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Kirov Ural Polytechnic Institute,
Sverdlovsk

U.D.C. 547.02:546.711.717

OXIDATION OF ORGANIC COMPOUNDS WITH ACTIVE MANGANESE DIOXIDE

S.P.Korshunov and L.I.Vereshchagin

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I. INTRODUCTION

New oxidants, possessing a wide range of action and great selectivity, have been discovered in recent years, among them being nickel peroxide[1], manganese(III) acetate[2], osmium tetroxide, the chromium trioxide–pyridine complex[3], selenium dioxide[4], etc. An important place in this series is occupied by active manganese dioxide, which since 1948 has found wide application for the oxidation of various classes of substances, especially unstable natural

compounds containing a hydroxy-group. Manganese dioxide exists in several crystalline forms[5], some of them being encountered in minerals.

Since the discovery by Ball et al.[6] of the method of selectively oxidising the polyene alcohol vitamin A_1 with specially prepared manganese dioxide, this oxidant has attracted the attention of a large number of research workers. The selective action of active manganese dioxide and the mild reaction conditions make this reagent very convenient for the oxidation of labile polyene and polyenyne alcohols, steroids, and vitamins. Whereas manganese dioxide was presented in the earlier paper as a specific reagent for the oxidation of $\alpha\beta$-unsaturated hydroxy-compounds, subsequent investigations have considerably extended the limits to its possible application.

Hitherto the method of oxidation with manganese dioxide has been presented in isolated papers and incomplete reviews[7-11], covering by no means all the experimental results. The aim of the present review is to systematise the main investigations in this field, attention being paid to oxidation with active manganese dioxide in neutral medium.

II. TYPES OF MANGANESE DIOXIDE AND METHODS OF PREPARATION

Following Ball's discovery, quite contradictory information appeared in the literature on the oxidation of alcohols by manganese dioxide. Thus Ball[6] and Turner[12] were unable to oxidise benzyl alcohol, whereas Harfenist[13] and Highet[14] obtained benzaldehyde in excellent yields under the same conditions. It can readily be seen that the reason for such discrepancies in the results is the varying oxidising power of the numerous modifications of manganese dioxide. The type of the manganese dioxide is determined primarily by the mode of preparation. Unfortunately, it is difficult to obtain a dioxide of standard activity which might serve as a criterion for comparing the oxidising efficiency of all its varieties. For a correct choice of oxidant and reaction conditions it is probably important to find the way in which the crystal structure influences the oxidising power. Many papers have been published[15-19] on the crystal lattice of the various modifications of manganese dioxide, but little attention has been paid to the effect of the fine structure of this reagent on its oxidising properties. In some cases[20] an analogy has been noted between depolarising and oxidising activities.

The crystal structure of manganese dioxide has been studied by electron diffraction, X-ray diffraction, and electron microscopy. The X-ray pattern of manganese dioxide powder was found to have changed quite markedly after oxidation, but the change disappeared after six repetitions of the reaction. The oxidising power of manganese dioxide is almost independent of crystal size, although microcrystalline forms exhibit a higher initial rate of oxidation. Detailed data on the correlation between the effectiveness and the lattice structure of the manganese dioxides could not be obtained. It was found empirically that the more active forms comprise those obtained by oxidising manganese sulphate with potassium permanganate in alkaline medium[21], the γ-dioxide obtained by treating the permanganate with concentrated hydrochloric acid[22], and colloidal manganese dioxide[23].

Several methods have now been worked out for the preparation of active forms of manganese dioxide. Among all the forms which have been described, those prepared by the methods of Attenburrow (ACC†)[21] and of Rosenkranz (RSM)[24] have become most widely accepted and used. The first of these methods consists in the interaction of hot (80–90°) solutions of potassium permanganate and manganese(II) sulphate in the presence of caustic soda. The precipitate is separated, washed with distilled water, and dried at 100–120°. The activity of such a dioxide is not diminished by carrying out the synthesis under acid conditions[25] or after washing with dilute nitric acid. Ball, Goodwin, and Morton[6] prepared manganese dioxide (BGM) by the interaction of potassium permanganate and manganese(II) sulphate in neutral medium at room temperature. The activity of the BGM dioxide is somewhat lower than that of the RSM form prepared from the same reactants but at 80–90°. The oxidising activity of the latter is increased by washing it with 15% nitric acid[24]. Good results were obtained with manganese dioxide prepared by the pyrolysis of manganese(II) salts[13,26]. It is noteworthy that each form of active dioxide exhibits specific features in the oxidation of various classes of compounds[27].

Gritter and Wallace[26] consider that the forms of the dioxide prepared from potassium or barium permanganate and also from manganese chromate possess the highest activity. They suggest that oxidation is accelerated by the presence of traces of potassium permanganate or of higher oxides of manganese, included in the crystal lattice or adsorbed on the surface of the manganese dioxide. The decrease in activity of the ACC dioxide produced by washing with organic solvents is explained by the desorption of impurities from the surface. However, the results of X-ray examination and the ineffectiveness of the addition of small quantities of potassium permanganate to the manganese dioxide during the oxidation contradict these hypotheses. This conclusion is inconsistent also with the high activity of certain oxidants prepared by the pyrolysis of manganese(II) salts, which excludes any catalytic effect due to contamination with potassium permanganate. Neither naturally occurring forms of manganese dioxide nor the commercial product possess appreciable oxidising power in neutral medium. Gritter[26] made a comparative study of the activities of a series of dioxides by oxidising benzyl alcohol with the five most widely used forms, and showed that the oxidising power falls in the sequence

$$MnO_2: BGM^{24} > ACC^{21} > HBL^{13} > GW^{26}.$$

III. REACTION CONDITIONS

In the oxidation of alcohols to the corresponding carbonyl compounds this method may be preferred to Oppenauer's method[29]. The reaction is conducted under a great variety of conditions — with different solvents, over a fairly wide temperature range, in air and in nitrogen, and with the components present in various proportions — the starting material being in most cases shaken at room temperature with the finely ground dioxide in an inert solvent, or a

† For brevity and convenience the various forms of manganese dioxide will henceforward be denoted by the initial letters of the surnames of the authors who have published the methods of preparation.

solution being slowly passed through a column filled with the oxidant[30]. The time required for completion of the reaction varies from 10 min to 10 days and longer depending on several factors, among them being the activity of the dioxide, the solvent, the temperature of the reaction, the substance to be oxidised, and the relative proportions of the components.

1. Solvent

It has been found empirically that in many cases the rate and the direction of the reaction are affected by the choice of solvent. Many workers have noted the deactivating effect of certain solvents on manganese dioxide. Polar solvents, which are strongly adsorbed on the surface of the active dioxide, lower the activity of the oxidant. These include primarily aliphatic, especially tertiary, alcohols. Acetone and ethyl acetate also deactivate the oxidant, but considerably more slowly; in this case the activity of the manganese dioxide is easily restored by drying in a vacuum. Gritter[28] determined the rate of oxidation of unsaturated alcohols by manganese dioxide in various solvents, and showed that the fall in the rate of oxidation of alcohols in the sequence — petroleum ether > carbon tetrachloride > benzene — corresponds to an increase in the affinity of solvent and dioxide: benzene forms the most stable "complex" with the active centres on the surface, which prevents contact between oxidant and alcohol molecule. The solvent has been found to have a strong influence on the yields of the oxidation products, sometimes even changing the direction of the reaction. Thus Morton[6] showed that vitamin A in petroleum ether is converted almost quantitatively into retinene, whereas in diethyl ether it forms anhydrovitamin A. The solvents most widely used for oxidation in the cold are light petroleum ether, saturated hydrocarbons (pentane, hexane, cyclohexane), ethers, and acetone; ethyl acetate, dimethylformamide, acetonitrile, dimethyl sulphoxide, etc. are also used. The same solvents are employed, as well as water and pyridine, for reactions at high temperatures.

2. Time and Temperature of Reaction

The time and the temperature of the reaction depend on the activity of the manganese dioxide, the material to be oxidised, and the relative proportions of the components. The duration of oxidation at room temperatures varies within wide limits: whereas the transformation of $\alpha\beta$-unsaturated alcohols is usually complete at room temperature after a few minutes[31], the oxidation of alkylanilines[32] and the formation of steroid dienones[33] occupy 16–24 h. In order to shorten the reaction time, oxidation is frequently conducted at an elevated temperature in the boiling solvent, the water formed sometimes being removed by azeotropic distillation. The rate of the reaction and the time at which it is complete can be assessed qualitatively from the liberation of water. Raising the temperature to 70–120° markedly shortens the reaction time, but the yields, the purity of the product, and the selectivity of action of the oxidant are diminished. In some cases, especially when carbon–carbon bonds undergo cleavage during the oxidation, the reaction is complete at 80–100° after 10–20 h.[34,35] When the reaction is conducted at room temperature, vigorous agitation is necessary for maximum contact of the material with the surface of the dioxide in order to avoid local overheating.

