OXIDATIONS WITH MANGANESE DIOXIDE

BY

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ABSTRACT

It has been found that a number of organic functional groups can be selectively oxidized with manganese dioxide, and the yields prove the method to be of preparative value.

A number of heterocyclic alcohols were oxidized to the corresponding aldehydes, namely, 2-, 3- and 4-pyridinemethanol, the corresponding N-oxides, 6-methyl-2-pyridinemethanol, 2,6-pyridinedimethanol and imidazole-4(5)-methanol.

Three thiols (thiophenol, allyl mercaptan, and benzyl mercaptan) were oxidized to the corresponding disulfides.

Two aliphatic acyloins (propionoin and butyroin) were oxidized to 1,2-diketones.

Finally β-phenylhydroxylamine was oxidized to nitrosobenzene.

The results of these oxidations appear to fit in the hypothesis that free radical intermediates are involved in manganese dioxide oxidations.

TABLE OF CONTENTS

	Page
I.- INTRODUCTION	1
1. Manganese dioxide as an oxidizing agent	1
2. Mode of action of manganese dioxide	14
3. Reported oxidation reactions leading to the products of this study	17
II.- DEFINITION OF THE PROBLEM	24
III.- SUMMARY OF RESULTS	25
IV.- DISCUSSION OF RESULTS	27
V.- EXPERIMENTAL	31
A. Preparation of manganese dioxide	31
B. Oxidation reactions	32
BIBLIOGRAPHY	51

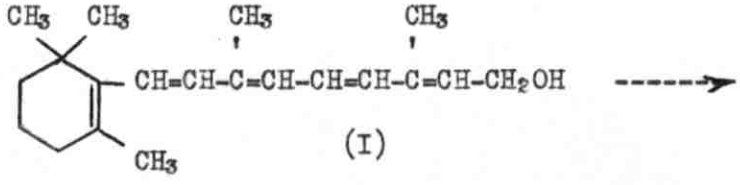
I. INTRODUCTION

1. Manganese Dioxide as an Oxidizing Agent

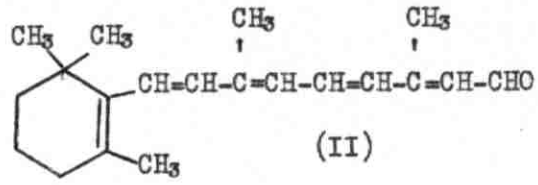
The use of manganese dioxide as an oxidizing agent has been established since the beginning of the last century. In organic chemistry it was originally used for the oxidation of methyl substituted aromatic compounds to the corresponding aldehydes in a mineral acid or in aqueous medium.

More recently the reagent has been used as an oxidizing agent in neutral non-aqueous media, where it has been found to be often effective at room temperature or at the boiling point of the solvent. The reagent has been established as a mild oxidizing agent with selective action on certain groups in the molecule.

The oxidation of unsaturated alcohols by manganese dioxide was first reported in 1948 by Morton and coworkers.[1] It was found that when vitamin A (I) in light petroleum ether was stirred at room temperature with manganese dioxide (prepared by oxidation of manganous sulfate with potassium permanganate in aqueous solution), it was smoothly converted to retinene (II) in an 80% yield.



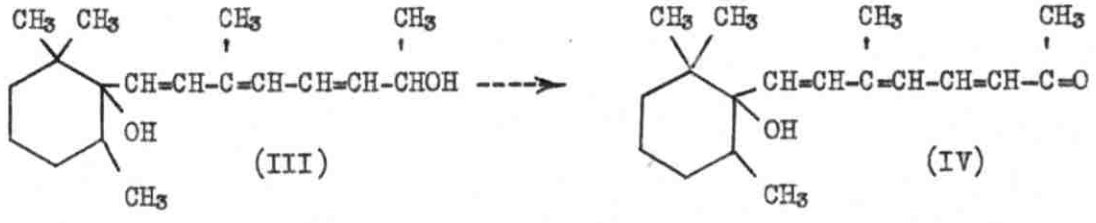
(I)



(II)

Under similar conditions, isopropyl alcohol, benzyl alcohol, octadecyl alcohol, cetyl alcohol and a mixture of C_{20} alcohols were unaffected. It was also found that the finer the state of subdivision of the oxide, the smaller its amount needed for the maximum yield. Various other solid oxidizing agents were tried as substitutes, but they failed to produce retinene. Thus chromium sesquioxide, chromic oxide, barium oxide, lead peroxide, lead tetroxide and silver oxide, all proved useless.

This type of reaction proved to be of particular value in the study of polyenes and polyenynes. Thus manganese dioxide was used in five oxidations during the synthesis of vitamin A from cyclohexene by Attenburrow and coworkers.[2] In these oxidations an activated alcohol group, whether primary or secondary, was oxidized to the carbonyl compound e.g. (III) was oxidized to (IV).



The dioxide was prepared by adding a solution of manganous sulfate tetrahydrate and a 40% solution of sodium hydroxide simultaneously during one hour, to a hot solution of potassium permanganate. The dioxide

precipitated as a fine solid, and stirring was continued for one hour more. The solid was collected by the centrifuge and washed with water until the washings were colorless. It was then dried at 100 - 120°C and ground to a fine powder before use.

During the following years, various forms of manganese dioxide were used for the oxidation of ethylenic and acetylenic α,β-unsaturated primary and secondary alcohols to the corresponding carbonyl compounds.

The mild nature of the reagent was established when Robeson and coworkers used a commercial type of the dioxide and dehydrogenated four geometrical isomers of vitamin A to the corresponding retinenes without any isomerisation.[3] It was also exemplified by the successful preparation of a number of β-aminoaldehydes from β-aminoalcohols of general formula $RCH(NH_2)CH_2CH_2OH$, where R = H, Me, Iso-Pr, Ph or p-$MeOC_6H_4$-, although here the yields were low.[4]

The manganese dioxide dehydrogenation of the simplest ethylenic alcohol, allyl alcohol, to acraldehyde, indicates that a single ethylenic bond provides sufficient activation to bring about the reaction.[2]

Although Morton and his coworkers failed to oxidize benzyl alcohol to benzaldehyde[1], more active forms of the dioxide achieved this in high yields. Thus a form of the dioxide prepared by heating manganous oxalate or carbonate at 220 - 280°C in the air, washing with dilute nitric acid, and then by water, and finally drying, was found to oxidize allyl and benzyl alcohol easily.[5] This oxide was called "form B", in contrast to "form A" which was prepared similarly, but not treated with

nitric acid. The reaction with "form B" was so fast that it could be effected by passing the alcohol through a column of the oxide.

It was found that the ease of oxidation of alcohols decreases in the order: multiply conjugated alcohols $\rangle$ benzyl and furyl alcohols $\rangle$ vinyl and ethinyl carbinols. This was attributed to the differences in the adsorptive ability; the more saturated the alcohol, the less readily adsorbed on the oxidant.

That this was not the only factor was shown by the addition of 1% water, or 5% tert-butyl alcohol, known to change the adsorptive characteristics of o-hydroxybenzyl alcohol to a marked extent, which affected the yield only slightly, if at all.

In another work, a yield of benzaldehyde as high as 89% was obtained by shaking a chloroform solution of the alcohol with manganese dioxide for 23 hours.[6] Veratryl alcohol was also oxidized in three hours in 58% yield, and 2-hydroxy tetrahydropyran was oxidized to the corresponding lactone.[6]

Various other examples in the literature indicate the activating effect of aromatic rings in the oxidations of alcohols by manganese dioxide. Thus by the use of the Attenburrow oxide, Turner reported the oxidation of benzhydrol (33%), xanthhydrol (100%) and furoin (88%).[7] He also reported the oxidation of 1,3-diphenyl propanol (V) and 1-hydroxy-1,2,3,4-tetrahydrophenanthrene (VII) to the corresponding ketones (VI) and (VIII).

(V) (VI)

(VII) (VIII)

In 1953, the use of manganese dioxide was extended to the steroid field.[8] The manganese dioxide used in this work was prepared by the addition of concentrated aqueous potassium permanganate to a stirred aqueous solution of manganous sulfate kept at 90°C until a slight excess was present (pink coloration of supernatent liquid). The mixture was then stirred at 90°C for 15 minutes, and the oxide was collected, washed with hot water, then with methanol and ether, and dried at 120 - 130°C to a constant weight. It was reported that only the allylic hydroxyl group was oxidized as shown by the conversion of androst-4-ene-3β:11β:17β-triol (IX) to 11β-hydroxytestosterone (X).

(IX) (X)

The oxidation was carried out in chloroform at room temperature.

In the same year appeared other reports of even more efficient conversions of similar systems. Thus compounds containing the systems Δ^{5}-7α-ol (XI) and $\Delta^{17(20)}$-21-ol (XIII) were converted to compounds with the systems Δ^{5}-7-one (XII) and $\Delta^{17(20)}$-21-al (XIV).[9]

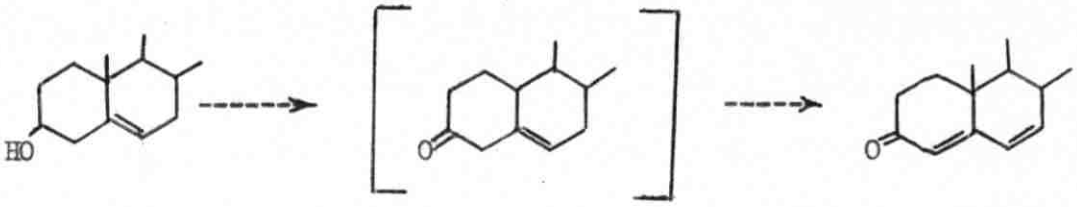
(XI) (XII)

(XIII) (XIV)

These oxidations were carried out in chloroform at room temperature, and yields higher than 90% were obtained.

