes that only one such operation takes place.

It has already been mentioned that aluminum alcoholates were originally intended for use as catalysts in the Tischtschenko reaction, hence it is not surprising that Meerwein has found that by reduction of benzaldehyde, approximately 6% conversion to the ester took place. To explain this he suggests that in the complex $R\text{-}\overset{H}{C}=O\ldots Al(OEt)_3$ a whole OEt group shifts instead of a hydrogen with formation of $R\text{-}\underset{OEt}{\overset{H}{C}}\text{-}O\text{-}Al(OEt)_2$, which thereupon reacts with more R-CHO to produce $R\text{-}\underset{OCH_2\text{-}R}{\overset{OAl(OEt)_2}{C}}\text{-}OEt$. The latter, an addition complex of a metal alcoholate to the carbonyl of an ester, is unstable and by loss of $Al(OEt)_3$ liberates the ester $R\text{-}CO\text{-}OCH_2\text{-}R$. Under the experimental conditions, the Tischtschenko reaction is of secondary importance only.

On this basis of the migration of an OR group from the alcoholate, Meerwein explains the preferential reducing action of alcoholates of metals such as Al, Zr and Sn^{IV} while under analogous conditions alkali metal alcoholates act as condensing agents. The formation of an ester is favored by a loose M - OR bond which allows ionization into M^+ and OR^- to take place. Clearly this is the situation for alcoholates of the alkali metals. With decreasing electropositive character of the metal atom (and hence increasing homopolar construction of the alcoholate) ester formation recedes in favor of reduction, e.g. for alcoholates of Al, Mg, Zr, etc. With the very pronounced homopolar construction of the alcoholates of B, Si, As and P, the alkoxyl group is too strongly attached to the central carbon atom. It is not easily removed so that neither condensation nor reduction (which also eventually involves loss of R-CH-O-) is possible.

The mechanism above does not, however, give any explanation for preferential reduction in the presence of alcohol, while in the absence of the latter, catalytic amounts of the alcoholate favor ester formation. Although this point has not been elucidated by Meerwein, it follows from a mechanism developed by Verley (9) for the reaction. The intermediate $R\text{-}CH_2\text{-}OAl(OEt)_2$ (which he arrives at in a rather indirect and perhaps unorthodox manner) he considers can undergo a group interchange with the ethyl alcohol present in the system during reduction:

$$\mathrm{R\text{-}CH_2\text{-}OAl(OEt)_2 + EtOH \rightleftharpoons R\text{-}CH_2\text{-}OH + Al(OEt)_3 \rightleftharpoons \begin{array}{l}\text{Further}\\ \text{reduction}\end{array}}$$

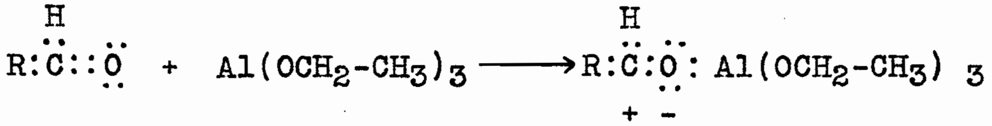
(This is a common metathetical reaction between salts and is made use of in the formation of other alcoholates by reaction of aluminum t-butoxide with the appropriate alcohol.) The alcoholate is thus freed for further reaction, and hence it should be possible to reduce the aldehyde R-CHO with an amount of alcoholate very much less than that required from the equation. This has been done in quite a number of cases. Thus Ponndorf (8) reduced 200 g. of C_6H_5-CH=CH-CHO (1.5 moles) in 80% yield using only 40 g. (0.12 moles) of aluminum benzylate in benzyl alcohol. A whole series of aldehydes (furfural, chloral, bromal and others) had been reduced by Meerwein himself in good yields (70-85%) using only one-seventh of the molar quantity of aluminum ethoxide required (7). It is noteworthy that these are the approximate ratios of aldehyde to catalyst which are employed in the absence of alcohol in the Tischtschenko reaction for ester formation. In the absence of alcohol, regeneration of the catalyst proceeds only through the ester intermediate  $\mathrm{R\text{-}\overset{\displaystyle OAl(OEt)_2}{\underset{\displaystyle OCH_2\text{-}R}{C}}\text{-}OEt}$, hence the Tischtschenko reaction ensues preferentially. With larger amounts of the alcoholate (equi-molar quantities or larger) presumably both reactions would take place simultaneously, since regeneration of the catalyst is no longer of any importance. Yields of the ester and alcohol would depend upon the relative rates at which each reaction proceeded. Young, Hartung and Crossley (14) reduced benzaldehyde to benzyl alcohol in benzene solution using these larger quantities of aluminum ethoxide in the absence of alcohol, to the extent of 28% with production of some benzoic acid and benzyl benzoate. Child and Adkins (15) obtained a 50% yield of benzyl benzoate using only catalytic amounts of the alcoholate in an inert solvent, while Meerwein (13), on introduction of ethyl alcohol obtained an 89% yield of benzyl alcohol. Although these experiments were not carried out under identical conditions, the existence of two simultaneous reactions seems to be beyond question.

In the last equation:

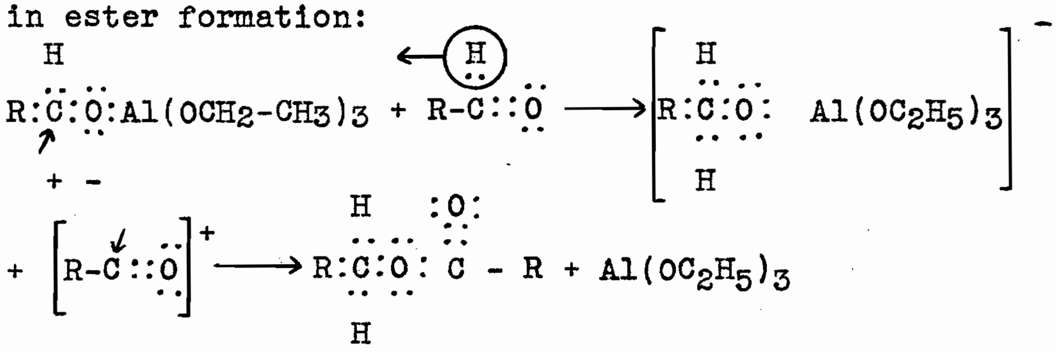
$$R\text{-}CH_2\text{-}OAl(OEt)_2 + CH_3\text{-}CH_2OH \rightleftharpoons R\text{-}CH_2OH + Al(OEt)_3 \rightleftharpoons \text{Further reaction}$$

the equilibrium to the right will be favored if the acidity of the ethanol is greater than that for the alcohol $R\text{-}CH_2OH$. Since ethanol is one of the most acidic alcohols, this would in general be the case; it would, however, be less favorable to regeneration of the alcoholate in the presence of isopropyl alcohol since the latter, being a secondary alcohol, is less acidic than a primary. It is recommended by Lund (1) that a 50-100% excess of aluminum isopropoxide always be used.

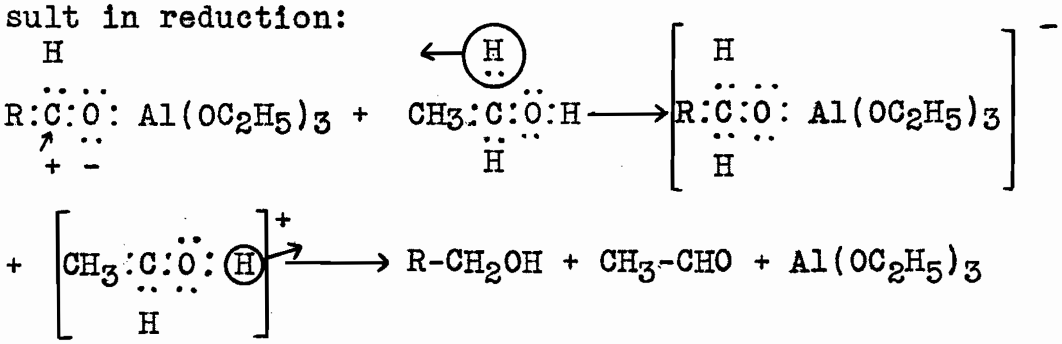
Comparatively recently (in 1940) Hammett* postulated a new mechanism for the reduction of carbonyl compounds with aluminum alcoholates based on modern electronic theories. The nature of and reason for the formation of the molecular compound is explained on the attraction of the electrophilic aluminum atom of the alcoholate to the nucleophilic oxygen atom of the carbonyl group causing increased polarization of the latter.



The carbon is made so positive that it is able to abstract a negative hydride ion from another compound such as an alcohol or aldehyde. Removal of a hydride ion from the aldehyde (which would occur in the absence of alcohol) results in ester formation:



Removal of a hydride ion from an alcohol molecule would result in reduction:



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* Physical Organic Chemistry -Hammett

In this new sense it is perhaps false to say that alcoholates of secondary alcohols are better for reducing purposes than primary. As a matter of fact, the reverse should actually be the case. The bond $R:\ddot{\underset{\cdot\cdot}{O}}:\!\downarrow\! H$ in a primary alcohol is weaker than that in a secondary, i.e. the electron density on the oxygen is higher in the case of the former. This means that in an alcoholate $R:\ddot{\underset{\cdot\cdot}{O}}:\mathrm{Al}\begin{smallmatrix}/\\ \backslash\end{smallmatrix}$, the electrophilic character of the aluminum is greater in a primary than in a secondary alcohol and hence primary alcoholates should be better *catalysts* for reduction purposes. It is true, however, that as the actual reducing *agent*, secondary alcohols are to be preferred because the higher electron density induced on the central carbon atom by the extra R group permits a hydride ion H^- to be more readily expelled. A better combination for reducing purposes would hence appear to be an aluminum alcoholate of a primary alcohol in a secondary alcohol as a solvent. This would tend to be supported by an observation made by Child and Adkins (15) that the catalytic activity of the alcoholates (in the Tischtschenko reaction) is increased by formation of molecular complexes with strongly electrophilic reagents such as aluminum chloride. This should apply equally well to their use as reducing agents (if Hammett's conception is correct) but no literature seems to be available on the subject. On further consideration, if the theory is correct, it should be possible to reduce a carbonyl group with an oxidizable alcohol in the presence of any common electrophilic agent (provided the latter is soluble in the medium used so that the mixture is homogeneous).

Hammett's mechanism does not explain the fact that reduction will take place in the absence of alcohol provided an excess of the alcoholate is used. Although he makes no mention of this, it could only be explained on the assumption of hydride ion removal from the OC_2H_5 group in the alcoholate itself - but then the alcoholate would cease to function as a true catalyst since it has taken an actual part in the reaction, and we revert back to Meerwein's original mechanism.

To sum up, there still seems to be some doubt concerning the true role of the alcoholate in the reaction. From all indications it possibly is a case of bifunctional action - the alcoholate can fulfil the functions of both a reducing agent (because of the OR present) and a catalyst (by virtue of the electrophilic aluminum). In the absence of alcohol and in the presence of but small amounts of alcoholate, the latter acts only in a catalytic manner and the Tischtschenko reaction can and does take precedence. In the presence of alcohol, or by using excess amounts of the alcoholate (at the same time removing the aldehyde or ketone produced by oxidation of the alcohol(ate)), reduction is favored to the practical exclusion of the Tischtschenko reaction. The catalytic activity is still vital, however, because on destruction of the electrophilic nature of the aluminum by combination with a nucleophilic compound such as ammonia, it is totally inactive as a reducing agent (13).

Limitations to the applicability of alcoholates as reducing agents.

The great utility of aluminum isopropoxide as a reducing agent has already been referred to and stressed. It is not without its limitations, however (13). In order to reduce compounds having very acidic hydrogens, e.g. phenol aldehydes, the OH group must be converted to a methoxyl, otherwise the alcoholate would be decomposed. In common with ammonia, amino-aldehydes such as p-dimethylaminobenzaldehyde coordinate with the aluminum of the alcoholate rendering it inactive as a reducing agent. Certain aliphatic hydroxyaldehydes such as aldol CH_3-CHOH-CH_2-CHO are difficultly reducible, the latter forming the glycol only in 30% yield after 4½ months reaction with aluminum ethoxide in the cold. Benzophenone C_6H_5-CO-C_6H_5 on reduction gives as a side reaction a 7% yield of the hydrocarbon diphenylmethane. Benzhydrol C_6H_5-CHOH-C_6H_5, which can be considered as the intermediate product, under similar conditions is reduced to the extent of 28% to diphenylmethane.

Since alcoholates are quite alkaline, under favorable circumstances they can extract halogen acid from compounds containing halogens -- as this research and other work by Stevens et al. (2,3,4) has shown. Presumably they could also extract water from a compound under certain conditions because of their powerful dehydrating action.

Easily polymerizable aldehydes give only fair yields of the corresponding alcohol (14). Crotonaldehyde can be reduced to the alcohol to the extent of 60%, the remainder going into the production of polymers. Butyraldehyde gives only a 28% yield of the alcohol, the rest forming high boiling materials - butyrates with some aldol condensation products. In spite of these limitations, for all-round general applicability to the reduction of aldehydes and ketones, a better reducing agent has as yet not been discovered.

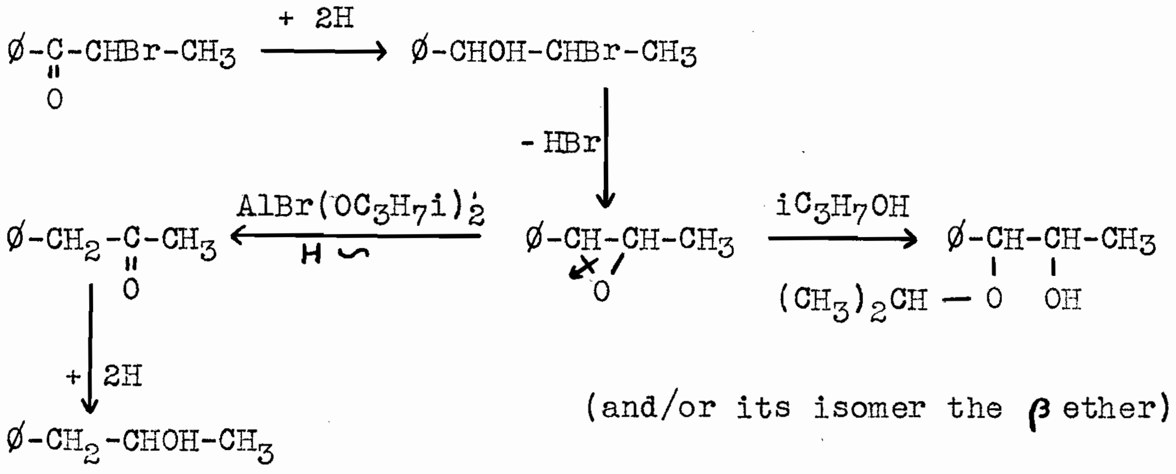
II THE REDUCTION OF α-BROMO KETONES WITH ALUMINUM ISOPROPOXIDE

Introduction

Meerwein, as a part of his program for showing the wide applicability of his new reducing agent, reduced a number of α-halogenated aldehydes and ketones with quite good results. Chloral and bromal gave the corresponding alcohols in 85% and 69% yields respectively, while ketones such as $\phi CO-CCl_3$ and $CH_3-CO-CCl_3$ gave yields of around 68%. The aldehyde $CH_3-CHCl-CCl_2-CHO$ was reduced nearly quantitatively (92%) to the alcohol. In 1937 Lund (1) obtained results on the reduction of $\phi CO-CH_2-Br$ and CBr_3-CHO with aluminum isopropoxide which corroborated these findings, yields of 85% and 77% of the corresponding alcohols being readily obtained.

The reduction of α-bromopropiophenone

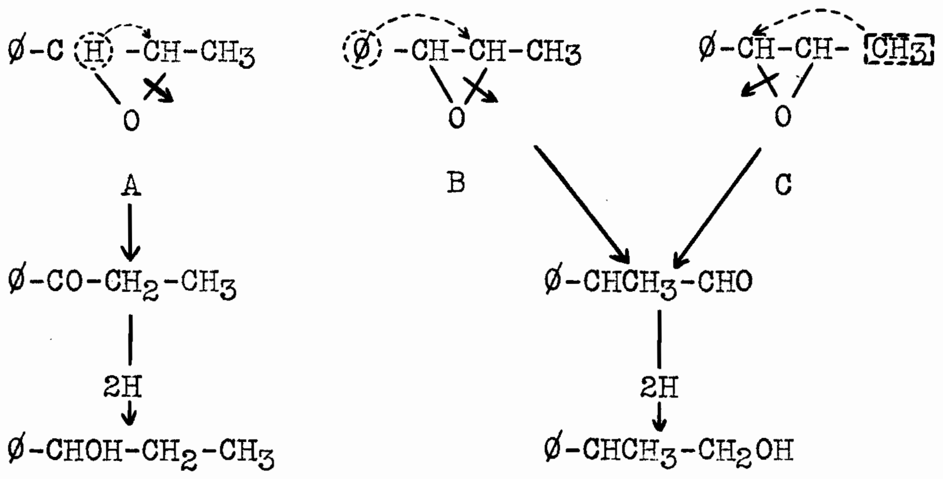
With the original idea that the presence of a β hydrogen in analogous compounds might allow removal of halogen acid, Stevens in 1938 reported for the first time the production of such halogen-free products in the reduction of α-bromoketones with aluminum isopropoxide. He found that α-bromopropiophenone gave the bromohydrin and halogen-free products in approximately equal quantities. A second paper published by Stevens, Allenby and Dubois (3) in 1940 greatly elucidated the question, the results obtained being explained most clearly on an intermediate oxide type of mechanism as follows:



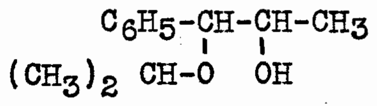
(and/or its isomer the β ether)

Reduction of α-bromopropiophenone with twice the molar quantity aluminum isopropoxide (1M solution) resulted in the formation of a liquid product, refractionation giving (after distillation of low boiling products) a second fraction analyzing for the bromohydrin (35% yield). This is the product which normally would be expected from the analogous work done by Meerwein and Lund. It was not particularly stable, redistillation always yielding considerable residue.

The low boiling material, after several refractionations at 16 mm. pressure, gave an alcohol fraction (b_{16} = 106-108°C.) from which was isolated, on treatment with phenylisocyanate, the phenylurethan of methylbenzylcarbinol $C_6H_5\text{-}CH_2\text{-}CHOH\text{-}CH_3$. Neither of the other two possible isomeric alcohols $C_6H_5\text{-}CHOH\text{-}CH_2\text{-}CH_3$ or $C_6H_5\text{-}\overset{CH_3}{CH}\text{-}CH_2OH$ (which could result from rearrangements of the type A, B and C illustrated) was isolated. According to Fourneau and Tiffeneau (16) (also Lévy and Gombinska (17,18)) these alternate rearrangements would be improbable. The low boiling fraction was not investigated further.



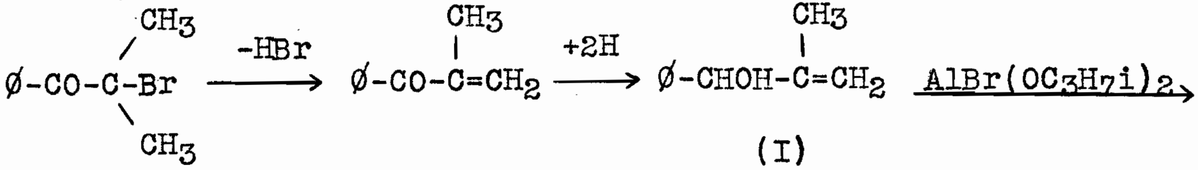
Although the presence of each of the various products isolated can be most clearly explained on Stevens' intermediate oxide mechanism just outlined, to give it further support, the various postulated intermediates were subjected to the same treatment as the parent starting material. From 10.75 g. of the bromohydrin, in addition to considerable tars, were obtained two fractions boiling over temperature ranges similar to those for reduction of the bromoketone. From the larger second fraction (1.1 g. boiling at 100-109°C. at 16 mm.) was isolated methylbenzylcarbinol, identified as its phenylurethan derivative.

It was discovered that in the acetone distillate, isopropyl bromide was present in an amount sufficient to account for 8% of the total bromine removed from the original bromoketone. This could only mean that the $Al(OC_3H_7\text{-}i)_2Br$ (which was presumably the salt formed by the remainder) was sufficiently acidic to react with isopropyl alcohol to form isopropyl bromide. This provided an explanation for the fact that in the event of intermediate oxide formation, the latter could cleave so easily under the conditions of the experiment (i.e. presence of aluminum isopropoxide). The complex salt could just as readily be available for reaction with the product alcohols or for isomerization of the oxide. Subsequent treatment of the oxide with aluminum isopropoxide both in the presence and absence of aluminum bromide confirmed this theory. In the absence of the salt, a very slow reaction took place and only a negligible carbinol fraction was isolated. The boiling point (b_{16} = 121-124°C.) of the main portion of the distillate and absence of residual odor of the oxide (b_{20} = 79-82°C.) eliminated the starting material as a possibility. A close analysis for a compound of the formula $C_{12}H_{18}O_2$ and the presence of a hydroxyl group gave reason for the belief that it was an ether of the type  $C_6H_5\text{-}\underset{(CH_3)_2CH\text{-}O}{CH}\text{-}\underset{OH}{CH}\text{-}CH_3$ formed by addition of isopropyl alcohol to the oxide. Its p-nitrobenzoate and phenylurethan derivatives gave nitrogen values corresponding closely to the values calculated for such a structure.

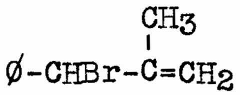
Similar treatment of the oxide in the presence of aluminum bromide resulted in a considerably increased rate of reaction with rapid evolution of acetone. Like the carbinol fraction obtained on reduction of α-bromopropiophenone, the boiling range of an analogous fraction in this case also was quite broad. Methylbenzylcarbinol was isolated as its phenylurethan derivative. The principal reason for the broad boiling point in both cases was considered to be the presence of the isopropyl ether.

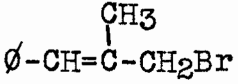
The reduction of α-bromoisobutyrophenone

In order to obtain better yields of these bromine-free products, Stevens turned his attention to the reduction of α-bromoisobutyrophenone, which, having a tertiary bromine, should give better results. To avoid complications which might occur at 80-85°C., the reduction was carried out at 33°C., the acetone being removed in vacuo. This procedure resulted in a most interesting new development. At this temperature reduction was very slow, the aluminum isopropoxide apparently acting first to remove HBr thus:



$$\phi\text{-CO-}\overset{CH_3}{\underset{CH_3}{C}}\text{-Br} \xrightarrow{-HBr} \phi\text{-CO-}\overset{CH_3}{C}{=}CH_2 \xrightarrow{+2H} \underset{(I)}{\phi\text{-CHOH-}\overset{CH_3}{C}{=}CH_2} \xrightarrow{AlBr(OC_3H_7i)_2}$$



$\phi\text{-CHBr-}\overset{CH_3}{C}{=}CH_2$ (II) The product analyzed correctly for this compound. However, since oxidation with chromic acid yielded benzoic acid, and hydrolysis with sodium hydroxide gave 2-methylcinnamyl alcohol ($\phi\text{-CH=}\overset{CH_3}{C}\text{-}CH_2OH$) (III), the bromide was very probably $\phi\text{-CH=}\overset{CH_3}{C}\text{-}CH_2Br$. This meant that an allylic rearrangement involving a 1:3 shift of the bromine must have occurred in the reaction, either spontaneously or under the influence of $AlBr(OC_3H_7i)_2$. Treatment of alcohol I with aqueous hydrobromic acid produced a bromide which on hydrolysis gave the alcohol III. The boiling points of the corresponding alcohol and bromide as well as the exaltation of the molecular refractivity of the latter gave further indication of the  $\phi\text{-CH=}\overset{\text{CH}_3}{\overset{|}{\text{C}}}\text{-CH}_2\text{Br}$ structure. Attempts to duplicate these experiments with ∝-bromopropiophenone were unsuccessful, but little reaction occurring. However, it is likely that both types of reactions can occur with ∝-halogenated ketones containing β-hydrogen, the preponderance of any one being dependent upon the experimental conditions and the structure of the bromo-ketone.

A certain amount of preliminary work was done by Stevens on the reduction of ∝-bromoisobutyrophenone in the usual manner. Reduction of 68 g. (0.3 moles) of the bromoketone (b_{10}=119-120°C.; n_D^{25}=1.5550; D_4^{25}=1.3663) with 1.0 moles of 1M aluminum isopropoxide gave, after working up in the usual way, two main fractions on repeated distillation at 9 mm. One boiling at 81-87°C., after further fractionation, yielded a substance having the following physical constants: b_9=83.8-84.5°C.; n_D^{25}=1.4756; D_4^{25}=0.8985. It gave no precipitate with hot alcoholic silver nitrate but reduced aqueous permanganate solution to some extent. It analyzed for $C_{13}H_{20}O$ -- a formula which might indicate an isopropyl ether of some carbinol.*

The second fraction, boiling at 100-103.5°C., con-

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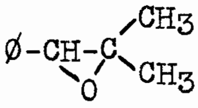
* The oxide  boils at 74°C. at 10 mm.

tained about 5% bromine and was probably a mixture of carbinols contaminated with a little bromohydrin. Purification through the phthalate gave a product still boiling over the same range, but bromine free. Analysis fitted the formula for $C_{10}H_{14}O$ (i.e., the expected alcohols). No bromohydrin (other than that as a slight impurity in the carbinol fraction) was isolated.

It was the object of this research to continue the work already done on this bromo-ketone and to attempt to identify the products formed. There was reason to believe that in this case, cleavage of the intermediate oxide could occur on both sides and subsequent rearrangement would produce a variety of alcohols. Their isolation and identification would provide even more striking evidence for the justification of the theory.

EXPERIMENTAL SECTION

I PREPARATION OF α-BROMOISOBUTYROPHENONE

To 184 ml. (2.10 moles) of benzene and 570 g. of aluminum chloride in 1 litre of carbon bisulfide was added 206 g. (1.93 moles) of purified isobutyryl chloride (b.p. 91-93°C.) in the usual Friedel-Crafts manner. The isobutyrophenone thus obtained boiled at 101-102°C. (14 mm.) and weighed 198.5 g., representing a yield of 69%. (n_D^{25}=1.5156, $n_D^{16.6}$=1.5195*). A semicarbazone derivative melted at 167-170°C.** after crystallization from alcohol. The ketone, on treatment with excess bromine in carbon tetrachloride solution in the usual way (21) gave a 91.5% yield of α-bromoisobutyrophenone ($b_{11.5}$=124-124.2°C.;*** n_D^{25}=1.5548).

II REDUCTION OF α-BROMOISOBUTYROPHENONE

α-bromoisobutyrophenone	318 g.;1.4 moles; $b_{11.5}$=124-124.2°C.
1 M. aluminum isopropoxide	4.2 moles

The preparation of the isopropoxide and the method of reduction were the same as described by Lund (1). Reaction between the aluminum turnings and alcohol was quite rapid once it had

* Faworski b_{10}=95-98°C.(19)
v.Auwers $n_D^{16.6}$=1.5192 (20)
** Faworski m.p.=166-167°C.(19)
*** Faworski b_{12}=129-130°C.(19)

been initiated by the addition of a little mercuric chloride. The mixture was generally warmed at the beginning but eventually the heat of reaction became so great that external cooling had to be applied. After the aluminum had gone completely into solution, the alcoholate was filtered (as rapidly as possible) through a Buchner funnel in order to free it from a small amount of dark residue.

The isopropoxide was heated nearly to the boiling point before the ketone was added. The acetone was continuously removed from the refluxing mixture by fractionation through an eight-plate Whitmore column (Figure 1), connection with the pot being made through a ground-glass joint.