3. Proportions of Reactants and Mode of Action of Active Manganese Dioxide

The oxidation of organic compounds in neutral solvents by active manganese dioxide is a heterogeneous reaction[6], so that the quantity of oxidant used is greatly dependent on the particle size of the dioxide. The particle size normally employed is 80–200 mesh. It is as yet impossible to determine theoretically, on the basis of known facts, the quantity of oxidant required. The ratio of substance to reagent usually varies within the range 1 : 5–20 by weight, and in some cases the excess of oxidant is increased to 1 : 50. The optimum proportions for the oxidation of $\alpha\beta$-unsaturated alcohols are 1 : 10 at room temperature, and 1 : 4–6 on boiling. In the opinion of many authors the ease of oxidation depends on the adsorbability of the given compound on the manganese dioxide. Ball et al.[6] consider this reaction to occur in three stages — adsorption of the substance from solution on the oxidant, oxidation, and desorption of the reaction product into the solution — from which it may be expected that more saturated compounds, which are more poorly adsorbed on the surface of the dioxide, should react at a lower rate. Results obtained by Harfenist[13] are fully consistent with Ball's conclusions. They showed that alcohols can be arranged in the sequence — conjugated polyene carbinols, benzyl and furfuryl alcohols, and vinyl- and ethynyl-carbinols — according to their ease of oxidation. However, the degree of adsorption is hardly the sole factor determining the reaction velocity.

Harfenist noted an interesting peculiarity in the oxidation of benzyl alcohols: the reaction does not usually go to completion, the product always being contaminated with the initial carbinol. In his view a permanent equilibrium is established at the surface of the dioxide between the starting material and the reaction product. Therefore oxidation proceeds successfully until a certain point is reached, at which the quantity of carbonyl compound formed attains a critical value, i.e. a concentration at which the final product begins to displace molecules of the initial alcohol from the dioxide surface. Henbest and Thomas[32] showed that only a small proportion of the oxygen in the manganese dioxide is consumed during oxidation. In their opinion water, bound to the manganese dioxide surface in the form of free hydroxyls, takes part in this reaction. Evans[8] points out that hydrated manganese dioxides contain available oxygen, the quantity of which has diminished by the theoretical amount after oxidation. The relative quantity of available oxygen in the various types of dioxide decreases in the sequence

$$MnO_2: GW > HBL > RSM > BGM > ACC.$$

The above sequence does not correspond to that based on the efficiencies of these forms of manganese dioxide in oxidising $\alpha\beta$-unsaturated alcohols. Consequently there is no direct link between the quantity of oxygen available in a sample of manganese dioxide and its oxidising power. If, however, we examine the dependence of rate of oxidation on the percentage contamination with other oxides of manganese, we find that the oxidising activity increases as the purity of the dioxide diminishes, the ACC dioxide forming an exception. Gritter[28] suggested that oxidising power is affected by the nature of the impurities present, especially cationic impurities. In his view, successful oxidation requires the presence on the manganese dioxide surface of centres of diminished electron density, capable of attracting the electron-rich oxygen of the alcoholic hydroxyl. The reaction velocity is determined by the number and type of these active centres.

The mechanism of oxidation by manganese dioxide has not yet been completely elucidated, and therefore the proposed schemes frequently contradict the experimental facts. Some investigators consider that compounds capable of forming more stable carbonium ions are more readily oxidised, but most authors deny the intermediate formation of a carbonium ion. Pratt[36] noted that the rate of oxidation of alcohols $C_6H_5CH(OH)-R$ increases roughly sevenfold as the radical R is varied in the sequence

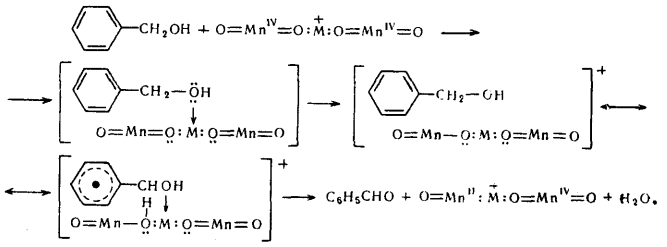
$$-\underset{\displaystyle CH_3}{\overset{|}{C}}H-C_6H_5;\ -\underset{\displaystyle CH_3}{\overset{|}{C}}H-CH_3;\ -CH_2C_6H_5;\ -CH_3;\ \overset{\cdot\cdot}{H};\ -C_6H_5;\ -CH=CH-C_6H_5;\ -COC_6H_5.$$

Replacement of the hydrogen atoms in the methyl group by radicals leads to a successive decrease in the rate of oxidation. Branched radicals probably cause steric hindrance to adsorption of the oxidisable molecule on the surface of the active dioxide. Nevertheless, these substituents govern the stability of the free radicals. A change in structure of the substituents which increases the stability of the free radical is accompanied by an increase in reaction velocity. Thus primary aliphatic alcohols are oxidised more slowly than secondary alcohols, and the latter in turn more slowly than phenylmethanols.

The free-radical mechanism suggested by Pratt[36-38] for the oxidation of organic compounds by manganese dioxide, combined with the adsorption theory, is probably the most successful in explaining the general features of the oxidation:

$$R_2CHOH + O{=}Mn^{IV}{=}O \rightarrow R_2\dot{C}OH + HO{-}Mn^{III}{=}O \rightarrow$$
$$\rightarrow R_2\dot{C}{-}\dot{O} + HO{-}Mn^{II}{-}OH \rightarrow R_2CO + MnO + H_2O.$$

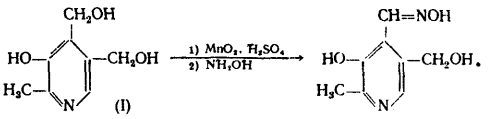
According to Gritter[28], in the course of the reaction the oxidisable substance forms a complex with the dioxide, ions of other metals, present as impurities in the oxidant, being involved in its formation:



An analogy can be traced between the oxidation of alcohols by manganese dioxide and the autoxidation of hydrocarbons in the presence of metal oxides, where similar complexes are probably formed[38].

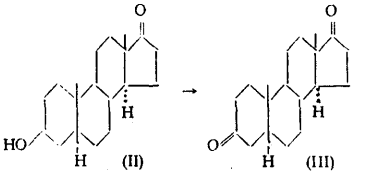
IV. OXIDATION OF ALCOHOLS

The oxidation of primary aliphatic alcohols with manganese dioxide in an acid medium was studied as early as the nineteenth century by Liebig[39], who converted ethanol into acetaldehyde with pyrolusite in sulphuric acid. β-Chloroacrylaldehyde[40], fluoroacetaldehyde[41,42], and several other aliphatic and aromatic carbonyl compounds have been obtained under similar conditions. The use has been described of manganese dioxide in acid medium for the oxidation of derivatives of vitamin A,[50] pyridoxol (I), and similar compounds[23,43-49]:

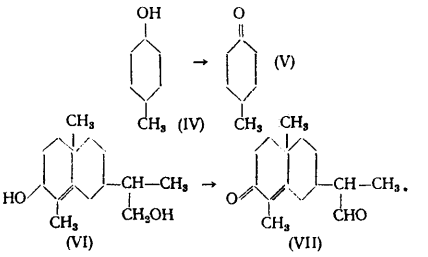


1. Oxidation of Saturated Alcohols in Neutral Medium

Comparison of the relative rates of oxidation of various types of alcohols shows that saturated alcohols are oxidised with great difficulty, while alcohols in which the hydroxyl is activated by a double or a triple bond, a system of conjugated bonds, an aromatic ring, or a carbonyl group are oxidised considerably more readily. The early work showed that neutral manganese dioxide (BGM) is inert towards primary and secondary aliphatic alcohols at room temperature. However, it was subsequently found that saturated alcohols can be oxidised to good yields of the corresponding aldehydes and ketones. In the oxidation with alkaline manganese dioxide (ACC) of ethanol, propan-2-ol, and isobutanol the yields of the carbonyl compounds reach 50%.[35] Gritter and Wallace[26] oxidised propan-1-ol and propan-2-ol under similar conditions, and obtained yields of 78% and 92% respectively. According to these workers, a long time or a high temperature is required for the reaction. The successful oxidation of saturated carbinols necessitates a large excess of the dioxide, as well as careful selection of the solvent[51]. For example, 3β-hydroxyandrostan-17-one (II) and its epimer when stirred in hexane or acetonitrile with ACC manganese dioxide for a day are converted into androstane-3,17-dione (III) in 99% yield:



Methylcyclohexanol (IV) in acetonitrile gives a 71% yield of 4-methylcyclohexanone (V):

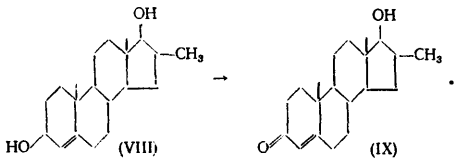


The analogue of α-santonin (VI)[52] is oxidised by manganese dioxide to the keto-aldehyde (VII).