In a second paper, the same authors found that, over a longer period of time, manganese dioxide was capable of dehydrogenating a Δ^{4}-3-one to a $\Delta^{4,6}$-dien-3-one, although the products were difficult to isolate.[10]

The expected product was however obtained when a Δ^{5}-3β-ol (XV) was refluxed with manganese dioxide in benzene for eight hours, where a rearrangement probably occurred to give (XVI).

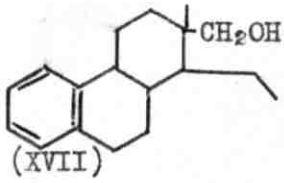


(XV) (XVI)

Cholesterol also gave $\Delta^{4,6}$-cholestadiene-3-one in 27% yield. The earlier reports indicated that manganese dioxide has no effect on saturated alcohols, both primary and secondary, but Harfenist and coworkers showed that this is not strictly true, although the rate of oxidation is low compared to α, β -unsaturated alcohols.[5]

It was however recently reported that given sufficient reagent and purified solvents, both primary and secondary saturated alcohols are oxidized in high yields.[11] Using 2 g of Attenburrow oxide, or a commercial oxide supplied by Bacon Inc. to oxidize 100 mg of 5α-androstan-17β-ol in hexane or acetonitrile for 20 hours, Harrison obtained the corresponding carbonyl compound in 99% yield. The rate of the reaction was found to depend on the solvent; thus it took four days to complete the reaction in dimethyl formamide, and seven days in dimethyl sulfoxide.

Similarly 4-methylcyclohexanol was oxidized in 71% yield, and n-butyl alcohol in 70% yield by passing a benzene solution through a column of the reagent, whereas the primary alcohol (XVII) was oxidized to the corresponding aldehyde in 76% yield after six hours in acetonitrile.



(XVII)

The author attributed the failure to observe such oxidations in the past to the smaller proportion of manganese dioxide used, to the use of solvents normally containing saturated alcohols as impurities like chloroform or acetone, or to the presence of the more reactive allylic alcohol which consumed most of the reagent.

Although the oxidizing properties of manganese dioxide were first investigated in connection with alcoholic hydroxyl groups, it proved to be less specific in this respect, and oxidations of other classes of compounds have been observed, some of them in the course of the present work.

This reagent was used for the dehydrogenation of the side chain in N-alkyl and NN-dialkylanilines where three main types of conversion were observed.[12]

a) Amide formation, as in the oxidation of monomethyl aniline to formanilide in over 80% yield.

$$PhNHCH_3 \longrightarrow PhNHCHO$$

b) Dealkylation with formation of an aliphatic aldehydes, as in the initial stage of the oxidation of diethylaniline where acetaldehyde was isolated (54%) by passing nitrogen through the reaction mixture.

$$PhNEt_2 \longrightarrow PhNHEt + MeCHO$$

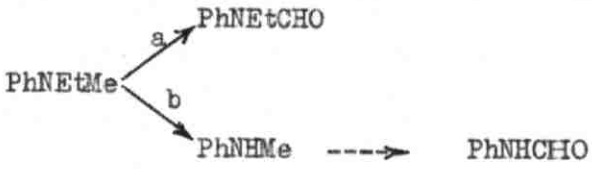
c) Dehydrogenation followed by oxidative cleavage of the resultant enamine, as in the conversion of monoethylaniline to formanilide.

$$PhNHEt \longrightarrow PhNHCH{:}CH_2 \longrightarrow PhNHCHO$$

Conversions(a) and (b) were found to be the major routes for the

oxidation of dimethylaniline and diethylaniline respectively.

It was found that ethylmethylaniline reacted according to both routes.



A large excess of the reagent was used in the oxidation of tertiary amines coupled with long periods of time.

Primary and secondary benzyl amines were oxidized to the Schiff bases but only in very low yields, and the reaction was very slow.[6] Infrared spectra of the reaction mixture after separation of the oxide showed the development of a strong C, N double bond absorption.

A further type of reaction is indicated by the oxidation of diallyl sulfide to the sulfoxide.[13]

At temperatures between 70°C and 120°C, the range of reactions brought about by manganese dioxide increases, but its selectivity decreases and so do the yields of polyene carbonyl compounds. Thus in refluxing benzene an oxo-steroid like Δ^4-22 α-spirosten-3-one containing the system (XVIII) could be dehydrogenated to $\Delta^{4,6}$-22α-spirostadiene-3-one containing the system (XIX).[10]

(XVIII) (XIX)

Oxidations where a C, C bond is broken were also reported. Thus 9,10-dihydroxystearic acid was cleaved in boiling chloroform to

azelaic acid aldehyde and pelargonaldehyde.[14] Under similar conditions mandelic and benzilic acids gave benzaldehyde and benzophenone respectively.

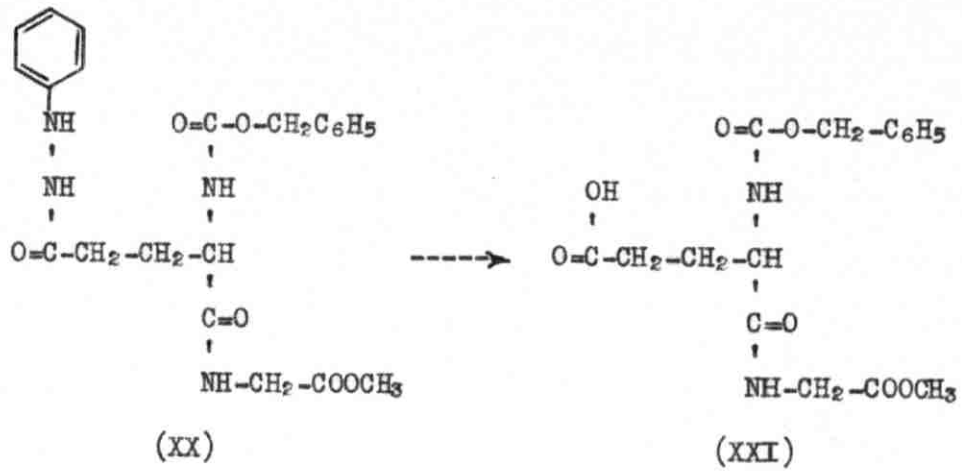
An extensive study[15] at the refluxing temperature of the solvent, and mostly in aqueous media, showed that several saturated primary and secondary alcohols were oxidized to carbonyl compounds. Thus ethyl, n-propyl and n-butyl alcohols were oxidized in aqueous medium to give the corresponding aldehydes in 50% yields. Ethylene glycol, glycerol and mannitol gave only carbon dioxide. Polybasic acids like oxalic, malonic, succinic, maleic and fumaric acids gave carbon dioxide accompanied by ethylene in the second and third and with acetylene in the last two of them. α-Hydroxyacids and α-aminoacids readily formed aldehydes or ketones with one carbon atom less. Aromatic aldehydes gave the corresponding carboxylic acids. Aromatic primary amines gave azo compounds; benzoin and substituted benzoins gave the diketones. Triphenylphosphine was also oxidized to the oxide.

In a recent investigation, manganese dioxide oxidized 2-hydroxymethylindole to 2-indolealdehyde in 65% yield.[16] The oxidation was carried out with "form B" of manganese dioxide prepared by Harfenist and coworkers.[5] A mixture of the alcohol and the oxidant in the weight ratio of 1:6 and ether was stirred for 24 hours.

The Attenburrow oxide was used for the oxidation of a large number of substituted anilines to symmetrical azo compounds.[17] The following compounds were oxidized readily and in yields exceeding 96%: aniline, p-fluoro, p-chloro, p-bromo, p-iodoaniline, p-anisidine, p-biphenylamine, m-chloro, o-fluoro, o-iodo, o-ethylaniline and o-anisidine.

The oxidations, as judged by the rate of separation of water[23], showed only small differences. However the p-substituted anilines generally reacted more rapidly and the order F > Cl > Br > I was observed. The three isomeric nitranilines had previously been recovered unchanged after refluxing in benzene for 24 hours.[15] A small yield (5%) was obtained from o- and p-nitranilines when refluxed in toluene for 24 hours.[17] The authors explained the failure of the nitranilines to react as due to the adsorption of the molecule on the solid surface through the nitro group, thus preventing the oxidation of the amino group. This was supported by the fact that 3,5-dichloro-4-nitraniline, in which adsorption through the nitro group is sterically prevented, could be oxidized in a low yield (10%) while 3,5-dichloro-2-nitraniline, which has the same electronic effects, but in which the nitro group is not hindered, was not oxidized. p-aminobenzoic acid and anthranilic acid were not affected and polycyclic aromatic amines like α- and β-naphthylamines and 1-aminoanthracene gave tarry products.

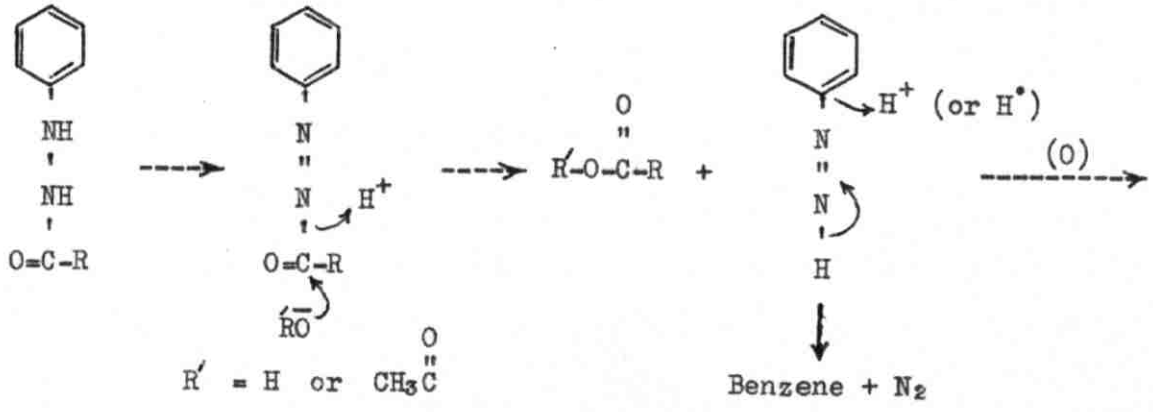
Kelly used Attenburrow oxide for the oxidation of several phenylhydrazides to carboxylic acids.[18] An example is the oxidation of N-carbobenzoxy-α-L-glutamylglycine methyl ester γ-phenylhydrazide (XX) to N-carbobenzoxy-α-L-glutamylglycine methyl ester (XXI) in 92% yield.