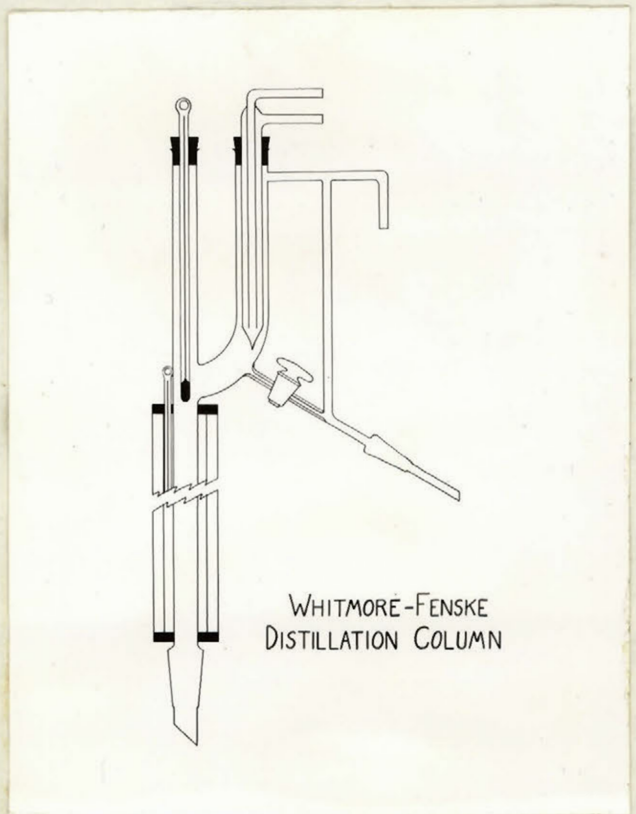


Figure 1

The column, which was packed with single turn glass helices, was equipped with an electrically heated jacket, the temperature being controlled so as to allow only the acetone to distil off. The total-reflux variable-take-off distilling head allowed high reflux ratios to be maintained. In this way, the acetone was removed very successfully without appreciable loss of isopropyl alcohol. Removal of distillate was continued until the temperature of the vapors rose to the boiling point of the isopropyl alcohol (82°C.) and a test for acetone with 2,4-dinitrophenylhydrazine was negative (total time 21 hours). A silver nitrate analysis for bromine made on this acetone and alcohol distillate established the fact that 22% of the total bromine in the α-bromoisobutyrophenone had been removed presumably as isopropyl bromide (b.p.60°C.).

Before the reaction product was worked up, a large part of the isopropyl alcohol was removed under reduced pressure. The gummy residue was decomposed with 250 ml. concentrated sulfuric acid in 1700 ml. water and 2 kg. crushed ice, and the mixture extracted several times with a total of 500 ml. ether. After first being treated with 60 ml. IN sulfuric acid, then dilute sodium carbonate solution to alkalinity, the ether solution was washed thoroughly with water and dried over sodium sulfate. The solvent was distilled off (the last traces being removed under partial vacuum) and the reduction products stripped from tars under low pressure (0.5-0.6 mm.). The total amount of distillable material was 215 g., residues 67.5 g.

The reduction products were redistilled a number of times through Whitmore columns of varying efficiencies (3 to 8 plates) cutting fractions at various points (with the aid of both b.p. and refractive index values) until finally three more or less main fractions were isolated. One of these corresponded to the lower boiling liquid already mentioned by Stevens et al. (3) and which will be referred to as an ether. This fraction boiled between 84.8 and 85°C. at 9 mm. pressure (n_D^{25}=1.4741). Another fraction boiling at 100.5-103°C. under a pressure of 9 mm. (n_D^{25}=1.5205) had also been mentioned previously by Stevens and will be referred to as the alcohol mixture. The third and smallest fraction boiling at 113°C. at 9 mm. (n_D^{25}=1.5175) was not reported by Stevens. A forerun (which probably contained appreciable quantities of the ether) amounted to about 6% of the total distillate.

III INVESTIGATION OF THE ETHER FRACTION

Physical and Chemical Properties

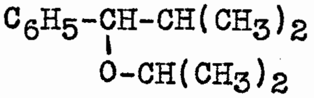
Yield $\doteq$ 30% of total

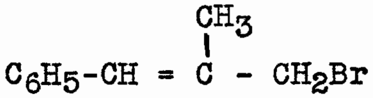
b_9 = 84.8-85°C.

b_{756} = 209.8°C.

n_D^{25} = 1.4741

D_4^{25} = 0.8881

The results of a carbon and hydrogen analysis are as follows: C, 81.04%; H, 10.50%; values which correspond almost exactly to an ether of the type  $C_6H_5\text{-}\underset{|\atop \mathrm{O\text{-}CH(CH_3)_2}}{\mathrm{CH}}\text{-}CH(CH_3)_2$ or one of its isomers (calculated for $C_{13}H_{20}O$: C, 81.25%; H, 10.42%; MR calculated, 60.28; found, 60.77)

The material gave no Baeyer Test for unsaturation with potassium permanganate and no Beilstein Test for halide. Hence it was free from any unsaturated bromide,  $C_6H_5\text{-}CH = \overset{\mathrm{CH_3}\atop |}{C} - CH_2Br$ which, it has been mentioned, was the main product on reduction at 33°C. (3). Originally an attempt had been made to determine the percentage of the latter compound present by means of a Hanus iodine number. The values obtained (20-40%), however, were obviously incorrect and from the negative permanganate test were undoubtedly due to bromination of the tertiary hydrogen (as in isobutyrophenone),of the ether itself.

Cleavage with hydrogen iodide

A 7.5-g. sample of the ether was heated with 30 g. of freshly distilled constant-boiling hydriodic acid, just to the point of slight refluxing. A non-homogeneous liquid, apparently an azeotropic mixture of some sort, distilled between 68.5 and 69°C. Heating was discontinued just as the brown decomposed hydriodic acid mixture began to come over. The distillate, on standing, separated into two layers; the lower layer (about 1 ml. in volume) was washed twice with water and dried over sodium sulfate. An attempt was made to form a quaternary ammonium compound with aqueous trimethylamine, but even after constant shaking for several hours, no reaction seemed to be taking place. However, on sealing a small amount in an ampoule with anhydrous trimethylamine (b.p. 3.5°C.) and warming to room temperature, a white solid appeared almost immediately. After the reaction was complete, the tube was opened, the excess amine evaporated off and the solid recrystallized from methyl alcohol containing a little ether. (m.p. 290°C.) A known sample of trimethylisopropylammonium iodide (no literature) was prepared in the same way. It also melted at 290°C. and a mixed melting point with the unknown showed no change.

Hence it seems to be certain that this fraction is an isopropyl ether of the alcohol mixture; whether only of one or of all the various isomeric alcohols present it was not determined, since this phase of the problem was not of primary importance in establishing a mechanism for the reduction process.

IV INVESTIGATION OF THE ALCOHOL FRACTION

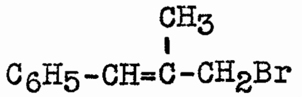
Physical and Chemical Properties

Yield $\doteq$ 40% of total

b_9 = 100.5-103°C.

n_D^{25} = 1.5205

A sodium fusion test for halide being negative, this fraction was presumably free from the unsaturated bromide



$\overset{CH_3}{C_6H_5\text{-}CH\text{=}\overset{|}{C}\text{-}CH_2Br}$ (b_8=115-117°C.)

Formation of derivatives

All attempts to form some sort of a solid derivative of the alcohol fraction which could subsequently be separated into its components by crystallization ended in failure. The benzoate, 3,5-dinitrobenzoate, p-nitrobenzoate, and 3-nitrophthalate all came down as oils, due undoubtedly to the complex nature of the mixture of possible isomeric alcohols of the general formula $C_{10}H_{14}O$ (of which $C_6H_5\text{-}\overset{CH_3}{\overset{|}{C}H}\text{---}\overset{CH_3}{\overset{|}{C}HOH}$, having two optically active centres would also be diameric).

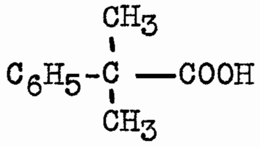
Oxidation with chromic oxide (22)

Oxidation of the alcohols to the corresponding carbonyl compounds was then tried in the hope that formation of derivatives of the latter would meet with more success.

Alcohol fraction	50 g.	0.3	equivalents (as $C_{10}H_{14}O$)
Chromic oxide	100 g.	0.45	"

From previous experience an excess of chromic oxide was found necessary to insure complete oxidation. Since the conditions were relatively mild (the temperature being kept below 23°C. throughout) no further degradation of the products would be expected. Each of the reactants was dissolved in 325 ml. of glacial acetic acid. The chromic oxide solution was added dropwise to the stirred and cooled alcohol solution over a period of 5 hours. After dilution with three litres of water, the mixture was extracted several times with a total of 250 ml. of chloroform. The chloroform extract was treated with sufficient dilute sodium carbonate solution to free it from most of the acetic acid it contained and the still acidic solution allowed to settle. Considerable difficulty was experienced throughout with emulsion formation between the chloroform and water. However, ether was found to be even less satisfactory, since on shaking, foam was generated which made the proper separation of the two layers almost impossible. The chloroform extract was washed several times with water (adding enough anhydrous sodium sulfate to break the emulsion) and the clear (slightly yellow) chloroform layer separated and dried. The solvent was partially removed by evaporation.

Isolation of



$$C_6H_5-\overset{CH_3}{\underset{CH_3}{C}}-COOH$$

The residue above was extracted twice with concentrated sodium carbonate solution to remove acids produced by the oxidation. This alkaline solution, after treatment with ether to remove foreign organic materials, was then acidified with acetic acid. Two ether extractions removed the acids set free and after drying over anhydrous sodium sulfate, the solvent was distilled off. The residue was dissolved in several millilitres of alcohol and then water added dropwise to the hot solution until a cloudiness was noticed. The product had a great tendency to separate as an oil, but by cooling the mixture to a solid mass in dry ice and scratching the sides of the vessel vigorously while warming up to room temperature, a solid came out, which after three recrystallizations from dilute alcohol melted at 77-78°C. (Weight of crude material 0.3 g.) A small amount was treated with thionyl chloride, heated on a steam cone and 50% ammonium hydroxide added. A solid amide was deposited, which after washing with water, then ether, was recrystallized twice from dilute alcohol.(m.p. 158-158.5°C.) The acid was undoubtedly $C_6H_5\text{-}C(CH_3)_2COOH$ (m.p.77-78°C., amide m.p. 160-161°C.) (23). Since no benzoic acid was isolated, degradation as the result of using excess chromic oxide could not have occurred to any significant extent.

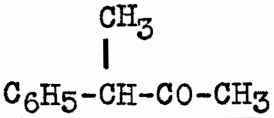
Identification of ketones

The original residue (remaining from the alkaline extraction above) after being just acidified with dilute acetic acid, was washed with water and dried over anhydrous potassium carbonate. The solvent was completely removed under vacuum, and since fractional distillation of the residue met with little success due to the wide boiling range of the various fractions, it was considered best to form first a solid derivative (if possible) and then to separate the various isomers by recrystallization. By comparison with known samples, their identity could readily be established. A 2,4-dinitrophenylhydrazone derivative was known to be practically ideal for this purpose -- it forms readily under the most difficult conditions, and being bulky is easy to handle and crystallize.

To 0.6 g. of 2,4-dinitrophenylhydrazine in 35 ml. of hot alcohol was added 0.5 g. of the ketone mixture along with 0.7 ml. of concentrated hydrochloric acid. A red precipitate was formed which was filtered from the cold solution. On making preliminary tests with various solvents, it was found that the material was a mixture of two hydrazones, one of which was fairly soluble in hot ethyl alcohol, the other quite insoluble. A digestion with hot alcohol followed by a hot filtration resulted in a partial separation of these two solids; the first (yellow and soluble in hot alcohol) constituting about 65% of the total (crude material) melted in the neighbourhood of 155°C.; the second (red and insoluble in hot alcohol) made up the remainder and melted around 230°C. Each was recrystallized repeatedly from alcohol-chloroform and alcohol-dioxan mixtures until melting points ceased to rise. Both materials were extremely soluble in chloroform and dioxan. The use of mixed solvents containing the latter served the dual purpose of decreasing the amount of alcohol necessary and also, by allowing a change in the solvent, of enabling the progress of the purification to be checked. The amount of chloroform (or dioxan) used in the mixed solvent for the recrystallization of the yellow compound was fairly small; in the recrystallization of the more difficultly soluble red product, a 35% solution gave best results. The melting points finally obtained were 159.5-160.5°C. for the yellow crystals and 241-242°C. for the red solid.

Isolation of isobutyrophenone

Mixed melting points made on a portion of the first material and a sample of isobutyrophenone-2,4-dinitrophenylhydrazone (m.p. 160-161°C.) prepared in the same way, all gave values between 159.5 and 161°C. Hence it is to be concluded that isobutyrophenone was present in the ketone mixture and $C_6H_5\text{-}CHOH\text{-}CH(CH_3)_2$ in the original alcohol (roughly in the proportion of 65% of total alcohols).

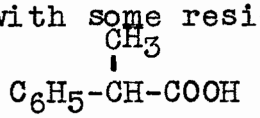


Evidence for presence of $C_6H_5\text{-}\overset{\overset{CH_3}{|}}{C}H\text{-}CO\text{-}CH_3$

Since an iodoform test on the ketone mixture was positive, it was reasonable to suppose that $C_6H_5\text{-}CH(CH_3)CO\text{-}CH_3$ also was present and that it formed the 2,4-dinitrophenylhydrazone melting at 241-242°C. (The melting point of 2,4-dinitrophenylhydrazine (red crystals) is 194°C. and it is fairly soluble in hot alcohol - hence it was eliminated as a possibility.) A larger hypoiodite oxidation was made on 10 g. of ketone in an attempt to cleave off the methyl group with formation of $C_6H_5\text{-}CH(CH_3)COOH$ (hydratropic acid).

Iodine	30 g.
Potassium iodide	60 g.
Water	240 ml.
Sodium hydroxide (10% solution)	enough

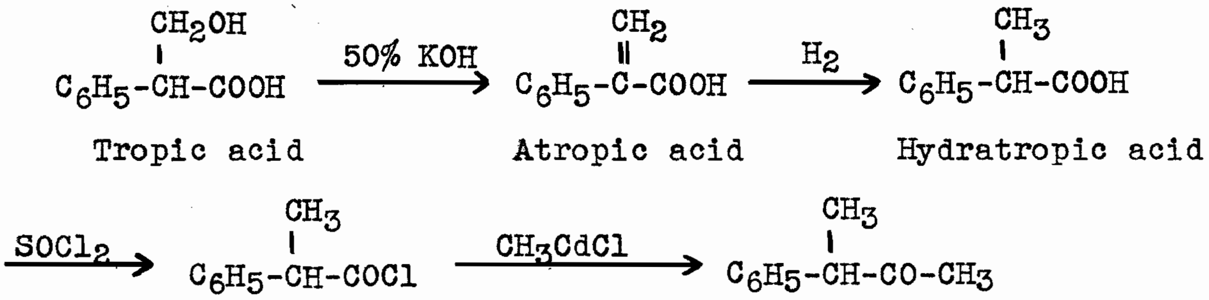
Ten grams of the ketone was run into the iodine-potassium iodide-water solution with stirring and then the sodium hydroxide solution added dropwise until the brown color of the iodine just disappeared. Stirring was continued for 2 hours, whereupon the mixture was heated to 50°C. and then stirred until cold. Due to the higher stability of sodium hypobromite over the hypoiodite it was decided (in order to ensure complete oxidation) to continue the reaction with the former. Accordingly 90 g. of bromine was added and the above procedure repeated. The mixture was then extracted with ether, the solvent evaporated off and the residue steam distilled. About 1 g. of brown liquid (bromoform?) followed by a few tenths of a gram of yellow solid was produced. The latter had the odor of iodoform and melted at the same temperature (119°C.)

The original alkaline oxidation mixture was acidified with sulfuric acid in order to liberate the acidic products and on removal of the halogens with bisulfite it was extracted with ether. After washing with water and drying, the solvent was removed by evaporation. A small residue (1-2 g.) was obtained, which consisted mainly of benzoic acid with some residual oil which had the odor of hydratropic acid  $C_6H_5\text{-}\overset{CH_3}{\overset{|}{C}H}\text{-}COOH$. The amount of the latter present was too small to isolate readily.

Too much significance should not be attached to the small amount of iodoform obtained, however, since the reaction was carried out in alkaline solution and the amount of oxidation would probably tend to be slight -- the tertiary hydrogen in the ketone very likely halogenating preferentially. This would be supported by the fact that the mixture had some lachrymatory properties.

V ATTEMPT TO SYNTHESIZE $C_6H_5\text{-}CH(CH_3)CO\text{-}CH_3$

An attempt was made to synthesize $C_6H_5\text{-}CH(CH_3)CO\text{-}CH_3$ by the following series of reactions:



$$\underset{\text{Tropic acid}}{C_6H_5\text{-}\overset{\overset{CH_2OH}{|}}{C}H\text{-}COOH} \xrightarrow{50\%\ KOH} \underset{\text{Atropic acid}}{C_6H_5\text{-}\overset{\overset{CH_2}{\|}}{C}\text{-}COOH} \xrightarrow{H_2} \underset{\text{Hydratropic acid}}{C_6H_5\text{-}\overset{\overset{CH_3}{|}}{C}H\text{-}COOH}$$

$$\xrightarrow{SOCl_2} C_6H_5\text{-}\overset{\overset{CH_3}{|}}{C}H\text{-}COCl \xrightarrow{CH_3CdCl} C_6H_5\text{-}\overset{\overset{CH_3}{|}}{C}H\text{-}CO\text{-}CH_3$$

Preparation of Atropic Acid

Tropic acid	30 g.
50% potassium hydroxide	180 ml.

The procedure for the dehydration was the same as that described by Baker and Eccles (24) for the most part. The solution of tropic acid and potassium hydroxide was boiled for one hour. After washing twice with ether (to remove any foreign organic matter) 100 ml. of water and enough 5N hydrochloric acid was added to make the solution acidic. The mixture was extracted with ether, washed twice with water and the solvent evaporated off. The solid residue was then extracted with carbon bisulfide (atropic acid alone is soluble) and the unreacted tropic acid filtered off. (This procedure was found to be an improvement over the original method which had involved purification by crystallization from alcohol.) The carbon bisulfide extract was washed once with water and dried over sodium sulfate. On removal of the solvent by evaporation, 13.5 g. of crude product was obtained which, after recrystallization from dilute alcohol, melted at 105.5-106°C.

Hydrogenation of Atropic Acid to Hydratropic Acid

Atropic acid 9 g. m.p.105.5-106°C.
Alcohol (distilled from silver nitrate) 75 ml.
Platinum oxide 0.2 g.

The acid was reduced in a typical hydrogenation apparatus (25), the theoretical amount of hydrogen being absorbed. The catalyst was removed from the solution by filtration and the alcohol distilled off. The residue was fractionated at 25 mm. There was no appreciable forerun, the main fraction coming off continuously at 162°C.* No afterrun was obtained though about 1 ml. of brown residue remained. Yield 5.6 g.

Preparation of hydratropic acid chloride

Hydratropic acid	7.1 g.	0.0475 moles.
Thionyl chloride (distilled)	7.0 g.	0.059 moles.

The hydratropic acid was added dropwise to the warmed thionyl chloride. The mixture was allowed to stand for 24 hours at room temperature, then heated over a steam cone until all of

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* Tiffeneau: b_{25}=160°C. (26)

the excess thionyl chloride was removed. The residue was vacuum distilled at a pressure of 12.5 mm. Approximately one-half ml. of forerun, boiling below 95°C. came over, followed by the main fraction (5-6 g.) distilling at 95-96°C.* The residue (1.6 g.) undoubtedly contained some residual hydratropic acid. An amide was made with a small amount of the main fraction which, after two recrystallizations from dilute alcohol, melted at 90-92°C.**

Reaction of hydratropic acid chloride with methyl cadmium chloride

The remainder of the acid chloride was treated with CH_3CdCl prepared in the following manner (29):

Magnesium turnings	1.35 g.	0.056 mole
Ether	100. ml.	
Methyl chloride gas	excess	

The reaction was started with 0.1 ml. of methyl iodide, then methyl chloride bubbled in until all of the magnesium had disappeared. The methyl chloride obtainable was not very pure, and even after passing it through a purification train of concentrated sulfuric acid, saturated potassium permanganate solution and drying towers of calcium chloride and phosphorus pentoxide, a certain amount of white sludge was deposited. (It would have been much simpler to make CH_3MgI; however, Gilman and Nelson (29) state that the reaction of the cadmium halide with this type of Grignard is unsatisfactory. They used CH_3MgBr; however, no methyl bromide was available at the time.)

* Rupe reported $b_{12.5}$=97-98°C. (27)

** m.p.=91-92°C. Janssen (28)

The remainder of the process was carried out under an atmosphere of purified nitrogen. The CH_3MgCl - ether solution was filtered in order to remove insoluble material and 11 g. of cadmium chloride was added slowly with stirring and cooling. Stirring at room temperature was continued until a negative test with Michler's ketone was obtained - indicating the absence of CH_3MgCl. The mixture was then heated to refluxing and 5 g. of hydratropic acid chloride in 50 ml. of dry ether was slowly added with continuous stirring. After refluxing and stirring for another two hours, the mixture was decomposed with ice and enough dilute sulfuric acid to prevent deposition of cadmium and magnesium hydroxides. The water layer was drawn off and the ether layer extracted with 10% sodium carbonate solution. After washing with water and drying over sodium sulfate, the ether was removed and the residue fractionally distilled at 11 mm. pressure. About 1 ml. of product boiling between 100 and 103°C. was obtained. A 2,4-dinitrophenylhydrazone derivative procedure gave two solids, one of which melted at 168-170°C. and another dark-red impure solid melting at 175-185°C. (impure 2,4-dinitrophenylhydrazine?).

Inasmuch as only a relatively small amount of product was isolated from the synthesis just described, it would be injudicious to state (without further evidence) that the material melting at 168-170°C. was the 2,4-dinitrophenylhydrazone derivative of the ketone C_6H_5-$CH(CH_3)CO$-CH_3. Due to circumstances beyond our control, this phase of the problem had to be left at this admittedly unsatisfactory stage of development.

VI. INVESTIGATION OF THE HIGH-BOILING FRACTION

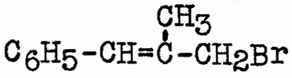
Physical constants

b_9 = 113°C.

n_D^{25} = 1.5175

Yield ≑ 7% of total

Chemical tests

Since a Beilstein test for halogen was negative, the fraction must have been free from the unsaturated bromide  $C_6H_5\text{-}CH{=}\overset{CH_3}{C}\text{-}CH_2Br$ (b_8=115-117°C.; n_D^{25}=1.5921 (3).) It was immediately oxidized by potassium permanganate but absorbed bromine only on standing a minute or two. The odor was similar to that of the ether; on the other hand, its higher boiling point and refractive index, coupled with the fact that it is oxidized by permanganate, may indicate the presence of a hydroxyl group. The compound is probably a hydroxy ether of the same type produced by the reduction of α-bromo propiophenone (3).

VII. ANALYSIS OF EXPERIMENTAL WORK

This experimental work has definitely established the fact that several products are formed by the action of aluminum isopropoxide on α-bromoisobutyrophenone. A chromic acid oxidation carried out on the alcohol fraction of the reduction mixture has shown that there is present in the latter (in estimated percentages of total volatile products):

(a) $C_6H_5-C(CH_3)_2CH_2OH$ in small amounts only (less than 1%)

(b) $C_6H_5-CHOH-CH(CH_3)_2$ (about 25%)

(c) $C_6H_5-CH(CH_3)CHOH-CH_3$ (about 15%) (?)

An isopropyl ether (d) of one or of all the above alcohols also was isolated and constituted roughly 30% of the total. A forerun boiling lower than the ether (6%) probably contained some of the latter. An unknown high boiling material (e) (which, as has already been suggested, may be a hydroxy ether) present in smaller amounts (7%) also was isolated. The remaining 17% consisted of residues and an after-run boiling even higher than the fraction (e), perhaps the unsaturated bromide $C_6H_5-CH=C(CH_3)CH_2Br$.

It should be stressed that the estimates of the amounts of products are approximate only. Due to the inefficiency of any purification process involving fractional distillation, it was very difficult to separate the fractions effectively since they boiled fairly close together. The amounts of intermediate fractions were in some cases appreciable. The percentages above, however, were calculated with this in mind and are reasonably correct.

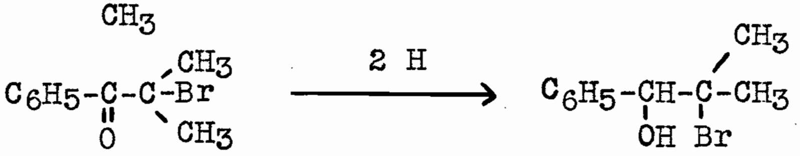
EXPERIMENTAL AND THEORETICAL DISCUSSION

Introduction

It would be difficult to understand how the various products of the reaction between aluminum isopropoxide and α-bromoisobutyrophenone could arise if the mechanism postulated for the reduction of α-bromopropiophenone by this same reagent were not also applicable here. In the discussion to follow, it is hoped that the additional evidence obtained as a result of this investigation will be sufficient to establish firmly the mechanism as a true picture of the reaction.

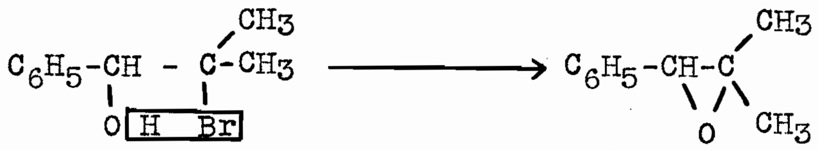
The intermediate oxide theory

At the temperature used (80°C.) reduction of the bromoketone apparently takes precedence over the removal of hydrogen bromide (which would result in the formation of $C_6H_5\text{-}CO\text{-}\underset{CH_3}{\underset{|}{C}}{=}CH_2$). The first stage then is:



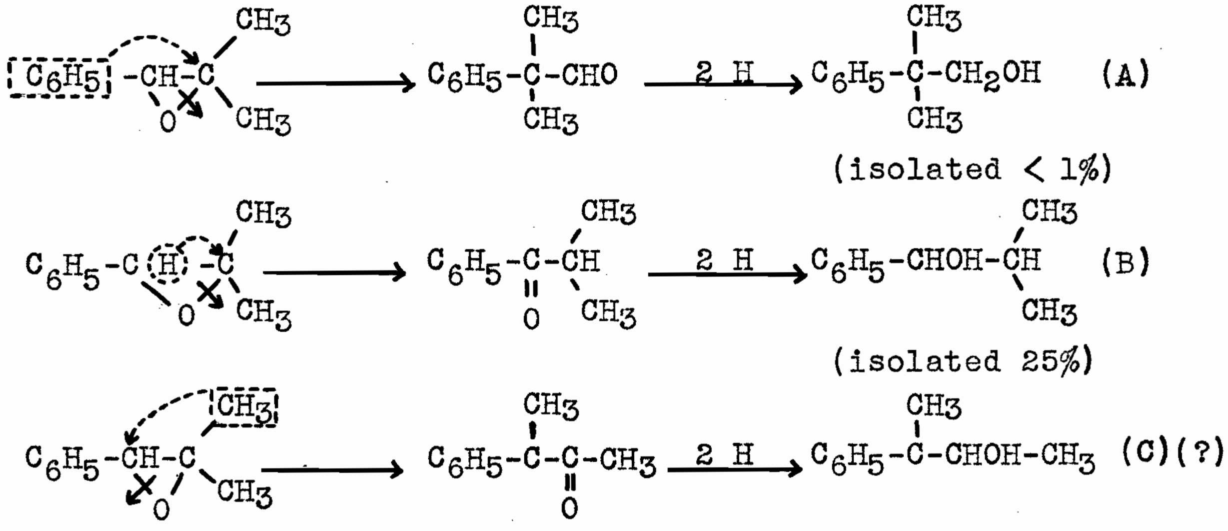
$$C_6H_5\text{-}\underset{O}{\underset{\|}{C}}\text{-}C\overset{CH_3}{\underset{CH_3}{\text{-}Br}} \xrightarrow{2\ H} C_6H_5\text{-}\underset{OH}{\underset{|}{CH}}\text{-}\overset{CH_3}{\underset{Br}{\underset{|}{C}}}\text{-}CH_3$$

A 35% yield of bromohydrin was obtained on reduction of α-bromopropiophenone (3). However, due undoubtedly to the greater reactivity of the tertiary bromine in the above formulated bromohydrin, and as a result of the aluminum isopropoxide functioning as a base, removal of halogen acid is favored so that none of the bromohydrin was isolated. Instead, an intermediate oxide is generated thus:



Such action is not surprising -- it takes place readily under analogous conditions as the result of the action of silver nitrate on similar bromohydrins (18).

The next stage involves cleavage of the oxide ring. There are only three possibilities, and it will be seen that the products formed are those which actually have been isolated.



(A)

(isolated < 1%)

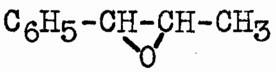
(B)

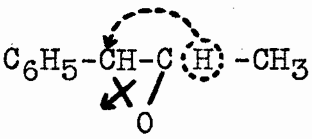
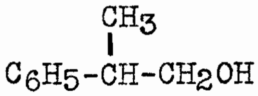
(isolated 25%)

(C)(?)