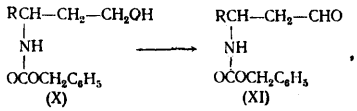
Thus the successful oxidation of saturated carbinols of various classes requires careful choice of reaction conditions and the form of the active dioxide. By means of active manganese dioxide it has proved possible to effect the oxidation of steroid alcohols[53], derivatives of gibberellic acid[54,55], alkaloids[56-59], cyclopropylmethanols[60], derivatives of tetrahydropyran-2- and -4-ols[14], bicyclo[3,3,0]-octanol[61], and other complex hydroxylated compounds[51,62-65].

The different positions of hydroxy-groups in polyols often permits selective oxidation of the hydroxyls[66-69]. A

clear example of such specific oxidation is provided by the preparation of 17α-hydroxy-16-methyl-13α,14β-androst--4-en-3-one (IX) from the corresponding 3,17-diol (VIII):[66]



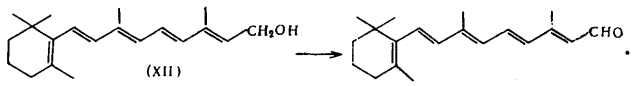
Here it is only the allylic hydroxyl which undergoes oxidation. Amino-alcohols and their benzyloxycarbonyl derivatives (X) are oxidised by the alkaline dioxide (ACC) with the formation of amino-aldehydes (XI):[70]



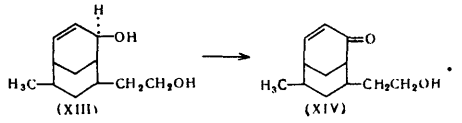
where R = C_6H_5, p-$CH_3OC_6H_4$.

2. Oxidation of αβ-Unsaturated Alcohols

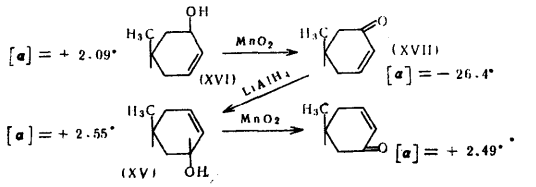
The first organic compound to be oxidised with active manganese dioxide in neutral medium was vitamin A_1 (XII), which contains a pentaene conjugated bond system and an allylic hydroxyl:



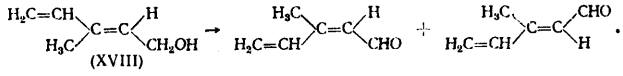
This work formed the start of a broad investigation into the oxidation of various unsaturated carbinols by manganese dioxide. During the following four or five years active manganese dioxide became firmly established as a convenient and efficient oxidant for the conversion of primary and secondary αβ-unsaturated alcohols into the corresponding carbonyl compounds. Detailed investigations of this reaction revealed certain relations between the structure and the ease of oxidation of the alcohols. Successful oxidation was found to require that the multiple bond in the unsaturated compounds should be located in the α-position with respect to the oxidisable hydroxyl. A break in conjugation sharply increases the inertness of the alcohols towards manganese dioxide. An example is provided by the oxidation of glycols containing only one allylic hydroxyl. Thus *cis*-8-2′-hydroxyethyl-6-methylbicyclo[3,3,1]non-3--en-2-ol (XIII) on treatment with active manganese dioxide gives only one oxidation product, 8-2′-hydroxyethyl-6--methylbicyclo[3,3,1]non-3-en-2-one (XIV):[71]



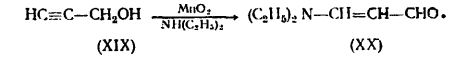
A characteristic feature of this reaction is the insensitivity of the carbon skeleton of unsaturated alcohols to the action of active manganese dioxide. In none of the work was cleavage of carbon–carbon bonds, change in the carbon skeleton, or allyl rearrangement noted, although these are so characteristic of many oxidations. However, some substances undergo stereochemical changes during oxidation. Cases have been reported[72] in which the angle of rotation of certain optically active alcohols changes on oxidation. The sign of rotation remains unchanged on treatment of (+)-*trans*-5-methylcyclohex-2-enol (XV) with manganese dioxide, whereas the (+)-*cis*-form (XVI) yields the *cis*--methylcyclohexenone (XVII), whose angle of rotation has the opposite sign:



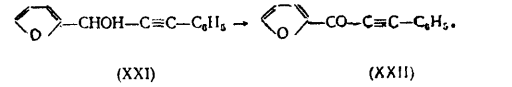
Sometimes the geometric configuration of the molecule changes during the reaction, with rearrangement of *cis*- and *trans*-substituents. Robeson[73] detected no change in the geometry of the molecule during oxidation of the geometric isomers of vitamin A_1 to the corresponding vitamin A aldehydes. Similar results were obtained by Wendler and Slates[74] in the oxidation of the *cis*- and *trans*-isomers of 2-ionylidene-ethanols. However, Boehm et al.[75,76] have observed *cis–trans* isomerisation in the transformation of pentadienols and pentenynols: *cis*-penta-2,4-dienol is oxidised by active manganese dioxide in pentane without geometric changes, whereas the *trans*-carbinol (XVIII) forms on oxidation a mixture of *cis*- and *trans*-isomers in the proportions 1 : 4:



Unsaturated alcohols containing one or more multiple bonds are very sensitive to oxidation by active manganese dioxide. This can be regarded as a classic method of synthesising unsaturated aldehydes and ketones, especially with the extremely labile naturally occurring polyene alcohols. Alcohols containing a double bond in the α-position to the hydroxy-group are oxidised by manganese dioxide to give a high yield of the corresponding carbonyl compounds, examples of this reaction being provided by the oxidation of allyl[26] and cinnamyl[36] alcohols to acrylaldehyde and cinnamaldehyde respectively. Good results have been obtained both with primary alcohols containing one double bond[77–82] or one triple bond[83] and with secondary alcohols[84–86]. The oxidation of prop-2-ynol (XIX) in the presence of diethylamine[87] gives the aminoacrylaldehyde (XX):

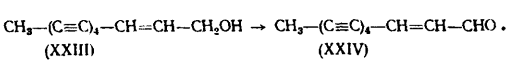


Alcohols in which the hydroxyl is activated by two multiple bonds[88–98] or by a multiple bond and an aromatic ring[99–102] are readily oxidised. Similarly, 1-fur-2′-yl--3-phenylprop-2-ynol (XXI) is converted into a high yield of 1-fur-2′-yl-3-phenylprop-2-ynone (XXII):[99]



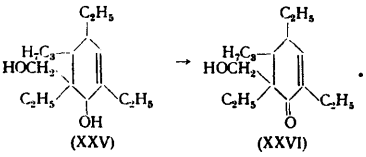
Active manganese dioxide has proved indispensable for the selective oxidation of such unstable compounds as the highly unsaturated polyene and polyenyne carbinols[103–114].

Thus treatment of dodec-2-ene-4,6,8,10-tetraynol (XXIII) with manganese dioxide gives dodec-2-ene-4,6,8,10-tetraynal (XXIV):[103]

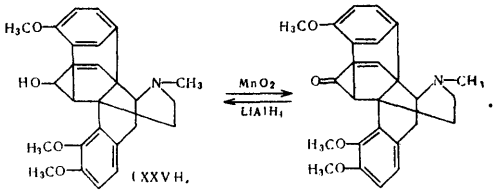


6-Methyl-8-phenylocta-3,5,7-trien-2-ol reacts similarly[104].