(XX) (XXI)

The oxidations were carried out in 60% acetic acid, and were complete within 30 minutes. The reaction was assumed to involve preliminary oxidation to an azo compound, followed by heterolytic elimination of nitrogen with addition of water or acetic acid to give a carboxylic acid, benzene and nitrogen. If the acetate ion was involved, a mixed anhydride would result, and would give the carboxylic acid on hydrolysis.

In a more recent paper Kelly and coworkers suggested the formation of a benzenediazonium ion by solvolysis of the azo compound and oxidation of the product.[19] The benzenediazonium ion was supposed to be the precursor of phenol and phenyl acetate which were isolated as products.



-----➤ Phenol + phenyl acetate + N_2.

A large number of N-benzylanilines were oxidized to benzalanilines in good yields by heating a suspension of manganese dioxide in benzene with the corresponding benzylaniline in an apparatus equipped with a Dean and Stark water trap.[20] The reaction was represented by the following equation:

$$p\text{-}RC_6H_4CH_2NHC_6H_4R'\text{-}p + MnO_2 \longrightarrow p\text{-}RC_6H_4CH{=}NC_6H_4R'\text{-}p + MnO + H_2O$$

where R, R' = H or any of various substituents.

The relative rates of reaction were determined by measuring the time necessary for 50% of the theoretical amount of water to collect in the trap. The results of the effect of structural changes on the rate were considered as confirmation of an earlier view that the reaction proceeds via radical intermediates.[23] A similar mechanism was proposed for the oxidation of benzylanilines.

Some hydrazobenzenes were also oxidized to the azo benzenes in good yields. Good yields of azobenzenes were obtained from a variety of anilines by a modified method which involved the distillation of water from a mixture of manganese dioxide and benzene before the amine was added.[20] Quinoline was also prepared from 1,2,3,4-tetrahydroquinoline, and indole and acridine were readily formed from 2,3-dihydroindole and 2,3-dihydroacridine.[20]

Manganese dioxide was recently found to oxidize active methyl groups in compounds like quinaldine, α- and γ-picolines, and 1-methylisoquinoline to give the corresponding acids in about 20% yield.[21]

β-Picoline did not react, and 3-methylquinoline and -isoquinoline were but little affected (below 5%). None of the picoline oxides could be oxidized.

2. Mode of Action of Manganese Dioxide

Morton and coworkers believed that the oxidation of vitamin A to retinene by manganese dioxide was due to surface catalysis.[1] They presumed that the process is triphasic comprising the following three stages:

a) Removal of the alcohol from the solution by adsorption on the surface of the reagent.

b) Conversion of the $-CH_2OH$ group to the $-CHO$ group.

c) Desorption of the product to the liquid phase.

To determine why the oxidation stops when unoxidized alcohol is still present, despite a large excess of the oxidizing agent, Harfenist and coworkers prepared artificial mixtures corresponding in all but one product to the results of completed oxidations of benzyl alcohol.[5] Additional benzyl alcohol was added to each in turn and the oxidation was allowed to continue. It was found that the extent of oxidation of the second portion of benzyl alcohol was low, and essentially the same in the cases in which the aldehyde was present at the start, whether with or without water. The addition of water and no aldehyde at the start gave a much less lowering of the yield (within the limits of reproducibility in successive runs.)

It therefore seemed that oxidation stops when the amount of the carbonyl compound reaches a critical value. It was presumed that

this represents a concentration at which the carbonyl compound can successfully displace the alcohol from some active sites of the solid surface.

A comparative study of different kinds of manganese dioxide was carried out by Gritter and Wallace who used allyl and benzyl alcohols as substrates.[22] They observed that the oxides prepared from potassium permanganate generally give rapid oxidations and high yields. They suggested that this is due to some occluded permanganate, but an attempt to detect the presence of permanganate by X-rays was unsuccessful. However, when a procedure was used to remove any occluded permanganate, the oxidation rate in the initial stages decreased appreciably. On the other hand, when a trace of permanganate was added to the oxide (less than 100 mg to 5 g) the initial oxidation rate showed only a slight increase. This study also showed that the method of washing and drying has a serious effect on the oxidizing power of the oxide. When washed with organic solvents the yield was lowered, possibly because any adsorbed permanganate or other species which causes rapid oxidation was removed by the organic solvent to a larger extent than by water.

By carrying the oxidation under nitrogen, it was shown that air oxidation in the reaction is negligible. It was finally found that a weight ratio (alcohol:oxide) of 1:5 or 1:10 is necessary to get effective oxidation. The initial rate in the second case was higher.

They concluded that the most powerful oxides were the Attenborrow[2] and the Ball, Goldwin and Morton oxide.[1]

A study of the effect of the structure of the alcohol on the rate of oxidation by manganese dioxide was carried out by Pratt and De Castle.[23] Oxidations were conducted in hot benzene, and the time necessary for 50% of the theoretical amount of water to collect in a Dean and Stark trap was taken as a measure of the relative rate.

A wide variety of phenylcarbinols were oxidized rapidly and in high yields. Some aliphatic secondary alcohols were also oxidized but slowly and in low yields. It was found that a change in the electron attracting ability of a para-substituent (CH_3O, $(CH_3)_2CH$, H, Cl, NO_2) has only a small effect on the rate, less than would be expected if carbonium ions are important intermediates. Anyway , except for CH_3O-, there was a small gradual increase in the rate with increasing electron attracting ability of the group, whereas a sharp decrease should be observed if carbonium ions were intermediates.

It was also found that addition of acid slightly decreases the rate of oxidation of benzyl alcohol although it would be expected to facilitate the formation of carbonium ions.

These authors considered the relatively minor effect of changing the para substituents to be consistent with the formation of free radicals as intermediates, e.g., $C_6H_5\dot{C}OH$, since free radicals can be stabilized by either electron release or electron withdrawal.

The addition of diphenylamine decreased the rate of oxidation of benzyl alcohol, as would be expected for a free radical reaction. Evidence for the formation of free radicals was also obtained from the fact that in the oxidation of alcohols of the general formula

C_6H_5CHOHR, the rate was three times larger when R = $-\overset{O}{\overset{\|}{C}}-C_6H_5$ than when R = $-CH_2C_6H_5$. This was interpreted as due to the ability of the carbonyl group to stabilize the radical $C_6H_5\dot{C}(OH)-R$.

The rapid oxidation of fluorenol compared with benzhydrol was also considered to be consistent with a free radical mechanism.

The oxidation of primary aliphatic alcohols was extremely slow, and the amount of the carbonyl compound was very low. The oxidation of secondary alcohols, both straight chain and alicyclic, was slow and gave poor yields. On the basis of free radical intermediates, primary alcohols would be expected to react slower than secondary alcohols, and these to react slower than phenylcarbinols, as was observed.

The authors suggested a simplified mechanism for the oxidation:

$$R_2CHOH + O=Mn^{+4}=O \longrightarrow R_2\dot{C}-OH + HO-Mn^{+3}=O \longrightarrow$$

$$R_2\dot{C}-\dot{O} + HO-Mn^{+2}-OH \longrightarrow R_2C=O + H_2O + Mn^{+2}=O$$

The nature of the manganese dioxide used in these oxidations, and in all the other cases cited before is difficult to define, but Pratt and De Castle noticed that its oxygen content was decreased by the amount demanded by the above equation. The nearly quantitative yield of water also supports this view.

3. Reported Oxidation Reactions Leading to the Products of this Study

A. Oxidation of pyridinemethanols and methylpyridines to pyridinecarboxaldehydes

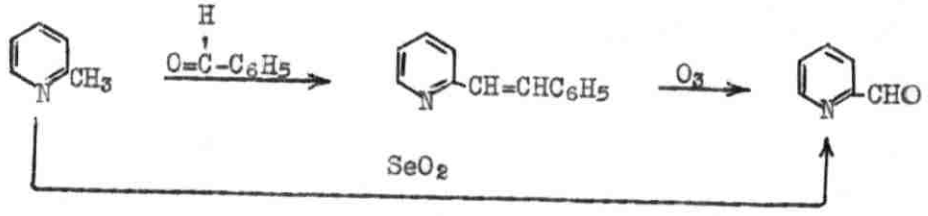
The aldehydes of the pyridine series are sensitive, rather

unstable compounds, and cannot be satisfactorily prepared by the usual methods. These compounds are important in the development of some bacteriostatic agents.

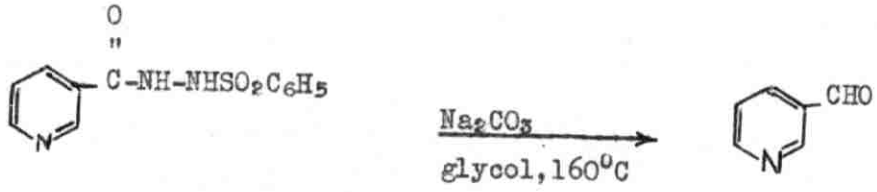
The older methods described in the literature for the preparation of pyridine aldehydes usually give poor yields not exceeding 30%.[24] Starting with picolines, pyridine aldehydes are made in two ways:

a) Condensation with benzaldehyde, and ozonolysis of the resulting stilbazoles.

b) Direct oxidation with selenium oxide, in poor yields.