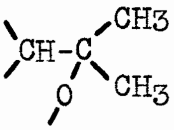
(believed to be present 15%)

(This type of ring opening and rearrangement is the main reaction on reduction of α-bromopropiophenone (3))

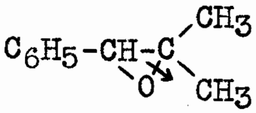
The isomerization reactions involve two distinct phenomena of the same nature -- the rupture of a bridge and the migration of a group. The relative percentages of each product formed will be dependent on the relative migration tendencies of the individual groups concerned and also on the influence of these same groups on the stability of the neighbouring C-O bond. As the result of a large number of experiments on the dehydration of glycols with subsequent cleavage and rearrangement of the oxides, as well as work on the oxides themselves, Tiffeneau et al. (30) have shown that invariably (under the dehydrating conditions they employed) cleavage of the oxide bond in compounds such as  $C_6H_5-CH-CH-CH_3$ (O) takes place on the side next to an aryl group and that aryl groups migrate in preference to alkyl radicals or a hydrogen. They have shown experimentally what would more or less be expected from the electronic standpoint -- namely that the stability of the C-O bond would be influenced by a phenyl group attached to the carbon for the same reason that the hydroxyl in benzyl alcohol is loosely attached.

Hence in the case of the oxide  $C_6H_5-CH-C(H)-CH_3$ (O) (the intermediate in the reduction of α-bromopropiophenone) cleavage and rearrangement in the manner shown would be most likely. Undoubtedly it was for this reason that by the reduction of the latter the only alcohol isolated was $C_6H_5-CH_2-CHOH-CH_3$ with no products corresponding to cleavage on the opposite side i.e.  $C_6H_5-CH(CH_3)-CH_2OH$ or $C_6H_5-CHOH-CH_2-CH_3$.

One would also predict that the C-O bond in a

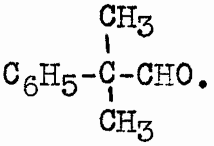

$>CH-C(CH_3)_2-O-$

radicle would be relatively weak (as evidenced by ready loss of water in tertiary alcohols). Tiffeneau showed in his experiments that such an arrangement was just as effective as a phenyl group (sometimes even more so) in loosening the C-O bond. Hence cleavage of the oxide



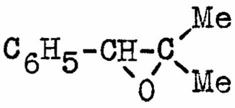
can take place equally well on the opposite side as shown, and we have the possibilities A and B.

From what has been said concerning group migrating tendencies, it would be reasonable to suppose that the most favored product would be that produced by rearrangement A. Knowing definitely that $C_6H_5-C(CH_3)_2CH_2OH$ was produced in small amounts only, and that the other alcohol $C_6H_5-CHOH-CH(CH_3)_2$ was found in considerable quantities (25% yield), it is not clear why the reverse seems to be the case. Poctivas and Tchoubar (31) on treating this oxide with magnesium bromide in boiling ether obtained a 90% yield of

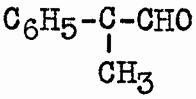


$C_6H_5-\underset{CH_3}{\overset{CH_3}{\underset{|}{\overset{|}{C}}}}-CHO$.

It is known however that both the conditions of the experiment and the medium in which the reaction is carried out are important factors in determining the direction of cleavage of the oxide ring. Lévy and Tabart (32) found that

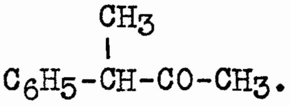


on being heated in the presence of infusorial earth gave



$C_6H_5-\underset{CH_3}{\overset{CH_3}{\underset{|}{\overset{|}{C}}}}-CHO$

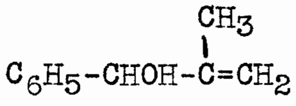
but that distillation or treatment with cold concentrated sulfuric acid produced

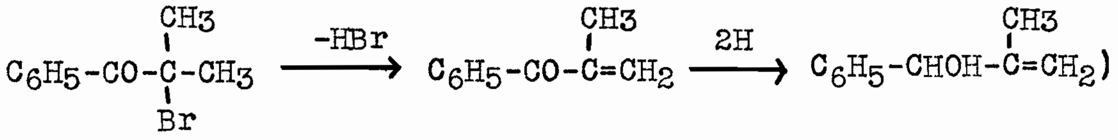


$C_6H_5-\overset{CH_3}{\overset{|}{CH}}-CO-CH_3$.

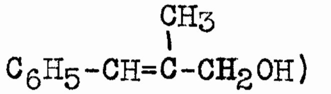
Tiffeneau and Orékhoff (33) obtained the first product on distilling the oxide in the presence of zinc chloride or dilute sulfuric acid.

Since both cleavage of a C:O bond and rearrangement of a radicle involve the same electronic principles, it would be surprising if the latter reaction were not also dependent on these factors. It is quite possible then, that in the presence of aluminum isopropoxide and aluminum bromide (or its complex salt) a hydrogen shift is favored over the rearrangement of a phenyl group.

In view of the rather unsatisfactory proof for the presence of the alcohol C_6H_5-$CHCH_3$-$CHOH$-CH_3, the structure of the red 2,4-dinitrophenylhydrazone derivative melting at 242°C. (prepared from the ketone mixture after oxidation of the carbinol fraction) is open to question. It would not ordinarily be expected that this derivative of the ketone C_6H_5-$CHCH_3$-CO-CH_3 should be red in color and have such a high melting point. On the other hand, some type of ring compound such as a pyrazolone or a hydrazone of an unsaturated aldehyde or ketone might be possibilities. If the original alcohol were  $C_6H_5\text{-}CHOH\text{-}\overset{CH_3}{\overset{|}{C}}{=}CH_2$ (I)(produced simply by elimination of HBr during reduction in the manner:



$$C_6H_5\text{-}CO\text{-}\underset{Br}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}\text{-}CH_3 \xrightarrow{-HBr} C_6H_5\text{-}CO\text{-}\overset{CH_3}{\overset{|}{C}}{=}CH_2 \xrightarrow{2H} C_6H_5\text{-}CHOH\text{-}\overset{CH_3}{\overset{|}{C}}{=}CH_2)$$

then pyrazolone formation of the corresponding ketone would very likely occur. According to Kohler (34), C_6H_5-CO-$CH{=}CH_2$ forms the 1,3-diphenylpyrazolone on treatment with phenyl hydrazine. The alcohol isomeric to I above (i.e.,  $C_6H_5\text{-}CH\text{=}C(CH_3)\text{-}CH_2OH$) (II) might also be produced in certain amounts by partial hydrolysis of the corresponding bromide which is known to be formed at 33°C. (3). A 2,4-dinitrophenylhydrazone derivative of the aldehyde, however, (although deep red in color) melts at 210°C.* The boiling point of the alcohol (b_8=124-124.3°C.(3)) is also too high to be included in the carbinol fraction (b_9=100.5-103°C.). The boiling point of I is within this range, however. Definite information concerning the alcohol $C_6H_5\text{-}CHCH_3\text{-}CHOH\text{-}CH_3$(III) is lacking. Since the publication of this work (4), a paper by Suter (35) in 1942 has considerably clarified a previous impression that the corresponding ketone $C_6H_5\text{-}CH(CH_3)\text{-}CO\text{-}CH_3$ had never been synthesized in a manner which was not open to question. The boiling point which he gives (b_{22}=106-107°C.) is fairly close to that of isobutyrophenone (b_{24}=118°C.(36)), so that conceivably the corresponding carbinols should boil at similar temperatures. Lacking more definite information, both of the alcohols I and III must be considered as possibilities.

Other mechanisms which explain the formation of $C_6H_5\text{-}CHOH\text{-}CH(CH_3)_2$

The intermediate oxide mechanism just described seems to provide the most reasonable explanation for the formation of the alcohol $C_6H_5\text{-}CHOH\text{-}CH(CH_3)_2$ though several others are possible. The series of reactions below results in the formation of the same compound:

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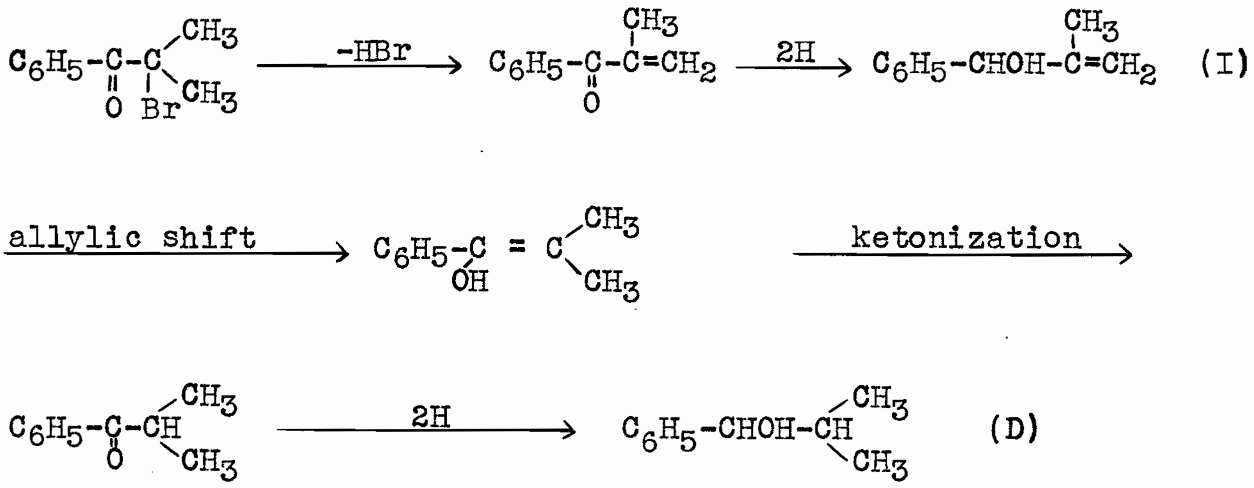
* Private communication
from Dr. P. G. Stevens



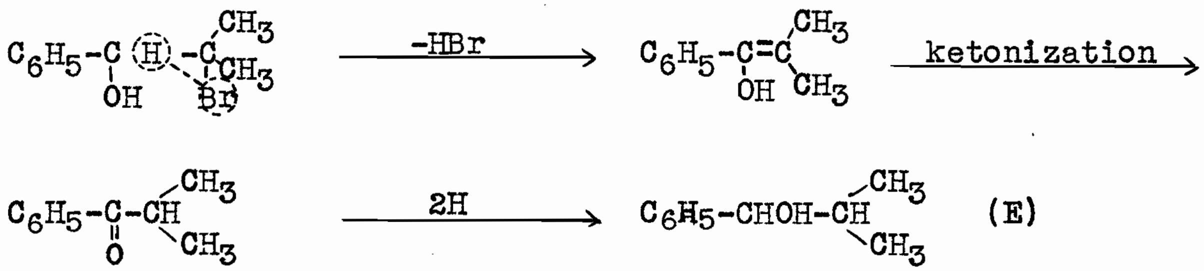
$$C_6H_5-\underset{\underset{O}{\|}}{C}-\underset{Br}{C}\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix} \xrightarrow{-HBr} C_6H_5-\underset{\underset{O}{\|}}{C}-\overset{CH_3}{C}=CH_2 \xrightarrow{2H} C_6H_5-CHOH-\overset{CH_3}{C}=CH_2 \quad (I)$$

$$\xrightarrow{\text{allylic shift}} C_6H_5-\underset{OH}{C}=C\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix} \xrightarrow{\text{ketonization}}$$

$$C_6H_5-\underset{\underset{O}{\|}}{C}-CH\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix} \xrightarrow{2H} C_6H_5-CHOH-CH\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix} \quad (D)$$

It was found however, that the alcohol (I) does not undergo an allylic rearrangement with aluminum isopropoxide but is recovered unchanged from the boiling solution.*

Another possibility would be a loss of hydrogen bromide after reduction in this manner:

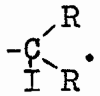


$$C_6H_5-\underset{OH}{C}\textcircled{H}-\underset{\textcircled{Br}}{C}\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix} \xrightarrow{-HBr} C_6H_5-\underset{OH}{C}=C\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix} \xrightarrow{\text{ketonization}}$$

$$C_6H_5-\underset{\underset{O}{\|}}{C}-CH\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix} \xrightarrow{2H} C_6H_5-CHOH-CH\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix} \quad (E)$$

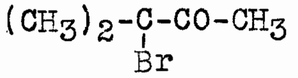
This is supported by a discovery of Lévy and Gombinska (I7) that although in the iodohydrin $C_6H_5-\underset{OH}{CH}-\underset{I}{CH}-CH_3$ loss of halogen acid on treatment with silver nitrate occurred as shown, in the case of $C_6H_5-\underset{OH}{C}\textcircled{H}-\underset{\textcircled{I}}{CH}-C_2H_5$ (orC_3H_7i) however

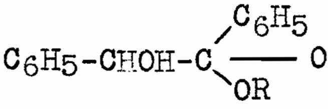
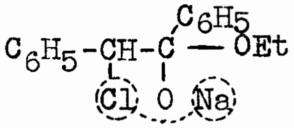
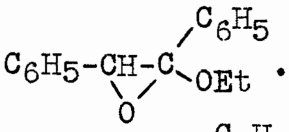
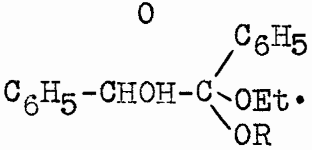
* Unpublished work by A.S. Dubois, McGill University, Montreal.

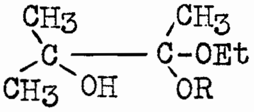
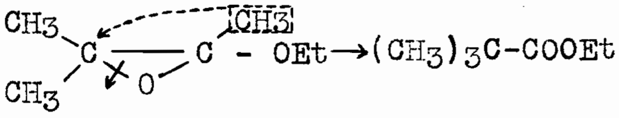
it took place in the second manner. No results are available for compounds of the type  $-\overset{R}{\underset{I}{C}}-R$.

It would be rather difficult to say definitely which of the three mechanisms B, D and E is most acceptable. Karl v. Auwers and E. Lämmerhirt (37) on boiling α-bromo-n-butyrophenone in N-diethylaniline obtained a product which was practically pure n-butyrophenone. Removal of bromine in this case could not take place through any of the mechanisms just outlined -- rather a direct interchange of hydrogen from the dimethylaniline and the bromine of the ketone has resulted. Inasmuch as the hydrogens in the alcohol component of aluminum isopropoxide are removable, such a direct group interchange may be operating here as well. However, since no phenylethylcarbinol was isolated from the reduction of α-bromopropiophenone it is difficult to understand how these alternative mechanisms could operate in one case and not the other. Explained on the basis of the intermediate oxide mechanism, on the other hand, the situation is considerably clarified.

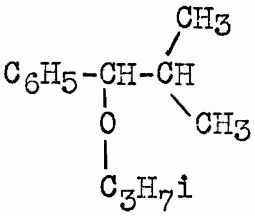
Additional support for the intermediate oxide mechanism

Results published in a paper by Aston and Greenburg (38) in 1940 on the reaction of sodium ethylate in alcoholic solution on α-halogenated ketones such as  $(CH_3)_2-\underset{Br}{C}-CO-CH_3$ (I) indicate a mechanism which is similar in most respects to that just outlined for the reduction of α-bromoketones. Originally

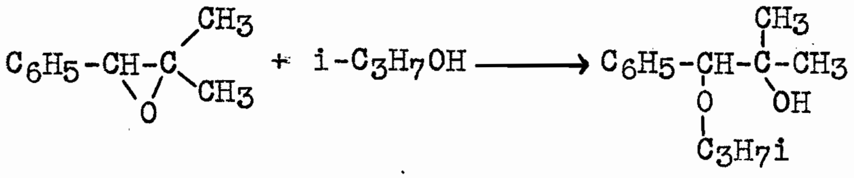
Ward (39) on treating desyl chloride ($C_6H_5-CHCl-CO-C_6H_5$) with equimolecular amounts of sodium ethylate in ROH had isolated the product  $C_6H_5-CHOH-\overset{C_6H_5}{\underset{OR}{C}}-OEt$. To explain this he postulated an intermediate addition compound with the sodium ethylate  $C_6H_5-\underset{Cl}{CH}-\overset{C_6H_5}{\underset{O\ \ Na}{C}}-OEt$ which subsequently lost sodium chloride giving the oxide  $C_6H_5-\underbrace{CH-C}_{O}{<}^{C_6H_5}_{OEt}$. Reaction of ROH with the latter produced  $C_6H_5-CHOH-C{<}^{C_6H_5}_{\underset{OR}{OEt}}$.

The mechanism was merely a suggestion, however, and had no experimental evidence to support it. It was given considerable weight when Aston found that in similar treatment of the bromo ketone I, there was produced the ester $(CH_3)_3C-COOEt$ in 13.5% yield along with the normal product  $\underset{CH_3}{\overset{CH_3}{>}}\underset{OH}{C}\text{——}\overset{CH_3}{\underset{OR}{C}}-OEt$ (32%). The formation of the ester of trimethylacetic acid was considered to be due to a rearrangement of the intermediate oxide  $\underset{CH_3}{\overset{CH_3}{>}}C\underbrace{\text{———}}_{O}\overset{CH_3}{C}-OEt \rightarrow (CH_3)_3C-COOEt$ as shown.

Mechanism of ether formation

The formation of the ether (or mixture of ethers) of the type  $C_6H_5-\underset{\underset{C_3H_7i}{O}}{CH}-CH{<}^{CH_3}_{CH_3}$ is easily understood by condensation of the two alcohols in the presence of the equivalent of HBr, after the manner of the formation of diisopropyl ether with acids.

The hydroxy-ether (which may constitute the high boiling fraction) would presumably be formed by reaction of the oxide with isopropyl alcohol thus:

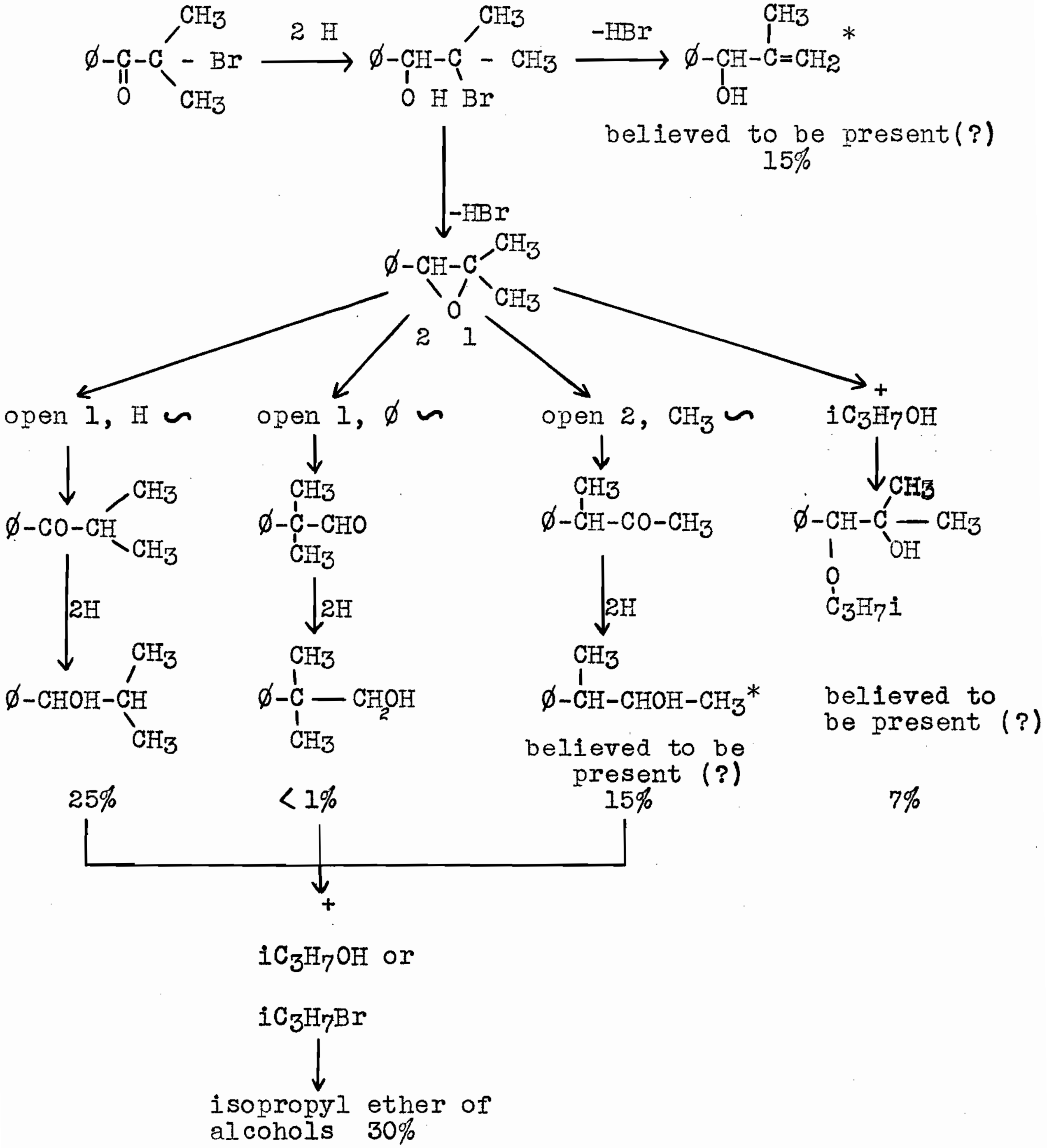


(I)

Unlike the corresponding hydroxy-ether produced from α-bromopropiophenone, it was present in relatively small amounts. The equilibrium above would undoubtedly be unfavorable to formation of I above, however, since the hydroxyl generated is tertiary and the reverse reaction might readily take place. Addition of isopropyl alcohol across the oxide bridge in the alternate direction might be greatly hindered sterically.

SUMMARY

From the reduction of α-bromoisobutyrophenone with aluminum isopropoxide at 80°C., a variety of products has been isolated. The more important of these have been identified conclusively, and by their very nature substantiate a postulated intermediate oxide mechanism which is presented below in full:



* indicates alternatives

BIBLIOGRAPHY

1. Lund, H., Ber. 70B, 1520-1525 (1937)
2. Stevens, P.G., J.Am.Chem.Soc. 60, 3089 (1938)
3. Stevens, P.G., Allenby, O.C.W. and Dubois, A.S., ibid, 62, 1424-1428 (1940)
4. Stevens, P.G., and Allenby, O.C.W., ibid, 62, 3264-3265 (1940)
5. Tischtschenko, W., Chem. zentr. 1906 II 1309 and 1552.
6. Claisen, L.,Ber. 20, 646-650 (1887)
7. Meerwein, H., and Schmidt, R., Ann. 444, 221-238 (1925)
8. Ponndorf, W., Z. Augew.Chem. 39, 138-143 (1926)
9. Verley, A., Bull.soc.chim.(4) 37, 871-874 (1925)
10. Adkins, H., and Cox, F.W., J.Am.Chem.Soc., 60,1151-1159 (1938)
11. Baker, R.H. and Adkins, H., ibid 62, 3305-3314 (1940)
12. Adkins, H., ibid 44, 2175-2186 (1922)
13. Meerwein, H., et al., J.prakt.Chem. 147, 211-225 (1936)
14. Young, W.G., Hartung, W.H. and Crossley, F.S., J.Am.Chem. Soc. 58, 100-102 (1936)
15. Child, W. C. and Adkins, H., ibid 47, 798-807 (1925)
16. Fourneau and Tiffeneau, Compt.rend.141, 662-663 (1905)
17. Lévy, J. and Gombinska, F.,ibid 188, 711-713 (1929)
18. Lévy, J. and Gombinska, D., Bull.soc.chim.(4), 49, 1765-1776 (1931)
19. Faworski,Al., and Mandryka, N., J.prakt.Chem.(2) 88, 690-693 (1913)

20. Auwers, K.v., Ber. 45, 2764-2781 (1912)

21. Ward, C.F., J.Chem.Soc. 123, 2207-2213 (1923)

22. Houben-Weyl: Die Methoden der organischen Chemie. Vol.II, p.47

23. Wallach, O., Chem.Zentr. 1899 II, 1047

24. Baker, J.W. and Eccles, A., J.Chem.Soc. 1927, 2125-2133

25. Organic Syntheses, Vol.VIII, p. 10

26. Tiffeneau, M., Ann.Chem.Phys.(8) 10, 352-353 (1907)

27. Rupe, H., Ann. 369, 311-369 (1909)

28. Janssen, H., Ann. 250, 125-140 (1889)

29. Gilman, H. and Nelson, J.F., Rec.trav.chim. 55, 518-530 (1936)

30. Tiffeneau, M. et al., Bull.soc.chim.(4) 49,1595-1851 (1931)

31. Poctivas, M. and Tchoubar, B., Compt.rend.205,287-288 (1937)

32. Lévy,J. and Tabart,A., Bull.soc.chim.(4) 49,1776-1788 (1931)

33. Tiffeneau,M. and Orékhoff,A., Bull.soc.chim. (4) 29,809-820 (1921)

34. Kohler,E.P., Am.Chem.J. 42, 375-401 (1909)

35. Suter,C.M. and Weston,A.W., J.Am.Chem.Soc.64,533-536 (1942)

36. Lapworth,A. and Steele,V., J.Chem.Soc.99,1882-1887 (1911)

37. Auwers,K.v. and Lämmerhirt, E.,Ber.53B, 428-443 (1920)

38. Aston,J.G. and Greenburg,R.B., J.Am.Chem.Soc. 62, 2590-2595 (1940)

39. Ward, A.M., J.Chem.Soc. 1929, 1541-1553.

SECTION II

THE NITRATION OF p-CYMENE

ACKNOWLEDGMENT

The author wishes to express his gratitude for the constant encouragement, continued cooperation and valuable suggestions tendered him by Dr. R. V. V. Nicholls.

CLAIMS TO ORIGINAL RESEARCH
AND CONTRIBUTIONS TO KNOWLEDGE

1. Based on a new method of analysis dependent on refractive index measurements, the relative and actual yields of dinitrotoluene and dinitrocymene produced by the nitration of cymene have for the first time been accurately determined.

2. Wide variations in temperature, water, nitric and sulfuric acid content of the system, addition and stirring times and other factors have been studied and optimum nitrating conditions have been established.

3. The constancy of the ratio of dinitrotoluene to dinitrocymene has been shown and various theories have been advanced for the slight variations which occasionally do occur.

4. Based on the use of Skelly Solve B, a method of solvent extraction for separation of the two components has been developed, replacing the previous unsatisfactory methods of recrystallization from alcohol and other solvents.

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EXPERIMENTAL SECTION

INTRODUCTION

This investigation of the nitration of p-cymene was made under the sponsorship of the Advisory Committee of the National Research Council of Canada and at the suggestion of Dr. J. H. Ross of the Allied War Supplies Board, and the Department of Chemistry, McGill University. The assumption was that the cymene being produced in the paper mills on this continent (amounting to several million gallons annually and at the present time being largely discarded) could perhaps be utilized in some manner for the furtherance of the war effort.

Cymene has been used in the past as a fungicide, a paint thinner and as the starting material for the preparation of resins, plasticizers, emulsifying agents, dyes, photographic developers, and as an intermediate in the manufacture of phenols, carvachrol, thymol and menthol. Substantial quantities of carvachrol are used by the essential oil industries in the manufacture of odorants used in soaps. Being concerned at this time, naturally enough, with the preparation of explosives, it was thought that, by a study of the nitration of cymene, valuable materials might well be obtained which would provide an outlet for some of this by-product.

With this in mind, a thorough survey of the literature was made in order to ascertain which particular phase of the problem merited attention. It was found that experimental conditions for the mononitration had been fairly well investigated and, since the procedure for the preparation of trinitrocymene is quite drastic, expensive, and yields are poor, attention was concentrated on the proper conditions for the formation of the dinitrated products, 2,6-dinitrocymene and 2,4-dinitrotoluene.

