OXIDATIONS BY FERRICYANIDE

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I. INTRODUCTION

In recent years several oxidizing agents, specific and selective to varying degrees, have been added to the literature of organic chemistry. Selenium dioxide, aluminum alkoxides, lead tetraacetate, osmium tetroxide, *tert*-butyl chromate, the chromium trioxide–pyridine complex, organic per acids, periodic acid, potassium ferricyanide, and peroxytrifluoroacetic acid have greatly enhanced the skill of the organic chemist in introducing and attacking particular groups in simple or large molecules.

Many of these reagents have been discussed in great detail in earlier reviews (27, 44, 88, 104). However, no extensive review or summary is available on potassium ferricyanide as an oxidizing agent in organic chemistry.

Potassium ferricyanide falls into the class of oxidizing agents comprising ceric sulfate, ammoniacal silver nitrate, and Fehling's solution, in all of which the oxidizing species is a complex electron-abstracting ion.

$$[Fe(CN)_6]^{3-} + e \rightarrow [Fe(CN)_6]^{4-}$$

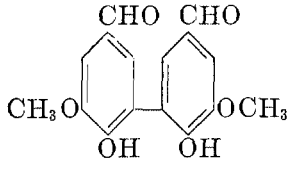
Consequently, ferricyanide has been used in systems obviously favored for oxidation in this manner, that is, extraction of an electron from an electron-rich site. Similar oxidations are also encountered in biological systems of the cytochrome type, where a "one-electron transfer" is involved. However, there are innumerable instances where the reagent has also been utilized with considerable success even though its capability was not originally apparent. The present review is an attempt to cover the extensive literature built around the various types of oxidations where alkaline ferricyanide has been successfully

employed. Since in recent times there has been a revival of interest particularly in the structures of the several products of oxidation of phenols with this reagent, this phase is dealt with first, followed by other applications in the order of relative utility.

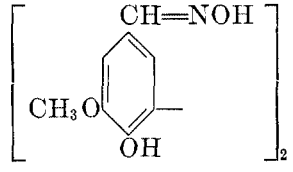
II. OXIDATION OF PHENOLS

Since potassium ferricyanide acts as a "one-electron abstracter," the primary action of this reagent on phenols is the formation of aryloxy radicals. The radical then reacts by decomposition and/or rearrangement to give the final product. Such radicals are a more stable species than alkyl radicals because of the spread of the odd electron by resonance over the ortho and para positions of the aromatic ring. As mesomeric radicals encounter each other, mutual perturbation of the electronic systems contributes alternative activated transition states, in each of which the unpaired electron is localized at a possible point of chemical reactivity. With the formation of the phenol radicals, conversion to a stable molecule may take place by any one of several processes. Nonradical products are formed by coupling with reactive molecules like oxygen or halogen, while self-coupling furnishes dimers and trimers. The latter could result from carbon–carbon coupling, carbon–oxygen linkage, or oxygen–oxygen union. In the aryloxy radicals, carbon–carbon coupling could occur at ortho-ortho, ortho-para, or para-para positions. It is this variety of possible types of union that leads to the different structures of the products of such oxidation.

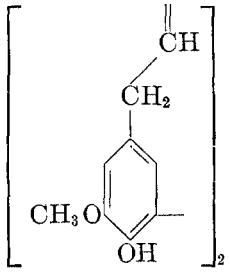
Dehydrodivanillin (I) obtained by the oxidation of vanillin, dehydrodivanillin oxime (II), dehydrodieugenol (III), dehydrodi-*o*-cresol (IV), dehydrodi-*p*-cresol (V), dehydrodi-β-naphthol (VI), and dehydrodi-2,4-dimethylphenol



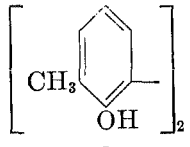
I
Dehydrodivanillin



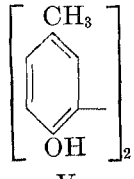
II
Dehydrodivanillin oxime



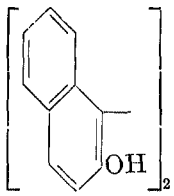
III
Dehydrodieugenol



IV
Dehydrodi-*o*-cresol

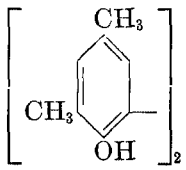


V
Dehydrodi-*p*-cresol



VI

Dehydrodi-β-naphthol

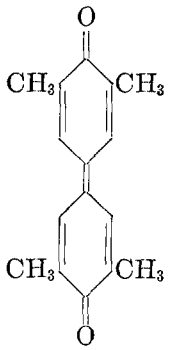


VII

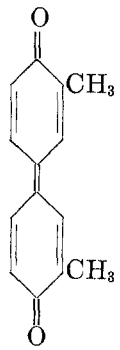
Dehydrodi-2,4-dimethylphenol

(VII) are examples of ortho-ortho carbon–carbon coupling (10, 19, 28, 34, 78, 83, 107).

Examples of para-para coupling are provided by the oxidation products of 2,6-dimethylphenol and *o*-cresol (10, 18, 19).



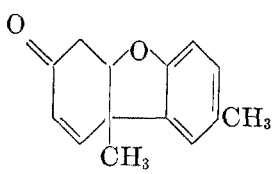
VIII



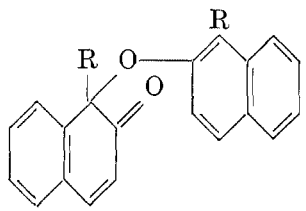
IX

The best example of ortho-para coupling is the case of the oxidation of *p*-cresol to the dimeric neutral ketone X (19, 83).

Carbon–oxygen union, although a less frequent occurrence, is still an authenticated process. 1-Bromo-2-naphthol and 1-methyl-2-naphthol afford compounds incorporating such a linkage (XI) (76, 87).



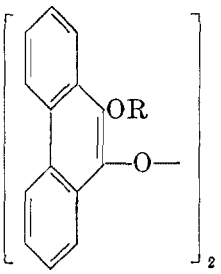
X



XI

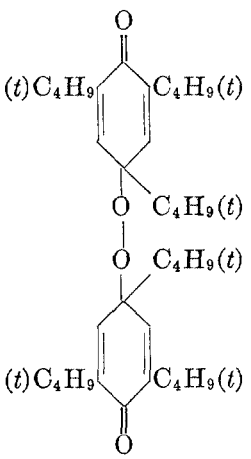
R = Br or CH_3

Oxygen–oxygen coupling is even rarer and is encountered in the product (XII) of the oxidation of the monoethyl and monomethyl ethers of phenanthrene hydroquinone (31).