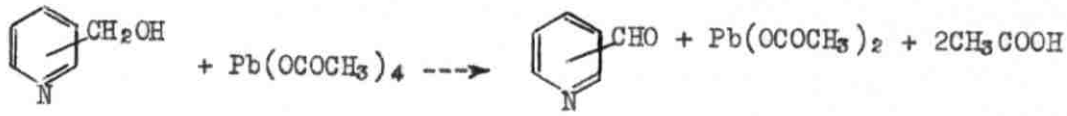
Panizzon[25] and Niewman[26] used the method of McFadyen and Stevens[27] to convert nicotinic acid into 3-pyridinecarboxaldehyde in 23-36% yield.



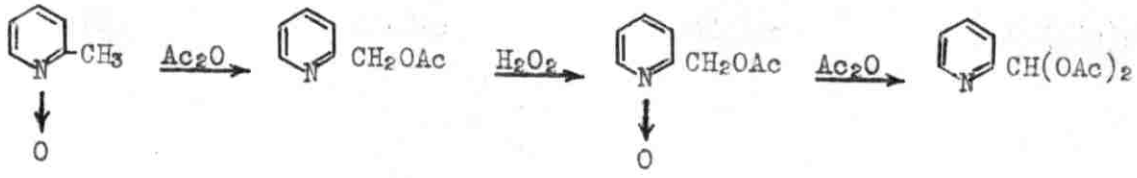
It is worth mentioning that none of the pyridine aldehydes could be obtained by the Rosenmund reduction of the corresponding acid chlorides with palladium as catalyst.[24]

The first successful preparation of these aldehydes in good yields was through the oxidation of the corresponding pyridine -

methanols with lead tetraacetate. 2-, 3-, and 4-Pyridinemethanols were obtained from the corresponding acids by reduction of the ethyl esters with lithium aluminum hydride, and they were oxidized with lead tetraacetate to the corresponding aldehydes in 65, 77 and 68% yield respectively.[28]



2-Pyridinecarboxaldehyde was also obtained as the diacetate in 46% yield by the rearrangement of 2-pyridinemethanol acetate 1-oxide by the action of acetic anhydride.[29] The starting material was obtained by the action of hydrogen peroxide on 2-pyridinemethanol acetate obtained by a similar rearrangement from 2-methylpyridine-1-oxide.



However, when 4-pyridinemethanol acetate was carried through the same sequence of reactions, the corresponding aldehyde was obtained in a very poor yield. Since 3-methylpyridine-1-oxide does not rearrange in the same manner, it was not possible to prepare 3-pyridinecarboxaldehyde by this method.

Some aldehydes of the pyridine series were also prepared by the oxidation of methyl substituted pyridines with selenium oxide.[30] 2-Pyridinecarboxaldehyde-1-oxide was obtained as the hydrate in 59% yield from 2-methylpyridine-1-oxide, when the oxidation was carried

out in pyridine, and in only 19%, when in dioxane. 4-Methylpyridine-1-oxide gave the corresponding carboxylic acid, while 3-methylpyridine-1-oxide could not be oxidized, and could even be used as solvent. 2,6-Pyridinedicarboxaldehyde-1-oxide was similarly obtained from the corresponding dimethyl derivative in 58% yield.

2-, 3-, and 4-Pyridinemethanols were also oxidized with selenium oxide to the corresponding aldehydes which were isolated as the pyridylhydroxymethanesulfonic acids in maximum yields of 100, 60, and 100% respectively.[31]

Further, several derivatives of 2-pyridinecarboxaldehyde were prepared, in unspecified yields, from the corresponding carbinols by oxidation with selenium oxide, such as the 4-nitro, 4-methoxy, 6-methyl-4-methoxy and 6-methyl-4-nitro-2-pyridinecarboxaldehydes.[32]

Another series of 2-, and 4-pyrdinecarboxaldehydes, and some methyl derivatives and 1-oxides were similarly prepared, but again no yields were reported.[33]

A single example of oxidation of a pyridinemethanol with manganese dioxide found in the literature, is the oxidation of 6-methyl-2-pyridinemethanol to the corresponding aldehyde in about 53% yield.[34]

The catalytic (V_2O_5/MoO_3), vapour phase (380 - 400°C) oxidation of 2,6-dimethylpyridine yielded a mixture of 6-methyl-2-pyridine-carboxaldehyde and 2,6-pyridinedicarboxaldehyde, in unspecified yields. However, a yield of 60% of 2,6-pyridinedicarboxaldehyde was obtained by oxidizing, in a similar way, a 5% solution of 6-methyl-2-pyridinecarboxaldehyde.[35]

B. Oxidation of 4(5)-Imidazolemethanol to 4(5)-Imidazole-carboxaldehyde.

4(5)-Imidazolecarboxaldehyde was obtained, in about 50% yield, by the oxidation of the carbinol by concentrated nitric acid.[36,37,38]

It was also obtained in 55% yield by the oxidation of the carbinol with concentrated hydrochloric acid.[39]

This aldehyde was further prepared in 50% yield from 4(5)-Imidazolemethanol hydrochloride by heating with an aqueous solution of potassium pyrosulfate or persulfate.[40,41]

C. Oxidation of Thiols to Disulfides.

Various oxidizing agents have been used for the conversion of thiols to disulfides e.g., nitric acid, hydrogen peroxide, oxygen, ferric chloride, lead peroxide, sodium hypochlorite, cupric salts like the chloride and the sulfate, and iodine.[42]

It was more recently found that thiols can also be oxidized to disulfides with lead tetraacetate. Benzenethiol and α-toluenethiol were converted to the disulfides in 88 and 80% yield respectively.[43] Alkyl disulfides prepared in this way were n-pentyl (83%), iso-propyl (71%) and tert-butyl (34%).

Thiols were also found to be oxidized to disulfides by dimethyl sulfoxide.[44] In these oxidations dimethyl sulfoxide played the role of both oxidizing agent and solvent. An almost quantitative yield of diphenyl disulfide, and an 88% yield of dibenzyl disulfide were obtained in this way. Several other thiols were oxidized, and high yields of disulfides were reported.

Further, some aromatic thiols were oxidized with nitroso-benzene in a mixture of dimethyl sulfoxide and tertiary butyl alcohol to give the aromatic disulfide in yields ranging between 50 - 70%.[45]

D. Oxidation of Acyloins to 1,2-Diketones.

Many methods for the oxidation of acyloins to 1,2-diketones have been described, such as the use of copper sulfate in pyridine,[46] and the use of a large excess of ammonium nitrate in acetic acid.[47]

Further, chromium trioxide was used, and very satisfactory results were obtained by the use of cupric acetate in dilute acetic acid.[48] This method was found to oxidize benzoin and other acyloins in 90% or better yields.

Nitrobenzene in excess was also used to oxidize acyloins, like furoin and anisoin to furil (80%) and anisil (90%), while benzoin was oxidized to benzil in a lower yield (34 - 40%).[49]

Propionoin was oxidized to bipropionyl in 70% yield by the use of cupric acetate in acetic acid, and in 62% yield when ferric chloride was used as the oxidizing agent.[50]

Acyloins were also readily oxidized to 1,2-diketones with bismuth oxide in acetic acid.[51] Butyroin was oxidized by this method in a 64% yield. With other acyloins like furoin and p-methoxy-benzoin the yields were 90% or more.

Finally, aromatic acyloins were oxidized in good yields by the action of thalium ethoxide in benzene.[52] Thus benzoin gave an 86% yield, and furoin gave an 82% yield. Aliphatic acyloins like $CH_3CH(OH)COCH_3$ and butyroin were not oxidized but gave a thalium

derivative instead.

In another paper the same authors reported that in the presence of thalium ethoxide aromatic acyloins were oxidized by aromatic nitro-compounds, the latter changing to azoxy compounds.[53] High yields were reported for most of the aromatic acyloins oxidized.

Manganese dioxide was used for the oxidation of benzoins.[15] A yield of 80% of benzil was obtained in the case of benzoin itself.

E. Oxidation of Phenylhydroxylamine to Nitrosobenzene.

Nitrosobenzene has been obtained by the oxidation of β-phenyl-hydroxylamine prepared by the reduction of nitrobenzene. When the oxidations were carried out with acidic potassium dichromate yields of 55 - 60% on nitrobenzene were obtained.[54,55]

Further, several nitroso compounds, including nitrosobenzene, were prepared from the nitro compounds by reduction to the corresponding phenylhydroxylamines and oxidation with ferric chloride. The yields varied from 30 - 60% on nitrobenzene.[56]

II. DEFINITION OF THE PROBLEM

An investigation of the use of manganese dioxide as a convenient and selective oxidizing agent of certain types of organic functional groups.