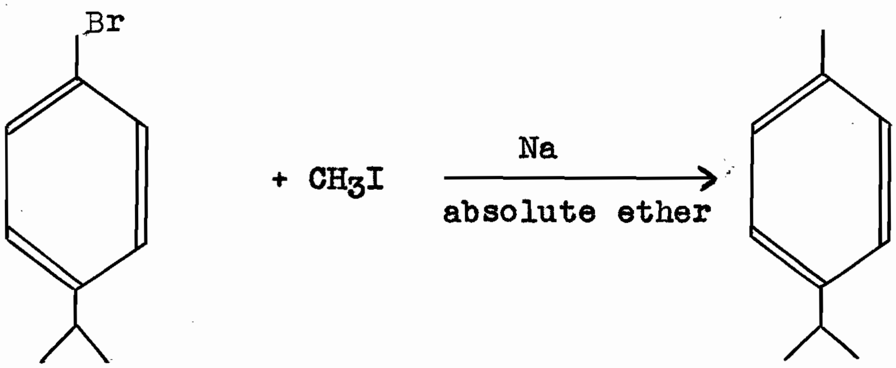
This phase of the problem was in a definitely unsatisfactory condition. Reliable figures for the amounts of these materials produced in the reaction were lacking and proper operating conditions were known only very approximately. Further, there seemed to be no really satisfactory method for separating the two compounds. It occurred to us that dinitrocymene might be useful as a phlegmatizer because of its exceedingly high stability and low melting point (54°C.). Dinitrotoluene is, of course, an intermediate in the preparation of trinitrotoluene, and if it ever became necessary to consider sources of supply other than those presently available from the petroleum and coal tar industries, then information concerning the amounts of this material formed during the nitration of cymene might be of definite value.

The investigation was planned to include a study of the effect of wide variations of sulfuric acid, nitric acid, and water content as well as the influence of temperature, nitration and cleavage catalysts and other factors in the relative and over-all yields of each of the products. It was anticipated that a considerable amount of work would have to be done on the most efficient means of separating the two constituents, since they would be of more value in the pure than in the mixed state. The results of these investigations are presented in this thesis.

HISTORICAL

Cymene - Its Sources and Methods of Purification

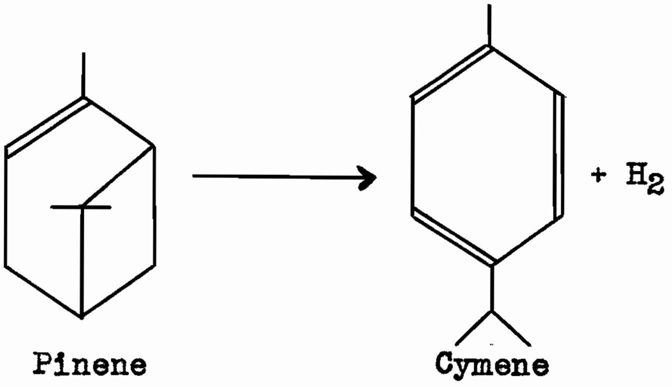
Originally discovered in 1837 by Dumas and Péligot (1) on heating a mixture of camphor and phosphoric anhydride (a process which is recognized even today as one of the best methods for the synthesis of this hydrocarbon),it was not until 1841 that cymene was given this name by Gerhardt and Cahours (2) after finding it in the essential oil of "cuminum cyminum." Originally thought to be p-methylpropylbenzene, the structure of p-cymene remained in doubt until 1891 when Widman (3) definitely established it as p-methylisopropylbenzene by means of a synthesis from p-bromisopropylbenzene, methyl iodide and sodium:



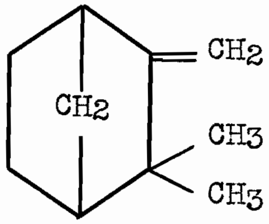
The identity of the synthetic and natural product was shown by a mixed melting point determination on the 2-sulfonamide derivative. Because of this uncertainty as to the structure of cymene, some very peculiar rearrangements were supposed to take place during the course of certain of its reactions. An extensive survey of these fifty years of investigation has been made by Bert (4).

Since that time, a number of syntheses have been developed by Sabatier (5), Bert (4,6), and others (7,8), which, along with the information available from pyrolysis studies, established the structure beyond any doubt whatsoever. Certain of these syntheses showed promise of industrial application though competition would be keen only in those countries where cymene was not available as an industrial by-product. The more important of these depended upon the condensation of isopropyl alcohol with toluene by means of sulfuric acid, the individual processes differing only in the mode of carrying this out (9,10,11). Another method developed by Malishev (12) which gave a 47% yield of cymene consisted in heating toluene and propylene under pressure in the presence of various catalysts. These are the products ordinarily obtained by pyrolysis of cymene: Malishev's operating conditions merely cause a reversal of this reaction.

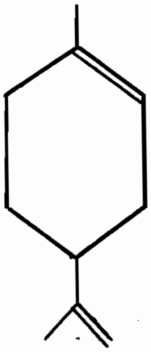
Cymene can also be readily synthesized from certain hydrocarbons having the same basic structure, by high temperature treatment over various materials. Most terpenes of the formula $C_{10}H_{16}$ and their derivatives undergo this transformation. A considerable amount of work has been done on this phase of the question, especially during the last ten years and a large number of materials have been found to serve as catalysts. The most important reactions are those involving cleavage of an internal ring (such as is found in pinene) with simultaneous dehydrogenation.



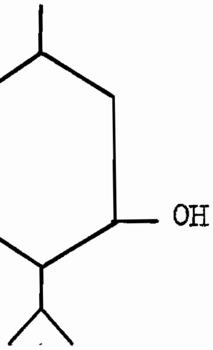
Brambilla (13) discovered that one of the best catalysts for this reaction was activated charcoal which gave a 90% yield of cymene at 200-400°C., though Fujita (14) states that camphene (I) is the main product and the production of cymene a side reaction if water vapor is passed through simultaneously. Linstead (15) obtained considerable dehydrogenation with 75-85% conversion to cymene on passing either pinene or limonene (II) over platinized charcoal at 305°C. Sulfur has been found by Komatsu (16) to be fairly effective in this connection, a 50% yield of cymene being obtained on heating pinene at 200°C. for 23 hours over this material. The menthenes (tetrahydrocymenes) and other terpenes of the formula $C_{10}H_{16}$ acted in the same manner; menthol (III) and borneol (IV) did not. The addition of materials used as vulcanization cataylsts in the rubber industry is stated by Austerweil (17) to have a beneficial effect. Dilute sulfuric acid also catalyzes the conversion of pinene, the normality influencing the course of the reaction quite markedly (18,19). In general, finely divided



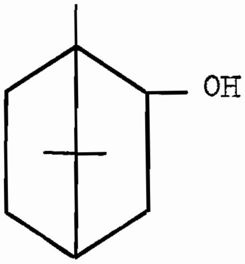
Camphene (I)



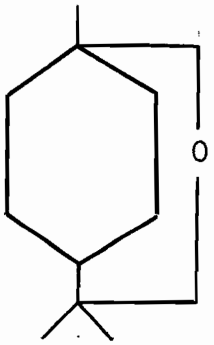
Limonene (II) or
Dipentene (VI)



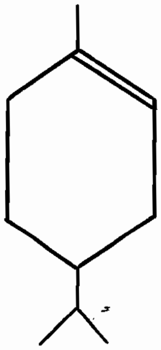
Menthol (III)



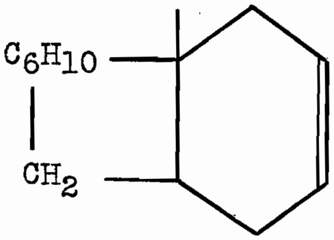
Borneol (IV)



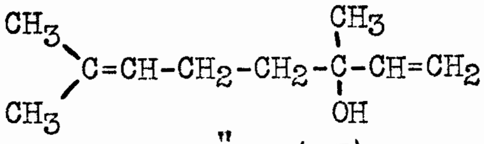
Cineol (V)



α- Phellandrene (VII)

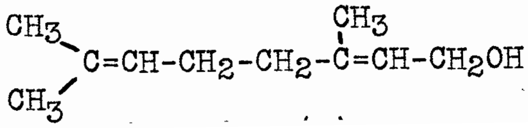


Cedrene (VIII)



$$\mathrm{\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C{=}CH{-}CH_2{-}CH_2{-}\underset{OH}{\overset{CH_3}{C}}{-}CH{=}CH_2}$$

Linalöol (IX)



$$\mathrm{\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C{=}CH{-}CH_2{-}CH_2{-}\overset{CH_3}{C}{=}CH{-}CH_2OH}$$

metals such as copper, iron, nickel or cobalt have been found by Sabatier (20) to be unsatisfactory - many products besides cymene being produced. Certain molybdates (ammoniates, sulfides, hydroxides or chlorides) on silica gel, pumice or active charcoal carriers have been used with some success (21).

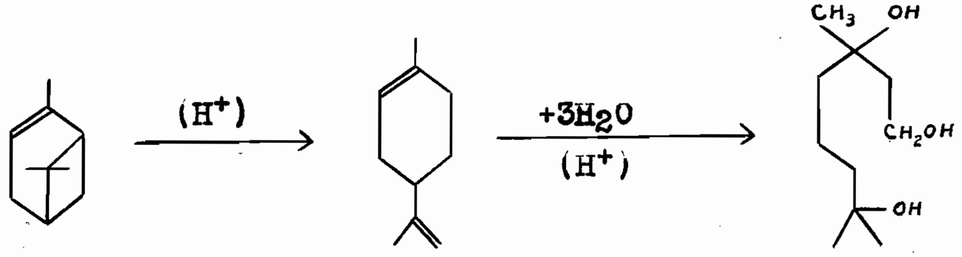
A unit for the production of synthetic p-cymene from liquid terpenes has been in the process of development for some time by the Hercules Powder Co., Wilmington, Delaware, and is now nearing completion (22). Although not mentioned, the raw material is very probably pinene, large quantities of which are obtained from the manufacture of wood pulp by the sulfate process.

Less important methods of producing cymene have been developed which have strictly limited applications for one reason or another. Cineol (V) from white camphor oil (or the crude oil itself) on being passed over hot activated charcoal (23,24), acid clays (24) or zinc chloride (24) produces good yields of cymene. On heating a terpene such as dipentene (VI) to 170-200°C. in the presence of Fuller's earth a partial conversion to p-cymene is effected. At higher temperatures (300-450°C.) cymene itself breaks down into toluene and propylene (25). Selenium dioxide will convert α-phellandrene (VII) in boiling ethyl alcohol into cymene and cuminaldehyde (26). Cedrene (VIII) if passed a number of times over nickel on a pumice carrier at 420-450°C., gives a 30% yield of crude cymene (27).

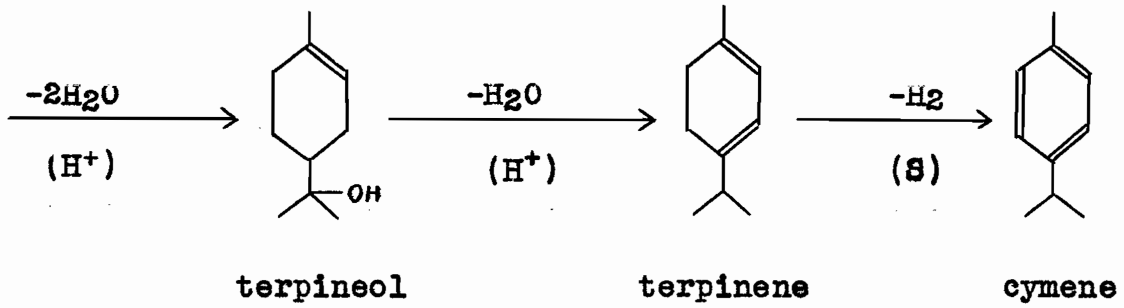
Certain straight chain compounds can be made to cyclize and lose hydrogen, water, etc. to form cymene. Linalöol (IX) if heated with an equal amount of water in an autoclave under a pressure of 60 At. at 300°C. for 5 hours is converted to the extent of 52% into hydrocarbons containing a high percentage of cymene (28). Geraniol (X) will not act in this manner though geranial, by distillation from iodine, is transformed, according to Bogert (29) to the extent of 68% into cymene. It is even possible to obtain cymene from 2,6-dimethyloctane (30) by vapor phase dehydrogenation over platinized charcoal at 305-310°C., though the yield is poor (10%).

The essential oils of a large number of plants contain varying quantities of cymene. By far the most important source (and the one which is of particular interest in this investigation) is that from the oil which collects on the surface of the sulfur dioxide recovery tanks in the sulfite process for the manufacture of wood pulp. Depending on the conditions of pulping and the quality of the wood, from 0.36 to 1.0 gallons of this by-product is obtained per ton of pulp (31). Spruce turpentine is from eighty to ninety percent p-cymene, whereas the turpentine from other soft woods may contain as little as fifty per cent. Along with the latter are present as impurities (in round figures) terpenes (5%), sesquiterpenes (10%), diterpenes (5%), borneol (2%), dicymene, fatty and resinous acids and considerable sulfur dioxide (18,32,33).

Little is known of the true role which the sulfite treatment itself plays in the conversion of certain of these materials into cymene. Routala and Pohjola (18) subjected pinene to the regular sulfite cooking process and obtained only 7% cymene. On heating dipentene with wood chips alone, 11.3% cymene was produced, though the addition of sulfur dioxide, lime and free sulfur raised this to 27%. It is known that dipentene, terpin hydrate and terpineol all yield terpinene on heating with sulfuric acid. Depending upon the particular process employed, the sulfite digestors are operated for a period varying from eight to thirty hours at a temperature of 125-155°C. Since the sulfite liquors are quite acidic (pH=2) these conditions could easily cause conversion of dipentene and other like materials into terpinene. Sulphur (which is liberated in the free state in the digestor) could complete the transformation of the terpinene into cymene either by dehydrogenation (16) or by oxidation to the alcohol followed by dehydration (34). Upon these facts Routala has based his mechanism for the conversion of pinene into cymene.



pinene dipentene terpin hydrate



According to Routala, a long cooking period and a solution rich in lime and sulfur dioxide are the most important factors in the formation of cymene.

Before the crude cymene can be used, it is desirable to free it from its impurities, and the development of a proper purification procedure has been the subject of considerable research. Piecing together the work of a number of different investigators, one finds that probably one of the best and simplest methods is as follows: The cymene is first freed from furfural, sulfur dioxide and soluble organic acids by treatment with 30% caustic solution. The furfural is changed into furoic acid and furfuryl alcohol by dismutation, the former being removed as its sodium salt by the alkali. Subsequent washing with 95% sulfuric acid resinifies the furfuryl alcohol and removes most of the other impurities, this being completed (after washing with water and drying) by a final refluxing and distillation over sodium. There is some disagreement as to the effectiveness of the sodium treatment (Mann (31) has found it to be unnecessary) but there seems to be no doubt that the sulfuric acid wash is absolutely essential (31,33,35,36,37,38). Impure cymene discolors on standing in sunlight, which, according to Wheeler (39), may be attributed to the presence of foreign materials such as p-anisidine. It will also discolor concentrated sulfuric acid; in fact, the latter is used by Schorger (35) as an indication of the purity of the material.

The procedure just outlined gives cymene of the highest quality; material of such purity is hardly needed for nitration purposes. Andrews (40,41) states that relatively impure cymene can be used here since the impurities, which are mainly terpenes, remain for the most part unchanged and can be removed later. Kobe and Doumani (42) have found that technical cymene has desirable emulsifying properties which aid intimate contact with the nitrating mixture and suggest the addition of an emulsifying agent if pure cymene is used. Fittica (43) and Wheeler and Smithy (36) on the contrary, recommend the removal of impurities.

There is some disagreement as to the correct physical constants for p-cymene, the boiling point in particular varying with the source from which the cymene was originally obtained (8,44). Richter and Wolff (45) went to great lengths in their purification of cymene from various sources and their values of b_{760} = 177.3-177.4°C. (corr.)D_4^{20} = 0.8570, n_D^{20} = 1.4904 can perhaps be taken as standard. These were the values for cymene obtained from camphor manufacture after treating the liquid repeatedly with permanganate solution, concentrated sulfuric acid, bromine, sodium and then subjecting it to a fractionation until the physical properties did not change. They agree closely with the physical constants of cymene synthesized from pure thymol by LeFèvre (46).

Mononitration of Cymene

Interest in the nitration of cymene in the past has centred to a great extent around the mononitration product 2-nitrocymene as a possible intermediate in the synthesis of various important chemicals such as thymol, menthol, p-aminocarvachrol (which is used as a photographic developer) and in the preparation of dyes. A rather complete survey of the literature involving this phase of the problem was made so that some idea would be had of the conditions which favored mononitration and hence of those which should be avoided in the preparation of dinitrated derivatives. A brief outline of this is presented here, the more important contributions only being included.

Three distinct methods for the mononitration have been used in the past. The addition of nitric acid alone to the cymene is very unsatisfactory, yields being practically nil even with fuming (d=1.5) acid at temperatures below 0°C. (47,48), though they are improved somewhat by operating at room temperature or higher (43,49). Considerable oxidation invariably takes place with the evolution of brown nitrogen-oxide fumes and darkening of the mixture. The main product is p-tolylmethylketone and p-toluic acid, with much cymene remaining unchanged, unless the cymene is added to the nitric acid when dinitrocymene and other compounds are obtained (50,51).

Widman and Bladin (50) in 1886 were the first to try a mixed sulfuric-nitric acid nitrating mixture. The careful addition of cymene to the calculated amount of nitric acid (d=1.4) in concentrated sulfuric acid gave some higher nitrated products with much cymene remaining unchanged. Widman and Söderbaum (52) a year or two later obtained much the same results using a method essentially the same - one which had proven satisfactory for other compounds having easily oxidizable groups. They noted particularly that increasing the sulfuric acid content of the nitrating mixture decreased the amount of unchanged cymene.

In 1918, Andrews (40,41) developed a method based on the above which he claimed gave an 80% yield of practically pure 2-nitrocymene (as shown by reduction to 2-aminocymene). He recognized the importance of vigorous stirring as a means of preventing local heating and oxidation (Widman et al. merely shook the mixture in a retort during addition) and also the necessity of adding the mixed acid to the cymene instead of the reverse. One-half mole (67 g.) of cymene along with an equal weight of concentrated sulfuric acid (d=1.84) was treated with a well-cooled mixture of nitric acid (d=1.42) in 10% excess in 105 g. of concentrated sulfuric acid, addition requiring five hours with efficient stirring below 0 °C. Much heat was evolved and the mixture became reddish brown in color, though no oxides of nitrogen were evolved. After pouring on ice, neutralizing and washing, the product was fractionally distilled in vacuo. Only 1 g. of p-tolylmethylketone was obtained as an oxidation by-product, though 10-12 g. of tars remained in the flask. Although he worked very carefully and made exhaustive tests, he was unable to isolate even a trace of the 3-nitro isomer.

Andrews' method was not entirely satisfactory as evidenced by the fact that other investigators were not successful in duplicating his yield, obtaining values ranging from 45% (53) to a high of 65% (54). This led to further research and a third method of nitration was developed which, in 1939, eventually gave consistently good results in the hands of Kobe and Doumani (55). It involved a new principle in the formation of an emulsion of cymene, sulfuric acid and glacial acetic acid which enabled immediate and intimate contact to be made with the entering nitrating acid preventing the troublesome local heating and consequent oxidation already mentioned. It had actually been originated by Wheeler and Smithy (56) in 1921 as a modification of the Andrews' technique, the main purpose of the acetic acid then being to prevent solidification of the mixture before completion of the reaction. This method was not any too reliable, however, yields varying widely for no apparent reason, and it was not until certain fundamentals of the reaction were recognized that consistent results were obtained.

Kobe and Doumani's procedure is as follows: To an emulsion of 500 g. of cymene, 1000 g. of sulfuric acid (d=1.84) and 300 ml. of acetic acid, is added at -10°C. with vigorous stirring a mixture of 369 g. of nitric acid (d=1.42) and 1000 g. of sulfuric acid over a period of two hours. To ensure completion of the reaction, the mixture is stirred a further ten minutes before pouring on ice. After washing with water to remove residual acids, the product is purified by fractional distillation under vacuum, yields ranging from 86-90%.

Efficient stirring and the maintenance of a good emulsion are extremely important, otherwise there is considerable darkening of the mixture with evolution of nitrogen oxides and an increase in tar formation. Technical cymene was found to be desirable because of its excellent emulsifying properties - any terpenic impurities remain unchanged and are removed either by steam or vacuum distillation. Kobe and Doumani do not even recommend a preliminary washing with sulfuric acid: they simply distilled crude cymene, taking off the fraction boiling at 174-178°C. It was not possible to maintain emulsification in the absence of acetic acid and substitution of phosphoric acid or acetic anhydride for the sulfuric acid gave very poor results. No emulsification problem was encountered if the cymene was added to the nitrating mixture but this method could not be used since it favored the formation of dinitration products.

By repeated fractionation of their nitration product, Kobe and Doumani isolated a small amount of p-nitrotoluene.(8-10%). Its presence had not been suspected by Andrews, though Mann, Montanna and Larian (31) using Wheeler and Smithy's modification (56) stated that it was present to the extent of 1-2%. Wide variations in nitric acid, sulfuric acid and acetic acid content, time of addition, and presence of emulsifying agents did not alter Kobe's value appreciably.

Their synthesis of 2-nitrocymene has been so successful that it has been accepted as the standard method for the preparation of this material.*

Dinitration of Cymene

Past interest in the dinitration of cymene has been largely academic, though undoubtedly there must have been some hope of putting the products to practical use

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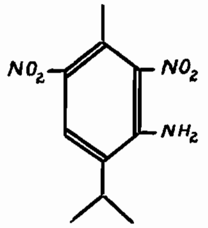
* Organic Syntheses, Vol.21, 96

from the fact that much of the original work was done during World War I. For instance, it has been proposed that dinitrocymene (like 2-nitrocymene) be used in the manufacture of dyes, since the colors are even more brilliant than those synthesized from nitrotoluene (41).

Kraut (57) first prepared dinitrocymene in 1854 by simply dropping cymene into a mixture of 2 parts of concentrated sulfuric acid and 1 part of fuming nitric acid. After raising the temperature to 50°C., the mixture was allowed to stand for several days, when, on the addition of water, a brown oil separated which later became solid. On crystallization from alcohol, a compound $C_{10}H_{12}(NO_2)_2$ was obtained in the form of colorless, very beautifully iridescent rhombic prisms melting at 54°C., and from the mother liquor several other uncrystallizable substances. The solid material was soluble in ether and alcohol, and tended to come out of saturated solutions as an oil. It exploded on heating in the air, leaving a very difficultly combustible ash. The structure of the compound was later proven to be 2,6-dinitrocymene by Mazzara (58) in 1889. He related it to 3-amino-2,6-dinitrocymene by treating the latter with ethyl nitrite, thus removing the NH_2 group. The structure of the dinitroaminocymene was independently shown to be as illustrated by an elaborate but thorough investigation.



3-amino-2,6-dinitrocymene

With the exception of this work by Mazzara, the compound drew scant attention until 1916 when Aschan (51)(in the laboratories of the University of Helsingfors) renewed the investigation. What particular interest he had in the material he does not say, though it may be inferred, from work published several years later by his student Alfthan (59), that he had hopes of preparing suitable dyestuffs. On the other hand, the explosive properties mentioned by Kraut may have been the motivating influence. Because the greater part of the experimental work since that date has been based on his technique, his procedures will be described in some detail.

He tried, first of all, the classical method of nitration - dropping cymene into well-cooled, concentrated (d=1.52) nitric acid with vigorous stirring. Besides 2,6-dinitrocymene he discovered the presence of a material which analyzed for $C_{18}H_{17}O_{10}N_5$, melted at 70°C. and crystallized in the form of yellow needles. (These same needles had been obtained by Fittig (60) in similar experiments done in 1868 on the nitration of cymene. He was unable to prove their structure, but stated that analysis seemed to indicate the loss of carbon.) Aschan's original nitro compound was undoubtedly 2,4-dinitrotoluene (m.p. 70.1°C.(61)) produced by cleavage of the isopropyl group from the benzene nucleus. His analysis (from which he obtained the formula $C_{18}H_{17}O_{10}N_5$) can be shown by calculation to fit the formula for dinitrotoluene $C_7H_6O_4N_2$ nearly as well. The reduction of the latter with ammonium sulfide yields golden needles of 2-nitro-4-aminotoluene melting at 77.5°C. (62), these properties checking with those of an amine obtained by Aschan on similar reduction of his material. The presence of dinitrotoluene as one of the components of the nitration product was later proven by Alfthan.

Aschan mentioned the fact that his two nitro compounds were separable only with great difficulty, prolonged fractional crystallization being necessary. This characteristic has been a constant barrier to the effective study of the reaction, and is one of the main reasons why so little progress has been made in the past. The sensitivity of the isopropyl group to oxidation was also confirmed by Aschan, who reported that even at comparatively low temperatures (0°C.), degradation products always are formed. Partial oxidation produces p-tolylmethylketone which invariably oxidizes further to p-toluic acid. Since the use of nitric acid alone seemed to favor this side reaction, he decided to try a sulfuric-nitric acid mixture. This, he hoped, would minimize local heating at the point of contact of the cymene with the acid, and also prevent excessive oxidation by dilution of the nitric acid with water.

The cymene was dropped into a mixture of 2 parts of nitric acid ($d=1.5$) and 4 parts of sulfuric acid ($d=1.84$)

with vigorous stirring. The temperature was kept below 0°C. by using a cooling mixture of ice and salt. After the addition was complete, the contents were allowed to stand another hour before pouring onto ice. The solid material which appeared was filtered off and freed of acid by washing five or six times with cold water. It was then given a treatment with carbonate solution in order to remove any p-toluic acid, and after a final washing with water, was dried at room temperature. The product thus obtained melted at 20-25°C., and was nearly white in color, the final dry weight representing an 88% yield (as dinitrocymene). A small amount (5%) of oily material was also produced, and was recovered from the various filtrates and wash-waters. Increasing the amount of sulfuric acid to 6 or 8 parts did not improve the yield materially; decreasing the amount of nitric acid lowered the over-all yield with an increase in the quantity of oil.

Using the above nitrating conditions, his student Alfthan (59), late in 1919, began a thorough investigation of the products produced in the reaction. It seemed to him that the best method of separating them would be by a vacuum distillation. After several such distillations at 5-6mm., he obtained a fraction boiling up to 161°C. which consisted of two kinds of crystals - needles and plates. By repeated recrystallization from alcohol these were separated, and proved to be 2,4-dinitrotoluene (needles melting at 70°C.)

and 2,6-dinitrocymene (plates melting at 54°C.). Mixed melting points with authentic samples gave no depression, and analyses agreed closely with the calculated values. Two other fractions boiling at 161-166°C. and 166-180°C. yielded 2,6-dinitrocymene. No mention was made of the relative amounts of each material present or whether he was successful in separating them completely. From results since published by other workers, it seems highly unlikely that the separation was particularly effective. Alfthan reported that about 10% of his total nitration product remained as tars in the distillation flask.

On reduction with tin and hydrochloric acid, the crude nitration product gave two diamines which were identified as 2,6-diaminocymene (already known to Aschan) and 2,4-diaminotoluene, thus establishing beyond a doubt the presence of 2,6-dinitrocymene and 2,4-dinitrotoluene in the original nitration mixture.

Alfthan also investigated the oily material, which as it has been mentioned was formed during the nitration. Several fractionations at 7-8 mm. pressure gave a small amount (4.5% of the total oil) of liquid boiling up to 110°C. - apparently containing cymene, p-tolylmethylketone (whose odor it had) as well as some mononitrocymene. A second fraction (8.5%) boiling from 110-125°C. would not solidify on strong cooling and had the odor of mononitrocymene (b_7 = 115-116°C., Andrews (40)). On further nitration it yielded 2,6-dinitrocymene melting at 53-54°C.

Higher boiling fractions constituted the remainder and consisted of dinitrocymene and dinitrotoluene.

Credit for the discovery that the isopropyl group in cymene is labile and can be removed during nitration must go to S. V. Hintikka (63) who published in 1917 the fact that p-nitrotoluene-o-sulfonic acid is produced along with a nitrocymene-o-sulfonic acid during the nitration of cymene-o-sulfonic acid. His results probably furnished the clue for the discoveries of Alfthan, and for the observation of Halse and Dedichen (64) in 1918 that trinitrotoluene was produced amongst other products in the nitration of cymene with concentrated nitric acid (d=1.5) and 20% oleum at 60-70°C. A year later, Lubs and Young (65), on nitrating 2-chlorocymene, obtained, as an impurity in the expected product 2-chloro-5,6-dinitrocymene, crystals melting at 88-89°C. and analyzing for $C_7H_6O_4N_2Cl$. Although they were unable to prove its structure, they suspected that it was a toluene derivative of some sort.