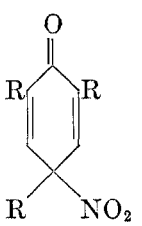


XII

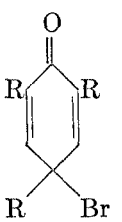
In all the instances referred to above, the radicals exist in equilibrium with their dimers only in solution; in the solid phase they exist solely as the more stable dimers. However, with suitably substituted phenols, much more stable radicals have been prepared and isolated and their stability clearly demonstrated. When 2,4,6-tri-*tert*-butylphenol is oxidized in ethereal or benzene solution with alkaline ferricyanide, an intensely blue colored solution is obtained. The color is attributed to the 2,4,6-tri-*tert*-butylphenoxy radical. The color is stable in the absence of air or oxygen, but in the presence of these the peroxide (XIII) was formed (12, 17, 61, 62, 63). The phenoxy radicals react rapidly with acidic solutions of sodium iodide, liberating iodine and the original phenol. With bromine and nitric oxide they give addition products (XIV, XV) which are thermally unstable and decompose around 90°C.



XIII

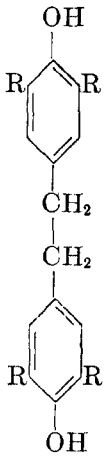


XIV

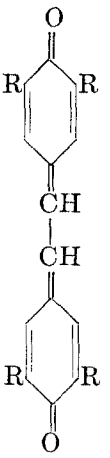


XV

The yields of the radicals are of the order of 99–100 per cent when the oxidation is carried out in a nitrogen atmosphere and with mechanical stirring. However, when the ortho or para position of the phenols carries a methyl group, as in 2,6-di-*tert*-butyl-4-methylphenol, the phenoxy radical rearranges to give two products (XVI, XVII) (14).

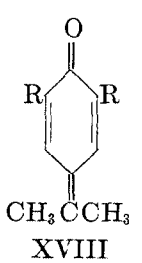


XVI

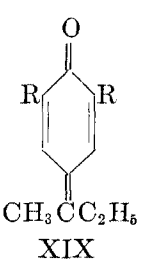


XVII

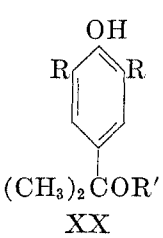
Quantitative measurements of these products (XVI and XVII) confirm the stoichiometry and suggest that the phenoxy radical immediately rearranges to the benzyl radical. Similarly, 2,4-di-*tert*-butyl-6-methylphenol (60), 2,4,6-trimethylphenol (18, 39), and 2,6-di-*tert*-butylphenol afford dimers on oxidation. On the other hand, 2,4,6-trialkylphenols without an α-hydrogen, like 2,4,6-tri-*tert*-amylphenol, 2,6-di-*tert*-butyl-4-methoxyphenol, 2,6-di-*tert*-butyl-4-ethoxyphenol, and 2,6-di-*tert*-butyl-4-butoxyphenol all yield stable phenoxy radicals on oxidation. The requirements for a stable monocyclic phenolic radical are therefore that the ortho and para positions must be substituted to prevent nuclear dimerization and the substituents must not have α-hydrogen atoms. This is well exemplified also by the behavior of 2,6-di-*tert*-butyl-4-isopropyl- and 4-*sec*-butylphenols, which carry a tertiary α-hydrogen in the side chain (15). The products in these cases are radicals which give blue solutions and as usual form the biscyclohexadienone peroxides with oxygen. However, continued oxidation produces the quinone methides (XVIII, XIX). Alcohols add to these methides giving the corresponding *p*-alkoxymethylphenols (XX), which then give stable radicals on oxidation in the same way as the tri-*tert*-butylphenols do. Reduction of the methides (XVIII, XIX) with lithium aluminum hydride regenerates the original phenols.



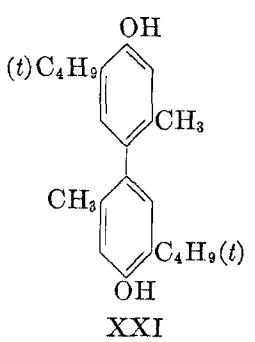
XVIII



XIX



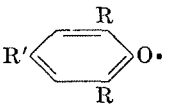
XX



XXI

TABLE 1

Phenoxy radicals



R	R′	Color of Radical	Infrared Peaks
tert-Butyl	*tert*-Butyl	Blue	1507 M, 1573 S
tert-Amyl	*tert*-Amyl	Blue	1507 M
tert-Butyl	Dimethylmethoxymethyl	Blue	
tert-Butyl	Dimethylethoxymethyl	Blue	
tert-Amyl	*tert*-Amyloxy	Red	
	Methoxy	Red	1590 S, 1509 M
tert-Butyl	Ethoxy	Red	1590 S, 1509 M
tert-Butyl	*tert*-Butoxy	Red	1590 S, 1509 M

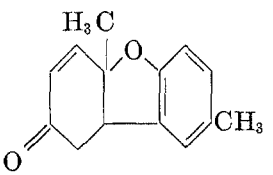
Attempts have also been made to produce stable oxygen diradicals (4). Only the bisphenol XXI could be oxidized with alkaline ferricyanide in benzene solution in a nitrogen atmosphere to produce a red glass whose electronic paramagnetic spin resonance showed the radical nature of the product.

In all the various phenoxy radicals discussed above, the color of the radical varies between red and blue depending on the substituents (see table 1).

The *p*-alkoxyphenoxy radicals appear to be considerably more stable than the *p*-alkylphenols. The infrared spectra of the phenoxy radicals show characteristic absorptions resembling a weak carbonyl absorption (13). Measurements of magnetic susceptibility show the presence of the unpaired electron.

III. MECHANISM OF OXIDATION OF PHENOLS

The uncertainty regarding the mechanism of the oxidation of phenols by ferricyanide is well exemplified by the erroneous formulation of several of the products obtained from various phenols. The structure assigned (XXII) for the neutral dimer from the oxidation of *p*-cresol by Pummerer (83) was accepted as correct even as late as 1953 (108).