III. SUMMARY OF RESULTS

Reaction No.	Compound oxidized	solvent	Time of reaction	Temp. °C.	Product	% yield
1	2-Pyridinemethanol	chloroform	5 hr	60-61	2-pyridinecarboxaldehyde	68
1	"	benzene	"	78-80	"	53.5
2	3-Pyridinemethanol	chloroform	"	60-61	3-pyridinecarboxaldehyde	67.3
2	"	benzene	"	78-80	"	78
3	4-Pyridinemethanol	chloroform	6 hr	60-61	4-pyridinecarboxaldehyde	73.4
3	"	benzene	"	78-80	"	67.9
4	6-Methyl-2-pyridinemethanol	chloroform	5 hr	60-61	6-Methyl-2-pyridinecarboxaldehyde	67.4
5	2-Pyridinemethanol-1-oxide	"	6 hr	60-61	2-pyridinecarboxaldehyde-1-oxide	62
6	3-Pyridinemethanol-1-oxide	"	5 hr	"	3-pyridinecarboxaldehyde-1-oxide	51

III. SUMMARY OF RESULTS (CONT'D.)

Reaction No.	Compound oxidized	solvent	Time of reaction	Temp. °C.	Product	% yield
7	4-Pyridinemethanol-1-oxide	chloroform	5 hr	60-61	4-pyridinecarboxaldehyde-1-oxide	68.8
8	2,6-pyridinedimethanol	"	"	"	2,6-pyridinedicarboxaldehyde	54.2
9	4(5)-Imidazolemethanol	dioxane	"	100	4(5)-Imidazolecarboxaldehyde	58.8
10	Thiophenol	chloroform	"	60-61	Phenyl disulfide	92.4
11	Allyl mercaptan	"	6 hr	"	Allyl disulfide	65.9
12	Benzyl mercaptan	"	5 hr	"	Benzyl disulfide	82
13	Butyroin	"	"	"	Bibutyryl	58
14	Propionoin	ether	"	35	Bipropionyl	51.9
15	β-Phenylhydroxylamine derived from nitrobenzene	water	3 hr	0	Nitrosobenzene	41.3 (on nitrobenzene)

IV. DISCUSSION OF RESULTS

Manganese dioxide, as prepared and used in the foregoing oxidations, appears to be an effective oxidizing agent for a number of heterocyclic carbinols which are converted to the corresponding aldehydes in yields comparable to and sometimes better than those obtained by other methods of oxidation.

The oxide is a cheap reagent, and the method of oxidation is simple and can therefore be used for the synthesis of these aldehydes.

A definite advantage of manganese dioxide, as compared to other oxidizing agents, is its mild oxidizing activity because of which other sensitive groups of the molecule undergoing oxidation are not affected.

Since some of the pyridine aldehydes are used in bacteriostatic researches, the advantage of the above method becomes clear.

It appears that 3-pyridinecarboxaldehyde-1-oxide is a new substance because no reference to it could be found in the literature. It should be noted that contrary to the 2- and 4-isomers, 3-pyridinecarboxaldehyde-1-oxide could not be obtained by selenium oxide oxidation of the corresponding picoline-N-oxide.

Manganese dioxide was also found to be very effective for the oxidation of mercaptans to the corresponding disulfides. High yields of pure disulfides were obtained.

It was further found to oxidize acyloins to the corresponding diketones, although the yields were not so high as in the oxidation of benzoin or other aromatic acyloins, where the -CHOH group is activated by the presence of aromatic centers.

The fact that a simple secondary alcohol group is not oxidized to a considerable extent was established by the results of the attempted oxidation of secondary butyl alcohol, when it was found, by vapour-phase chromatography, that the ketone was formed in a yield not exceeding 15%.

It was finally observed that manganese dioxide oxidizes β-phenylhydroxylamine to nitrosobenzene in a yield approaching that obtained by the conventional method of oxidation by potassium dichromate and concentrated sulfuric acid.

It was thought that the method used to prepare nitrosobenzene from nitrobenzene might be applied to the preparation of nitrosobenzaldehydes from nitrobenzaldehydes, since the aldehyde group would remain intact during the reaction. The method was only partially successful with m-nitrobenzaldehyde, where a very low yield of the impure nitroso compound was obtained, as indicated by the green color of the distillate. This product was, however, very difficult to purify by recrystallization, because it dissolved very readily in most of the common solvents. With o-nitrobenzaldehyde there was no indication that even a small amount of the nitroso compound was formed. Instead a dark brown tarry material was obtained. This part of the work was therefore discontinued.

In most of the oxidations the ratio of substrate to oxide was

1:5 by weight, and the time of the reaction was five or six hours. Higher ratios of the oxide were used in only a few cases.

It was concluded, from the first few oxidations, that chloroform was a suitable solvent, and most of the oxidations were carried out in chloroform, except for the oxidations of β-phenylhydroxylamine and propionoin.

The results of the present work fit the hypothesis offered by Pratt and De Castle[9], that the manganese dioxide oxidations proceed through free radical intermediates. It should be noted that the manganese dioxide used by these investigators is quite similar to the reagent used in this work.

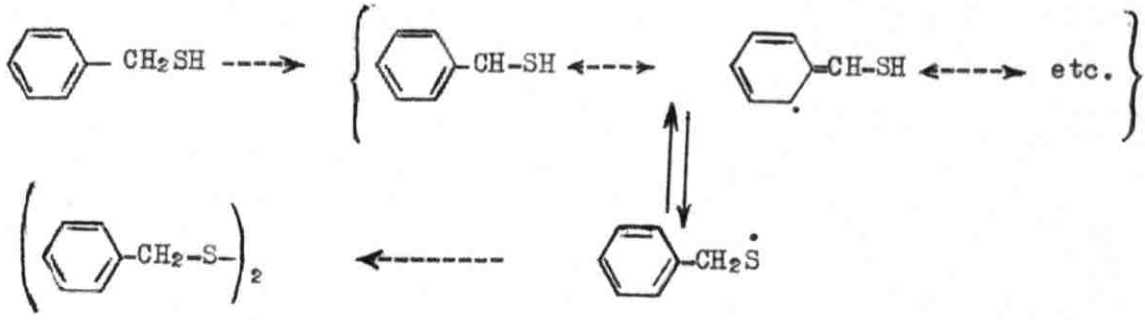
On the basis of this hypothesis, primary aliphatic alcohols would be expected to react very slowly and to show little conversion, if at all, in the comparatively short time of the reaction. This was established by the attempted oxidation of n-heptanol, when it was found, by vapour phase chromatography, that most of the alcohol was unchanged.

Secondary alcohols would be expected to react slowly, and this was observed in the oxidation of secondary butyl alcohol.

All the alcoholic functional groups oxidized were attached directly to an unsaturated center, the heterocyclic ring in the heterocyclic carbinols, or the carbonyl group in propionoin and butyroin. It would be expected that a free radical intermediate would be relatively stable in such cases, and the degree of stabilization would be expected to be reflected in the yield as was roughly observed. For instance, the markedly lower yield of 3-pyridinecarboxaldehyde and

its 1-oxide, as compared with the 2- and 4-isomers, can be accounted for by the smaller resonance stabilization of the corresponding free radical intermediates.

The same arguments can be offered for the oxidation of mercaptans, where a sulfur free radical could conceivably be the intermediate. In the case of allyl and benzyl mercaptans, an equilibrium might be supposed to exist between a sulfur and a carbon free radical. As the sulfur free radical is consumed by dimerization, the equilibrium is shifted to form more of it.



V. EXPERIMENTAL

A. Preparation of Manganese Dioxide

A solution of 55 g of manganous sulfate monohydrate in 150 ml of distilled water was placed in a 2-liter, three-neck flask, fitted with a thermometer and mechanical stirrer, and it was heated with stirring to 86°C. A solution of potassium permanganate was prepared by mixing 60 g of the salt with 400 ml of water and heating on a hot plate to 70 - 85°C. The permanganate solution was added to the sulfate solution in portions of 35 - 40 ml. When the first 340 ml had been added the reaction mixture was heated with stirring for 20 minutes. After the addition of another 35 ml the mixture was stirred for 10 minutes before the remainder of the permanganate solution was added. Heating was continued for another 30 minutes, by which time the supernatent liquid had become colorless.

The total operation up to this point took about one hour and 40 minutes, and the temperature varied in the range 84 - 93°C.

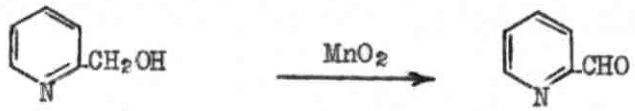
The reaction mixture was then filtered while hot, and the solid was washed with three 250 ml portions of hot water. It was then dried for 48 hours in an oven at 110 - 120°C. The dry product (about 70 g) was brown and could be powdered easily.

After it had been dried, the oxide was kept in a calcium chloride desiccator, and was ground to a fine powder just before its use. Relatively fresh preparations of the oxide were used for all the

oxidations carried out.

B. Oxidation Reactions

1. Oxidation of 2-pyridinemethanol to 2-pyridinecarboxaldehyde.



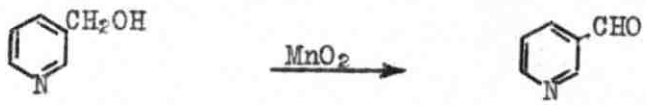
The commercial alcohol supplied by Raschig Co. was distilled under reduced pressure. The fraction boiling at 112°/15-16 mm was collected and used.

To a solution of 20 g of the alcohol in 1000 ml of chloroform, 100 g of manganese dioxide was added, and the mixture was refluxed with stirring for five hours. It was then filtered while hot through a sintered glass funnel, the solid was washed five times with 200 ml portions of dry ether, and the washings were combined with the filtrate.

The bulk of the solvents was removed by evaporation at the aspirator, keeping the temperature of the water bath around 50°C. The residual liquid was distilled under reduced pressure, and the fraction boiling at 68 - 70°/13-14 mm (Reported b.p.: 70-73°/13 mm)[28] was collected. The yield was 13.6 g (68%) of 2-pyridinecarboxaldehyde.

The same oxidation was repeated with benzene as the solvent, and 10.5 g (53.5%) of the aldehyde was obtained. A Dean and Stark distilling receiver was used in which 5 ml of water was collected.

2. Oxidation of 3-pyridinemethanol to 3-pyridinecarboxaldehyde.

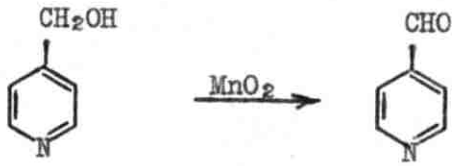


The commercial alcohol supplied by Raschig Co. was distilled under reduced pressure, and the fraction boiling at 138 - 140°/10-11 mm was collected and used.