No further contribution to the problem of the dinitration of cymene was made until 1927, when Wheeler and Harris (66) for the first time reported figures which gave some indication of the relative and absolute yields of each of the two products. After trying variations in acid concentration and nitrating temperature without materially improving Alfthan's technique, they fell back on his original method. They carried the reaction out below 0°C., taking four hours for complete addition of the cymene. After stirring another hour, the mixture was poured onto ice and washed free of acid with dilute sodium carbonate solution. From 200 g. of cymene were obtained 190 g. of solid and 100 g. of oil. Fractional distillation of the latter failed to yield any solid material. Repeated recrystallization of the solid from hot alcohol and precipitation from carbon tetrachloride by the addition of petroleum ether gave a final yield of 114 g. of 2,6-dinitrocymene (29%) and 40 g. of 2,4-dinitrotoluene (7%). The remainder of the material (save for 3% p-nitrotoluene) stayed as an oil and was not investigated further. Their method of analysis was still obviously very unsatisfactory, and since such a large percentage of the product was uncrystallizable, their figures mean little.

In 1939, as a side issue in the preparation of 2-amino-6-nitrocymene, Kyker and Bost (67), working under Wheeler, have reported the most thorough study of the nitrating conditions made to date. They concentrated principally on the effect of temperature on the course of the reaction. For the separation of the two components, they employed crystallization, using pure instead of mixed solvents. Dioxan, ethyl ether, dichlorethyl ether, isopropyl ether, petroleum ether, heptane, toluene, carbon disulfide, chloroform, carbon tetrachloride, methanol and ethanol were all tried. Methanol was found to be far superior for both yield and purity of the product. After three recrystallizations from this solvent, the melting point of the crude mixture rose to 51-53°C., whereas it was only 41-42°C. after six recrystallizations from ethanol.

Their results are summarized in Table I (500 g. samples of cymene were used throughout.

TABLE I

Temperature	-3 to -5°C.	-5 to -7°C.	-10 to -12°C.
Time (hrs.)	12	20	33
Wt.of product	670 g.	750 g.	785 g.
Color (in shades of yellow)	brown	deep	light
Physical state at 0°C.	semi-solid	solid	crystalline
	(no oil found in filtrates or washings)		
Material crystallizing from methanol	230 g.	346 g.	420 g.
M.p.	30-32°C.	34-36°C.	38-40°C.
Oil from mother liquors	435 g.	400 g.	360 g.

It will be noted that as the temperature is lowered, the quantity of solid material, the melting point and reaction time increase. On the other hand, the color of the product (and hence the degree of oxidation) and the quantity of oils from mother crystallizing liquors decrease.

They used the same relative acid quantities specified by Alfthan, and also confirmed the need of efficient stirring.

In Table II are the yields of nitroaminocymene and nitroaminotoluene which were obtained on reduction of both oil and solid material with ammonium sulfide.

TABLE II

Temperature of nitration	6-nitro-2-cymidine.HCl yield (based on cymene) %	2-nitro-p-toluidine yield (based on cymene) %
-3 to -5°C.	19.7	11.4
-5 to -7°C.	29.8	9.9
-10 to -12°C.	36.8	9.0

From these figures they concluded that with decrease in temperature, the ratio of 2,6-dinitrocymene to 2,4-dinitrotoluene in the original nitration product increased. Since reduction of the latter to the monamino compounds was not complete, conclusions which they have based on the above may well be erroneous. They give, at best, only a very general idea of the relative amounts of dinitrocymene and dinitrotoluene present.

As far as is reasonably certain, this represents the sum total of the material available up to the moment on the dinitration of cymene. Its inadequacy need not be questioned, and it is hoped that the results of this investigation will provide a much clearer picture of the whole field.

Tri-nitration of Cymene

Because of the great difficulty with which a third nitro group can be made to enter the cymene nucleus, the tri-nitration of this compound has received very little attention in the past. Fittig, Köbrich and Jilke (60) first prepared trinitrocymene in 1868 by heating p-cymene with a mixture of concentrated sulfuric acid and fuming nitric acid for long periods of time. They found that the cymene was changed largely into dinitrotoluic acid, only a relatively small amount being converted without oxidation into nitro compounds. From the solid material remaining after a thorough alkaline wash, two different kinds of crystals were deposited on solution in alcohol. Fittig et al. were able to separate them by further "judicious" recrystallization into colorless iridescent plates (m.p.118°C.) which analyzed for trinitrocymene, and another compound in the form of long fine needles, melting at 69.5-70°C., analysis indicating the loss of carbon. The latter, we now have reason to believe, were probably crystals of dinitrotoluene. Trinitrocymene was also obtained by Ehrnrooth (68) in 1931 by further nitration of 2,6-dinitrocymene using essentially the same operating conditions. The melting point of this material was reported as 124-125°C., however it is very probable that both it and Fittig's compound had the same structure -i.e. 2,3,6-trinitrocymene. It is unlikely that the nitro groups are on the 2,3,5 positions (the only other possibility.)

The substitution of 20% oleum for the concentrated sulfuric acid was a modification introduced by Halse and Dedichen (64). Trinitrocymene was the main product at 20-30°C.,trinitrotoluene with some dinitro-p-toluic acid at 60-70°C. In the literature available no yields are reported for any of these methods of preparation, but from results obtained in our laboratories, they are all probably fairly low.

EXPERIMENTAL SECTION

Introduction

From the information just presented in the Historical Section on the dinitration of cymene, it is obvious that a nitric-sulfuric acid mixture should give best results. Attention was accordingly centred on an investigation of the effect of a variation in the operating conditions on the yield of products using such a mixture. It was also clear that in order that results should be readily reproducible, experimental conditions would have to be clearly defined and standardized. Accordingly, wherever possible, any chance variables were eliminated, or at least made constant by suitable operating techniques.

Experimental Procedure

The sulfite turpentine (p-cymene)* which was available for experimental purposes was already in a fairly high state of purity. It had previously been partially refined by treatment with one-quarter of its weight of 34% caustic soda solution. After the addition of water, the mixture had then been refluxed for a period of at least two hours, the cymene being steam distilled out and dried over calcium chloride. It was only slightly yellow in color and had a refractive index of n_D^{20}=1.4910. Nevertheless, although nitration of this material gave results which differed only

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* Kindly donated by the Brown Company, Berlin, N.H.

slightly from those obtained from high-grade cymene, it was considered important for purposes of absolute control to remove all impurities. The previous alkali treatment had removed sulfur dioxide, organic acids and furfural; the terpenes were now removed by treatment with concentrated sulfuric acid. The following is a typical procedure employed:

To 1750 ml. (1500 g.) of the crude material in a separatory funnel was added 250 ml. of 95% sulfuric acid. After thorough shaking (with cooling, since considerable warming occurred), the acid was allowed to separate and was drawn off. It was almost black in color. The operation was repeated with two more 250-ml. portions, the last washing being practically colorless. Upon removal of traces of residual acid remaining in the cymene with dilute sodium bicarbonate solution, the material was dried over 8-mesh calcium chloride. It was noted that the total loss in volume after this treatment was about 200 ml. Of this, 150 ml. was due to loss by removal both of impurities and cymene in the acid wash. A large proportion of this total could be traced to the removal of cymene itself as the soluble sulfonic acid. On shaking some of the purified cymene with sulfuric acid, it was found that even with only moderate warming, the amount of sulfonation which occurred would easily account for the total loss. If this side reaction is to be reduced to a minimum, it is suggested that the first 250 ml. of sulfuric acid be added in small portions, keeping the cymene cooled to well below room temperature. The remaining 50 ml. loss was caused by absorption of the cymene on the drying agent. Hence there remained about 1550 ml. (1330 g.) of water white material, having a refractive index n_D^{20} = 1.4911.

As the final step in the purification, the cymene was subjected to efficient fractionation. Several types of modified and packed columns were used, each being equipped with a constant reflux, variable take-off head (Figure 1).

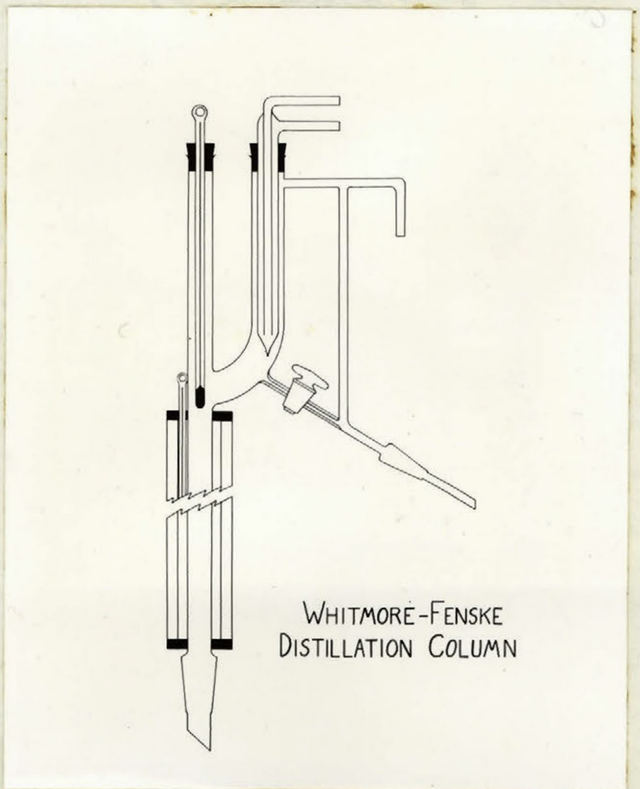

Figure 1

The latter provided fine adjustment of the distillation take-off (which was generally about 75 ml. per hour) and also allowed high reflux ratios (1 to 10 or better) to be maintained. Three separate techniques were tried; (a) the cymene was distilled directly without previous sodium treatment, or (b) first refluxed from three to five hours over 25 g. of sodium, then decanted and distilled, or (c) after refluxing, distilling directly from the sodium. Table III below shows that as far as the main fraction is concerned, there is no appreciable difference between the various products obtained.

TABLE III

Purification of cymene by distillation

	(a)	(b)	(c)
Forerun	5.0%	3.1%	2.5%
High boiling fraction	5.0%	13.5%	18.0%
Residue	1.9%	2.1%	3.5%
Main fraction	88.1%	81.3%	76.0%
n_D^{20} (average of all main fractions)	1.4909	1.4906	1.4908 *
boiling range (corr.)	176.8-177.3°C.	176.8-177.3°C.	176.8-177.3°C.

In the figures above, "high boiling" material represents all cymene having refractive indices above 1.4911 and boiling above 177.3°C. These percentages tend

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* Richter and Wolff reported b_{760} = 177.3-177.4°C.

n_D^{20} = 1.4904 (45)

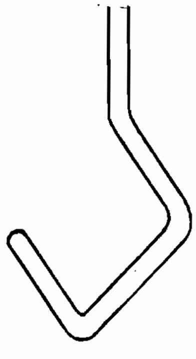
to be misleading since this fraction contains a very high percentage of cymene. However, they do show certain trends which can be summarized as follows:

(1) The sodium treatment partially removes low boiling materials, which subsequently appear in the residue.

(2) An increase in the refractive index value of the cymene as a whole takes place (as evidenced by an increase in the amounts of high boiling fractions), presumably caused by chemical action of the sodium on the cymene. These results tend to corroborate a statement by Mann (31) to the effect that the sodium treatment is unnecessary.

Nitration of cymene

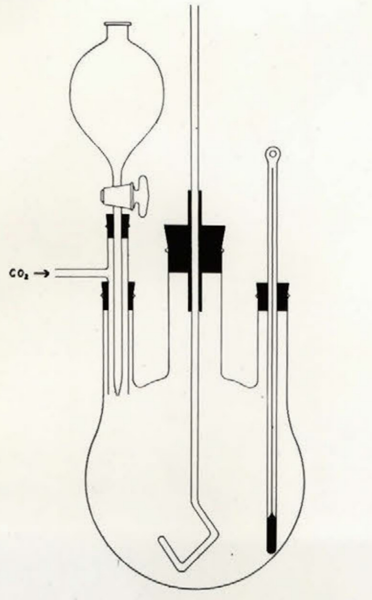
In the past, practically every publication on the nitration of cymene has stressed the importance of rapid and complete emulsification of the cymene with the acid if excessive local heating, charring and oxidation are to be avoided. From the controversy over yields obtained from the mononitration especially, it was suspected that improper stirring was one of the most important difficulties to be eliminated. After a number of trials, the best type of stirrer for this purpose was found to be one having the general shape illustrated. When correctly adjusted for speed and depth in the nitrating mixture, a film of liquid was thrown from the centre upwards and outwards to the walls of the flask where it descended, mixing with the main liquid at the



Stirrer used
Figure 2

outer boundary. Thus the contents were rapidly cycled from the inside to the outside and back again, without the formation of vortices where the cymene could collect and remain for any length of time. A fair amount of heat is given off during the reaction. In most of the experiments to be described, the outside bath had to be maintained at least 5 or 6°C. below the actual nitration temperature desired.

The apparatus used was of the simplest type. A three-neck flask (with or without ground glass joints), equipped with the stirrer described above, a thermometer, separatory funnel and adapter, was all that was required. (Figure 3).



NITRATION APPARATUS

Figure 3

For temperatures above 40°C., ground glass joints were found to be necessary. Below 40°C. (where most of the reactions were carried out) a flask having necks somewhat longer than usual (three to five inches) was found to be entirely satisfactory. Rubber stoppers coated with Vinylite resin stood up very well against the nitrogen oxide fumes. To make the use of mercury seals unnecessary and to standardize further nitrating conditions, all reactions were done under an atmosphere of dry carbon dioxide.

Except when otherwise specified, the nitrations were carried out as follows: To the mixed acids in the reaction flask, the cymene was added at such a rate that complete addition occurred in two hours. This was accomplished quite easily with a maximum error of ± 10 minutes by drawing the end of the funnel down to a fine jet and calibrating carefully. During the addition, the mixture was rapidly stirred and by regulating the bath temperature, the inside temperature could be maintained to within a degree of that desired. Stirring was continued for another hour at the same temperature before the mixture was poured onto ice.

At 0°C., the product in all cases was a solid of varying degrees of consistency, softening and in some instances liquefaction occurring at room temperature. The water layer was separated and extracted three times with 25-ml. portions of benzene. This seemed to be the best solvent for the anticipated products. The extracts were combined and added to the nitration product proper. After washing the benzene solution with water containing a little sodium sulfate to aid separation, the mixture was extracted two or three times to alkalinity with 10% sodium carbonate solution. The solubility of both dinitrocymene and dinitrotoluene in sodium carbonate solution of this concentration was found to be imperceptible by actual test. Proper separation of the two layers in most cases was difficult if not impossible without first filtering off the small amount of solid which invariably was formed as a suspension. This material (which was insoluble in water or dilute bicarbonate solution) presumably was not removed by the alkaline wash given the solid nitration product by other workers. No mention of such a solid has been found in the literature. Under certain conditions the amount of this material produced was quite considerable. Any important changes from the normal will be mentioned after each separate series of runs.

After washing the benzene solution free from alkali, it was allowed to dry thoroughly over anhydrous sodium sulfate in an ice-chest. The drying agent was removed by filtration through a sintered glass funnel, which was found to be far more convenient and satisfactory than an ordinary filter paper. Since in practically all cases (to save time in distillation) runs were made using only 30-g. samples of cymene, all precipitates, etc. were washed with fresh solvent to remove any adhering products. The benzene was removed under reduced pressure (100 mm.). The boiling point of p-cymene under these conditions is about 110°C., the benzene coming off at room temperature or slightly above, so that any unreacted cymene remained behind with the nitration products. The residue varied in color from a light yellow to a dark red.

Although this investigation was primarily a study of the effect of reaction conditions on the relative and over-all yields of the products, it was apparent that an efficient means of separating them would have to be developed before this could be properly carried out. Accordingly attention was centred at first on this phase of the problem. Separation of the volatile compounds by vacuum distillation would circumvent difficulties which would certainly arise from the unavoidable production of tars in certain of the nitration runs. At the same time, it would be possible to separate mono from dinitrated derivatives, since the former would have lower boiling points, and with the aid of a good column, a fair separation of the dinitrocymene from the dinitrotoluene might even be achieved. Alfthan (59) had obtained some separation by such treatment. He did not state what type of distilling flask he used but in all probability at that date (1920) a modified Claisen was the best he had.

Boiling point curves for the dinitration products were entirely lacking, though Mann (31) had obtained them for 2-nitrocymene and p-nitrotoluene. Since such data would be needed for fractionation purposes, the variation of the boiling point with pressure was determined for pure samples of p-nitrotoluene, 2-nitrocymene, 2,4-dinitrotoluene and 2,6-dinitrocymene. Solids were crystallized to constant melting point beforehand, while the only liquid (2-nitrocymene) was first fractionated through a Whitmore column (Figure 1) and the appropriate cut taken. The physical constants for these purified materials were as follows:

2-nitrocymene liquid b_{10}=123°C. n_D^{20}=1.5291
p-nitrotoluene solid m.p. 52-53.5°C.
2,4-dinitrotoluene solid m.p. 71-72°C. (calcd. for $C_{10}H_{12}O_4N_2$; N, 12.7. Found N, 12.7*)
2,6-dinitrocymene solid m.p. 53-54°C.

TABLE IV

Variation of Boiling Points with Pressure

2-Nitrocymene				p-Nitrotoluene			
		(Mann)				(Mann)	
P. mm.	b.p. °C.	P. mm.	b.p. °C.	P. mm.	b.p. °C.	P. mm.	b.p. °C.
2.5	84.0	2.0	97.6	2.3	60.0	3.0	86.0
5.0	108.0	3.0	104.3	5.2	87.0	5.0	93.4
7.5	116.5	5.0	112.0	9.0	101.0	8.0	103.5
11.5	126.8	8.0	121.5	14.0	112.0	10.0	108.0
15.0	134.0	10.0	126.2	18.5	119.5	13.0	112.0
19.2	140.0	13.0	131.4	25.0	126.0	20.0	120.8
28.5	150.5	20.0	141.0	30.3	131.0	-	-

2,4-Dinitrotoluene		2,6-Dinitrocymene	
P. mm.	b.p. °C.	P. mm.	b.p. °C.
2.1	110.0	2.6	125.0
2.5	123.0	3.3	135.0
3.5	131.5	5.2	148.5
4.8	141.0	6.5	154.5
6.1	149.0	9.0	164.0
7.5	155.0	10.5	168.5
11.0	164.0		

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* Courtesy of S.A.V.Deans,
McGill University, Montreal

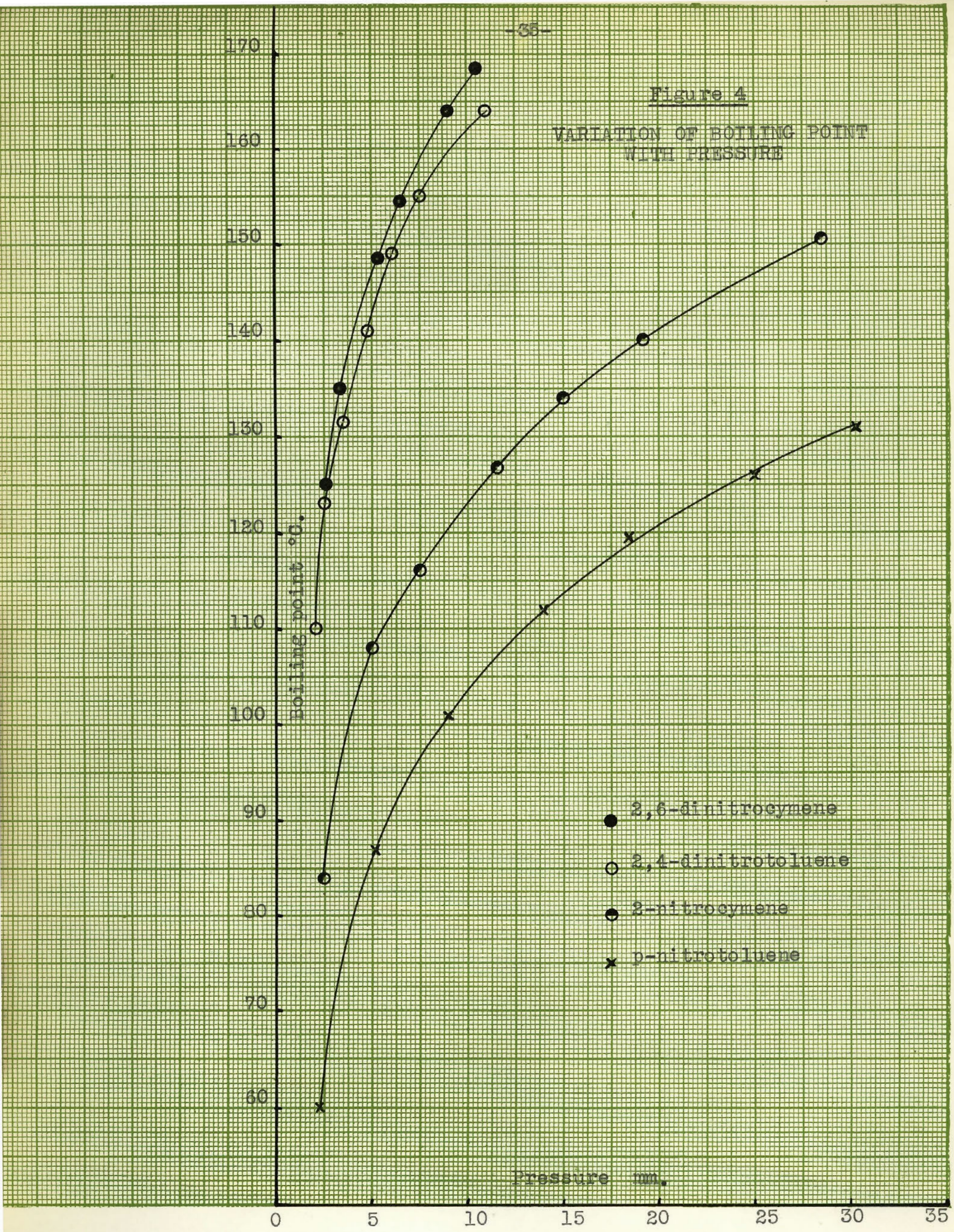


Figure 4

VARIATION OF BOILING POINT WITH PRESSURE

These figures are presented in the form of a graph (Figure 4).

For the fractionation of the nitration mixture, a number of various columns were employed. Several types of modified and unmodified Claisens were found to be unsatisfactory because of low efficiency. A Whitmore column 23 inches long, having an internal diameter of 12 mm. and packed with single turn glass helices also proved to be a failure because of the extraordinarily high viscosity of the liquid even near its boiling point. With the jacket temperature as much as 50°C. above the temperature of the refluxing liquid and a pot temperature 70 to 80°C. higher, the distillation rate was extremely slow and plugging and flooding of the column tended to occur. A shorter column, 12 inches in length, gave the same trouble. The latter, however, when packed with two and three turn helices, operated very satisfactorily, though the jacket had to be kept about 15°C. above the temperature of the vapor for best results. Under these conditions and with a pot temperature 50 to 60°C. higher than the boiling point of the liquid, a fairly rapid reflux rate was possible (40 drops per minute). A ground glass connection between pot and column prevented contamination of the distillate.

In order to keep decomposition of the nitration product as low as possible during distillation, a low pressure (generally from 2.5 to 4.0 mm.) was used. The products were remarkably stable to heat, however. A distillation ordinarily required about four hours, but even when extended to as long as seven hours, the amount of residue remaining in the pot was practically the same.

Since a number of the products are solids at room temperature, it is not surprising that plugging of the take-off head tended to occur. This was prevented by wrapping the head with an electrically-heated Nichrome ribbon, heat being brought even to the tips of the take-off arms on the "cow" by means of heavy wire leads pushed through the rubber stoppers to which the receivers were attached. The ribbon used for wrapping the portion of the arms actually inside the receivers was attached to these terminals.

The rate of take-off at the start of the distillation was adjusted so that only from three to four drops were removed per minute. This enabled very effective separation of the low boiling components (mono-nitrated products,etc.) to be brought about. The cut between the forerun and main fractions was quite sharp, in most cases only a few drops distilling in the intermediate temperature range. After the temperature of the vapor had risen to that corresponding to dinitrated products, a new receiver was rotated into position and the distillation rate increased somewhat. Further cuts were taken at arbitrary points since the distillation temperature rose gradually and more or less uniformly from this point on. The boiling point curves indicate that separation of the dinitrated products would not be particularly good. It was found in practice, however, that the first fractions were fairly rich in dinitrotoluene. It did not seem advantageous to fractionate more than once since unavoidable losses would more than offset the advantages gained by further separation. Towards the end of the distillation, the pot and jacket temperatures were raised in order completely to drive off volatile material. A few grams of black tar always remained behind.

The product was thus separated by the distillation into several fractions. The foreruns came off at temperatures corresponding to 2-nitrocymene in the main with occasionally a little p-nitrotoluene (any residual cymene remaining unnitrated was removed at 100 mm.). These fractions in practically all cases constituted only a very small percentage of the total distillate. The main bulk of the product was removed at temperatures well within the boiling range of 2,4-dinitrotoluene and 2,6-dinitrocymene. This was followed by a small amount of material which boiled a few degrees higher, due probably in large part to the higher temperatures of pot and jacket necessary to remove last traces. Under the conditions of the nitration, the amounts of very high boiling trinitro derivatives which would be formed would be insignificant.

The first fraction, being rich in dinitrotoluene, often solidified spontaneously. The main bulk of the distillate, however, remained as an oil which occasionally solidified on standing a number of days. By seeding this oil with pure dinitrocymene and allowing crystallization to proceed slowly and undisturbed at room temperature, very large crystal formations (one to one and one-half inches long), uncontaminated with needles of dinitrotoluene, would often occur. The residual oil was then removed by decantation, and on seeding with needles, dinitrotoluene would crystallize out. By such careful handling it was possible to separate fair amounts of quite pure materials. Care had to be taken not to cool or agitate the oil unduly or invariably both products would come out together.

This obviously was a long and tedious procedure, so that for the main separation, it was clear that recourse would have to be made to crystallization. From the experience of other workers it was clear that the separation of these two materials even by such a procedure would be difficult. Using methyl and ethyl alcohol as solvents as recommended by Alfthan (59) and Kyker and Bost (67), the problem seemed to be hopeless. The products always tended to come out as oils from which a fair amount of quite pure material could be isolated provided solidification was not pushed too far. If the mixture was cooled too much, the whole mass solidified into a mixture of needles and plates having practically the same melting point as the parent material. (An estimate of the purity was better and more easily obtained by examination under a microscope rather than by melting-point determinations.) By cooling only slightly, however, it was possible to isolate products of high purity, though a considerable amount of oil remained unsolidified. This so-called recrystallization was hardly more satisfactory than the previously described procedure for isolating the pure products from the oil itself. The solubilities of dinitrocymene and dinitrotoluene are so similar in these solvents that the effect of the latter as far as aiding purification is concerned was negligible. Kyker and Bost's claim to good results using methanol would appear to be founded mainly on the fact that, on the average, half of their total product was not crystallized at all but left as an oil.

Most of the other solvents which had been tested by previous workers as well as some that had not (nitromethane and isopropyl alcohol) were tried and found to be unsatisfactory. Kyker and Bost had reported that heptane and petroleum ether were unsuitable. It seemed inconceivable, however, that the presence of an isopropyl group on the dinitrocymene would not confer on it a higher solubility in paraffinic hydrocarbons. In actual fact, it was found that the difference in solubility in Skelly Solve B (b.p.60-68°C.) was truly remarkable. By actual test, dinitrocymene was from thirty to forty times more soluble than dinitrotoluene at 40°C. Both Skelly Solve A (b.p. 28-30°C.) and Skelly Solve C (b.p. 90-100°C.) were unsatisfactory, however.

Unfortunately, due no doubt to the fact that dinitrocymene and dinitrotoluene are so mutually soluble as oils, the nitration mixture went completely into solution at 40°C.

with an amount of Skelly Solve B very much less than that theoretically required to remove all the dinitrotoluene present. However, since this solvent seemed to offer the only hope of a solution to the problem, work was continued on it until finally a satisfactory method of operation was evolved.

The nitration product was shaken up with from three to four times its weight of Skelly Solve B at room temperature. After settling, the solvent was decanted and cooled to 0°C. The oil which separated was removed and the supernatant liquid either boiled off or simply cooled down in dry ice to a temperature just above the freezing point of the solvent. The solubility of the product is very low at this temperature (about 1 g. per 100 ml.). The solid which separated was very rich in 2,6-dinitrocymene (about 94%) for a starting material containing as much as 30% dinitrotoluene.

The value of cooling first to 0°C. and separating the condensed oil before cooling further is to add in effect another complete recrystallization. For example, in an actual test, 50.7 g. of a nitration mixture containing 30% by weight of dinitrotoluene was shaken with 150 g. of Skelly Solve B at 23°C., the solvent then being decanted and cooled to 0°C. A yield of 6.9 g. of oil containing 19% by weight of dinitrotoluene was obtained. On cooling the solvent further in dry ice, 11.7 g. of solid containing only 6.3% of dinitrotoluene was deposited. It can be calculated from these figures that if the solvent had been cooled down immediately from room temperature to -70°C., the same weight of product would result but the percentage dinitrotoluene would be higher (11%). This procedure is also better than shaking up the nitration mixture with the solvent at 0°C., decanting and then cooling. For although about 11.7 g. of solid should be deposited in each case, the percentage dinitrotoluene will be higher in the latter because of the higher percentage of dinitrotoluene in the oil with which it is in contact (30% instead of 19%).