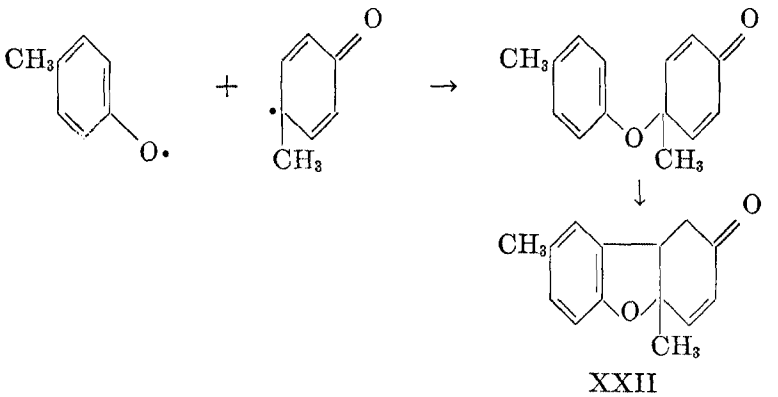
XXII

The synthesis of the same compound by oxidizing *p*-cresol in neutral solution with dilute hydrogen peroxide together with the enzyme peroxidase was taken as conclusive evidence for the above structure.

However, the brilliant two-step synthesis of the lichen substance usnic acid from the dimerization of methylphloroacetophenone under the action of alkaline ferricyanide (2, 3) established decisively the erroneous nature of the earlier representations for these dimers.

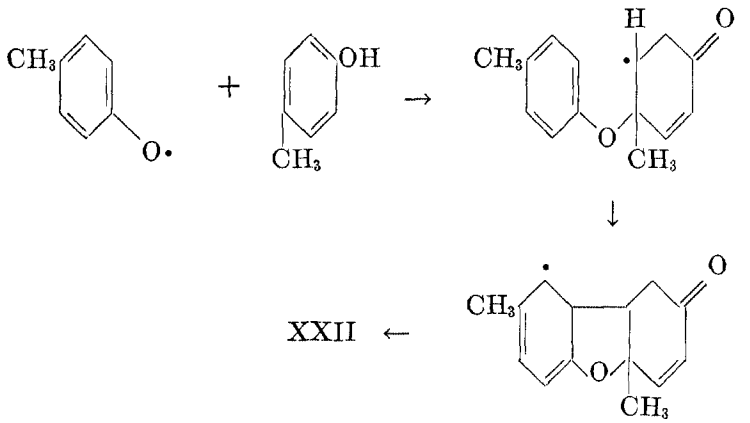
The mode of formation of a compound originally postulated by Pummerer as the dimer (XXII) involved an intermediate of the type shown in schemes I and II.

Scheme I:



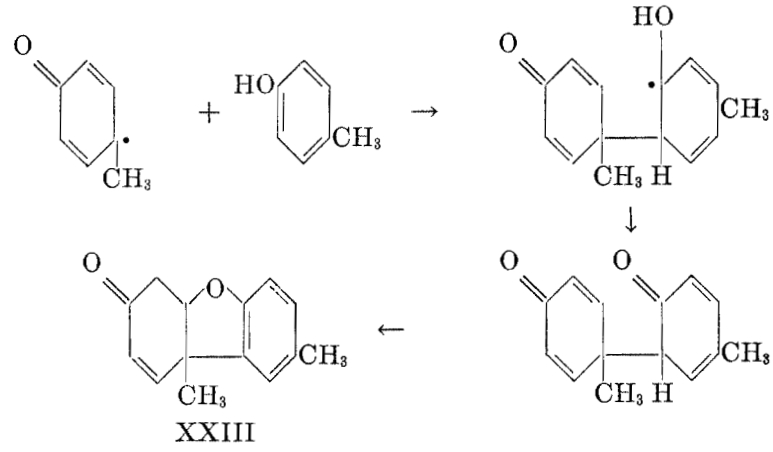
XXII

Scheme II:



In the two schemes, the last step of cyclization to a furan derivative is considered improbable, since the hemiquinone formation would be the more likely step on the basis of analogy with similar hemiquinone radicals encountered in the oxidation of quinols and catechols. A third scheme, which was verified by the synthesis of usnic acid, involves on the other hand a carbon–carbon coupling ortho to the hydroxyl by substitution of the radical on the phenol molecule and subsequent addition of the phenolic hydroxyl to the β-enone system resulting in the formation of Pummerer's ketone.

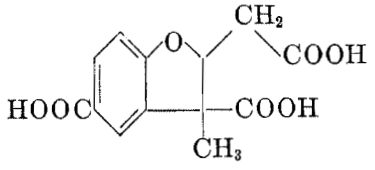
Scheme III:



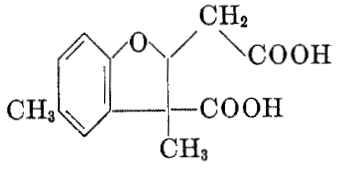
XXIII

Even here, an alternate scheme involving radical pairing instead of radical substitution has been advanced for the formation of the same product, and no special reason exists for preferring one scheme to the other in biogenetic arguments.

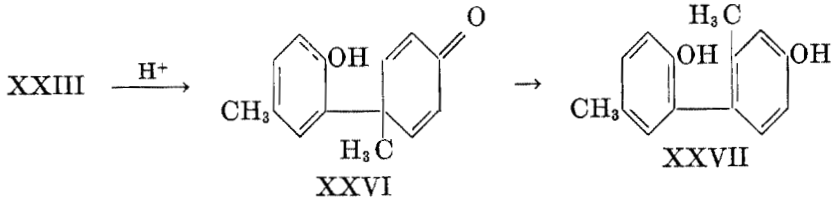
The new formulation for Pummerer's ketone accords well with the degradation products of the compound. Acid cleavage to yield 2,3′-dicresol can be explained by a dienone–phenol rearrangement (XXVI, XXVII), while the di-



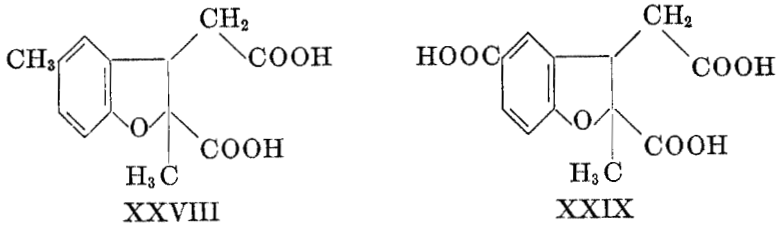
XXIV



XXV



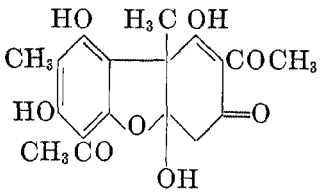
XXVI XXVII



XXVIII XXIX

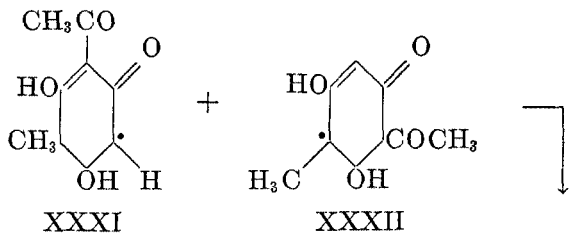
carboxylic acid and tricarboxylic acid obtained by permanganate oxidation (84, 109) would be formulated as shown in formulas XXV and XXIV instead of as in formulas XXVIII and XXIX

By a similar line of arguments, the oxidation of methylphloroacetophenone should yield the dimer XXX.