To a solution of 15 g of the alcohol in 750 ml of chloroform was added 75 g of manganese dioxide and the mixture was refluxed with stirring for five hours. It was then treated as in reaction number 1, and the product was collected at 78 -80°/10-11 mm (Reported b.p.: 86-90/13 mm).[28] The yield was 9.9 g (67.3%) of 3-pyridinecarboxaldehyde.

The same oxidation was repeated in benzene with a reflux period of six hours. This time 11.5 g (78%) of the aldehyde was collected. In the course of the reaction 4 ml of water was collected in a Dean and Stark distilling receiver.

3. Oxidation of 4-pyridinemethanol to 4-pyridinecarboxaldehyde.



The commercial product supplied by Raschig Co. was purified by distillation at reduced pressure, and the fraction boiling at 160°/21 mm was collected. The reported boiling point is 145°/10 mm.

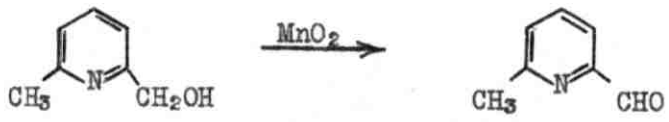
To a solution of 15 g of the alcohol in 750 ml of chloroform was added 75 g of manganese dioxide, and the mixture was refluxed with stirring for six hours. The mixture was then treated as in reaction number 1, and the product boiling at 77 - 78°/11-12 mm was collected. (Reported b.p.: 77-78°/12 mm).[67] The yield was 10.8 g (73.4%) of 4-pyridinecarboxaldehyde.

The same oxidation was repeated in benzene with a refluxing period of six hours. A yield of 10 g (67.9%) of the aldehyde was obtained.

Preparation of the semicarbazone of 4-pyridinecarboxaldehyde.[57]

To one ml of 4-pyridinecarboxaldehyde in 10 ml of ethyl alcohol was added water until the solution became faintly turbid, and the turbidity was removed with a few drops of ethyl alcohol. Then 1 g of semicarbazide hydrochloride, and 1.5 g of sodium acetate were added. The mixture was vigorously shaken and heated for 10 minutes in a water bath. It was then allowed to cool to room temperature, and was further cooled in ice. The semicarbazone was collected and recrystallized from 50% ethanol. Its m.p. was 215°C (Reported m.p.: 216°C.).[58]

4. Oxidation of 6-methyl-2-pyridinemethanol to 6-methyl-2-pyridinecarboxaldehyde.



The commercial alcohol supplied by Raschig Co. was purified by distillation under reduced pressure. The fraction boiling at 109 - 110/11 mm was collected.

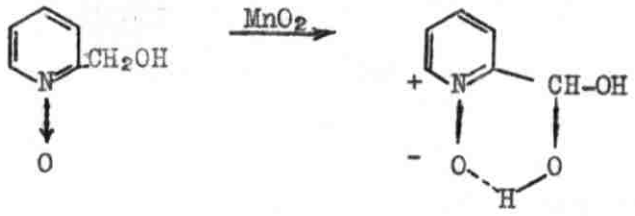
To a solution of 15 g of the pure alcohol in 600 ml of chloroform was added 75 g of manganese dioxide, and the mixture was refluxed for five hours. Subsequent treatment was as described before. The light brown liquid left after evaporation of the solvents was distilled under reduced pressure, and the fraction boiling at 71°C/11 mm was collected (Reported b.p.: 70-72°C/9 mm).[34] The yield was 9.96 g (67.4%) of

6-methyl-2-pyridinecarboxaldehyde.

Preparation of the semicarbazone of 6-methyl-2-pyridine-carboxaldehyde.[57]

The semicarbazone, prepared as in reaction number 3, melted at 218°C (Reported m.p.: 216°C.).[34]

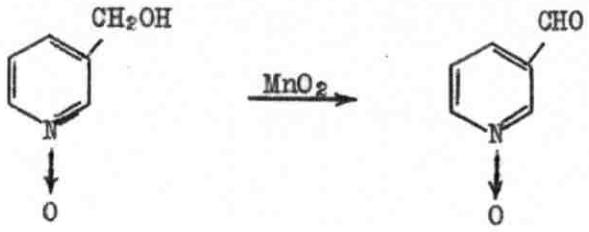
5. Oxidation of 2-pyridinemethanol-1-oxide to 2-pyridine-carboxaldehyde-1-oxide hydrate.



The commercial compound supplied by Raschig Co. melted at 140°C (Reported m.p.: 141°C)[59] and it was used without further purification.

To a solution of 15 g of the compound in 900 ml of chloroform, (prepared by heating and stirring), was added 75 g of manganese dioxide, and the mixture was refluxed with stirring for six hours. The mixture was then filtered while hot, and the solid was washed with five 150 ml portions of dry ether. After evaporation of the solvents an oily residue was obtained. To induce crystallization pentane was added and the wall of the flask was scratched with a glass rod. The mixture was then cooled and filtered. The dried solid melted at 75 - 77°C. The yield was 10.5 g (62%) of the aldehyde monohydrate. After recrystallization from benzene, the product melted at 80°C (Reported m.p.: 78-80°).[30]

6. Oxidation of 3-pyridinemethanol-1-oxide to 3-pyridine-carboxaldehyde-1-oxide.



The commercial compound supplied by Raschig Co. melted at 86°C. (Reported m.p. 84-86°C)[33], and it was used without further purification.

To a solution of 10 g of the compound in 500 ml of chloroform, was added 50 g of manganese dioxide, and the mixture was refluxed with stirring for five hours. The mixture was then filtered while hot, and the solid was washed with five 100 ml portions of dry ether. The combined filtrate and washings were evaporated to dryness at the aspirator. The solid obtained melted at 131 - 133°C after recrystallization from benzene. The yield was 5 g (51%).

Preparation of the oxime of 3-pyridinecarboxaldehyde-1-oxide.[57]

To about 0.5 g of hydroxylamine hydrochloride dissolved in 3 ml of water, was added 2 ml of 10% sodium hydroxide solution and about 0.2 g of the aldehyde. Enough ethanol was then added to give a clear solution. The mixture was warmed on a water bath for 10 minutes, and subsequently was cooled in ice. The side of the test tube was scratched with a glass rod to induce crystallization. The precipitate obtained was recrystallized from 50% aqueous ethanol. After several recrystallizations it melted at 230 - 231°C.

Since no information could be found about 3-pyridinecarboxaldehyde-1-oxide, the derivative obtained above was analysed for carbon,

hydrogen and nitrogen.

Anal. Calcd. for $C_6H_6N_2O_2$: C, 52.17; H, 4.35; N, 20.29

Found: C, 52.40; H, 4.47; N, 20.46

7. Oxidation of 4-pyridinemethanol-1-oxide to 4-pyridine-carboxaldehyde-1-oxide

The commercial compound supplied by Raschig Co. was found to melt at 121 - 122°C (Reported m.p.: 124-125°),[34] and it was used without further purification.

To a solution of 10 g of the compound in 500 ml of chloroform, was added 50 g of manganese dioxide and the mixture was refluxed with stirring for five hours. It was then filtered while hot, and the solid was washed with five 100 ml portions of dry ether. The combined filtrate and washings were evaporated to dryness at the aspirator. A yield of 6.75 g (68.8%) of the aldehyde was obtained. The product melted at 149 - 150°C without recrystallization (Reported m.p.: 148 - 150°C).[33]

Preparation of the semicarbazone of 4-pyridinecarboxaldehyde-1-oxide.[57]

The semicarbazone was prepared as in reaction number 3. It was found to melt at 248 - 250°C (decomp.) (Reported m.p.: 246-248 (decomp.)).[33]

8. Oxidation of 2,6-pyridinedimethanol to 2,6-pyridinedicarboxaldehyde.

a) Preparation of 2,6-pyridinedimethanol.[28]

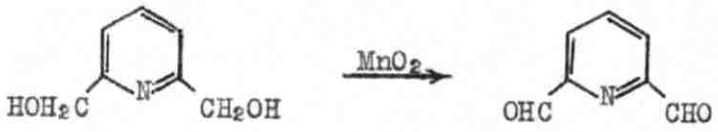
Commercial di-n-butyl ester of 2,6-pyridinedicarboxylic acid, supplied by Raschig Co., was recrystallized from ligroin before use.

In a one-liter, three-neck, round-bottom flask equipped with a dropping funnel, condenser, calcium chloride tube, mechanical stirrer and an inlet for nitrogen was placed 9.5 g (0.25 mole) of lithium aluminum hydride and 400 ml of dry ether. The flask was then cooled in an ice-salt mixture. While a slow stream of nitrogen was passed through the system, a filtered solution of 27.9 g (0.1 mole) of di-n-butyl ester of 2,6-pyridinedicarboxylic acid in 350 ml of dry ether was added with stirring. The addition of the solution was completed in 60 minutes, after which the reaction mixture was decomposed with 30 ml of water added dropwise through the funnel. The mixture was then filtered through a sintered glass funnel, and the solid was extracted ten times with 200 ml portions of boiling methanol. This was done by suspending the solid in methanol, passing carbon dioxide for 3 - 4 minutes and refluxing the mixture on a water bath for 3 - 4 minutes.

The filtrate and washings were combined, and carbon dioxide was passed through the solution for 3 - 4 minutes. The solvents were then evaporated at the aspirator. The solid residue was extracted with portions of boiling benzene until the benzene filtrate gave no precipitate on cooling. The yield was 8.1 g (58%). The crystals of the alcohol from the benzene solution melted at 118°C (Reported m.p.: 114 -

118°C).[60]

b) Oxidation procedure.