When only 6% dinitrotoluene was present, it was a relatively simple matter to obtain the dinitrocymene in a pure state. The best method found was simply to dissolve up the mixture in warm alcohol, allow it to stand until the product oiled out (which incidentally it always tended to do unless violently agitated) and then to seed it with pure dinitrocymene. A large percentage of the oil would thereupon solidify in the form of large plates of pure dinitrocymene. Excessive cooling is to be avoided for needles of dinitrotoluene may come out as well. A very pure product is obtained in this way, and may be granulated by dissolving up in alcohol, cooling just to the saturation point, seeding and then shaking rapidly while cooling in cold water.

It would obviously be a very difficult task to determine rapidly and quantitatively the amounts of dinitrocymene and dinitrotoluene found in a large number of nitration runs even by this process. Some method of rapid and accurate analysis would be necessary before it would be possible to investigate the problem fully in a reasonable length of time. A refractive index measurement was decided upon as being the best. This method, of course, is not new. As a matter of fact, Andrews (40) used it for the determination of 2-nitrocymene and p-nitrotoluene percentages in his mononitration work on cymene.

An Abbe refractometer equipped with heating jackets was used. In order to prevent crystallization of the material induced by contact with the lower ground glass plate, measurements had to be made at 40°C. The persistency with which dinitrocymene tends to remain as an oil enabled a measurement to be taken at 40°C. even with the pure material though it melts at 53-54°C. Artificial mixtures of varying composition were made up and are given below in Table V with the refractive index values found.

TABLE V

Percent dinitrotoluene by weight	n_D^{40}
0	1.5368
8.97	1.5400
17.20	1.5428
22.75	1.5447
28.10	1.5468
35.15	1.5491
50.00	1.5543
60.35	1.5580

m.p. dinitrocymene	53-54°C.
m.p. dinitrotoluene	71-72°C.

Mixtures containing 70% dinitrotoluene solidified immediately. The range covered was adequate, however, for the problem at hand, though higher values could have been obtained using a Pulfrich refractometer, which is equipped with a cell. These results have been expressed in the form of a graph (Figure 5). It will be noticed that the values lie along a straight line. No change in refractive index took place when the mixtures were heated for twenty hours at 50-60°C., or allowed to stand in the sun for five hours, though some darkening took place. This confirms what has already been said concerning the stability of the nitration mixture to heat during distillation. The temperature coefficient of the refractive index was found to be 0.0004 per °C. All readings were taken to within ± 0.1°C. so that the maximum error from this source was 0.0001.

With this new method of analysis it became unnecessary to separate the main distillate into various fractions. After carefully removing low boiling products (fraction 1), the remainder of the volatile material was taken off fairly rapidly (fraction 2) though the last few millilitres were collected in a separate receiver (fraction 3). Distillation time was thus shortened to about two hours.

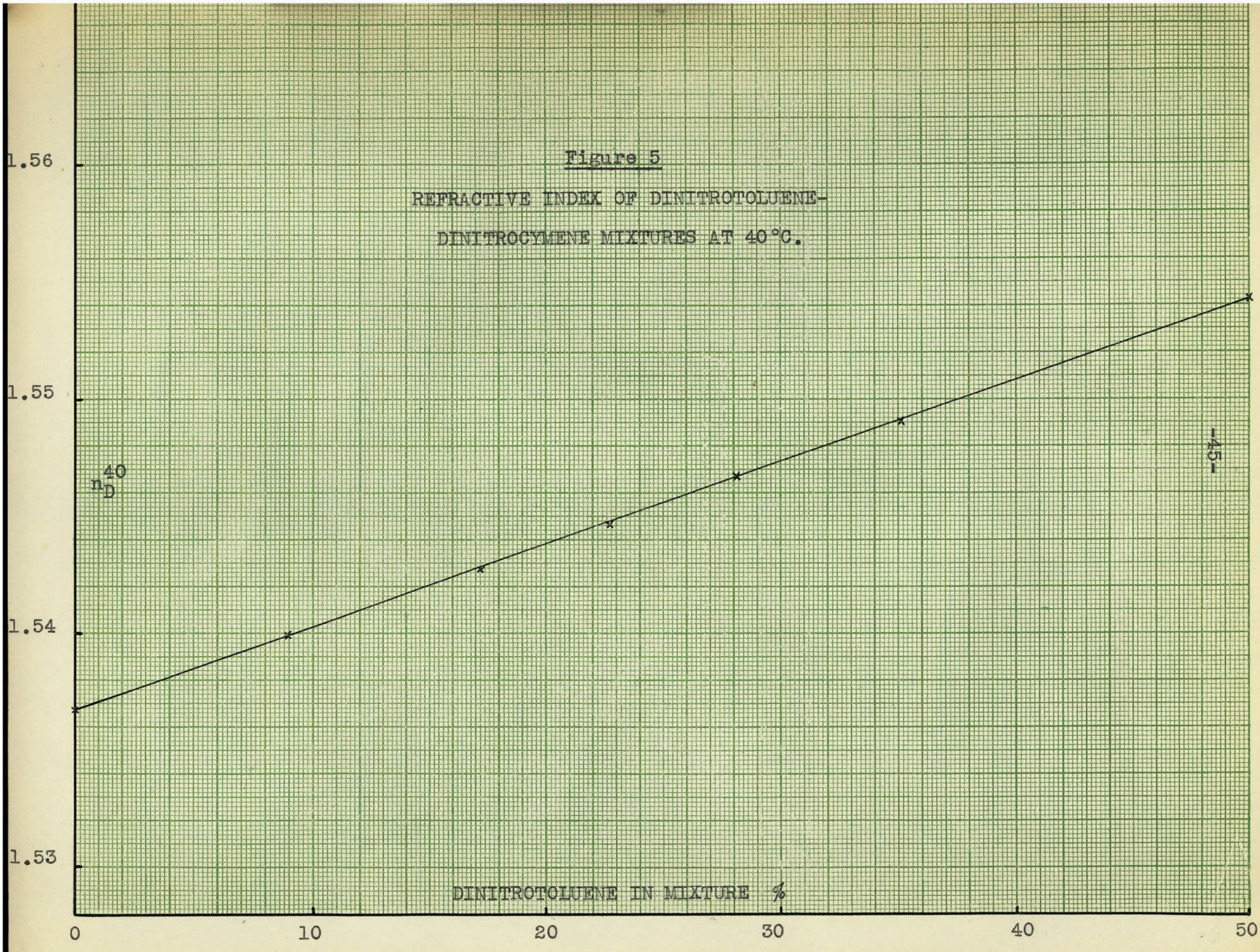


Figure 5

REFRACTIVE INDEX OF DINITROTOLUENE-DINITROCYMENE MIXTURES AT 40°C.

Experimental Results Variation of Temperature (Table VII)

It would be difficult and unprofitable to carry out a very complete investigation of the nitration of cymene in which all of the possible combinations of the variables, temperature, acid concentrations, addition time, etc. were studied. A very good indication of the effect of each of these factors would, however, be conveniently obtained by adhering to a set of arbitrarily chosen nitrating conditions. For example, in the present investigation the effect of temperature was studied by standardizing the cymene: nitric acid: sulfuric acid proportion at 30 g.: 60 g.: 120 g., the addition time at 2 hours and the stirring time at one hour -- conditions chosen because they had been so often used by other workers. Each of the remaining variables was in turn studied at 30°C. (a temperature readily maintained in the laboratory), the independent variables in each case being maintained at the above arbitrarily chosen values.

The results of such an investigation of the effect of temperature on the nitration of cymene have been summarized in Table VI. The lower limit was defined by the temperature at which the nitrating acids and products solidified, the upper one by the amount of oxidation which occurred. It may be mentioned that temperature regulation below 0°C. was most conveniently achieved by using an acetone bath cooled with dry ice; ice-salt mixtures were found to be very inflexible and difficult to control.

All nitrations done below +6°C. gave crude products which were only slightly lemon-yellow in color, progressive darkening occurring with rise in temperature until at 60°C. they were almost black. In these, as in all other cases, the appearance of the final products obtained on distillation of the crude material was independent of the quality of the latter and all had the same yellow color. The yield of alkali-soluble oxidation products also increased with ascending temperature, a very marked rise taking place at 60°C. especially (from 2.2 g. at 40°C. to 7.7 g. at 60°C.). Production of nitrogen oxide fumes varied in an analogous manner; at 60°C. oxidation was so violent that the mixture had to be cooled momentarily to prevent fuming off. Below 0°C. oxidation seemed to be insignificant. The amount of residue insoluble in both benzene and alkali was a minimum at 30°C. (1.8 g.) reaching a maximum at both extremes of temperature (3.5 g.). Even when yields of products were low, no unchanged cymene was recovered.

In Table VI (and in all of those to follow) "total weight of product" means the weight of all distillable material, excluding any residual unreacted cymene. The yields of dinitrotoluene and dinitrocymene have been calculated on the total amount of cymene used in the nitration (30 g. samples throughout), no allowance being made for any cymene which might have been subsequently recovered. By "percent dinitrotoluene in mixture" is meant the percent dinitrotoluene in the dinitration fractions as found by analysis. This figure gives an indication of the extent to which the isopropyl group has been removed. Runs marked by an asterisk are those which have been brought over from other tables for purposes of comparison.

TABLE VI. EFFECT OF VARIATION OF TEMPERATURE ON NITRATION OF CYMENE

No.	Temp.	Fraction I		Fraction II			Fraction III			Residue	Total wt. Prod.	Yield based on p-cymene		D.N.T. in mixture
		Wt.	n_D^{40}	Wt.	n_D^{40}	D.N.T.	Wt.	n_D^{40}	D.N.T.			D.N.T.	D.N.C.	
	°C.	g.		g.		%	g.		%	g.	g.	%	%	%
1	-20	-	-	32.9	1.5479	31.4	4.3	1.5385	4.9	4.8	37.2	25.9	53.1	28.4
2	-20	-	-	31.9	1.5479	31.4	5.5	1.5400	9.0	4.6	37.4	25.8	53.5	28.1
3	-6	-	-	32.8	1.5477	30.9	6.0	1.5399	8.7	5.0	38.8	26.1	56.0	27.5
4	+6	0.1	1.4650	29.1	1.5481	32.1	9.8	1.5410	11.8	2.6	39.0	25.8	56.6	27.0
5	+16	-	-	30.1	1.5477	30.9	7.8	1.5410	11.8	3.9	37.9	25.1	55.2	27.0
6	+30	1.1	1.5254	29.1	1.5478	31.2	5.5	1.5388	5.6	4.3	35.7	23.0	50.2	27.1
7	+30	1.2	1.5240	30.3	1.5472	29.5	4.4	1.5405	10.5	5.7	35.9	23.0	50.4	27.1
8	+40	2.2	1.5240	23.8	1.5481	32.1	6.5	1.5409	11.6	5.3	32.5	20.6	43.6	27.7
9	+60	1.6	1.5250	14.3	1.5506	39.2	7.2	1.5446	22.0	6.9	23.1	17.6	28.5	33.4

Cymene	30 g.	0.224 moles
Nitric acid (96%)	60 g.	0.915 moles
Sulfuric acid (96%)	120 g.	1.175 moles
Addition time	2 hours	
Stirring time	1 hour	

Note: (2) Mixture stirred for 2 hours after complete addition
(6,7) Check runs
(9) Mixture stirred for one-half hour after complete addition

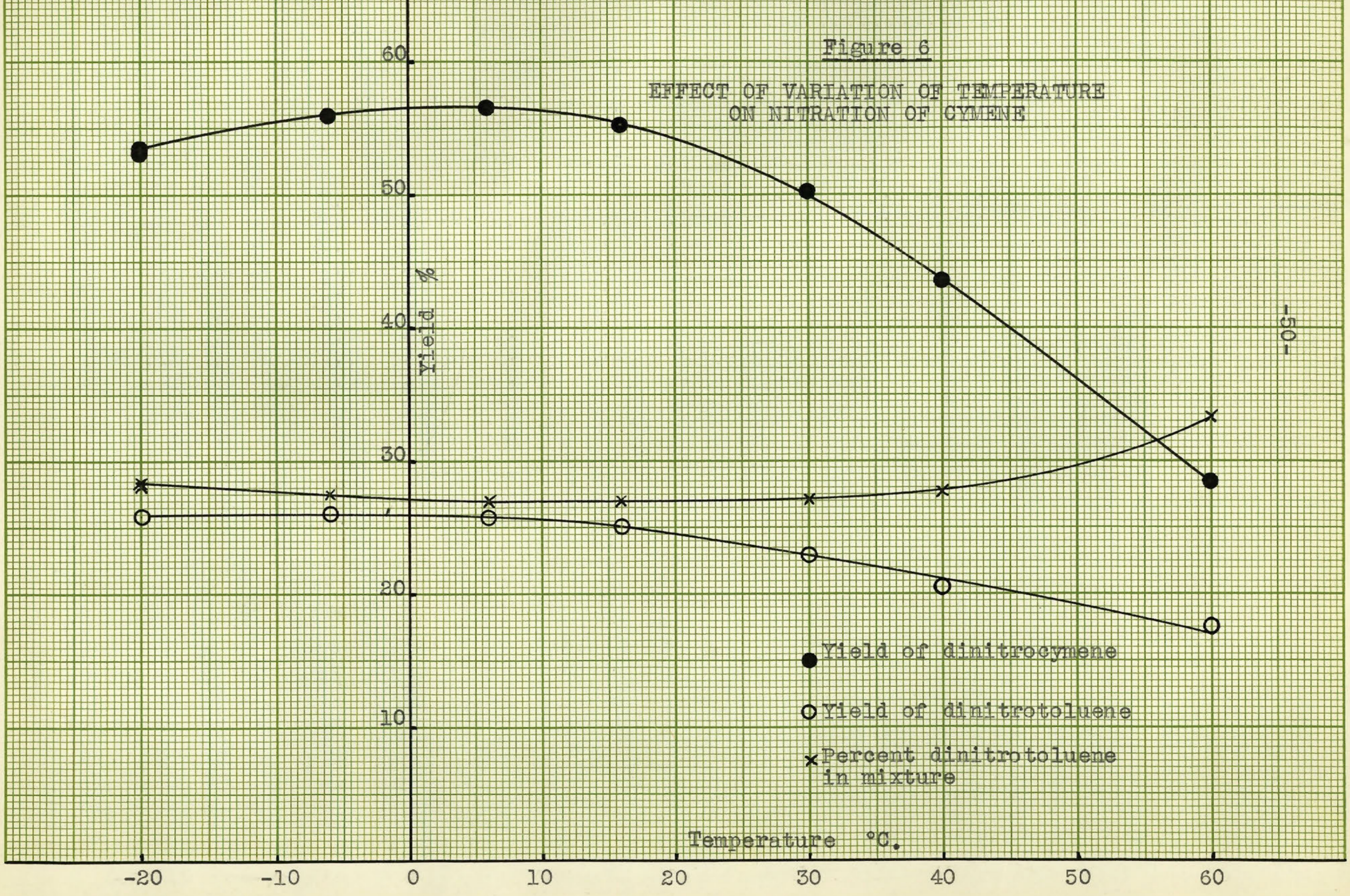


Figure 6

EFFECT OF VARIATION OF TEMPERATURE ON NITRATION OF CYMENE

Effect of Dilution of the Nitrating Acids Table VII.

The results obtained on addition of varying amounts of water to the standard nitrating acid (120 g. 96% sulfuric acid, 60 g. 96% nitric acid) have been expressed in the form of a graph (Figure 7). In Table VII, the"concentration of the nitric acid," for purposes of convenience, has been calculated on the assumption that the concentration of the sulfuric acid has remained constant at 96%, the water added serving exclusively as a diluent for the former. The results have been plotted against the percentage water in the system taken as a whole - assuming the concentration of both acids is 100%.

Oxidation increased with dilution (as might be expected) to the point where, using 29.3% nitric acid, the mixture was continually on the verge of fuming off. The color of the crude product and the amount of alkali-soluble oxidation products (which increased from 1.8 g. using the regular acid mixture to 8.1 g. in the case of the most dilute solution) as well as the increase in tar formation, confirmed this. Alkali and benzene insoluble residues behaved in the opposite manner, falling from 1.8 g. to zero for the higher dilutions. No unchanged cymene was recovered. In all cases it apparently had reacted completely.

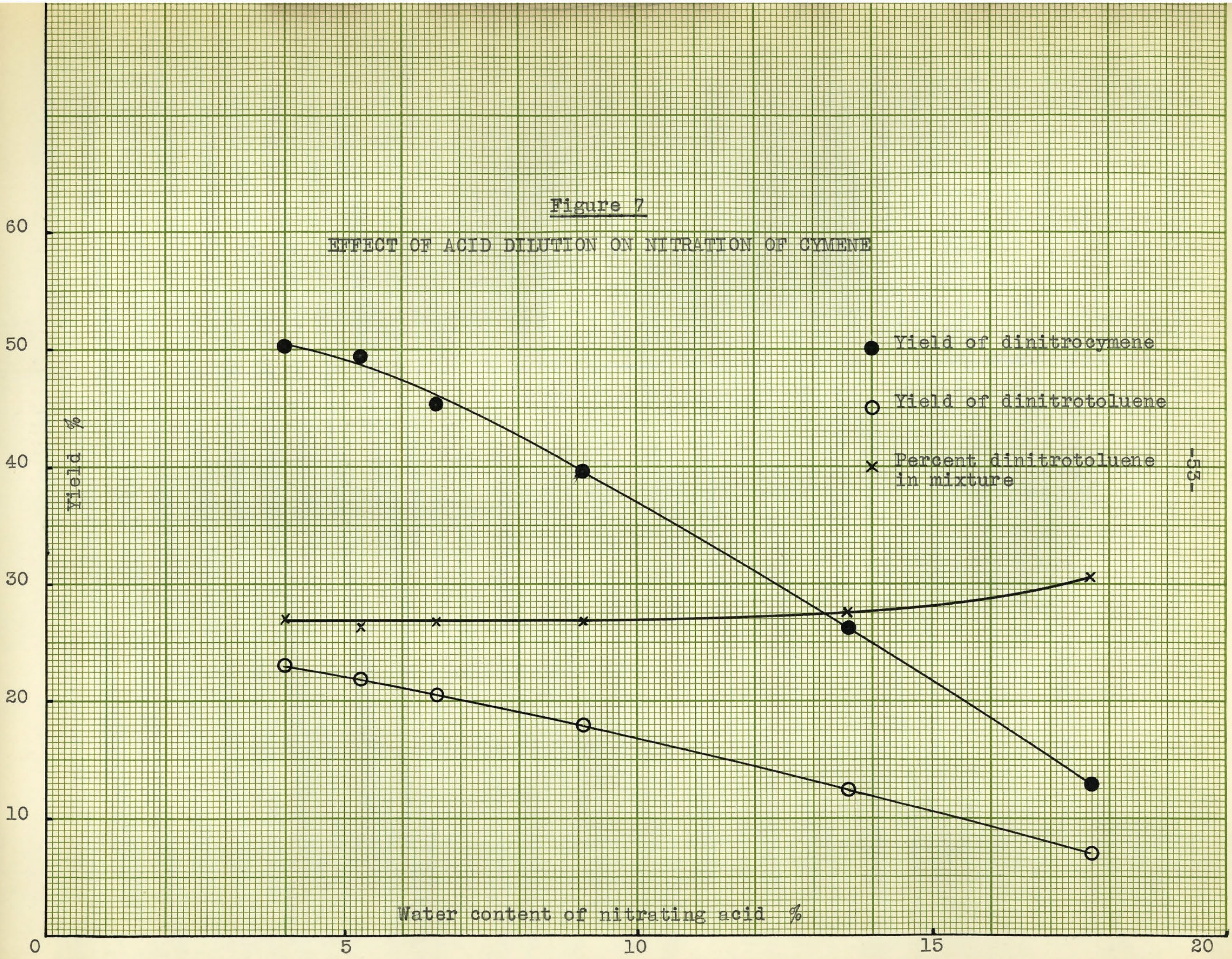
TABLE VII. EFFECT OF VARIATION OF NITRIC ACID CONCENTRATION ON NITRATION OF CYMENE

No.	Conc. of HNO_3	Water in system	Fraction I		Fraction II			Fraction III			Residue	Total wt. Prod.	Yield based on p-cymene		D.N.T in mixt.
			Wt.	n_D^{40}	Wt.	n_D^{40}	D.N.T.	Wt.	n_D^{40}	D.N.T.			D.N.T.	D.N.C.	
	%	%	g.		g.		%	g.		%	g.	g.	%	%	%
10*	96.0	4.0	1.1	1.5254	29.1	1.5478	31.2	5.5	1.5388	5.6	4.3	35.7	23.0	50.2	27.1
11	91.8	5.3	2.4	1.5242	25.0	1.5480	31.8	8.7	1.5405	10.5	4.1	36.1	21.8	49.5	26.3
12	87.7	6.6	4.0	1.5231	27.0	1.5474	30.0	4.1	1.5389	5.9	4.0	35.1	20.5	45.3	26.8
13	79.3	9.1	6.8	1.5232	14.3	1.5491	34.9	12.9	1.5432	18.0	4.4	34.0	17.9	39.6	26.9
14	62.6	13.6	9.4	1.5233	13.7	1.5481	32.1	4.5	1.5418	14.0	5.1	27.6	12.4	26.2	27.6
15	46.0	17.7	11.1	1.5243	6.1	1.5485	33.2	3.2	1.5459	25.7	8.4	20.4	7.0	12.9	30.6
16	29.3	21.4	13.4	1.5252	-	-	-	-	-	-	8.2	13.4	-	-	-

Cymene	30 g.	0.224 moles
Nitric acid (96%)	60 g.	0.915 moles
Sulfuric acid (96%)	120 g.	1.175 moles
Addition time	2 hours	
Stirring time	1 hour	
Temperature	30°C.	

Figure 7

EFFECT OF ACID DILUTION ON NITRATION OF CYMENE



Variation of Sulfuric Acid Content (Table VIII.)

The amount of oxidation which occurred was dependent on the quantity of sulfuric acid present in the nitrating mixture - for quantities of 40 g. and less it was considerable, the mixture at the end of the reaction being quite black in color, with the production of copious amounts of nitrogen oxide fumes. Alkali-soluble oxidation products decreased from 4.1 g. when nitric acid alone was used to 1.1 g. for a mixture containing 200 g. of sulfuric acid. The decrease in tar formation, though not considerable, illustrated the same tendency. In Run No. 17 (nitric acid alone) 2.9 g. of unchanged cymene was recovered.

TABLE VIII. EFFECT OF VARIATION OF SULFURIC ACID CONTENT ON NITRATION OF CYMENE

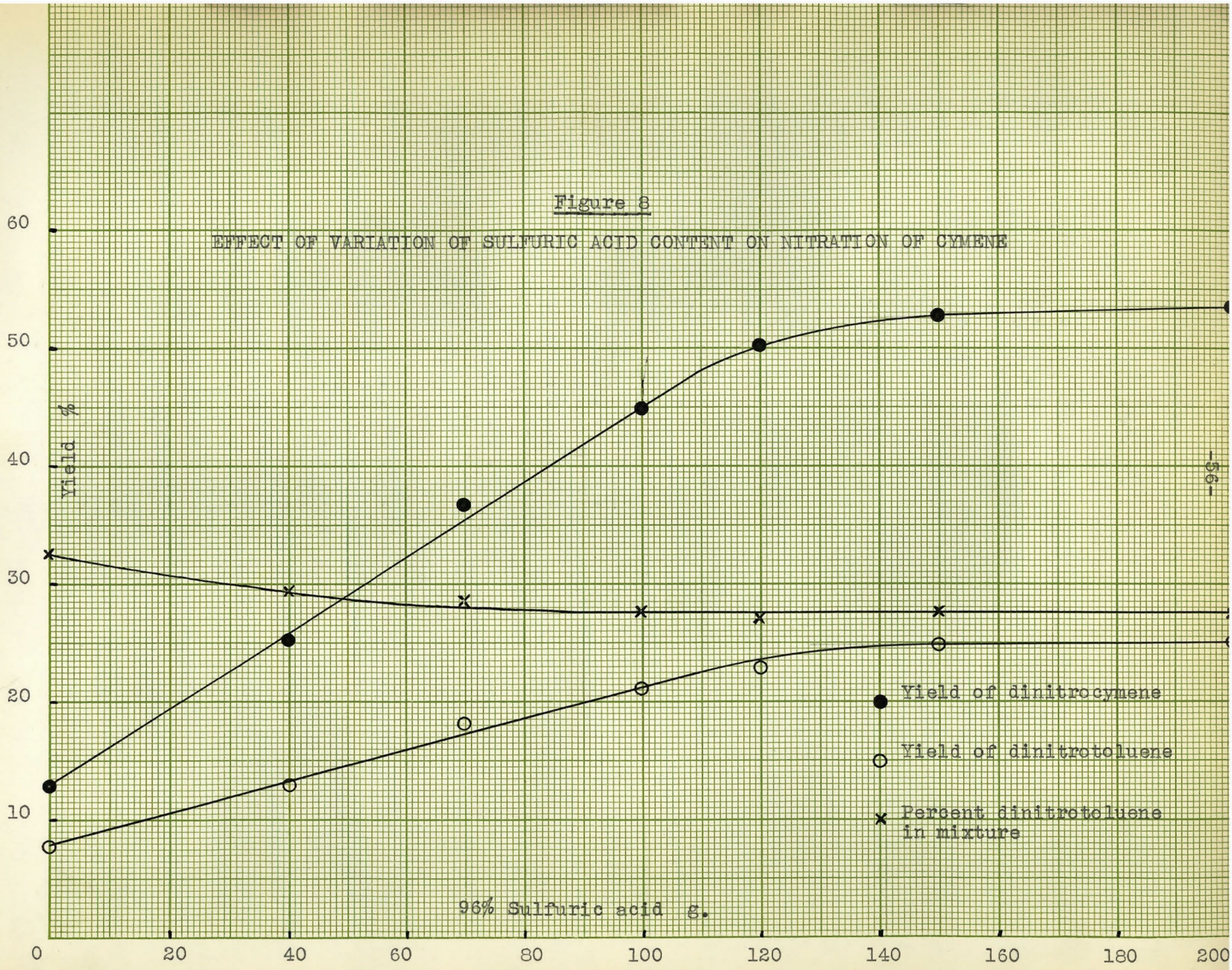
No.	96% H_2SO_4		Fraction I		Fraction II			Fraction III			Residue	Total wt. Prod.	Yield based on p-cymene		D.N.T. in mixture
	Wt. g.	Moles	Wt. g.	n_D^{40}	Wt. g.	n_D^{40}	D.N.T. %	Wt. g.	n_D^{40}	D.N.T. %	g.	g.	D.N.T. %	D.N.C. %	%
17	-	-	7.9	1.5259	2.6	1.5483	32.7	7.1	1.5483	32.7	5.6	17.6	7.8	12.9	32.7
18	40	0.392	8.5	1.5267	11.7	1.5490	34.6	6.3	1.5439	20.0	5.5	26.5	13.0	25.3	29.5
19	70	0.686	7.1	1.5234	22.8	1.5479	31.4	3.1	1.5398	8.4	5.4	33.0	18.2	36.8	28.6
20	100	0.980	4.3	1.5235	26.6	1.5479	31.4	4.6	1.5390	6.2	4.3	35.5	21.2	44.9	27.7
21*	120	1.175	1.1	1.5254	29.1	1.5478	31.2	5.5	1.5388	5.6	4.3	35.7	23.0	50.2	27.1
22	150	1.469	0.3	1.4565	29.3	1.5479	31.4	7.3	1.5415	13.2	4.1	36.9	24.9	52.7	27.7
23	200	1.959	0.3	1.4651	27.0	1.5489	34.3	10.1	1.5402	9.6	4.1	37.4	25.1	53.5	27.6

Cymene	30 g.	0.224 moles
Nitric acid (96%)	60 g.	0.915 moles
Addition time	2 hours	
Stirring time	1 hour	
Temperature	30°C.	