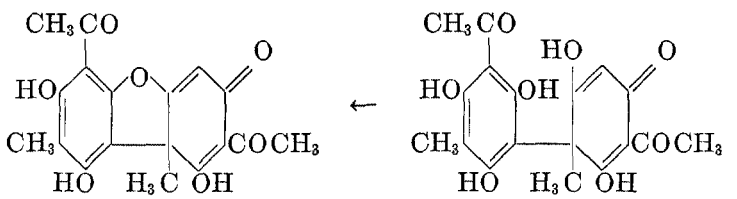


XXX

That the usnic acid molecule is divisible into two *C*-methylphloracetophenone units has been appreciated for many years. Hence the revision of the constitution of the *p*-cresol dimer led directly to the brilliant synthesis of this lichen substance on the following lines (XXXI to XXXIV).

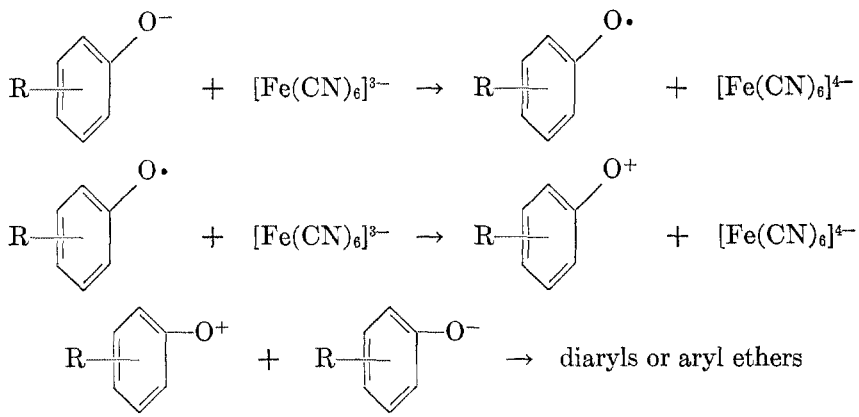


XXXI XXXII



XXXIV XXXIII

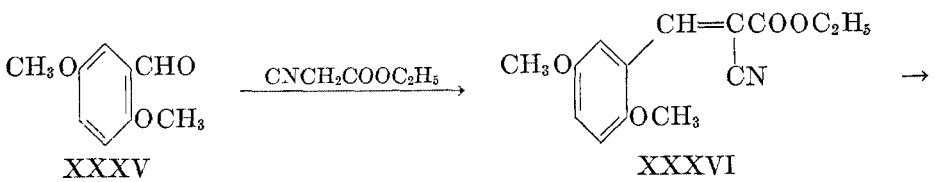
Although the formation of products of the kind discussed above is well understood as resulting from the radical substitution or radical pairing of the mesomeric aryloxy radicals, kinetic studies of the oxidation of phenols by ferricyanide show that the dimers could well be represented as arising from condensations between phenol molecules and mesomeric aryloxy cations (40). This would mean that the coupling process is not homolytic but heterolytic, involving a cationoid substitution of a phenol molecule by a mesomeric aryloxy cation formed by a second-stage oxidation of the aryloxy radical.



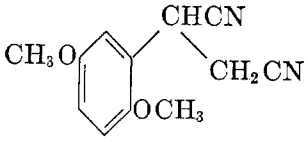
Evidence in support of this observation has been derived from the fact that under varied conditions the oxidation always requires the consumption of more than one equivalent of ferricyanide. In many instances it is also found that the products carry aromatic nuclei coupled together only in the ortho or para position to the original hydroxyl groups. However, in all these oxidations only part of the products is often separated into ketonic or phenolic compounds, while considerable amounts are chemically intractable resins probably arising out of consecutive oxidations of the dimers. These factors complicate the interpretation of the kinetic data. However, certain conclusions emerge from these measurements. In the oxidation of *p*-cresol, for instance, the complexity of the reaction increases with the alkalinity of the medium but the yield of Pummerer's ketone is constant. In general, also, the velocity of oxidation increases with alkalinity in such a way as to indicate that the oxidizable species are aryloxy anions and not phenol molecules. At all stages, the velocities of oxidation decrease with increase of ferrocyanide concentration, a result which is to be expected if the primary step in the oxidation is the reversible one-electron transfer. Still, the complexity of the oxidation is so great as to invalidate any conclusion concerning the order of the reaction with respect to the phenol. No simple kinetic expression can therefore be derived for these oxidations.

IV. SYNTHESIS OF INDOLE DERIVATIVES

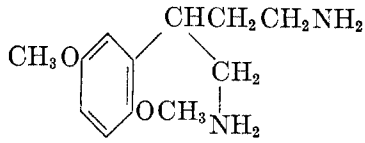
Another reaction involving a phenolic starting material is the synthesis of selected indoles. Several natural products like bufotenine, serotonine, physostigmine, eseroline, and eserethole have been made by the alkaline ferricyanide oxidation of appropriate phenethylamines or tryptamines (36, 37, 38). Other 5-hydroxy- and 7-hydroxyindoles have also been made by this procedure. The syntheses of serotonine and bufotenine are illustrated in the following schemes:



XXXV XXXVI



XXXVII



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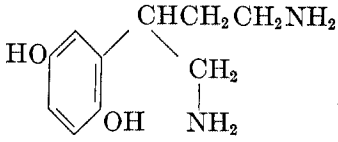

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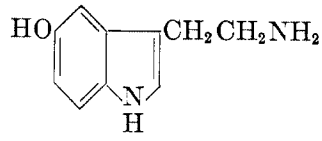

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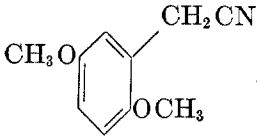
Serotonine



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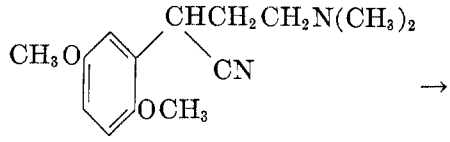