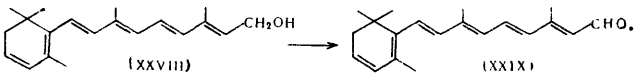
This method has been successfully applied to the oxidation of unsaturated cyclic carbinols[115-127]:



The cyclohexenone (XXVI) is obtained in 80% yield by oxidation of the corresponding alcohol (XXV) in cyclohexane at 20°.[115] Active manganese dioxide has been used for the oxidation of hydroxy-groups in certain alkaloids and other natural products[128-140]. This has enabled their structure to be established, e.g. in the case of flavothebaone (XXVII):[129]

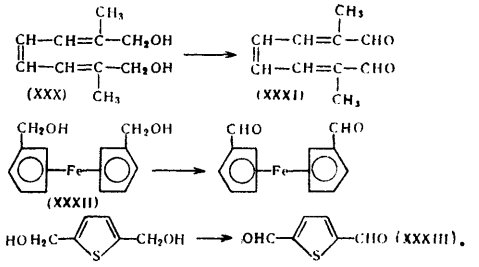


The exceptionally mild action of the active dioxide has enabled it to be used for the preparation of difficultly accessible carbonyl derivatives of vitamin A. In this case none of the known oxidants gave positive results. Numerous papers have been published on the synthesis of the corresponding aldehyde from vitamin A_1,[6,30,141] α- and β-ionylideneacetaldehydes[142-145], and β-ionone[146] by means of manganese dioxide in inert solvents at room temperature. A similar conversion is characteristic also of vitamin A_2 (XXVIII), which is readily oxidised to the aldehyde (XXIX),[147-149] and also of 8,9-dehydrovitamin A,[21] neovitamin A,[150] and several other similar compounds[151-155]:

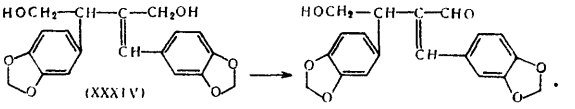


Vitamin A_1 aldehyde has been prepared also from vitamin A_1[156] and β-carotene[157] by oxidation with air in the presence of manganese dioxide. The use of these methods has enabled a convenient and cheap process to be developed for obtaining vitamin A aldehyde identical with the product isolated from the retina.

In the oxidation of polyols several reactions are possible, involving one or more hydroxyls depending on their degree of activation by multiple bonds, or accompanied by cleavage of skeletal carbon bonds (under more severe conditions). Special interest attaches to the synthesis of polyene and aromatic dialdehydes and diketones[158-172]. An example is provided by the oxidation of 2,7-dimethylocta-2,4,6-triene-1,8-diol (XXX)[164] in 94% yield to the corresponding dialdehyde (XXXI), of 1,1′-bishydroxymethylferrocene (XXXII),[171] and of 2,5-bishydroxymethylthiophen (XXXIII):[172]

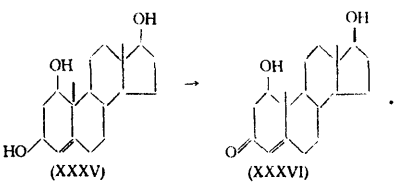


Glycols in which the hydroxy-groups are activated to different extents behave somewhat differently. Thus several publications have indicated the possibility of oxidising only an allylic type of hydroxyl[173-175]. A break in the chain of conjugation in an unsaturated bond system, even by only one carbon atom, for example, as in (XXXIV),[173] markedly decreases the rate of oxidation:



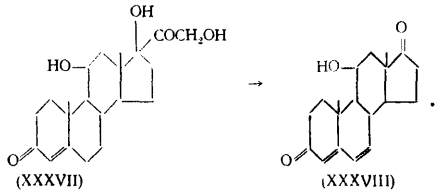
Barakat et al.[35] were able to obtain benzil and *pp′*-dimethoxybenzil in good yields from the corresponding α-hydroxy-ketones. This work also showed that ethylene glycol, glycerol, mannitol, and inositol are oxidised to carbon dioxide and water when boiled with an aqueous suspension of active manganese dioxide. The oxidation of hydroxy-acids is also anomalous: reaction is very rapid, and is accompanied by the evolution of carbon dioxide, aldehydes and ketones being formed containing one fewer carbon atoms than in the initial acid. Under milder conditions esters of hydroxy-acids undergo the usual type of oxidation[176-179].

The specificity of the action of active manganese dioxide has enabled it to be used for the oxidation of several steroid hydroxy-compounds[180-203]. The reaction goes mainly by the usual route, with conversion of only an allylic hydroxyl. Androst-4-ene-1β,3β,17β-triol (XXXV) is oxidised, in propan-2-ol at room temperature, to 1β,17β-dihydroxyandrost-4-en-3-one (XXXVI):[180]



It is advisable to conduct the reaction at room temperature in order to ensure that the structure of the molecule shall be preserved. Otherwise, oxidation of the hydroxyl may be accompanied by dehydrogenation of the olefinic to a diene system, migration of double bonds[204-208], and even rupture of carbon–carbon bonds.

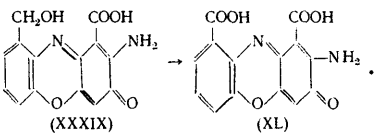
Special interest attaches to the oxidation of steroid 5-en-3β-ols, which in hot benzene are converted into 4,6-dienones[33], whereas in dimethylformamide or pyridine at 20° they give 4-en-3-ones, although the rate of reaction is not very high[51]. This extends the possibilities of synthesis of steroid products. Manganese dioxide in boiling chloroform splits off the side-chain in dihydroxy-acetonyl steroid alcohols to give 17-oxosteroids[34]. Hydrocortisone (XXXVII) is converted into 11β-hydroxyandrosta-4,6--diene-3,17-dione (XXXVIII):[209]



(XXXVII) (XXXVIII)

3. Oxidation of Aromatic Alcohols

The oxidation of benzyl alcohols and similar compounds by active manganese dioxide has been studied in some detail. As already mentioned, this oxidant has been regarded as ineffective for these alcohols. These views have now been completely refuted, and manganese dioxide has become widely used in the synthesis of aromatic aldehydes and ketones. Turner[12] was able to effect the mild oxidation of diphenylmethanol, xanthen-9-ol, furoin, 1-1'-naphthylethanol, tetrahydrophenanthren-1-ol, and several other alcohols. During recent years the successful oxidation has been accomplished of substituted benzyl alcohols[210-215], 2- and 4-hydroxymethylindoles[216,217], hydroxymethylferrocene[218], triazolylmethanols[219], secondary phenylmethanols[220,221], 1-thienylethanol[222], 1-furylalkanols[83], 2-hydroxyarylalkylbenzimidazoles[223], 4-pyranylmethanols[224], etc. The oxidation of benzyl alcohols usually goes readily, and stops at the carbonyl stage. Only one example has been reported in which the corresponding acid could be isolated as the main product: 2-amino-9-hydroxymethyl-3-oxophenoxazine-1-carboxylic acid (XXXIX), with manganese dioxide in chloroform at room temperature, gives the dicarboxylic acid (XL) as the sole product[225]:

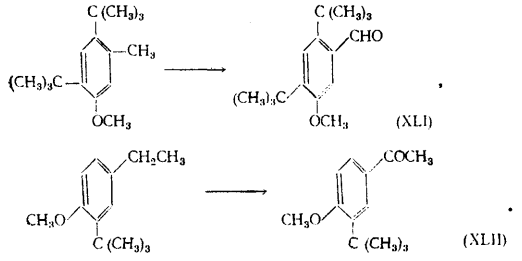


(XXXIX) (XL)

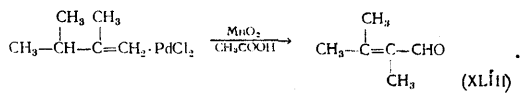
Insufficient study has hitherto been made of the mechanism of the oxidation of benzyl alcohols and similar compounds. Pratt[36] established that electron-acceptor properties of *para*-substituents in phenylmethanols have considerably less effect on their rate of oxidation than would have been expected on the hypothesis of a carbonium-ion mechanism. Moreover, Gritter and Wallace[28] have shown that methyl, methoxyl, and nitro-groups in the *ortho*-, *meta*, and *para*--positions always increase the rate of oxidation of the phenylmethanols in comparison with that of unsubstituted benzyl alcohol. This phenomenon is explained by a free-radical mechanism for the reaction. The insignificant effect of the nature of substituents becomes understandable, for radical reactions are accelerated by both electron-acceptor and electron-donor substituents. This mechanism is confirmed by the decrease in the rate of oxidation produced by the addition of diphenylamine. In a study of the oxidation of the alcohols $C_6H_5CH(OH)-R$ (where R = H, Alk, C_6H_5, $C_6H_5CH_2$, $C_6H_5CH{:}CH$, C_6H_5CO, etc.), Pratt explained the differences in the rates of oxidation of the α-substituted benzyl alcohols as due to two effects — the steric effect of substituents capable of preventing rapid adsorption of the alcohol on the surface of the active manganese dioxide, and the effect of the stabilisation of free radicals formed in the first stage of oxidation. Similar results were obtained by Gritter.