A mixture of 5.7 g of 2,6-pyridinedimethanol and 500 ml of chloroform was refluxed with stirring until the solid had dissolved, then 60 g of manganese dioxide was added, and the mixture was refluxed with stirring for five hours. It was filtered while hot, and the solid was washed with five 100 ml portions of dry ether. The combined filtrate and washings were evaporated to dryness at the aspirator, and the solid residue was extracted with ligroin mixed with some light petroleum ether. After a first crop of crystals had been collected, the mother liquor was concentrated and a second crop was obtained. The yield was 3 g (54.2%) of 2,6-pyridinedicarboxaldehyde melting at 122 - 123°C. (Reported m.p.: 124°C).[35]

Preparation of 2,6-pyridinedialdoxime.[57]

To 1 g of hydroxylamine hydrochloride dissolved in 6 ml of water was added 4 ml of 10% sodium hydroxide solution and 0.4 g of the dialdehyde. Ethyl alcohol was added dropwise until a clear solution had been obtained. The mixture was then heated for 10 minutes on the water bath, and subsequently was cooled in ice. To induce crystallization the side of the tube was scratched with a glass rod, and about 2 ml of water was added dropwise to the solution. The precipitate was filtered and was recrystallized from water. Almost colorless needles melting at 212° (decomp.) were obtained (Reported m.p.: 211.5°C).[35]

Anal. Calcd. for $C_7H_7N_3O_2$: C, 50.9; H, 4.2; N, 25.5

Found: C, 50.79; H, 4.12; N, 25.58

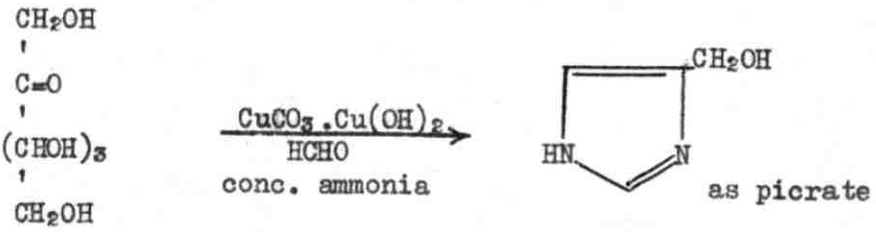
Preparation of the phenylhydrazone of 2,6-pyridinedicarboxaldehyde.[57]

To 0.5 g of the aldehyde dissolved in 20 ml of ethyl alcohol, water was added dropwise until a faint cloudiness was obtained. To this mixture 0.5 ml of phenylhydrazine was added, and a yellow precipitate was obtained in a few minutes. The mixture was warmed for five minutes, and then it was cooled. The solid was recrystallized from alcohol. The small yellow crystals melted at 198 - 199°C (Reported m.p.: 199.5°C).[35]

9. Oxidation of imidazole-4(5)-methanol to imidazole-4(5)-carboxaldehyde.

I. Preparation of imidazole-4(5)-methanol

a) Preparation of imidazole-4(5)-methanol picrate[61]

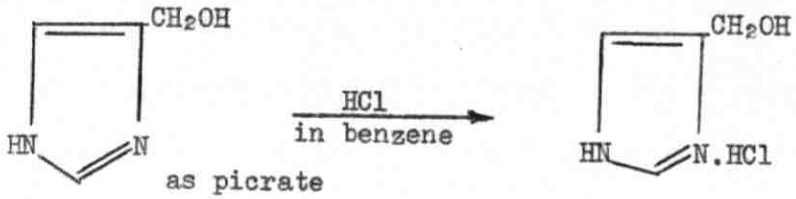


To 222 g (1 mole) of basic copper carbonate in a 5-liter flask was added 1.5 liter of distilled water, and 720 g (800 ml) of 28% ammonia. The bulk of the copper carbonate was brought into solution by swirling, and 112 g (100 ml) of 37% formaldehyde and 90 g (0.475 mole) of commercial 95% fructose were added. The contents were mixed well and placed in a water bath under a hood. After 30 minutes of heating with occasional shaking a moderate current of air was bubbled through the

mixture, and heating was continued for two more hours. The reaction mixture was then chilled in ice for three hours, and the olive-brown precipitate of the copper complex of the imidazole derivative was filtered off and washed with 500 ml of cold water. It was then suspended while moist in one liter of water, and made slightly acidic by the addition of concentrated hydrochloric acid (about 40 ml). Hydrogen sulfide gas was then passed through the solution with frequent shaking until the copper sulfide had precipitated out (3 hours). The precipitate was filtered and extracted with 500 ml of hot water in two or three portions. The filtrate, light-brown to reddish-brown, was boiled for 15 minutes, then 60 g (0.26 mole) of picric acid was added with stirring; heating was continued until solution was complete.

The greenish yellow plates which separated as the solution was cooled to room temperature were filtered, washed three times with 150 - 200 ml portions of water, and air dried. The filtrate and first washing were combined and heated, 10 g of picric acid was added, and the mixture was cooled and filtered. Both fractions were found to melt above 200°C. They were combined, and recrystallized from water, by adding 700 ml of water for every 30 g of solid, treating with charcoal and filtering through a hot funnel. Crystals deposited upon slight cooling as long yellow needles, which were filtered, washed with water and air-dried. The yield of crude product was 60% (Reported 61 - 64%).

b) Conversion of imidazole-4(5)-methanol picrate to imidazole-4(5)-methanol hydrochloride.[61]



as picrate

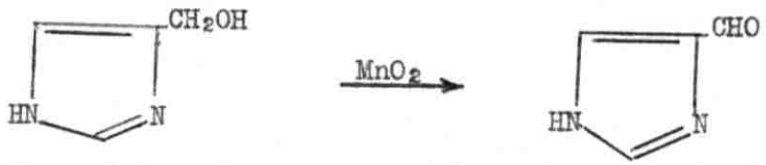
In a 2-liter flask immersed in a water bath at 80°C were placed 60 ml of concentrated hydrochloric acid, 150 ml of water and 300 ml of benzene. To this mixture was added 60 g of the pure picrate with shaking until the picrate had dissolved. The benzene layer was decanted, and the aqueous layer was extracted five times with 200 ml portions of benzene, treated with about 3 g of animal charcoal and filtered. The clear pale yellow filtrate was evaporated to dryness under vacuum. The resulting solid was dissolved in the minimum quantity of hot absolute ethanol (about 20 ml). Colorless needles deposited on cooling. Three volumes of dry ether were added, and the mixture was kept in the refrigerator overnight. The crystals were filtered, washed with a little ether and dried in a vacuum desiccator. This gave 23 g (95%) of the chloride salt (Reported 90-95%).

c) Isolation of imidazole-4(5)-methanol from the hydrochloride.[38]

A solution of 22 g of the hydrochloride in water was treated with 25 ml of saturated aqueous sodium carbonate solution. The resulting solution was distilled to dryness under vacuum. The remaining residue was extracted twice with 30 ml of anhydrous ethanol and filtered. After

addition of 30 ml of benzene, the solution was concentrated to 10 ml. It was then cooled in the refrigerator and induced to crystallize by scratching with a glass rod. After several days in the cold, the large somewhat yellow crystals were filtered. Their m.p. was 89 - 90°C (Reported m.p.: 91°C). A second crop of the same m.p. was obtained from the mother liquor. The total yield was 9.3 g (58%) (Reported 85%).

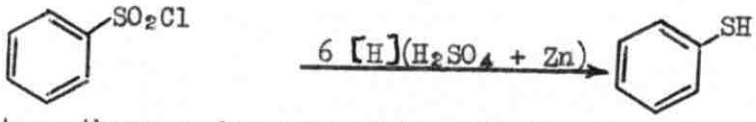
II. Oxidation procedure[62]



A solution of 8 g of imidazole-4(5)-methanol in 800 ml of dioxane was prepared by stirring the mixture vigorously at 60 - 70°C until the solid had dissolved. To this solution was added 80 g of manganese dioxide and the mixture was stirred at 80°C for four hours. The mixture was then filtered while hot, and the solid was washed with five 100 ml portions of ether. The combined filtrate and washings were evaporated to dryness at the aspirator, and the solid obtained was dried in a vacuum desiccator. The yield was 4.6 g (58.8%) of imidazole-4(5)-carboxaldehyde melting at 174°C without recrystallization (Reported m.p.: 174°).[38]

10. Oxidation of thiophenol to phenyl disulfide

a) Preparation of thiophenol[63]

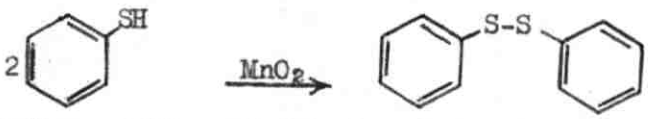


In a 3-liter, three-neck, round-bottom flask fitted with a thermometer and a mechanical stirrer was placed 720 g of crushed ice, and to this was added 130 ml of concentrated sulfuric acid. After the mixture had

been cooled to 0°C by placing the flask in an ice-salt bath, 60 g of benzenesulfonyl chloride was added slowly over half an hour. Zinc was then added in small portions to keep the temperature at 0°C. Efficient stirring was continued because benzenesulfonyl chloride solidified when added to the cold mixture. The contents of the flask were stirred for one hour more at the same temperature. An efficient condenser was then attached to the flask, the cold bath was removed and the flask was allowed to warm spontaneously to room temperature with continued stirring. The mixture was then boiled until it became clear with continued vigorous stirring (a total of seven hours of heating was found necessary).

The mixture was subsequently steam-distilled. Thiophenol was separated from water and dried by shaking with calcium chloride for five minutes, and distilled at 169°C (Reported b.p.: 169.5°C.). The yield was 34 g (90%) as reported. The crude product was redistilled under reduced pressure to give colorless thiophenol b.p. 70°C/15 mm.

b) Oxidation procedure



To a solution of 10 g of thiophenol in 500 ml of chloroform was added 50 g of manganese dioxide, and the mixture was refluxed with stirring for five hours. It was then filtered while hot, and the solid was washed five times with 100 ml portions of ether. The combined filtrate and washings were evaporated at the aspirator. An oily residue was obtained which solidified on chilling the flask in ice. The solid was recrystallized from absolute ethanol. Colorless needles

melting at 60°C were obtained (Reported m.p.: 61°C)[64]. A second crop melting at 58°C was obtained by concentrating the mother liquor, cooling and seeding. A total of 9.25 g (92.4%) of phenyl disulfide (8.25 g from the first crop and 1 g from the second) was obtained.