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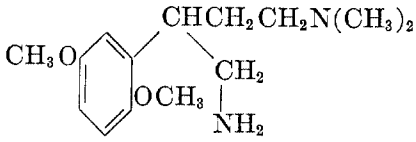

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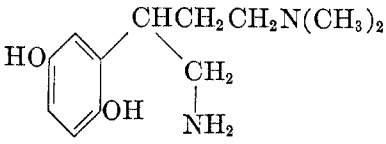

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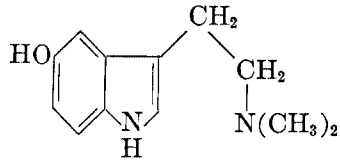

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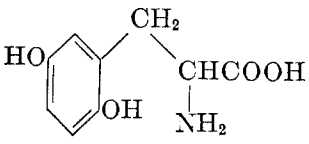
Bufotenine

The yields of the indoles in the final step of oxidation with alkaline ferricyanide in the two cases of bufotenine and serotonine are 45 and 48 per cent, respectively. However, their 6-hydroxy derivatives could be obtained only in traces.

Substituted phenylalanines also give the hydroxyindoles in high yields with decarboxylation in the last step from the 2-indolecarboxylic acid. However, again 2,3-dihydroxyphenylalanine and 2,3-dihydroxyphenethylamine gave only traces of the corresponding indoles (20, 21).



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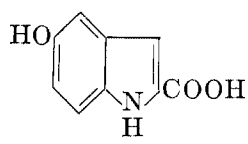

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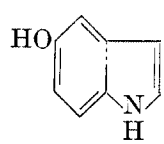

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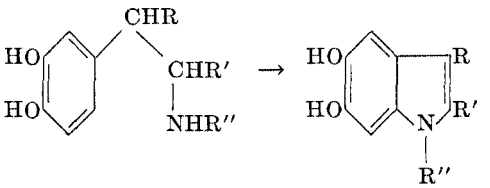
TABLE 2

Yields of 5,6-dihydroxyindoles obtained by the oxidation of amines with alkaline ferricyanide



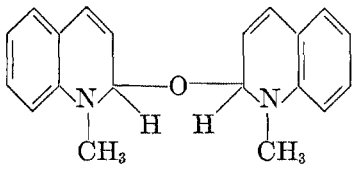
Substituents	Yield	Substituents	Yield
	per cent		*per cent*
R = R′ = R″ = H	Traces	R = OH; R′ = R″ = H	0
R = R″ = H; R′ = CH_3	Traces	R = OH; R′ = H; R″ = CH_3	62
R = R′ = H; R″ = CH_3	60	R = OH; R′ = H; R″ = i-C_3H_7	40
R = R″ = H; R′ = COOH	5–30	R = OH; R′ = CH_3; R″ = H	20
R = H; R′ = COOH; R″ = CH_3	40		

The yields of 5,6-dihydroxyindoles vary according to the nature of the substituent on the side chain. Thus, while adrenaline and *N*-isopropyladrenaline afford 3,5,6-trihydroxy-1-methyl- and 1-isopropylindoles in 62 and 40 per cent yields, respectively, others range from 0 to 30 per cent. The yields are summarized in table 2 (7, 8, 9).

The synthesis of these indole derivatives demonstrates the role of phenol oxidation in the possible biogenetic modes of formation of the indole alkaloids like lycorine, tazettine, caranine, lycorenine, galanthamine, and the erythrina bases. There are numerous other plant products whose biogenesis by such phenol coupling is self-evident.

V. OXIDATION OF HETEROCYCLIC QUATERNARY SALTS

Aside from the oxidation of phenols, a reaction in which alkaline ferricyanide has been most extensively used is the oxidation of *N*-substituted pyridinium, quinolinium, and similar heterocyclic quaternary salts to the corresponding pyridones (70). The earliest account of such oxidation is the preparation of *N*-methyl- and *N*-ethylpyridone, *N*-methyl- and *N*-ethylquinolone, and *N*-methylisoquinolone (22, 23, 29, 30). The possibility of two α-pyridones arising out of unsymmetrically substituted pyridinium salts was considered even then. The oxidation was supposed to proceed in two steps: viz., formation of the pseudobase and dehydrogenation of the pseudobase. However, in solution the pseudobase does not appear to be the main form, since conductivity measurements on pyridine methiodide before and after neutralization with alkali show no decrease. Methylquinolinium iodide, on the other hand, showed the formation of an ether when it was treated with silver oxide and the reaction was followed titrimetrically (24, 25, 26, 35). This has been confirmed by subsequent investigations on the kinetics and mechanism of formation of the pseudobase from 1-methylquinolinium salts (1, 35). While the pyridinium salts do not form the dimolecular ethers, quinolinium compounds do. This has been attributed to the fact that systems



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with a small concentration of quaternary ion and hydroxyl ions or with insufficient pseudobase formation do not form the ether and in pyridine salts very little or no pseudobase formation occurs at all.

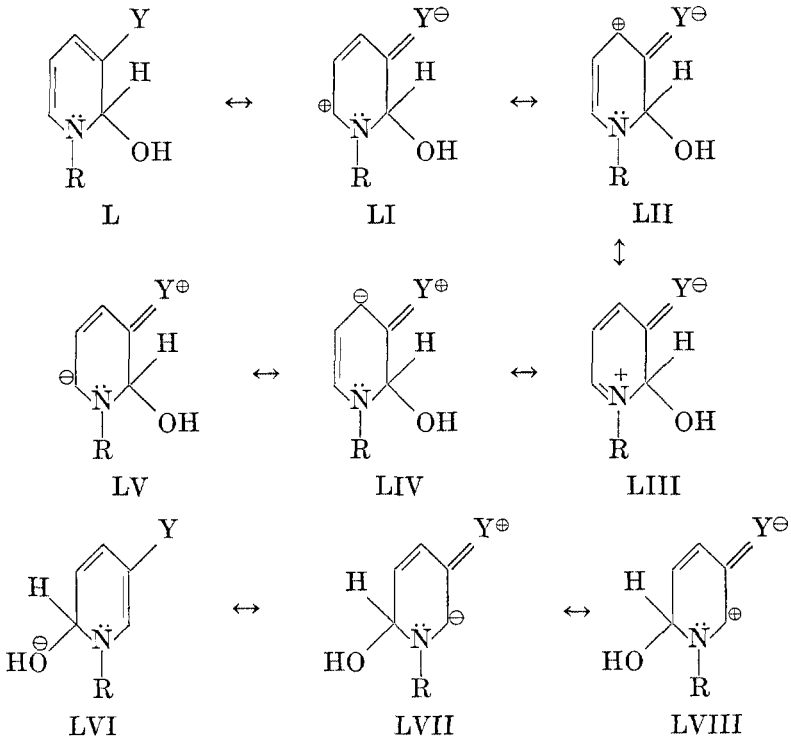
The preparation of pyridones by this method has greatly facilitated the synthesis of pyridone alkaloids like cytisine and anagyrine or the preparation of intermediates towards their synthesis. This has also opened up a new method of synthesis of benzoquinolizines (102, 106).