V. OXIDATION OF HYDROCARBONS

For a long time a great deal of attention has been paid in the chemical literature to the problem of the oxidation of alkylbenzenes. Among oxidising agents used for this reaction an important place is occupied by natural manganese dioxide, pyrolusite. In all cases oxidation is found to involve only the alkyl substituent in the benzene ring. Thus Fel'dman[226] heated 2,4-dichlorotoluene in the presence of pyrolusite and 58% sulphuric acid at 80° for 16–19 h, and obtained an 80% yield of 2,4-dichlorobenzoic acid, whereas *p*-nitrotoluene gives *p*-nitrobenzoic acid[227]. Alkylpyridines undergo similar oxidation[228]. When toluene is nitrated with a mixture of sulphuric and nitric acids in the presence of manganese dioxide, a mixture of *p*-nitrotoluene and 2,4-dinitrobenzaldehyde is formed[229]. It has been suggested[230] that terephthalic acid can be prepared by the oxidation of *p*-cymene with manganese dioxide in sulphuric acid. Thus the aromatic ring and certain functional substituents remain unchanged during the reaction, whereas a methyl group is converted into carbonyl or carboxyl depending on the conditions. The reaction conditions can be so chosen that oxidation is halted at the carbonyl stage. Lifshits[231] obtained a mixture of benzyl alcohol and benzaldehyde by the interaction of toluene and manganese dioxide in the presence of sulphuric acid. Carpenter et al.[232] were able to oxidise substituted methyl- and ethyl-benzenes to the corresponding benzaldehyde (XLI) and acetophenone (XLII) respectively:

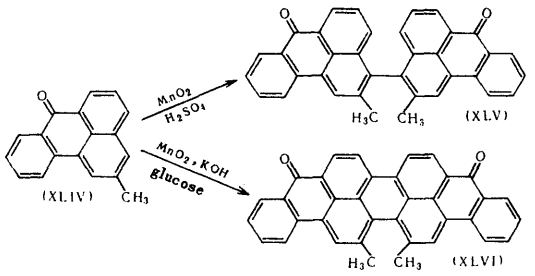


Recently Hüttel and Christ[233] have proposed a new method for synthesising αβ-unsaturated carbonyl compounds (XLIII) by oxidising palladium dichloride–alkene complexes with various reagents, including manganese dioxide in an acid medium:



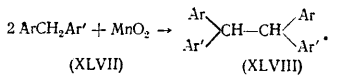
Manganese dioxide is used also for the oxidative dimerisation and even polymerisation of aromatic hydrocarbons. Travkin[234] heated 2-naphthol with manganese dioxide at

260° for 3 h, and obtained a quantitative yield of binaphthyl-2,2′-diol. Oxidation[235] of 2-methylmesobenzanthrone (XLIV) with manganese dioxide in sulphuric acid at 0–5° gives a 78% yield of 2,2′-dimethyl-3,3′-bibenzanthryl-7,7′-dione (XLV), whereas in alkaline medium containing glucose the product is 16,17-dimethylviolanthrone (XLVI):



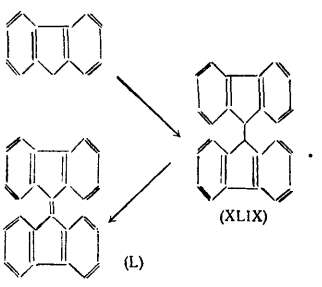
A convenient method for synthesising *p*-polyphenyls from benzene has been worked out by Kowacic[236]: the polyphenyls are formed by the action of manganese dioxide, copper(II) chloride, lead dioxide, and other oxidising agents in the presence of catalytic quantities of aluminium chloride.

The oxidative dimerisation of diarylmethanes (XLVII) by active manganese dioxide in neutral medium can be regarded as the same type of reaction[37]:



Three types of product — (1) tetra-arylethanes (XLVIII), (2) tetra-arylethylenes, or (3) diaryl ketones — may be formed depending on the conditions. Pratt made a detailed study of this process, and found it to be a general reaction with all symmetrical and unsymmetrical diarylmethanes, the rate of the reaction and the yield of tetra-arylethylenes depending on the electronic properties of the aryl ring.

The oxidation of *pp*′-dinitrodiphenylmethane, fluorene, and xanthen in a mixture of benzene and biphenyl at 211° is accompanied by the liberation of double the theoretical quantity of water. This suggests that, in the course of oxidation, tetra-arylethanes are dehydrogenated to the corresponding ethylenes, which were isolated in 15–30% yields. In order to demonstrate the formation of tetra-arylethylenes at the expense of tetra-arylethanes, 9,9′-bifluorenyl (XLIX) was converted into a 75% yield of 9,9′-bifluorenylidene (L) by the same method:



In view of the great stability of diarylmethane radicals, Pratt suggested a free-radical mechanism of oxidation:

$$Ar_2CH_2 + O{=}Mn{=}O \rightarrow Ar_2\dot{C}H + HO{-}Mn{=}O, \quad (1)$$

$$Ar_2CH_2 + HO{-}Mn{=}O \rightarrow Ar_2\dot{C}H + HO{-}MnOH, \quad (2)$$

$$2\,Ar_2\dot{C}H \rightarrow Ar_2CH{-}CH{\cdot}Ar_2. \quad (3)$$

This scheme is confirmed by the increase in rate of oxidation in the sequence — diphenylmethane, 1-benzylnaphthalene, *p*-benzylbiphenyl, di-*p*-biphenylylmethane — which corresponds to increasing stability of the corresponding free radicals. Dehydrogenation of tetra-arylethanes to the ethylenes may pass through analogous stages. Good yields of the former were obtained by stirring with a fourfold excess of manganese dioxide by weight in a 20 : 1 biphenyl–benzene mixture at 211°. The yields of tetra-arylethanes diminish with fall in temperature, although the theoretical quantity of water is liberated.

Simultaneous formation of diaryl ketones was also noted, their yields increasing with fall in temperature and increase in the quantity of active dioxide. The corresponding diarylmethanols are probably intermediate products in the oxidation of diarylmethanes to diaryl ketones. Manganese dioxide is normally used for the abstraction of hydrogen atoms, the oxidation of hydrocarbons to ketones representing a rare though not unique case of the introduction of oxygen into the carbon skeleton[227]. A possible source of hydroxy-groups is hydrated manganese dioxide, on whose surface hydroxyls are present as free radicals or as HO–Mn=O. The reaction can then be written

$$Ar_2\dot{C}H + HO{-}Mn{=}O \rightarrow Ar_2CHOH + MnO. \quad (4)$$

Reaction (4) together with reaction (1) explains the increased yield of ketones when the solvent is not distilled off during the reaction and when the latter is conducted at lower temperatures, since active manganese dioxide is rapidly dehydrated during the azeotropic distillation of water and solvent, which diminishes the possibility of attack by a hydroxyl on the free radical. At the same time, a reaction in which water and solvent are distilled off promotes the desorption and recombination of radicals, i.e. reaction (3). Thus

$$Ar_2\dot{C}H + HOMnO \rightarrow Ar_2CHOH + MnO,$$

$$Ar{-}CH{-}Ar \rightarrow Ar{-}CHOH{-}Ar + MnO,$$



$$Ar_2CHOH \rightarrow Ar_2CO + H_2O.$$

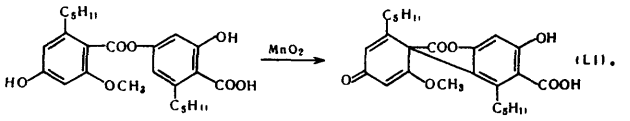
The above mechanism is confirmed by the oxidation of diphenylmethane with manganese dioxide which has first been dehydrated by being boiled in toluene. When the hydrocarbon is oxidised with this dioxide in the absence of solvent, the yield of benzophenone falls from 74% to 2%. Since the dioxide undergoes still greater dehydration in reaction with a solvent at high temperatures, it follows that in this case practically no ketone will be formed.