Note: (17) 2.9 g. unchanged cymene recovered

Figure 8

EFFECT OF VARIATION OF SULFURIC ACID CONTENT ON NITRATION OF CYMENE



Variation of Nitric Acid Content (Table IX)

The quantity of alkali-soluble material produced in those reactions where the nitrating mixture was low in nitric acid was considerable. This amounted to as much as 9.0 g. when only 24.5 g. of nitric acid was used, though the value dropped rapidly to the normal of 2 g. in Run 26 (41.2 g. of acid). This indicated extensive oxidation, evidenced also by production of large volumes of nitrogen oxide fumes and darkening of the nitration mixture and crude nitration product. In such cases also, difficulty was experienced in preventing fuming off, though considerable amounts of cymene came through unchanged. (For Run 24, this amounted to about 15 g.) It was noticed that about half-way through the addition in the latter reaction, no further heat was evolved, probably indicating that nitration had ceased.

TABLE IX. EFFECT OF VARIATION OF NITRIC ACID CONTENT ON NITRATION OF CYMENE

No.	Temp.	96% HNO_3	Fraction I		Fraction II			Fraction III			Residue	Total wt. Prod.	Yield based on p-cymene		D.N.T. in mixtur
			Wt.	n_D^{40}	Wt.	n_D^{40}	D.N.T.	Wt.	n_D^{40}	D.N.T.			D.N.T.	D.N.C.	
	°C.	Wt.-g.	g.		g.		%	g.		%	g.	g.	%	%	%
24	15	24.5	-	-	4.4	1.5475	30.3	4.9	1.5460	26.0	2.5	9.3	6.4	13.3	28.0
25	30	24.5	0.3	1.5000	12.5	1.5472	29.5	0.5	1.5385	4.9	4.0	13.3	9.1	18.5	28.5
26	30	41.2	2.3	1.5236	16.2	1.5495	36.0	8.0	1.5407	11.0	3.0	26.5	16.5	34.8	27.8
27	15	48.7	1.1	1.5350	29.9	1.5470	28.9	3.2	1.5370	0.6	3.0	34.2	21.2	48.7	26.2
28	30	48.7	3.4	1.5230	27.2	1.5470	28.9	1.4	1.5365	0.0	3.7	32.0	19.3	41.3	27.5
29*	30	60.0	1.1	1.5254	29.1	1.5478	31.2	5.5	1.5388	5.6	4.3	35.7	23.0	50.2	27.1
30	16	60.0	-	-	30.1	1.5477	30.9	7.8	1.5410	11.8	3.9	37.9	25.1	55.2	27.0
31	30	67.5	0.2	1.5270	29.3	1.5475	30.3	6.0	1.5390	6.2	5.0	35.5	22.7	51.9	26.2
32	30	70.0	-	-	30.4	1.5475	30.3	6.6	1.5400	9.0	4.9	37.0	24.1	54.2	26.5
33	30	100.0	0.1	1.4848	27.7	1.5488	34.0	10.1	1.5412	12.4	4.3	37.9	26.2	54.0	28.2

Cymene	30 g.	0.224 moles
Sulfuric acid (96%)	120 g.	1.175 moles
Addition time	2 hours	
Stirring time	1 hour	

Note: (24,25) Considerable amounts of unchanged cymene recovered

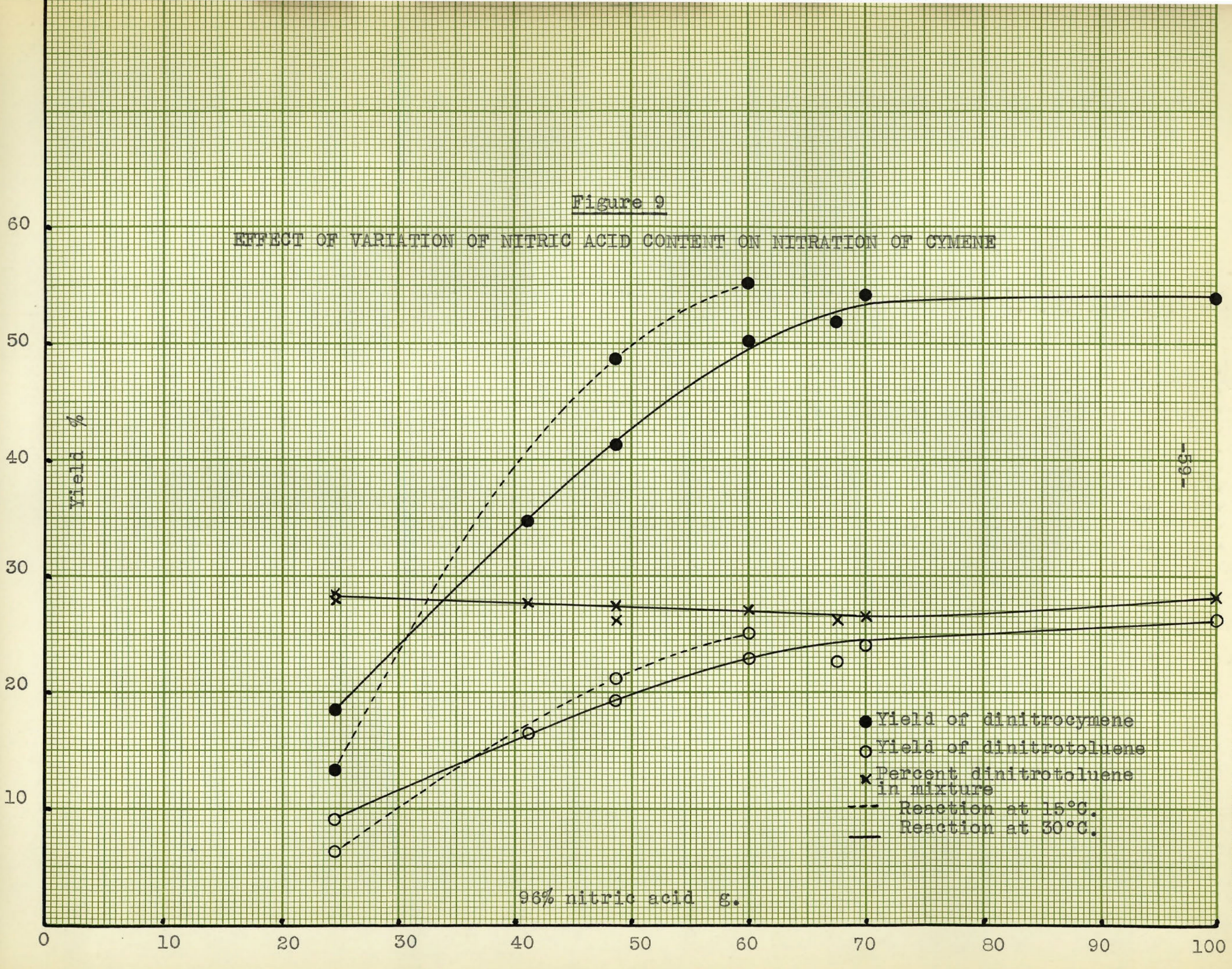


Figure 9

EFFECT OF VARIATION OF NITRIC ACID CONTENT ON NITRATION OF CYMENE

Variation of Stirring Time (Table X)

No appreciable change in color of product, oxidation residues or tar formation took place on varying stirring time from 1/2 to 3 hours.

Variation of Addition Time (Table XI)

Very little change in the amount of oxidation occurred even with wide variations in the addition times of the cymene (1/3 hour to 11 hours). From the amount of alkali-soluble oxidation products and tar formation, however, the trend appeared to be towards an increase in the amount of oxidation with slower addition. Runs 40 and 41 show that there is very little change on nitrating in the absence of a dry carbon dioxide atmosphere.

It will be noticed that Run 41 and Run 6 differ slightly from one another though the nitrating conditions are identical. In all of the experiments in Table XI, the nitric acid used had been obtained from a different source. Although the density was the same as that of the acid regularly employed, it was considerably lighter in color and always gave somewhat better results. The difference is slight, however, and the conclusions drawn from such a variation in the addition time will still be valid.

TABLE X. EFFECT OF VARIATION OF STIRRING TIME AFTER COMPLETE ADDITION ON NITRATION OF CYMENE

No.	Stirring time hours	Fraction I		Fraction II			Fraction III			Residue	Total	Yield based on p-cymene		D.N.T. in mixture
		Wt. g.	n_D^{40}	Wt. g.	n_D^{40}	D.N.T. %	Wt. g.	n_D^{40}	D.N.T. %	g.	wt. g.	D.N.T. %	D.N.C. %	%
34	1/2	1.4	1.5232	31.5	1.5468	28.3	2.4	1.5384	4.6	4.4	35.3	22.2	49.6	26.6
35*	1	1.1	1.5254	29.1	1.5478	31.2	5.5	1.5388	5.6	4.3	35.7	23.0	50.2	27.1
36	2	1.2	1.5256	31.0	1.5470	28.9	4.9	1.5387	5.4	4.2	35.8	22.5	50.8	26.4
37	3	0.8	1.5244	29.6	1.5475	30.3	6.0	1.5400	9.0		36.4	23.4	52.0	26.7

Cymene	30 g.	0.224 moles
Nitric acid (96%)	60 g.	0.915 moles
Sulfuric acid (96%)	120 g.	1.175 moles
Addition time	2 hours	
Temperature	30°C.	

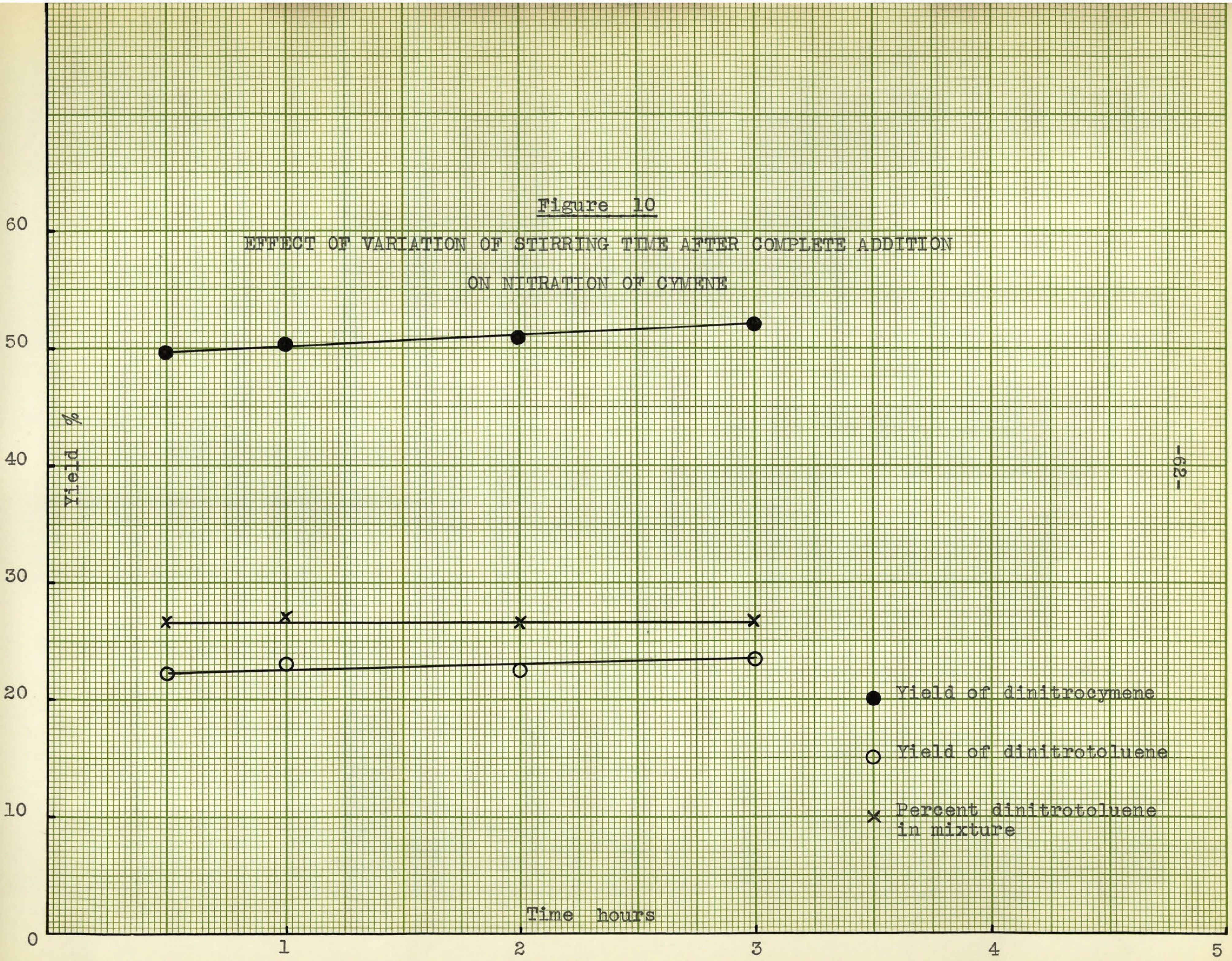


Figure 10

EFFECT OF VARIATION OF STIRRING TIME AFTER COMPLETE ADDITION ON NITRATION OF CYMENE

TABLE XI. EFFECT OF VARIATION OF ADDITION TIME ON NITRATION OF CYMENE

No.	Addition time hours	Fraction I		Fraction II			Fraction III			Residue	Total wt. Prod.	Yield based on p-cymene		D.N.T. in mixture
		Wt. g.	n_D^{40}	Wt. g.	n_D^{40}	D.N.T. %	Wt. g.	n_D^{40}	D.N.T. %	g.	g.	D.N.T. %	D.N.C. %	%
38	1/3	-	-	33.5	1.5468	28.3	5.0	1.5400	9.0	3.6	38.5	24.3	56.8	25.8
39	1	0.1	1.5272	33.1	1.5469	28.6	4.6	1.5404	10.2	3.5	37.8	24.3	55.3	26.3
40	2	1.3	1.5224	28.7	1.5474	30.0	6.9	1.5411	12.1	4.0	36.9	23.2	52.1	26.6
41	2	1.2	1.5232	31.0	1.5472	29.4	5.2	1.5407	11.0	4.1	37.4	23.7	52.8	26.8
42	5	2.1	1.5232	29.8	1.5472	29.4	3.6	1.5413	12.7	4.1	35.5	22.6	48.2	27.6
43	8	2.6	1.5234	25.8	1.5485	33.2	5.2	1.5408	11.2	5.3	33.6	22.4	43.5	29.5
44	11	2.1	1.5232	27.0	1.5478	31.2	3.0	1.5414	13.0	5.6	32.1	21.6	42.2	29.4

Cymene	30 g.	0.224 moles
Nitric acid (96%)	60 g.	0.915 moles
Sulfuric acid (96%)	120 g.	1.175 moles
Stirring time	1 hour	
Temperature	30°C.	

Note: (40) Not done under CO_2 atmosphere

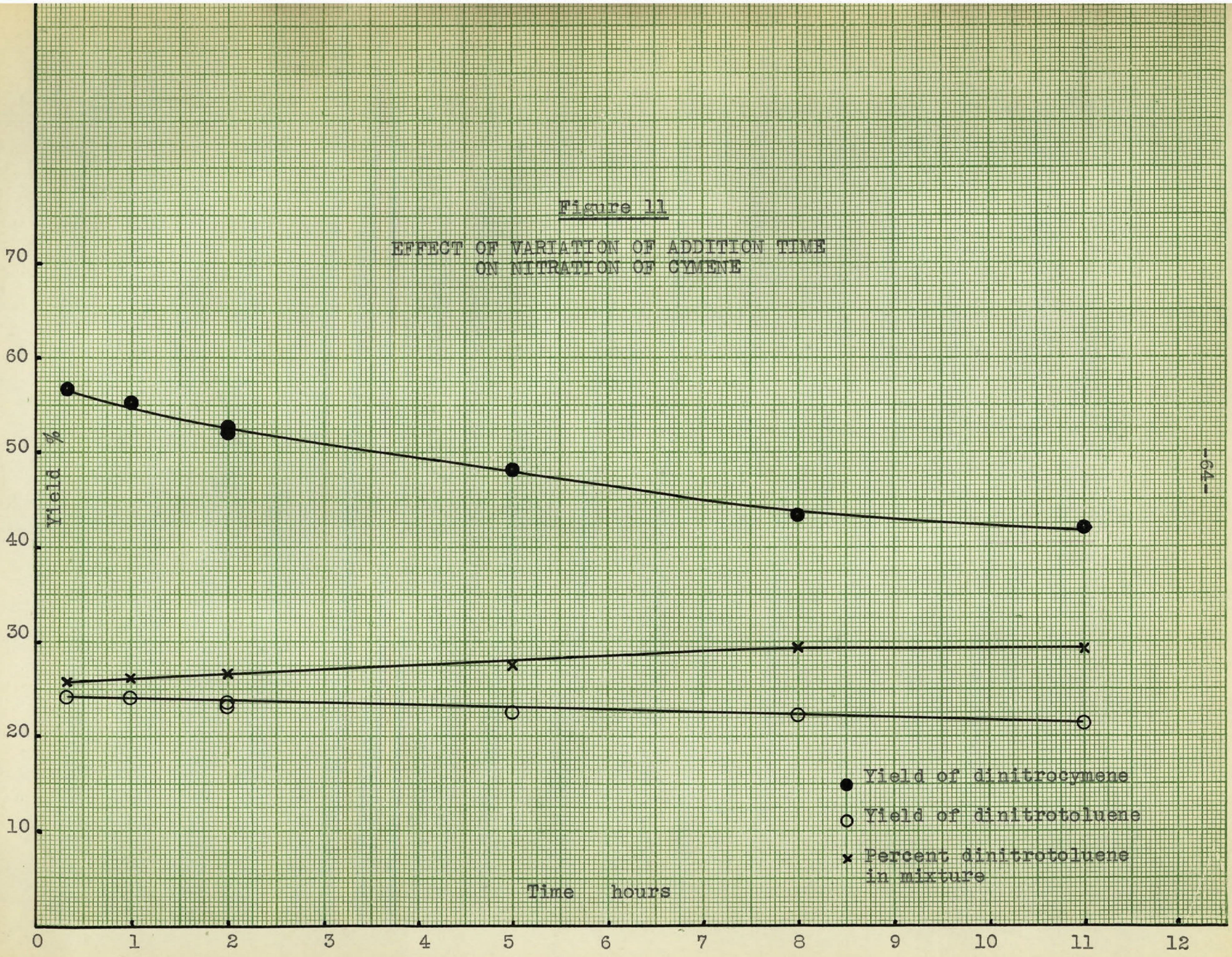


Figure 11

EFFECT OF VARIATION OF ADDITION TIME ON NITRATION OF CYMENE

TABLE XII. MISCELLANEOUS

No.	Fraction I		Fraction II			Fraction III			Residue	Total wt. Prod.	Yield based on p-cymene		D.N.T. in mixture
	Wt. g.	n_D^{40}	Wt. g.	n_D^{40}	D.N.T. %	Wt. g.	n_D^{40}	D.N.T. %	g.	g.	D.N.T. %	D.N.C. %	%
45*	1.1	1.5254	29.1	1.5478	31.2	5.5	1.5388	5.6	4.3	35.7	23.0	50.2	27.1
46	1.5	1.5250	31.0	1.5472	29.5	4.2	1.5405	10.5	3.9	36.7	23.5	51.0	27.2
47	1.4	1.5232	30.2	1.5471	29.2	4.6	1.5412	12.4	4.4	36.2	23.0	50.6	27.0
48	1.6	1.5232	28.3	1.5472	29.5	5.8	1.5424	15.8	5.0	35.7	22.8	49.5	27.2
49	4.1	1.5255	-	-	-	-	-	-	39.8	4.1	-	-	-
50	0.1	1.4642	29.7	1.5470	28.9	5.7	1.5401	9.4	5.2	35.5	22.4	52.4	25.8
51	1.2	1.5210	29.5	1.5479	31.5	6.0	1.5402	9.6	4.7	36.7	24.2	51.1	27.7
52	2.1	1.5235	28.9	1.5471	29.2	3.4	1.5389	5.9	5.2	34.4	21.3	47.2	26.8
53	3.3	1.5212	18.7	1.5486	33.4	8.6	1.5413	12.7	5.0	30.6	18.0	39.8	26.9
54	-	-	1.4	1.5430	17.5	0.9	1.5455	24.5	3.3	2.3	1.2	3.6	20.4
55	-	-	13.8	1.5492	35.2	6.7	1.5430	17.5	9.9	20.5	14.8	28.9	29.4
59	11.7	$\{n_D^{20} = 1.5295$	4.5	1.5467	28.0	7.4	1.5420	14.6	2.7	23.6	7.7	19.0	25.5
60	0.8	1.5068	22.0	1.5252	23.7	5.4	1.5365	0.0	3.7	28.2	17.1	59.0	19.0
63	1.7	1.5237	41.0	1.5519	42.9	2.5	1.5434	18.6	3.8	35.2	19.8	50.7	
64	-	-	33.3	1.5470	28.9	5.4	1.5417	13.8	3.8	38.7	25.4	56.4	26.8

Note 45: Run done under standard conditions.

MISCELLANEOUS (Table XII, page 64a)

Addition of nitration catalysts (Runs 46,47 and 48)

The influence of various metallic salts which were known to be effective as cleavage and nitration catalysts was investigated, the previously defined standardized conditions being used throughout. Only those nitrates were employed which were soluble either in the mixed acid or in concentrated nitric acid alone, when by slow addition of the sulfuric acid they were precipitated in a very finely divided form. The nitrates of lead, aluminum, iron, copper and mercury did not fulfil these conditions. The nitrates of cobalt (Run 46), zinc (Run 47) and nickel (Run 48) were suitable in this respect; however, the change in yields of products was so slight that further investigation was discontinued. Max Phillips (69) reported that in the sulfonation of cymene the addition of small quantities of such metallic salts also had little effect.

Substitution of acetic anhydride for sulfuric acid (Run 49)

The orientation of a nitro group entering the benzene nucleus is in certain cases very appreciably affected by the nitrating agent employed. In order to test this factor in the nitration of cymene, a reaction was attempted in which acetic anhydride was substituted for the sulfuric acid. The same molar amount of acetic anhydride (119 g.) was used and the regular standard conditions were adhered to. Only a very insignificant amount of nitration occurred, the products

(4.1 g.) being entirely low boiling. The remainder, a black tarry residue (39.8 g.), was unstable, and appeared to undergo decomposition during distillation as evidenced by excessive foaming and gas evolution. It was insoluble in hot Skelly Solve B so that no dinitrocymene could have been present. Only a very small amount of alkali soluble oxidation products was isolated.

Substitution of 20% oleum for 96% sulfuric acid (Run 50)

Instead of 120 g. of sulfuric acid, the same weight of 20% oleum was used. Excessive evolution of sulfur trioxide fumes on addition of the cymene at both 30°C. and 20°C. limited the operating temperature to 10°C. -- otherwise the nitrating conditions were standard. The percentage yield of both dinitrocymene and dinitrotoluene was somewhat lower than the values obtained for a normal nitration at the same temperature (cf.Figure 6). No appreciable variation was noticed in the production of tars and other oxidation products.

Effect of decolorizing the nitric acid with urea nitrate (Run 51)

The nitric acid (which ordinarily was slightly brown in color) was decolorized before use by bubbling dry air through it while boiling with 2% of its weight of urea nitrate. Results were only slightly better than those obtained using the colored acid.

Nitration of very crude cymene (Runs 52 and 53)

Although on nitrating cymene partially purified as described on page 25, results were obtained (Run 52) which checked fairly closely with those in which cymene of the best quality had been used (Run 45), very crude cymene (as obtained directly from the settling tanks) gave somewhat different results (Run 53). The latter was very dark yellow in color, and after several washings with 10% sodium carbonate solution to free it from sulfur dioxide, had a refractive index value of $n_D^{20} = 1.4920$. As can be seen from Table XII, the yield of dinitrocymene decreased by 10%, from 50% to 40%, and the dinitrotoluene correspondingly. Oxidation products and tars were produced in the ordinary amounts.

Effect of reverse addition (Runs 54 and 55)

In Run 54, the nitric acid was added dropwise to the mixture of cymene and sulfuric acid -- the nitrating conditions otherwise being standard. Considerably more heat was given off than in a normal run and the mixture had a great tendency to fume off with the evolution of large amounts of nitrogen oxides. On pouring on ice, a small lump of sticky brown material was obtained which, however, was worked up in the usual way. Surprisingly enough, only a very little alkali soluble oxidation product was obtained. Since the amount of dinitrated material isolated was extremely small (see Table XII) the value for "D.N.T. in mixture" (20.4%) means little.

In Run 55, the combined mixed acids were run into the cymene, much the same results being obtained, though considerable tar formation occurred. It would appear that in order for the nitration of cymene to be a success, the cymene has to be added to the nitrating mixture and not the reverse, differing markedly from benzene and toluene in this respect.

Vapor phase nitration (Runs 56 and 57)

With the original object of determining the effect of very high nitrating temperatures on the cleavage of the isopropyl group, a vapor phase nitration of cymene was carried out. A glass tube 36 inches long with an internal diameter of 20 mm., kept at a temperature of 190-200°C. by means of an electrically heated Nichrome wire, was used as the reaction chamber. Thermometers inserted in wells at each end of the tube provided a constant check on the temperature; heavy lagging with asbestos paper keeping heat losses to a minimum. The reactants (cymene and nitric acid) were led in separately as gases at the upper end. Vaporization was attained simply by running the liquid dropwise from a funnel into a distillation flask heated to a temperature well above the boiling point of the liquid in question.

The neck and arm of the flask were also heated electrically, the latter being connected to the reaction tube simply by inserting it in the open end and sealing well with powdered asbestos. Wherever it was necessary to use rubber stoppers, they were protected with a coating of Vinylite resin.

A separate vaporizer was provided for each liquid.

Using this apparatus, 30 g. of cymene and 17.6 g. of 96% nitric acid (25% excess over that required to cause complete mononitration) were passed through simultaneously at a uniform rate over a period of 3 hours. The product, after neutralization with dilute bicarbonate solution and drying, weighed 24.6 g. It was light yellow in color and had an odor of cymene. On fractionation, 18.8 g. of unchanged cymene was recovered along with 4.4 g. of product distilling over a temperature range corresponding to mononitrotoluene and mononitrocymene (105°C. at 17 mm. to 113°C. at 5 mm.). The quantity was too small for proper identification of the products. Residues amounted to 1.4 g. It would be difficult to say whether the small amount of products formed was the result of nitration in the vapor phase or in the liquid phase subsequent to condensation of the reactants.

A similar experiment (Run 57) was tried in which as a nitration catalyst boron trifluoride was added (70) at the rate of 30-40 bubbles per minute. The results obtained were much the same, the total weight of product being 21.3 g., of which 17.0 g. was unchanged cymene and 3.4 g. material boiling over ranges corresponding to mononitration products. The remainder (0.9 g.) was residue. Considerable tar formation occurred inside the tube.

Investigation of typically aromatic nitration procedures (Runs 58-62)

With the object of comparing the relative ease of the nitration of cymene with other simple aromatic compounds, the mononitration of cymene was attempted following a typical procedure employed in the mononitration of benzene (Run 58). A nitrating mixture consisting of 25.5 g. 96% sulfuric acid and 20.1 g. 70% nitric acid was added dropwise over a period of 70 minutes to 30 g. of cymene at 30°C. with vigorous stirring. The mixture was then heated to 56°C. and maintained at this temperature for 50 minutes, with continuous stirring. The now nearly black solution was poured onto ice and worked up in the usual manner. A forerun of 13.6 g. of unchanged cymene was followed by 5.3 g. of yellow product boiling over a wide range (65-122°C. at 14.8 mm.) though the main fraction came off at temperatures corresponding to mononitrated material. A considerable amount of residue (9.3 g.) remained in the pot.

The investigation was continued by determining the ease of addition of a second nitro group to mononitrocymene, using one of the common procedures which was known to operate successfully in a similar nitration stage in the production of T.N.T. (Run 59). To an acid mixture composed of 15.6 g. of 96% nitric acid, 42.4 g. 96% sulfuric acid and 4.95 g. of water at 85°C., 30 g. of mononitrocymene (n_D^{20}=1.4291) was added over a 20-minute period with stirring. After being held at 92°C. for 10 minutes, the mixture was allowed to stand for a similar length of time before pouring on ice. After working up in the previously described manner, the mixture was fractionally distilled. The results are tabulated in Table XII. It will be noticed that a considerable amount of mononitrocymene was recovered unchanged.

The production of dinitrocymene from mononitrocymene using the previously described standard conditions for the dinitration of cymene was also studied (Run 60). For a 30-g. sample of mononitrocymene the quantities of acid were just one-half those ordinarily employed, though the remaining conditions of a standard run were adhered to. There was a marked decrease in the ratio of dinitrotoluene to dinitrocymene, though the overall yield of dinitrated products remained practically unchanged. The amount of oxidation was quite noticeably less than that which occurred when cymene was used as the starting material.