However, ambiguity exists in the case of unsymmetrically substituted *N*-alkylpyridinium salts, since the pyridone formation can occur either at the 2- or the 6-position. The determination of the orientation of such compounds becomes imperative in the synthesis of products like emetine (5, 71, 93) or in establishing the structures of compounds like the nicotinamide moiety of the coenzymes I and II.

The most controversial compound in this series is the pyridone obtained by the oxidation of the *N*-methyl derivative of nicotinic acid or its amide (5, 74, 75). The earliest report on this compound (89) suggested that the product was a 6-pyridone, since it showed no fluorescence in the ultraviolet while 2-pyridone compounds like ricinine and ricinidine did so. Subsequently, the same compound was prepared by the oxidation with alkaline ferricyanide of trigonelline acid sulfate and was isolated by extraction with ether from the reaction mixture. The product was again characterized as a 6-pyridone (42). However, when the methiodide of nicotinamide was oxidized similarly (41), the product was a 2-pyridone having ultraviolet absorption different from that of the 6-pyridone and fluorescing strongly in ultraviolet light. On hydrolysis, it gave the nicotinic acid *N*-methyl-2-pyridone melting at 183–183.5°C., while the 6-pyridone melts at 237–238°C. A more extensive investigation of this question (5) led to the observation that *N*-methyl-β-picolinium sulfate, *N*-ethyl-β-picolinium iodide, 3-bromopyridine methiodide, and nicotinamide methiodide all gave the corresponding 2-pyridone only. While 3-cyanopyridine methiodide gave both the 2- and the 6-pyridone, the methosulfate of nicotinic acid itself gave predominantly the 6-pyridone. These results were explained on the basis of the argument that it is the formation of the pseudobase and its subsequent oxidation which determine the nature of the product. Therefore, it is the orientation of the pseudobase formation which determines ultimately the site of the pyridone. On the contrary, if the ease of oxidation of the two pseudobases was the decisive factor, the formation of the pseudobase would not affect the direction of the pyridone formation.

However, the 2-hydroxy compound has greater resonance stabilization from the interaction of the substituent with the ring than the 6-hydroxy compound,

irrespective of the fact that the β-substituent is electron-withdrawing or electron-donating.



Therefore any substituent capable of resonance interaction with the ring double bonds would favor the formation of the pseudobase at the 2-position and on oxidation yield the 2-pyridone.

In the case of the 3-cyano- and 3-carboxy-substituted pyridines, the electrostatic repulsion of these groups to the hydroxy group (a field effect or proximity effect) tends to prevent the formation of the pseudobase at the 2-position, whereas no such situation exists at the 6-position. The spatial interaction of the negative nitrile and carboxy groups also tends to interact with the hydrogen of the 2-hydroxy group, thereby decreasing its acidity and inhibiting oxidation at this position. This results in the preferential formation of the 6-pyridone.

Contrary to these conclusions, a subsequent investigation of the oxidation of nicotinamide methiodide (74) showed that nearly equal yields of the 2- and 6-pyridone were obtained and that the predominance of one compound over the other was due to preferential extraction of the component in the isolation procedure. Further confirmation of this point was made through oxidation of the nicotinamide moiety of the deuterium-labelled diphosphopyridine nucleotide, when both 2- and 6-pyridones containing the deuterium were obtained in equal yields (75).

The importance of steric factors in the oxidation of these 3-substituted py-

ridines was well emphasized by the extensive work of Sugasawa and coworkers (92, 95). It was found that 3-ethylpyridine methiodide always gave only the corresponding 2-pyridone. Although 3-acetylpyridine could not be directly oxidized through its metho salt, the corresponding ethylene ketal gave the 6-pyridone in 85 per cent yield. The corresponding ethylenethioketal also gave the 6-pyridone in 89 per cent yield (95). Hydrolysis and Huang-Minlon reduction of both compounds afforded 3-ethyl-1-methyl-6-pyridone, a product different from that obtained by the direct oxidation of the metho salt of 3-ethylpyridine. The diethylacetal of 3-acetylpyridine also gave only the 6-pyridone, although in somewhat lower yield. It is interesting to note that alkaline ferricyanide does not affect the mercapto group, as was confirmed by the quantitative recovery of acetophenone ethylenethioketal after treatment with alkaline ferricyanide.

It has also been shown that when the β-substituent is alkoxycarbonyl or carboxamide (97), 3-pyridyl, *N*-methyl-2-pyrrolidyl (96, 98), 6,7-methylenedioxy-2-quinolyl (105), 2-methyl-4-thiazolyl (101), or 3-phenyl (94, 95), the 6-pyridone is the main if not the sole product. Methyl, ethyl, and bromo groups in the 3-position gave only the 2-pyridone (99, 100). The direction of oxidation was not affected by a change in the nature of the *N*-alkyl group with the same β-substituent (98, 101).

In view of the fact that the 3-carbamylpyridine yields equal amounts of the 2- and 6-pyridones and the 3-pyridyl- and 3-phenyl-substituted pyridines yield the 6-pyridones predominantly, the electronic interpretation of the role of the β-substituent does not appear to be convincing. Greater influence must be attributed to the steric factors (98, 101).

VI. OXIDATION OF TERTIARY AMINES

In a few instances the direct oxidation of tertiary amines with alkaline ferricyanide has afforded the corresponding pyridones. *d,l*-Sparteine gives *d,l*-oxysparteine in 35 per cent yield, while β-isosparteine affords oxo-β-isosparteine in 25 per cent yield (11, 59).

However, *N*-demethylations have been reported to occur during oxidations with alkaline ferricyanide of *N*-methyl tertiary amines where the nitrogen atom is attached to a secondary or tertiary carbon atom (73). Tropine yields nortropine in 87 per cent yield and not tropinone. Several other bases like 3-dimethylaminocyclohexanol, dimethyl-*tert*-octylamine, *N*-methyldicyclohexylamine, dimethylcyclohexylamine, 2-dimethylamino-1,2,3,4-tetrahydronaphthalene, and 1,2,6-trimethylpiperidine undergo such *N*-demethylation. However, *N*-methylmorpholine, codeine, nicotine, and dimethylaniline do not undergo such demethylation. No mechanism for this demethylation has been offered, nor has any reason been given for the failure of the reaction in the cases mentioned (73).