11. Oxidation of allyl mercaptan to allyl disulfide

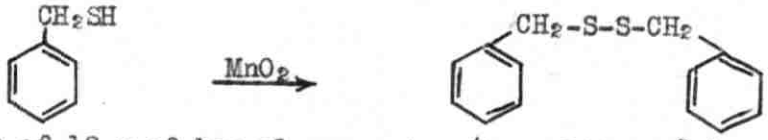
$$2\ CH_2{=}CH{-}CH_2SH \xrightarrow{MnO_2} CH_2{=}CH.CH_2{-}S{-}S{-}CH_2.CH{=}CH_2$$

The commercial product supplied by Aldrich Chemical Co. was distilled a nd the fraction boiling at 67 - 68°C was collected.

To a sclution of 10 g of the mercaptan in 500 ml of chloroform was added 50 g of manganese dioxide, and the mixture was refluxed for six hours. It was then filtered while hot, and the solid was washed five times with 100 ml portions of ether. The combined filtrate and washings were evaporated at the aspirator to a small volume (about 25 ml). This liquid was distilled under reduced pressure, and a yellow liquid boiling at 74 - 76°C/15 mm was collected (Reported b.p.: 78 - 80°/16 mm).[64] The yield was 6.5 g (65.9%) of allyl disulfide.

To confirm its nature, the product was mixed with zinc dust and was distilled. The infrared spectrum of the distillate was identical with that of diallyl sulfide.

12. Oxidation of benzyl mercaptan to benzyl disulfide



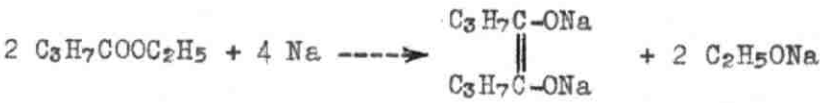
To a solution of 12 g of benzyl mercaptan (b.p. 194-195°C) in 600 ml of chloroform was added 60 g of manganese dioxide, and the mixture was

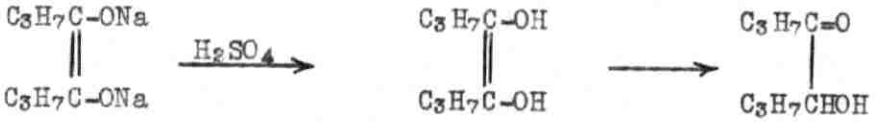
refluxed for five hours. It was then filtered while hot, and the solid was washed five times with 100 ml portions of ether. The filtrate and washings were combined and evaporated until a solid had started to deposit. The flask was then cooled, and the solid obtained on filtration was recrystallized from absolute alcohol.

A total of 9.87 g (82%) of benzyl disulfide was obtained. Of this 9.1 g (m.p. 69 - 70°C) was collected as a first crop, and 0.77 g (m.p. 68°C) was obtained by concentrating the mother liquor (Reported m.p.: 71 - 72°C and 69 - 70°C).[64]

13. Oxidation of butyroin to bibutyryl

a) Preparation of butyroin[65]





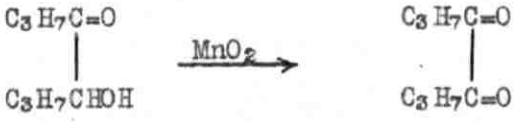
In a one-liter, three-neck, round-bottomed flask fitted with a reflux condenser and a stirrer was placed 23 g of clean sodium and about 60 ml of xylene. The flask was heated until the sodium had melted, then it was cooled with vigorous stirring whereupon the metal was changed to small pieces. The cooled xylene was decanted and the metal was washed five times with dry alcohol-free ether, and was finally covered with 300 ml of absolute ether. The flask was then fitted with a dropping funnel in which was placed 58 g (0.5 mole) of ethyl butyrate. About 10 ml of the ester was added, and this caused the ether to boil.

Subsequent addition was regulated so that a constant gentle ebullition was maintained. This addition took about two hours, and the mixture was refluxed for a further half an hour, by which time there was no more reaction and practically all the sodium had been changed to the yellowish white precipitate which appeared in the first stages of the reaction.

The flask was then placed in an ice bath, and the contents were stirred vigorously while a cooled solution of 52.5 g of sulfuric acid (sp.g.: 1.84) in 87.5 ml of water was carefully run through the funnel. The stirrer was removed, and the flask was kept in the ice bath until the lower layer of hydrated sodium sulfate had solidified. The ether layer was decanted, and the solid was washed with 100 ml of ether.

The combined solution and washing were dried overnight over anhydrous potassium carbonate. The ether and alcohol were removed by distillation at the aspirator, and the remaining liquid was distilled under reduced pressure. The fraction boiling at 80°C/12 mm was collected. It was colored light yellow probably due to traces of the diketone. (Reported b.p.: 80 - 86°C/12 mm).

b) Oxidation procedure



To a solution of 7.8 g of butyroin in 400 ml of chloroform was added 40 g of manganese dioxide and the mixture was refluxed with stirring for five hours.

The mixture was then filtered while hot and the solid was washed five times with 80 ml portions of anhydrous ether. The bulk of the

solvents was removed by distillation at the aspirator, and the residual liquid was distilled under reduced pressure. The fraction boiling at 56 - 58°C/12 mm was collected (Reported b.p. of bibutyryl: 58-58.5°C/11 mm).[64] The yield was 4.5 g (58%) of bibutyryl. The infrared spectrum of the product showed it to be essentially free of -OH absorption. The infrared spectrum of the residue left in the distilling flask was that of practically unchanged butyroin.

Preparation of the dioxime of bibutyryl[57]

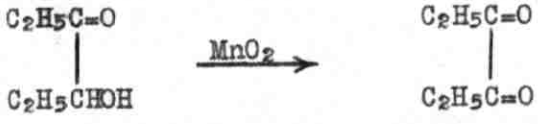
To a solution of about 2.5 g of hydroxylamine hydrochloride in 15 ml of water were added 10 ml of 10% sodium hydroxide solution and about 0.8 g of the product, and the solution was made clear by the addition of ethyl alcohol. The mixture was left in a water bath for 10 minutes and was then cooled in ice. The solid collected was recrystallized from dilute ethanol and yielded colorless needle-shaped crystals, melting at 183°C (sealed tube) (Reported m.p. of bibutyryl dioxime: 186-187°C).[64]

14. Oxidation of propionoin to bipropionyl

a) Preparation of propionoin

Propionoin was prepared by the same procedure as that used for butyroin except that ethyl propionate was used as the starting material. The product distilled at 55 - 60°C/11-12 mm (Reported b.p.: 60-65°C/12 mm).[65]

b) Oxidation procedure



To a solution of 10 g of propionoin in 500 ml of dry ether was added

50 g of manganese dioxide, and the mixture was refluxed with stirring for five hours. Subsequent treatment was similar to that used in the oxidation of butyroin. Upon vacuum distillation of the product a yellow oil, b.p. 34 - 36°C/12 mm, was obtained (Reported b.p. of bipropionyl: 32°C/10 mm).[64] The yield was 5.1 g (51.9%).

Preparation of derivatives

a) Dioxime: It was prepared as for bibutyryl. It melted at 190°C (Reported m.p.: 185°C).[64]

b) Semicarbazone: It was prepared as in reaction number 3. It melted at 271°C (decomp.) (Reported m.p.: 270°C (decomp.)).[64]

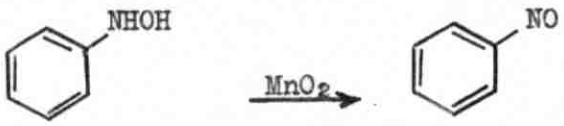
15. Oxidation of β-phenylhydroxylamine to nitrosobenzene

A solution of β-phenylhydroxylamine was prepared, and without prior isolation the product was oxidized with manganese dioxide.

a) Preparation of β-phenylhydroxylamine[66]

In a one-liter flask were placed 12.5 g of ammonium chloride, 400 ml of distilled water and 24 g of pure nitrobenzene, and the mixture was stirred vigorously. In the course of 15 - 20 minutes, 31 g of zinc dust of 85% purity was added. During this addition the temperature rose to 60 - 65°C. Stirring was continued for 15 minutes after all the zinc had been added. The temperature ceased to rise indicating complete reaction. The mixture was filtered, and the filtrate was received in a flask cooled in an ice-salt mixture. The zinc oxide was washed on the funnel with 200 ml of boiling water, and the washings were added to the main solution.

b) Oxidation procedure



To the above solution cooled to 0°C, was added 70 g of manganese dioxide and the mixture was stirred at 0°C for three hours. It was then immediately subjected to steam distillation. A green distillate passed through the condenser, and was received in a thoroughly cooled receiver where a white solid (slightly colored green) was formed. The distillate solidified partly in the condenser, and the stream of water was stopped occasionally to avoid blocking of the condenser. Steam distillation was continued until the green liquid was no more detectable in the condenser, and an oily yellow substance started condensing there.

After filtration, the solid was dried by pressing it between several sheets of filter paper. It melted at 60 - 62°C. When recrystallized from alcohol its m.p. became 64-65°C (Reported m.p. of nitrosobenzene: 64-67°C).[66] The yield was 8.7 g (41.3% from nitrobenzene). This corresponds to a 63.5% yield from phenylhydroxylamine, since the best yield of β-phenylhydroxylamine obtained by isolation from the yellow solution before oxidation (salting out at 0°C with 150 g of sodium chloride) was 14.5 g (68%) (reported 68%).[66]

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