VI. OXIDATION OF PHENOLS

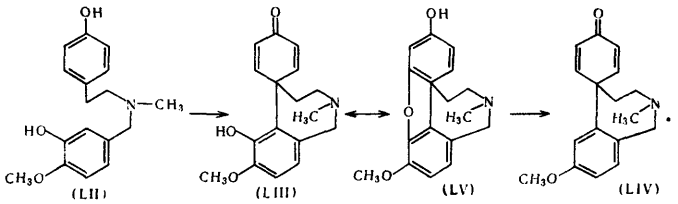
In recent years several successful syntheses, involving the oxidative linking of phenols, have been made of important natural products from readily available and inexpensive substances[238-241]. This method is based on the free-radical coupling of certain phenol derivatives, the reaction

being regarded as analogous to biochemical processes occurring in the living cell. Various oxidants convert phenols into mono- or di-radicals, which can then react intramolecularly or dimerise, new carbon–carbon, carbon–nitrogen, or carbon–oxygen bonds being formed. Active manganese dioxide occupies a special place[241] among the numerous oxidising systems (lead dioxide, potassium hexacyanoferrate(III), hydrogen peroxide, etc.) employed for this purpose.

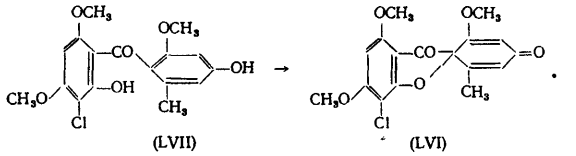
Scott and Davidson[242,243] have synthesised picrolichenic acid (LI), previously isolated from *Pertusaria amara*:



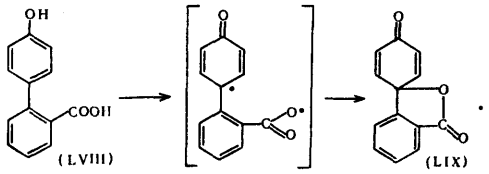
Under similar conditions Barton and Kirby[244,245] have obtained from *p*-hydroxy-*N*-(3-hydroxy-4-methoxybenzyl)-*N*-methylphenethylamine (LII) the alkaloid galanthamine (LIII), which can be further oxidised via (LV) to narwedine (LIV):[246,247]



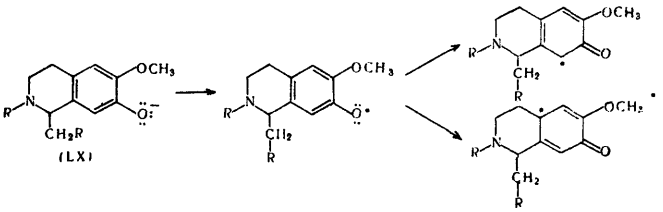
Several morphine alkaloids[248] and geodin[241] have been synthesised by a similar scheme. A new carbon–carbon bond is formed also in the oxidation of bisphenols[249]. In other cases the oxidative coupling of phenols leads to the formation of a carbon–oxygen bond. This can be seen in the synthesis of depsidone and diploicin[250,251] and of dehydrogriseofulvin (LVI)[252,253] from 3-chloro-2,4′-dihydroxy-2′,4,6-trimethoxy-6′-methylbenzophenone (LVII):



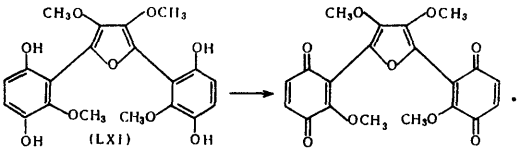
Oxidation of 4′-hydroxybiphenyl-2-carboxylic acid (LVIII) with manganese dioxide in ether[254] gives a 25% yield of phthalan-1-spiro-1′-cyclohexadiene-3,4′-dione (LIX):



Interaction of phenolic tetrahydroisoquinoline bases with active manganese dioxide at room temperature results in formation of the isoquinoline system[241,255]. At higher temperatures hydrogen is detached from the hydroxyl with formation of polymeric products. The phenoxide ion (LX) is converted into a mixture of radicals having their unpaired electron on the oxygen atom or in the *ortho*- or *para*-positions of the cyclohexadiene ring, and these radicals then interact to form the polymeric products[256,257].

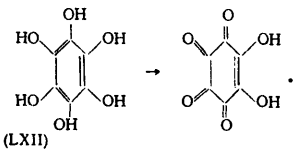


Oxidation of the mono- and di-adducts of 3,4-dimethoxyfuran with acetylbenzoquinone (LXI) involves conversion of the 2,5-dihydroxyphenyl into *p*-quinonoid substituents[258]:



These reactions have been used for the purification of industrial waste waters from *p*-t-butylphenol, bishydroxyphenylpropane, and other phenols[259].

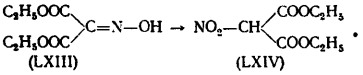
The oxidation of phenols with manganese dioxide in acid and alkaline media has been known for a long time. As early as the nineteenth century Clark[260] oxidised quinol to *p*-benzoquinone with manganese dioxide in sulphuric acid. The most interesting of recent investigations is that by Fatiadi[261] on the oxidation of benzenehexaol (hexahydroxybenzene) (LXII) with a specially prepared highly active dioxide in alkaline medium:



VII. OXIDATION OF AMINES

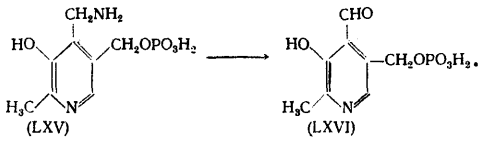
An important field for the application of active manganese dioxide is the oxidation of various amino-compounds. This reaction occurs in several ways, and covers a wide range of compounds containing nitrogen. Their interaction with manganese dioxide may involve oxidation of alkyl groups, cleavage of carbon–carbon bonds, and dehydrogenation of carbon–carbon and carbon–nitrogen bonds. The process may be either unimolecular or bimolecular.

The oxidation of amino-compounds with manganese dioxide in acid medium is widely used for the synthesis of various classes of compounds. An example is provided by the oxidation of aniline with the natural dioxide in acid medium to form *p*-benzoquinone[262]. In dilute acetic acid the oxime (LXIII) is readily converted into the nitro-compound (LXIV):[263]



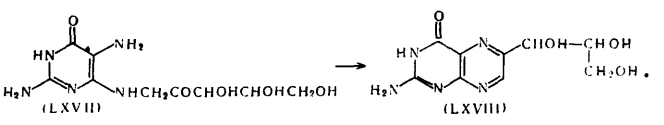
3-(2-Piperidyl)pyridine (anabasine) on oxidation with manganese dioxide in sulphuric acid gives a 45% yield of nicotinic acid[264]. Isonicotinic acid has been obtained by the oxidation of 4-ethylpyridine[228] and 4-methylpyridine[265].

When pyridoxamine (LXV) is subjected to prolonged heating with manganese dioxide in water containing sulphuric or phosphoric acid[45,266], the aminomethyl group is converted into an aldehyde group (LXVI):



(LXV) (LXVI)

Among recent work mention must be made of the paper by Lagowski and Forrest[267] describing the preparation of 2-amino-3,4-dihydro-4-oxo-6-(L-*erythro*-1,2,3-trihydroxypropyl)pteridine (LXVIII) by oxidation of the 1-pyrimidinylamino-1-deoxypentulose (LXVII):



(LXVII) (LXVIII)

In 1955 Highet and Wildman[14] accomplished the oxidation of benzylamine, *N*-methylbenzylamine, and *N*-methylpiperonylamine with manganese dioxide in chloroform. The infrared spectrum of the oxidation product of benzylamine was almost identical with that of hydrobenzamide, which confirms the intermediate formation of the imine (LXIX):

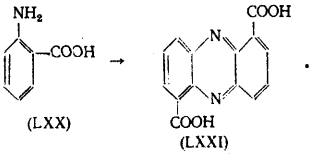
$$R{-}CH_2NH{-}CH_3 \rightarrow R{-}CH{=}N{-}CH_3.$$
(LXIX).

Tertiary amines do not undergo this reaction, which was subsequently extended to anilines, *N*-alkylanilines, hydrazines, and hydrazones of carbonyl-containing compounds.