VII. OXIDATION OF HYDRAZIDES

Yet another application of potassium ferricyanide consists in the formation of aromatic and heterocyclic aldehydes from the corresponding carboxylic acids by

TABLE 3

Oxidation of hydrazides to aldehydes by ferricyanide

Hydrazide	Yield of Aldehyde	Hydrazide	Yield of Aldehyde
	per cent		*per cent*
Benzoic acid hydrazide	64	3-Hydroxybenzoic acid hydrazide	52
4-Methylbenzoic acid hydrazide	60	4-Hydroxybenzoic acid hydrazide	
2-Chlorobenzoic acid hydrazide	32	2-Methoxybenzoic acid hydrazide	30
2-Bromobenzoic acid hydrazide	51	4-Hydroxy-3-methoxybenzoic acid hydrazide	
3-Bromobenzoic acid hydrazide	56	3,4,5-Trimethoxybenzoic acid hydrazide	59
4-Bromobenzoic acid hydrazide	45	2-Nitro-5-aminobenzoic acid hydrazide	
2-Nitrobenzoic acid hydrazide	0	Isophthalic acid hydrazide	50
3-Nitrobenzoic acid hydrazide	23	Terephthalic acid hydrazide	
4-Nitrobenzoic acid hydrazide	0	Diphenic acid hydrazide	
2-Aminobenzoic acid hydrazide	26	β-Naphthoic acid hydrazide	55
3-Aminobenzoic acid hydrazide	52	Cinchoninic acid hydrazide	0
4-Aminobenzoic acid hydrazide	34	Cinnamic acid hydrazide	0
2-Hydroxybenzoic acid hydrazide	37	Phenylacetic acid hydrazide	0

way of the hydrazides. The method has had only a limited investigation and appears to merit more detailed examination.

The earliest reference to such an oxidation as this (46) mentions varying conditions from one acid to another for the most favorable yields of the aldehydes. The reaction proceeds thus:

$$2RCONHNH_2 + O \rightarrow RCH{=}NNHCOR + H_2O + N_2$$
$$RCONHNH_2 + O \rightarrow [RCON{=}NH] \rightarrow RCHO + N_2$$

More often the calculated amount of 2 moles of ferricyanide is not completely used up. However, an excess sometimes appears to be favorable. Although the oxidation is often conducted at room temperature, better yields are obtained when it is carried out at higher temperatures. 2-Aminobenzoic acid hydrazide, for example, gives *o*-aminobenzaldehyde in 26 per cent yield at 100°C., 23 per cent at 60°C., 21 per cent at 20°C., and only 10 per cent at 0°C. The oxidations are carried out in aqueous or aqueous alcoholic solutions with 2 equivalents of potassium ferricyanide in 10 equivalents of ammonia. The yields of the aldehydes from the various benzoic acid hydrazides are listed in table 3.

In all these oxidations, only 1–2 g. of the hydrazide has been employed and experiments with larger amounts are not described. The results show that in aryl acyl hydrazides carrying a strongly meta-directing group in a position ortho or para to the hydrazide side chain, the product is the symmetrical diacylhydrazide:

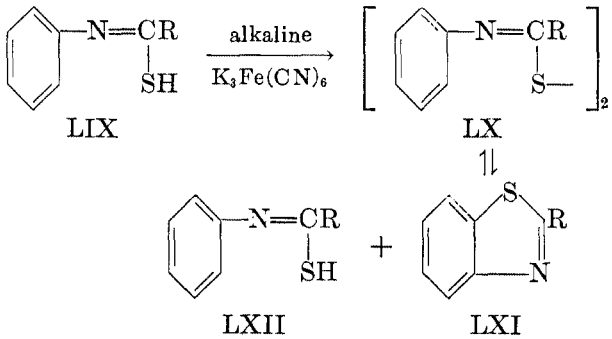
$$2RCONHNH_2 + 4OH^- - 4e \rightarrow RCONHNHCOR + N_2 + 4H_2O$$

The reaction also fails in the production of aliphatic aldehydes and is essentially equivalent in this respect to the McFadyen–Stevens reaction.

VIII. SYNTHESIS OF BENZOTHIAZOLE DERIVATIVES

Potassium ferricyanide has also been extensively used in the synthesis of innumerable benzothiazole derivatives from alkylthioanilides and alkylamides

(45). Many compounds which are pharmacologically active or are useful dyestuffs have been prepared by this method. The benzothiazole was considered to arise from a reversible dismutation of an intermediate disulfide (56).



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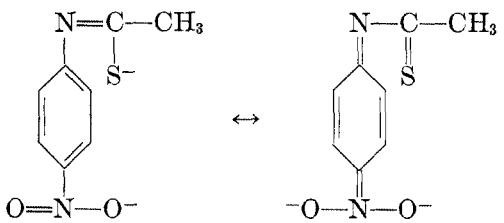
However, such a mechanism has been considered improbable because of the high temperature required for the conversion of arylthiourethans into ethoxybenzothiazoles as compared with their oxidation to the disulfides. Besides, phenylthiourethan disulfide was unaffected by being maintained at its melting point for half an hour, and no trace of this substance could be obtained by heating an equimolecular mixture of phenylthiourethan and 1-ethoxybenzothiazole slightly above the melting point for an equal time (43).

More detailed studies on differently substituted thioacetanilides show that the ease of cyclization was greater when the para position of the anilide carried anionoid groups like methyl, methoxy, chloro, etc., while cationoid groups like nitro gave poor yields of the benzothiazole (57, 58). In the ortho position, even the anionoid groups gave poor yields of the benzothiazoles. It has been suggested that electron-withdrawing groups in the para position reduced the contribution of the enol form of the thiocarbonyl group by resonance of the type



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thereby favoring the formation of *p*-nitroacetanilide to ring formation.

The relative yields of the variously substituted benzothiazoles are listed in table 4.

o-Nitrothioacetanilide, *p*-nitrothioacetanilide, and *p*-methylsulfonylthioacetanilide did not undergo cyclization. *m*-Nitrothioacetanilide formed only 2-methyl-7-nitrobenzothiazole and not 2-methyl-5-nitrobenzothiazole.