Several typical last stage nitration procedures for the preparation of trinitrotoluene gave very poor results when applied to a similar nitration of dinitrocymene (Runs 61 and 62). From 20 g. of the latter was obtained (after preliminary treatment of the product with Skelly Solve B to remove unreacted dinitrocymene) about 2 g. of material melting at 118°C. after crystallization from methanol -- supposedly trinitrocymene (m.p.118°C.(60)).

Influence of added D.N.T. on the nitration of cymene (Run 63)

A nitration was carried out at 30°C. under the standard conditions, 10 g. of dinitrotoluene having first been added to the nitration mixture. The results are given in Table XII. It will be noticed that within experimental error the yield of dinitrocymene has not been altered (compare Run 45). The yield of dinitrotoluene is lower, but this may be due to the fact that the assumption of complete recovery of the D.N.T. added (on which these yields have been calculated) is false. This seems to be borne out by the fact that no corresponding increase in the yield of dinitrocymene occurred.

Nitration done under optimum conditions (Run 64)

A survey of the various graphs will indicate that optimum conditions are as follows (for a 30 g. sample of cymene): 96% nitric acid, 75 g.; 96% sulfuric acid, 150 g.; temperature, around 0°C.; addition time, as short as possible; stirring time, not critical but conveniently one hour. The results of a nitration carried out under these conditions will be found in Table XII (an addition time of 15 minutes being used). It will be noticed that the yields were not appreciably better than those obtained under the conditions of optimum addition time alone (Run 38). It would appear, then, that there is but slight chance of increasing these values beyond this point.

Method of analysis by solvent extraction

Although the original procedure for the analysis of the nitration mixture, based on the method of solvent extraction, gave results which can hardly be called duplicable, at least they were of the same order of magnitude as those obtained by refractive index measurements. In Table XIII below, the results obtained for a temperature variation in the standard conditions using the two methods of analysis are listed, to give some indication of their comparative degrees of precision.

TABLE XIII

	Solvent Extraction			Refractive index measurement		
Temp.	D.N.T. %	D.N.C. %	D.N.T.in mixture %	D.N.T. %	D.N.C. %	D.N.T. in mixture %
0°C.	25.8	52.9	28.4	26.0	56.7	27.2
10°C.	29.7	52.2	31.6	25.6	56.3	26.7
20°C.	21.0	51.9	24.8	24.6	54.2	26.7

Report of Explosive Tests on 2,6-Dinitrocymene* (Table XIV)

Ignition Temperature Test:

Ignites at..............Negative at 360°C.

Brown fumes begin at.....None

Friction Test on Unglazed Porcelain:

Evidence of decomposition.....None

Crackling....................None

Reaction to litmus paper......Neutral

Machine Impact Test:

Hammer drop.............Negative at maximum drop

---

*Courtesy of M.C.Fletcher,
Department of Mines and Resources,
Explosives Laboratory
Ottawa, Ontario

Trauzl Lead Block Test:

Net expansion.......No detonation with No.6 detonator.

EXPERIMENTAL AND THEORETICAL DISCUSSION

The formation of dinitrotoluene.

It has been mentioned previously that Kobe and Doumani (55), during an investigation of the mononitration of cymene, discovered that the production of p-nitrotoluene as a side reaction was independent of operating conditions, remaining constant at approximately eight per cent of the total for wide changes in acid concentrations, presence of emulsifying agents and other factors. It was more or less expected then that the production of dinitrotoluene during the dinitration of cymene should behave in a similar manner. A glance at the various graphs which have been drawn (Figures 7-11) will indicate that extreme variations in water content, sulfuric and nitric acid content of the system as well as stirring and addition times caused but slight changes in the mean value of 27% for "percentage dinitrotoluene in the dinitration product." In view of the considerably more drastic conditions which are necessary for the introduction of a second nitro group, this really remarkable constancy was rather unexpected.

The widest variation occurred with changes in temperature (Figure 6), though this was little enough, being only 7% for an alteration of eighty degrees. It will also be noticed that there is a minimum in the curve for"percentage dinitrotoluene in the mixture." There is no possible doubt that such a minimum actually exists -- indeed a similar series of curves was obtained in preliminary experiments done before the nitrating conditions had been standardized. The most obvious reason for this is that two opposing reactions balance one another at this point. Since the production of dinitrotoluene involves removal of an isopropyl group, then any factor affecting the lability of the latter will result in a change in the ratio of dinitrotoluene:dinitrocymene. Pyrolytic reactions in which cleavages occur are favored by rise in temperature, and assuming that removal of the isopropyl group during nitration is of the same character, then "percent dinitrotoluene in the mixture" should necessarily increase with rise in temperature and the curve slopes upward to the right. Another factor is working in the opposite sense, however. It is known that lower temperatures favor para substitution in a benzene ring (71). Hence, although a decrease in temperature would cause a lowering of the ratio as a result of the first influence, at a certain stage the second factor would predominate, with ensuing formation of a minimum followed by a rise in the curve to the left.

This is a very reasonable explanation for the presence of a minimum but it is by no means the only one. It has already been mentioned that a marked increase in oxidation occurred with rise in temperature above 30°C. It is very probable that, due to the presence of an isopropyl group which furnishes a point of attack, dinitrocymene would oxidize more readily than dinitrotoluene. The resultant removal of the former from the reaction products would produce an increase in the dinitrotoluene:dinitrocymene ratio.

This theory naturally is not applicable to the increase in the ratio with lowering of temperature after the minimum in the curve has been reached. It will be noticed, however, that below 0°C. the absolute yield of dinitrocymene falls fairly rapidly while the absolute yield of dinitrotoluene remains substantially the same. This may mean that at these temperatures a secondary reaction of some sort is occurring, which, by operating on dinitrocymene preferentially, causes a lowering of its yield. The isolation of an alkali-and-benzene-insoluble residue from these nitrations has already been referred to, and it also has been mentioned that the amounts of this material increased with lower temperatures.

The first explanation for the increase in the dinitrotoluene-dinitrocymene ratio at lower temperatures (based on increased p-orientation) would lead one to expect a lowering of the absolute dinitrocymene percentage, but at the same time, a corresponding increase in the amount of dinitrotoluene formed. Actually the latter varies but little (if anything, a slight decrease is noticeable). Due to the presence of the secondary reaction at these lower temperatures however, it becomes impossible to settle the question definitely. One might equally well say that dinitrotoluene was removed by this secondary reaction, but that the loss was made up by increased p-orientation at the expense of the yield of dinitrocymene. Due to the necessity of obtaining information on the actual operating conditions for the nitration, investigation of these less important side-issues was extremely cursory. In view of the presence of at least three reactions occurring simultaneously in the system (nitration, oxidation and cleavage) considerably more facts would have to be accumulated before the relative effects of these factors on the yields could be correctly determined.

The ratio of dinitrotoluene to dinitrocymene was found to be practically independent of the amount of nitric acid present (Figure 9), though a minimum occurs at a point corresponding to optimum conditions. This is practically within experimental error, however -- there seems to be no a priori reason why the point of attack in the nitration of the aromatic nucleus should depend on the amount of nitric acid available.

The percentage dinitrotoluene in the mixture was found to remain constant at 26.8% on dilution of the acid mixture with water (Figure 7), though a slight increase with very high dilution is apparent. Practically the same phenomenon occurred on changing the sulfuric acid content of the nitrating mixture (Figure 8), a slight increase also taking place for the lower concentrations. Although it is perhaps not expedient to theorize too greatly on such slight changes, the effect of increased oxidation which has been shown to be theoretically capable of increasing this value can be operating equally well in these cases. It has been mentioned previously that a marked increase in oxidation occurred on dilution or on decreasing the sulfuric acid content of the system.

No change in the ratio occurred on varying the stirring time (Figure 10). A slight increase did take place, however, with increase in addition time (Figure 11). Since nitration seemed to be practically instantaneous, it is not clear what factors can be operating in one case and not in the other. A decrease in absolute yield of products with increased addition time has never been mentioned previously by other workers, but as can be seen from Figure 11, it is very marked. It might be argued that secondary reactions resulting from longer contact time of the products with the nitration mixture were responsible. However, this can hardly be the case since increasing the stirring time actually resulted in a slight increase in yield.

The manner in which cleavage of the isopropyl group takes place has been the subject of some discussion in the past. In 1920, Alfthan (59) reviewed the facts which were definitely known at that time. On the basis of the formation of p-nitrotoluic-o-sulfonic acid by nitration of the corresponding sulfonic acid of cymene as discovered by Hintikka (63) Alfthan considered that formation of dinitrotoluene by dinitration of cymene might proceed through this sulfonic acid as an intermediate. The presence of a sulfonic acid group in the ortho position would assist greatly the replacement of an isopropyl group meta to it. However, he found that p-nitrotoluic-o-sulfonic acid underwent no further reaction with nitric acid no matter what concentrations or temperatures were employed.

As for the possibility that removal of the isopropyl group proceeded through preliminary oxidation to the ketone p-CH_3-C_6H_4-CO-CH_3 or the acid p-CH_3-C_6H_4-COOH, other workers had shown that although nitration in positions 2 and 6 occurred in the normal manner, the products were resistant to further nitration. Alfthan confirmed these facts and provided the additional information that trinitrocymene also was resistant to further nitration.

No further important contributions to the subject appeared until 1942, when Doumani and Kobe (72), continuing their work on the mononitration of cymene, investigated the fate of the isopropyl group which must of necessity have been set free as the result of the formation of p-nitrotoluene. From the spent acids after nitration they were able to isolate isopropyl alcohol in considerable amounts. On the basis of this discovery they believed that direct replacement of the isopropyl group by a nitro group takes place without preliminary oxidation by the nitric acid.

From one of the experiments carried out in this investigation (Run 63) in which the addition of 10 g. of dinitrotoluene to the nitrating acid caused no appreciable variation in the amount of dinitrocymene produced, it would appear that the reaction is not reversible. This fact effectively contradicts another conceivable explanation for the increase in the dinitrotoluene:dinitrocymene ratio on increasing the water content or decreasing the sulfuric acid content of the system. In the event of an equilibrium, since concentrated sulfuric acid is known to cause condensation of isopropyl alcohol with toluene and 2-nitrotoluene (9,10,11), the reverse reaction (removal of an isopropyl group with accompanying increase in dinitrotoluene formation) should be favored by the first conditions.

It is interesting to note that on mononitrating pure 2-nitrocymene by the standard conditions (Run 60), the percent dinitrotoluene in the mixture dropped from 27% to 19%, that is by a percentage equal to the amount of p-nitrotoluene produced in the mononitration of cymene as found by Doumani and Kobe. In other words, dinitration appears to proceed in two steps, in the mononitration stage the percent cleavage of the isopropyl group amounts to 8%, in the next stage a further 19% is removed. The greater cleavage which occurs in the second stage would more or less be anticipated knowing that the nitro group (like the sulfonic acid group) is meta directing -- hence aiding removal of the isopropyl group which in 2-nitrocymene is meta to it. Since the total yield of dinitrated products is approximately the same on starting with either cymene or 2-nitrocymene, most of the nitration loss must necessarily take place during the introduction of the second nitro group. The accuracy with which these interdependent results check with one another is excellent evidence for the precision of the method of analysis.

Optimum conditions

With the exception of stirring time, the variables in every case are seen to alter in such a manner that definite optimum conditions can be selected for best yields of products. In the case of temperature variation, these conditions also occur at a maximum, differing from the results obtained by Kyker and Bost (67) who reported that the absolute yields steadily increased with fall in temperature. Because of decreased oxidation which occurred on lowering the temperature, it is clear why yields should rise. An explanation for the subsequent decrease below 0°C. has already been given.

Maximum yield, as might be expected, is coincident with minimum water content (a general characteristic of the nitration of aromatics). The concentration of pseudo acid ($HONO_2$) which is regarded as the effective nitrating agent is greater the more highly concentrated the nitric acid used. Hence success in aromatic nitrations depends upon such provisions as have been made against dilution. Introduction of sulfuric acid ensures the presence of high concentrations of pseudo acid or its anhydride N_2O_5, hence the nearly linear increase in both dinitration products with decrease in water content (Figure 7) or increase in sulfuric acid content (Figure 8). In Run 50, where 20% oleum has been substituted for the sulfuric acid, the yields of dinitrotoluene and dinitrocymene (after correction for temperature from 10°C. to 30°C.) are 20% and 47% respectively, well below the maxima in either Figure 7 or Figure 8. One would expect from what has just been said that the yields should be higher. However, secondary reactions seem to be favored in this case as indicated by the higher amounts of oxidation by-products formed. It is clear from Figure 8 that a definite maximum in the yield of both products is obtained at 140-150 g. of sulfuric acid. The amount of acid needed to keep the mixture completely anhydrous during the nitration (calculated on the basis of formation of $H_2SO_4.H_2O$) is only about 77 g. No explanation has been discovered for the fact that optimum conditions require nearly double this amount.

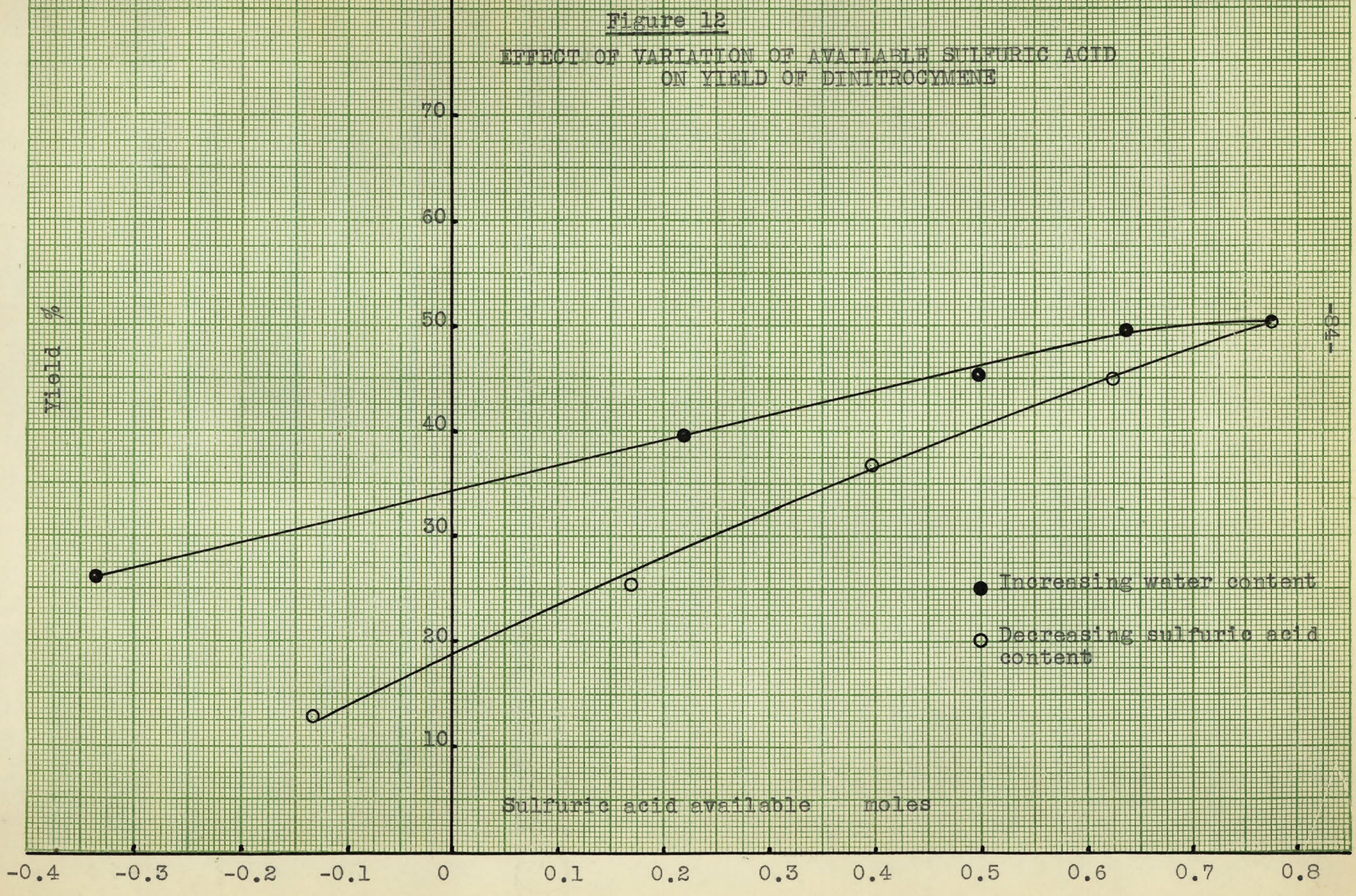
If the sulfuric acid acts only to remove the water in the system, then yields of products plotted against the amount of free sulfuric acid available for dehydration should be independent of the manner in which the quantity of this available acid has been varied. In Table VII this has been done by increasing the water content, in Table VIII by decreasing the sulfuric acid content of the system; in Table XV below the amounts of available sulfuric acid have been determined for both sets of conditions.

TABLE XV

Increasing water content			Decreasing H_2SO_4 content		
Run No.	H_2SO_4 available moles	D.N.C. %	Run No.	H_2SO_4 available moles	D.N.C. %
10	0.776	50.2	21	0.776	50.2
11	0.637	49.5	20	0.624	44.9
12	0.498	45.3	19	0.397	36.8
13	0.220	39.6	18	0.170	25.3
14	-0.335	26.2	17	-0.133	12.9

Figure 12

EFFECT OF VARIATION OF AVAILABLE SULFURIC ACID
ON YIELD OF DINITROCYMENE



In Figure 12 the yield of dinitrocymene has been plotted against these values. It will be noticed that the curve for the first set of conditions in which water content has been varied is considerably higher, except in the case of the common point for Runs 10 and 21 (identical conditions). This seems to indicate that the presence of $H_2SO_4.H_2O$ favors nitration of cymene under conditions which are otherwise identical. This may be simply the result of the larger volume of nitrating acid reducing oxidation and other side reactions, in which case it also provides an explanation for the fact that conditions of maximum yield require an amount of sulfuric acid nearly double that needed to remove all of the water present as $H_2SO_4.H_2O$

The yield of dinitrated products increases in direct proportion with the amount of nitric acid used until at 70-75 g. the yield becomes practically constant (Figure 9). This weight of nitric acid is within several percent of that which would be required assuming quantitative dinitration of the cymene and allowing sufficient acid to convert the isopropyl groups removed (as the result of dinitrotoluene formation) into isopropyl nitrate.

In Run 64 in which a nitration was carried out under optimum conditions based upon the various graphs, the yields were not appreciably better than those obtained under the conditions of optimum addition time alone (Run 38). It would appear that the amount of cymene removed as the result of side reactions has been reduced to a minimum, and that there is little chance of bettering the total over-all yield of 81.8%.

Note on possible uses for dinitrocymene

The procedure for the separation of the nitration products which has been employed in this investigation has been of necessity conditioned by the fact that it was the most accurate method of determining the relative and overall yields of dinitrotoluene and dinitrocymene (the principal object of this research). It would not be commercially feasible to distil fractionally the products from residues. This is not necessary, however, for the crude product obtained under optimum conditions is very light in color and contains no low boiling materials, and should be fairly pure after a preliminary alkaline wash. It is not known just what products give rise to tars by decomposition during distillation, but they are present in but minor amounts under the best conditions. In those instances where a mixture of the two products can be employed, a single recrystallization from alcohol should be sufficient. If the materials are to be used in their pure state, the method of extraction with Skelly Solve B which has been developed should be capable of commercial use with appropriate adaptations.

The very stable character of dinitrocymene (Table XIV) combined with its low melting point of 54°C. would indicate that this compound should have very desirable phlegmatizing properties. It has been found by actual test* that dinitrocymene either pure or mixed with dinitrotoluene in the proportions obtained by the nitration of cymene, is just as, if not more, efficient than beeswax (at the present time used as a standard by the British authorities) for the desensitization of Pentolite. Dinitrocymene should also prove valuable in lowering the melting points of desirable explosives which otherwise are difficultly fusible.

At the present time nitrated compounds (in particular nitrobenzene) are used in reclaiming vulcanized rubber. Dinitrocymene possibly could be used in this instance also, the isopropyl group and the extra nitro groups conferring on the material even more desirable terpenic solubility properties which should be valuable in this respect. Investigation of this possibility is to be begun shortly.

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SUMMARY

1. An investigation of the dinitration of p-cymene has been made. An intensive study has been completed of the effects of variations in the temperature, the water, sulfuric and nitric acid contents of the system, the rate of addition and the stirring time, together with the influence of nitration and cleavage catalysts upon the relative and absolute yields of dinitrotoluene and of dinitrocymene.
2. A method has been devised for the rapid analysis of the reaction products after a preliminary purification by distillation.
3. A method of solvent extraction of the two components has been developed using Skelly Solve B, replacing the previous, unsatisfactory methods of recrystallization using alcohol and other solvents.
4. Some attention has also been given to such factors as: differing methods of addition of reactants, use of typically aromatic nitration procedures, substitution of acetic anhydride and of 20% oleum for the sulfuric acid, preliminary decolorization of the nitric acid, etc.
5. Optimum nitrating conditions have been determined for the first time and the constancy of the dinitrotoluene: dinitrocymene ratio has been established. Various theories have been advanced to explain such slight variations which do occasionally occur in that ratio.

BIBLIOGRAPHY

1. Dumas, M.M. and Péligot, E., Compt.rend. 4, 496 (1837)
2. Gerhardt and Cahours, Ann.Chim.Phys. (iii) 1, 102,372 (1841)
3. Widman, O., Ber. 24, 439-456 (1891)
4. Bert, L., Bull.soc.chim. 37, 1252-1270 (1925)
5. Sabatier, P. and Murat, M., Compt.rend. 156, 184-187 (1913)
6. Bert, L., Compt.rend. 176, 840-842 (1923)
7. Fittig, R., Ann. 149, 337 (1869)
8. Auwers, K.v., Ann. 419, 92-120 (1919)
9. Verley, A., Can. 279,590 (1928) C.A. 22:2754
   U.S. 1,756,575 (1930) C.A. 24:3022
10. Desseigne, G., Compt.rend. 200, 466-468 (1935)
11. Meyer, H. and Bernhauer, K., Monatsch. 53 & 54, 721-52 (1929)
12. Malishev, B.W., J.Am.Chem.Soc. 57, 883-884 (1935)
13. Brambilla, M., Ann.chim.applicata 26, 572-580 (1936)
    C.A. 31:7594
14. Fujita, Y., J.Chem.Soc. Japan, 55, 11-14 (1934)
    C.A. 28:2345
15. Linstead, R.P., Michaelis, K.O.A. and Thomas, S.L.S.,
    J. Chem. Soc. 1139-1147 (1940)
16. Komatsu, S., Nakamura, H. and Kurata, M., Mem.Coll.Sci.
    Kyoto Imp. Univ. 6, No.4, 183-186 (1923) C.A. 17:2577
17. Austerweil, G. and Peufaillit, L., Brit. 206,848 (1923)
    C.A. 18:1180
18. Routala, O. and Pohjola, A., Pappers-Trävarutid. Finland
    1934, 289-294. C.A. 28:4227

19. Hirao, N. and Takano, T., J.Chem.Soc.Japan <u>58</u>, 213-221 (1937) C.A.31:3468

20. Sabatier, P., Mailhe, A. and Gaudion,G., Compt.rend.<u>168</u>, 926-930 (1919)

21. Bergström, H.O.V., Cederquist, K.N. and Trobeck, K.G., Swed. 85,993/4 (1936) C.A.30:6012

22. A.C.S.News. Feb.10, 1942

23. Asahina, Y. and Nakanishi, S., J.Pharm.Soc.Japan, <u>48</u>, 1-20, (1928) C.A.22:1767

24. Kimura, S., J.Soc.Chem.Ind. Japan <u>37</u>, Suppl.binding, 4 (1934) C.A.28:1990

25. Rheinische Kampfer-Fabrik G.m.b.H. Ger.483,640 (1928) C.A. 24:630

26. Hirao, N. and Takano, T., J.Chem.Soc.Japan <u>59</u>, 95-101 (1938) C.A.32:4970

27. Treibs, W.,Ber. <u>68B</u>, 1041-1049 (1935)

28. Ikeda, T. and Wakatsuki, K., J.Chem.Soc.Japan <u>57</u>, 555-564 (1936) C.A.30:7538

29. Bogert, M.T. and Fourman, V.G., Am.Perfumer <u>28</u>, 345-347 (1933) C.A. 28:101

30. Kazanskii, B.A., Plate, A.F. and Goldman,E.E., Compt.rend. acad.sci. U.R.R.S. <u>23</u>, 250-251 (1939) C.A. 33:8180

31. Mann, C.A., Montonna, R.E., and Larian, M.G., Ind.Eng.Chem. <u>28</u>, 598-601 (1936)

32. Private communication from Brown Co., Berlin, N.H.

33. Boedtker, E., J. Pharm.Chim. (8) <u>9</u>, 417-434 (1929)

34. Murto, J.O., Teknillinen Aikahanslehti <u>22</u>, 539-544 (1932) C.A. 27:411

35. Schorger, A.W., J.Am.Chem.Soc. <u>39</u>, 2671 (1917)

36. Wheeler, A.S. and Smithy, I.W. ibid 43, 2611-8 (1921)
37. Karvonen, A., Ber. 56, 1824-1828 (1923)
38. Austerweil, G. and Lemay, L., Bull.soc.chim. 41, 454-457 (1927)
39. Wheeler, A.S., J.Am.Chem.Soc. 42, 1842-1846 (1920)
40. Andrews, C.E., J. Ind. Eng. Chem. 10, 453-456 (1918)
41. Andrews, C.E., U.S. 1,314,920 (1919) C.A. 13:2765
42. Kobe, K.A. and Doumani, T.F., Ind.Eng.Chem.31, 262 (1939)
43. Fittica, F., Ann. 172, 303-330 (1874)
44. Auwers, K.v., and Kòlligs, H., Ber. 55B, 3872-9 (1922)
45. Richter, F. and Wolff, W., Ber. 63B, 1721-1725 (1930)
46. Le Fèvre, C.G., LeFèvre, R.J.W., and Robertson, K.W., J. Chem.Soc. 1935, 480-8.
47. Barlow, J., Ann. 98, 245-253 (1856)
48. Landolph, Fr., Ber. 6, 936-938 (1873)
49. Fittica, F., Ber. 6, 938-943 (1873)
50. Widman, O. and Bladin, J.A., Ber. 19, 583-589 (1886)
51. Aschan, O., Teräsvuori and Per Ekwall Finska Kem. Medd. 1918, 5 pp. C.A.13:2868
52. Widman, O., and Söderbaum, H.G., Ber. 21, 2126-2129 (1888)
53. Phillips, M., J.Am.Chem.Soc. 44, 1775 (1922)
54. Demonbreun, W.A. and Kremers, R.E., J.Am.Pharm.Assoc. 12, 296-300 (1923)
55. Kobe, K.A. and Doumani, T.F., Ind.Eng.Chem.31, 261,(1939)
56. Wheeler, A.S. and Smithy, I.W., loc.cit.
57. Kraut, C., Ann. 92, 66-71 (1854)
58. Mazzara, G., Gazz.Chem.Italiana 19, 160-8 (1889); ibid, 20, 140-149 (1890)

59. Alfthan, J., Ber. 53, 78-98 (1920)

60. Fittig, R., Köbrich, A. and Jilke, T., Ann. 145, 129-157 (1868)

61. Sirks, M.H.A., Rec.trav.chim. 27, 207-250 (1908)

62. Beilstein, F. and Kuhlberg, A., Ann. 155, 1-29 (1870)

63. Hintikka, S.V., Teknillinen Aikakanslehti 7, 27 (1917)

64. Halse, O.M. and Dedichen, H., Tidsskrift for Kemi 15, 301 (1918)

65. Lubs, H.A. and Young, R.C., J.Ind.Eng.Chem. 11, 1130-1133 (1919)

66. Wheeler, A.S. and Harris, C.R., J.Am.Chem.Soc. 49, 494-499 (1927)

67. Kyker, G.C. and Bost, R.W., J.Am.Chem.Soc. 61, 2469-70 (1939)

68. Ehrnrooth, E., Finska Kemistsamfundets Medd. 40, 142-143 (1931) C.A.26:2716

69. Phillips, M., J.Am.Chem.Soc. 46, 686-694 (1924)

70. Thomas, R.J., Anzilotti, W.F. and Hennion, G.F., Ind.Eng. Chem. 32, 408-410 (1940)

71. Groggins: Unit Processes in Organic Syntheses. p.5

72. Doumani, T.F., and Kobe, K.A., J.Org.Chem.7, 1-5 (1942)