Great attention has been paid to the oxidation of various ring-substituted anilines to azobenzenes. Various oxidising agents — including per-acids[268], diacetoxyiodobenzene[269], sodium borate[270], lead tetra-acetate[271], etc. — have previously been used for this purpose. The simplicity of the oxidation procedure and the availability of manganese dioxide have made this method the most widely used in the synthesis of azobenzenes. Barakat et al.[35] investigated the oxidation of aniline, *o*- and *p*-chloroanilines, *p*-toluidine, 1- and 2-naphthylamines, and also *o*-, *p*-, and *m*-nitroanilines with alkaline manganese dioxide in petroleum ether. Aniline and methyl- and chloro-anilines gave the corresponding azobenzenes in excellent yields.

Wheeler and Gonsalez[272] derived several general rules from a study of the oxidation with active manganese dioxide of a series of ring-substituted anilines. One of their main conclusions was that the electronic character of the substituent has no appreciable effect on the reaction velocity or the yield of the oxidation product, although a slight electronic effect is nevertheless present. Thus *para*-substituted anilines react somewhat faster than other isomers. In a series of halogenoanilines the rate of oxidation falls in the sequence F > Cl > Br > I. 3,5-Dichloro- and 2,6-dimethoxy-anilines react normally, as does 3-chloro-4,6-dimethoxyaniline. However, several substituted nitroanilines — 2-iodo-4-nitro-, 2,6-di-iodo-4-nitro-, and 2-methyl-5-nitro-anilines — do not react with manganese dioxide. This cannot be explained by the electronic effects of the substituents, for in some cases the nitro-group facilitates oxidation. One possible explanation is that the nitro-group itself may be adsorbed on the surface of the manganese dioxide, and thereby prevent oxidation of the amino-group. Therefore 3,5-dichloro-4-nitroaniline, in which adsorption of the nitro-group is impeded by the neighbouring chlorine atoms, forms the azobenzene to a slight extent, whereas 3,5-dichloro-2-nitroaniline, in which the electronic effect of the chlorine atoms is the same as in the 4-nitro-isomer, is completely incapable of being oxidised.

Carboxyl resembles the nitro-group in having an unfavourable effect. The diminished polarity of the carboxyl in ethyl *p*-aminobenzoate, and the consequently diminished adsorbability of carboxyl on the manganese dioxide surface, make it possible to obtain a low yield of diethyl azobenzene-*pp'*-dicarboxylate. It has recently been found[273] that anthranilic acid (LXX) is oxidised in low yields to phenazine-1,6-dicarboxylic acid (LXXI):



(LXX) (LXXI)

The relatively minor influence of the nature of the substituents in the oxidation of amines can be regarded as an indication that this reaction has a free-radical mechanism. The formation of free radicals as intermediate products in the oxidation of amines has been suggested by Henbest and Stafford[274]. It must not be overlooked, however, that adsorption phenomena may mask the influence of the electronic structure of substituents in the actual oxidising step. Thus the oxidation of primary aromatic amines is a bimolecular adsorption dehydrogenation of the amino-group.

This idea has been developed by Pratt and McGovern[38], who have studied the oxidation of *N*-benzylanilines (LXXII) to benzylideneanilines (LXXIII):

$$X{-}C_6H_4CH_2NH{-}C_6H_4{-}X' \xrightarrow{MnO_2} X{-}C_6H_4CH{=}N{-}C_6H_4{-}X'.$$
(LXXII) (LXXIII)

Since an important part is played by the adsorption of anilines on the surface of the manganese dioxide, *ortho*-substituted benzylanilines react more slowly than the *para*-substituted isomers, and the *o*-methoxy-derivatives are oxidised far more slowly than the *o*-methylated compounds, since the former contain a more bulky substituent. Furthermore, the rate of oxidation of benzylanilines is independent of the electronic characteristics of the substituents.

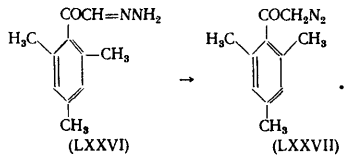
Hydrazobenzenes (LXXIV) are extremely readily dehydrogenated to azobenzenes (LXXV) in high yields:

$$X{-}C_6H_4{-}NH{-}NH{-}C_6H_4{-}X \rightarrow X{-}C_6H_4N{=}N{-}C_6H_4X.$$
(LXXIV) (LXXV)

The rate of this oxidation is hardly affected at all by substituents.

The oxidation of hydrazones of carbonyl compounds by manganese dioxide represents a unimolecular dehydrogenation of the amino-group. Barakat showed that the active dioxide is able to oxidise hydrazones of ketones to azines. The appearance of a violet colour in the solution suggests formation of a diazo-compound as an intermediate stage in the oxidation. Schroeter[275] reported that active manganese dioxide oxidised hydrazones of substituted benzophenones to diazo-derivatives, though in lower yields than with oxidation by silver oxide. The dihydrazone of dibenzoylbenzene is converted under these conditions into a bisdiazo-compound[276,277]. Morrison and Danishefsky[278] used alkaline manganese dioxide to prepare diazo-ketones from

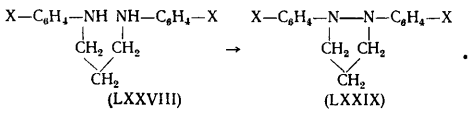
monohydrazones of diketones and keto-aldehydes. Mesitylglyoxal hydrazone (LXXVI) when shaken with the active dioxide forms diazomethyl mesityl ketone (LXXVII):



(LXXVI) (LXXVII)

Diekmann[279] obtained by means of manganese dioxide a 55% yield of bisphenylsulphonyldiazomethane from the hydrazone of bisphenylsulphonylformaldehyde. A similar reaction has been described with dihydrazones[280], where it is probable that diazo-compounds are also intermediate products[281]. Phenylhydrazides of acids form, with manganese dioxide in dilute acetic acid, aromatic hydrocarbons[282,283], while methylhydrazine in the presence of alkali forms ethane[284].

The oxidation of trimethylenediamines also consists in the oxidative dehydrogenation of the two amino-groups with subsequent intramolecular cyclisation to a pyrazoline. Wittig[285] obtained from *NN'*-diphenyltrimethylenediamine a 31% yield of 1,2-diphenylpyrazolidine. A more detailed study of this reaction has been made by Daniels and Martin[286], who found that the oxidation depends to a considerable extent on the type of active dioxide used. The conversion was investigated of a large number of 1,3-bisarylaminopropanes (LXXVIII) into the corresponding 1,2-diarylpyrazolidines (LXXIX):



(LXXVIII) (LXXIX)

In the case of *NN'*-di-*p*-methoxyphenyltrimethylenediamine the product is *pp'*-dimethoxyazobenzene[287]. Nevertheless, the corresponding ethoxy-derivative reacts normally, with formation of a pyrazolidine ring. *NN'*-Dialkyltrimethylenediamines do not undergo this reaction.

N-Alkylanilines undergo a different type of reaction with active manganese dioxide, alkyl and methylene groups in the amines being involved. Henbest et al.[32,288] studied the oxidation of *N*-alkyl- and *NN*-dialkyl-anilines with a large excess of manganese dioxide (ratio of reactants 1 : 50–100), and showed that three types of reactions could occur in this case — (*a*) formation of an amide

$$\rangle N{-}CH_3 \rightarrow \rangle N{-}CHO;$$

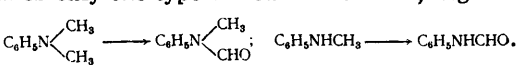
(*b*) dealkylation with formation of an aliphatic aldehyde

$$\rangle N{-}CH_2R \rightarrow \rangle NH + RCHO;$$

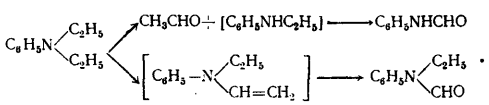
(*c*) dehydrogenation at an alkyl C–C bond followed by cleavage of the resulting enamine

$$\rangle N{-}CH_2CH_2R \rightarrow \left[\rangle N{-}CH{=}CH{-}R\right] \rightarrow \rangle NCHO + RCHO.$$

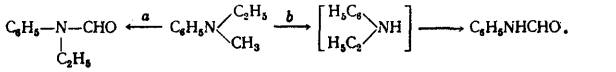
Sometimes only one type of reaction occurs, e.g.