IX. OXIDATION OF AROMATIC HYDROCARBONS

One of the earliest uses of alkaline ferricyanide has been in the oxidation of toluene, xylene, and their derivatives to the corresponding benzoic acids (64,

TABLE 4

Conversion of thioacetanilides to benzothiazoles by oxidation with ferricyanide

Benzothiazole	Yield	References	Benzothiazole	Yield	References
	per cent			*per cent*	
2-Methyl	71	(58)	2-Methyl-7-nitro	33	(58)
2,4-Dimethyl	73	(57)	2-Methyl-6-cyano	32	(103)
2,7-Dimethyl	52	(57, 58)	2-Methyl-6-nitro-4-methoxy	24	(103)
2-Methyl-4-methoxy	70.3	(54, 58)	2-Methyl-5-methoxy	7	(103)
2-Methyl-6-methoxy	5–6	(48, 58)			
2-Methyl-4-chloro	88	(58)	2-Methyl-7-methoxy	37.8	(52)
2-Methyl-5-chloro	87	(58)	2-Methyl-4,5-tetramethylene	55	(50, 51)
2-Methyl-4-nitro	0	(58)	2-Methyl-7-dimethylamino	52	(51)
			2,5,6-Trimethyl	10	(53)

TABLE 5

Oxidation of aromatic hydrocarbons to benzoic acid by ferricyanide

Hydrocarbon	Yield of Benzoic Acid per Gram of Hydrocarbon	Reference	Hydrocarbon	Yield of Benzoic Acid per Gram of Hydrocarbon	Reference
	grams			*grams*	
Toluene	0.009	(64)	*m*-Bromotoluene	0.0115	(68)
o-Nitrotoluene	0.69	(64)	*p*-Bromotoluene	0.0065	(68)
m-Nitrotoluene	0.052	(64)	*o*-Toluenesulfamide	0.59	(66)
p-Nitrotoluene	0.73	(65)	*m*-Toluenesulfamide	0.75	(66)
o-Bromotoluene	0.0044	(55)	*p*-Toluenesulfamide	0.80	(69)

65, 66, 67, 68, 69). The hydrocarbon in aqueous solution was boiled with a large excess of ferricyanide. However, the yields have been poor except in the case of the relatively activated toluenes. The yields are listed in table 5.

X. OXIDATION OF FURAN DERIVATIVES

Nearly all oxidations of furan compounds result in breaking the ring. Alkaline ferricyanide appears to be a general oxidant for all furan compounds that are stable to alkali. Nitrofuran compounds are oxidized in the presence of potassium acetate instead of potassium hydroxide (6). The amount of ferricyanide used varies according to the substance oxidized. The relative yields of the various furan derivatives obtained by this method are listed in table 6.

XI. OXIDATION OF HYDROXYLAMINES

Among the reactions of ferricyanide which have not been fully explored is the conversion of hydroxylamines to *N*-substituted oximes (33). Oxidation of *N*,*N*-dialkylhydroxylamines with alkaline ferricyanide gives excellent yields of the corresponding *N*-alkyl ketoximes. Thus, *N*,*N*-bis(1-phenylpropyl)hydroxylamine yields almost quantitatively propiophenone-*N*-(1-phenylpropyl) oxime. Similar oxidation of *N*-acyl-*N*-alkylhydroxylamines yields *N*-acyl oximes almost quantitatively. *N*-Acetyl-*N*-benzylhydroxylamine gives *N*-acetylbenzaldoxime.

TABLE 6

Oxidation of furan derivatives by ferricyanide

Potassium Ferricyanide	Furan derivative (1 g.)	Product	Yield
grams			*grams*
50	Sylvan	Furoic acid	0.05
25	Dimethylfuran	Dehydromucic acid	0.01
25	Furyl methyl ketone	Furoic acid	0.51
25	Furylacrylic acid	Not oxidized	
25	5-Methyl-2-furoic acid	Dehydromucic acid	0.35
25	Furfural	Furoic acid	0.22
25	5-Bromofuryl methyl ketone	Bromofuroic acid	0.45
25	Furyl methyl ketone in potassium acetate	Furoic acid	0.30
25	5-Nitrosylvan in potassium acetate	5-Nitrofuroic acid	0.54
25	Furfuryl alcohol	Furoic acid	0.21
25	Furfuralacetone	Furylacrylic acid	0.10
25	Furil (0.5 g.)	Furoic acid	0.41
75	2-Methyl-3-furoic acid	2,3-Dicarboxyfuran	0.35
50	*tert*-Butylfuroic acid (0.5 g.)	Dehydromucic acid	0.01
25	Furylethylene	Furoic acid	0.02

XII. OXIDATION OF THIOPHENOLS

Thiophenol is quantitatively oxidized by alkaline ferricyanide to diphenyl disulfide (47, 55). This reaction has been used extensively in the preparation of synthetic rubber, employing ferricyanide and *n*-dodecyl mercaptan as catalysts for polymerization. The proposed mechanism involves the generation of a thioalkyl free radical which serves both as initiator and as chain-transfer agent.

$$RSH + Fe(CN)_6^{3-} \rightarrow RS\cdot + H^+ + Fe(CN)_6^{4-}$$

Ferricyanide has also been employed as a catalyst for emulsion polymerizations of butadiene and styrene and also as an accelerator for the polymerization of several other unsaturated organic compounds (49, 110). The reversible equilibria of mercaptan–disulfide and ferricyanide–ferrocyanide have been utilized in the potentiometric titration of cysteine (32).

XIII. OXIDATION OF GLYCOLS

The action of alkaline ferricyanide has been utilized in working out a micro method for the estimation of fructose in the presence of glucose (91). The oxidation has been carried out under such conditions of pH, temperature, and duration that glucose is not affected. The relative velocities of oxidation of the various monosaccharides have been studied (90) and found to be as follows: fructose, 100; glucose, 15.3; arabinose, 9.3; mannose, 5.1; galactose, 14.2. All these oxidations were carried out at 60°C. for 2 hr.

The only other instance of an oxidation of a glycol is the oxidation of the tetralol obtained by the oxidation of anthracene with osmium tetroxide. The product was 2,3-naphthalenedicarboxylic acid (16).

In retrospect, ferricyanide has been mainly employed in systems that are obviously favorable for the extraction of a single electron from an electron-rich

site in a molecule, but many other uses for the reagent have also been found in cases where its potentialities have not been originally apparent. Perhaps the capacity of this reagent as an oxidant has not been exhausted.

The author is grateful to Professor S. Sugasawa of the University of Tokyo for encouragement and assistance in writing this paper.

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