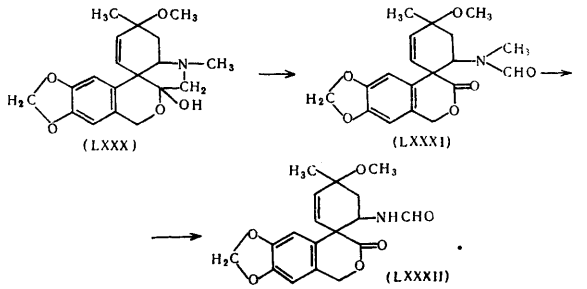
With diethylaniline the course of the reaction is more complicated:



Enamines are readily cleaved by manganese dioxide, as has been shown by the oxidation of *NN*-dibenzylstyrylamine to *NN*-dibenzylformamide[288], and also in the oxidation of sporidesmin[289] with a freshly prepared active dioxide. Introduction of a *p*-methyl group was found to facilitate the reaction, whereas a *p*-nitro-group impeded it. Small quantities of azobenzenes are formed as side-products in the oxidation of *N*-ethyl-*N*-methyl- and *NN*-diethyl-anilines. *N*-Ethyl-*N*-methylaniline yields both *N*-ethylformanilide and formanilide itself:

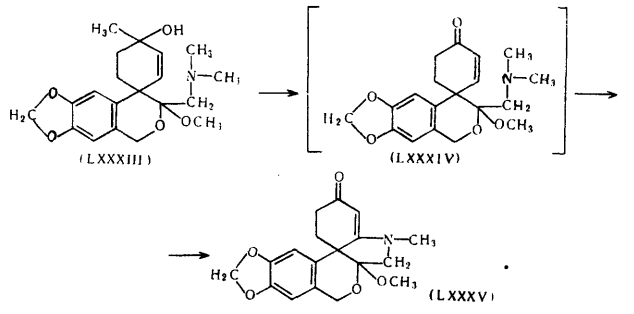


1,4-Diphenylpiperazine forms *NN'*-diformyl-*NN'*-diphenylethylenediamine, the process consisting in oxidative cleavage of a carbon–carbon single bond. This reaction is of great importance, for it represents the only known method of converting ethylenediamines into *N*-formyl derivatives. It has been used for the oxidation of tazettine to tazettamide, and of dihydrotazettine to dihydrotazettamide[290], and also in analytical practice for the determination of ethyl groups in diethylamino-compounds[291]. Japanese workers[292,293] have been able to isolate from oxidation of the alkaloid tazettine (LXXX), besides tazettamide (LXXXI), products of further oxidation, including *N*-desmethyltazettamide (LXXXII):



(LXXX) (LXXXI) (LXXXII)

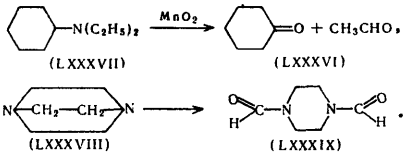
It is interesting that oxidation of a similar dimethylamino-derivative (LXXXIII)[294] produces, instead of the expected cyclohexenone (LXXXIV), oxidative elimination of one *N*-methyl group with cyclisation to dihydro-*O*-methyltazettinone (LXXXV):



(LXXXIII) (LXXXIV) (LXXXV)

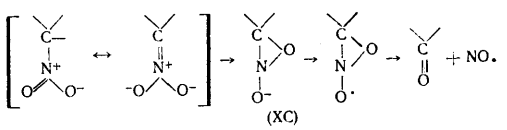
In some cases oxidation with manganese dioxide does not affect a dimethylamino-group[295]. With dialkylbenzylamines[296] the reaction consists in oxidation of the methylene group of the benzyl radical with detachment of the amino-group, various yields of benzaldehyde being formed in all cases. Tribenzylamine reacts very slowly, probably owing to steric hindrance to adsorption on the surface of the dioxide. Dialkylcyclohexylamines are transformed in good

yields into cyclohexanone (LXXXVI), the diethyl derivative (LXXXVII) being oxidised also at the ethyl group to form acetaldehyde[288]. Triethyleneamine (LXXXVIII) is oxidised with cleavage of a C–C bond to 1,4-diformylpiperazine (LXXXIX):

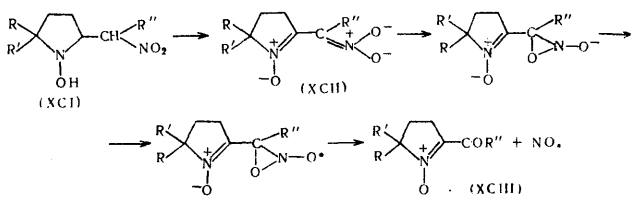


Active manganese dioxide has been successfully used for dehydrogenation at a carbon–nitrogen bond in nitrogen heterocycles. Thus tetrahydroquinazoline derivatives are converted into good yields of the corresponding dihydroquinazolines[297], and similarly pyrrolidine into pyrroline derivatives[298].

The oxidative elimination of nitric oxide from nitro-compounds represents a special case of the use of active manganese dioxide. The literature contains examples of analogous reactions in the presence of per-acids and quinones. Thus Jones[299] showed that 4-nitro-2,6-diphenylphenol when heated with an oxidising agent loses nitric oxide and is converted in good yield into 2,6-diphenyl-1,4-benzoquinone. Such reactions are regarded as taking place according to the following scheme



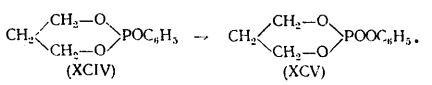
The oxaziran ring (XC), which is formed when a C=N double bond is present, breaks down to form a carbonyl compound and nitric oxide. Bowering et al.[300] have shown that a similar reaction is possible with 2-nitroalkylhydroxylamines:



Ethyl 1-hydroxy-2-methyl-5-(1-nitroethyl)pyrrolidine-2-carboxylate (XCI; R = $COOC_2H_5$, R′ = R″ = CH_3) is oxidised to the pyrroline anion (XCII), which is then converted according to the above scheme into the *N*-hydroxypyrroline (XCIII). The reaction takes place in petroleum ether at room temperature and lasts 4–6 h.

VIII. OXIDATION OF OTHER CLASSES OF COMPOUNDS

Active manganese dioxide is a good oxidising agent for tervalent phosphorus compounds. This reaction was first used for the conversion of triphenylphosphine into triphenylphosphine oxide[35]. Phenyl trimethylene phosphite (XCIV), obtained by reaction of triphenyl phosphite with trimethylene glycol, gives when shaken with manganese dioxide a 56% yield of the corresponding phosphate (XCV):[301]



Kabachnik and his coworkers have described the oxidation by means of active manganese dioxide of tertiary vinylphosphines[302], dibutyl-2-piperidinoethylphosphine, and dibutyl 2-piperidinoethyl phosphite to the corresponding oxides[303]. They have also studied the oxidation of vinyl-, allyl-, and vinylphenyl-phosphonous esters[304]. In all these cases reaction takes place readily, to give high yields without the formation of side-products.

Edwards and Stenlake[305] successfully used manganese dioxide for the oxidation of alkyl sulphides, and a paper has recently been published on the oxidation of various thiols with this oxidant[306].

Several papers have been published on the action of manganese dioxide on carbohydrates[307,308] — aldohexoses (galactose, ribose, erythrose, etc.), ketoses (inosose, fructose), disaccharides (sophorose, maltose, cellobiose, and melibiose). The oxidation of aldohexoses involves mainly elimination of $C_{(1)}$ with formation of the corresponding aldopentoses. These are accompanied by a certain quantity of epimerisation products and a mixture of C_{6-3} acids. Results of the oxidation of 3-*O*-methyl-D-glucose and of rhamnose indicate that this reaction may be of preparative value, e.g. for the synthesis of *O*-methylpentoses or deoxypentoses. Disaccharides react similarly: hexosylhexoses give hexosylpentoses. Interesting results have been obtained for the oxidation of D-fructose[309]: the manganese dioxide reacts with the carbonyl group adjacent to the first carbon atom of D-fructose with the formation of the 2-oxo-D-arabinoaldohexose, but with inadequate selectivity.

Manganese dioxide has been used in aqueous medium for the oxidation of derivatives of nucleic acids and similar compounds. Thymidine 5′-phosphate[310], adenine, 6-methylaminopurine, guanine, and 9-ethylguanine[311] have been subjected to oxidation. The latter compounds are oxidised fairly rapidly, products of the degradation of the purine ring — urea, alkylureas, guanidine, biuret, etc. — being formed. Purine nucleosides — adenosine and guanosine — are oxidised rather more slowly. Pyrimidine nucleosides — uridine, cytidine, and thymidine — remain unchanged during the same conditions.

The present review shows that during recent years active manganese dioxide in its various modifications has been finding ever wider use for numerous reactions of an oxidising character involving diverse classes of organic compounds.

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Institute of Petroleum-Chemical and
Coal-Chemical Synthesis, Zhdanov Irkutsk
State University, Angarsk

