TABLE II

BIOLOGICAL TESTING OF APOCUPREICINE AND QUINOLINE DERIVATIVES[a]

Substance	*In vitro* Bacteriostasis in broth at concn. of	Intraperitoneal toxicity Deaths at dosages in mg. per 20 g. mouse 2	3	4
Quinicine·HCl		0/30	11/30	30/30
Ethylapocupreicine·HCl	1:50,000	7/30	28/30	
Hydroxyethylapocupreicine·2HCl	1:50,000		5/30	28/30

Substance	Oral toxicity Deaths at dosages in mg. per 20 g. mouse 3	5	6	12	50	80	90	Mouse protection *vs.* Pnc. II.
N-*p*-Aminobenzenesulfonylhydroxyethyl-apocupreicine				0/10				neg.
6-N⁴-Acetylsulfanilamidoquinoline[b]					0/10		1/10	neg.
6-Sulfanilamidoquinoline[b,c]	1:100,000	7/30	13/30	21/30				neg.
6-Amino-5-(*p*-sulfamidophenylazo)-quinoline				0/30				neg.
8-Amino-5-(*p*-sulfamidophenylazo)-quinoline						6/10		neg.

[a] The experimental testing was carried out by Drs. Bracken, Patrick, Maclachlan and Johnston of the Mercy Hospital, Pittsburgh, Pa. For methods see ref. 1 and earlier papers. [b] Winterbottom, THIS JOURNAL, **62**, 160 (1940); Bobranski, *Arch. Pharm.*, **277**, 75 (1939); Ganapathi, *Indian J. Med. Research*, **27**, 971 (1940). [c] *In vitro* tests were made with the dihydrochloride.

Ethylapocupreicine Monohydrochloride.—Ethylapocupreicine was dissolved in alcohol and converted to the monohydrochloride. After repeated concentration of the alcoholic solution *in vacuo*, the salt crystallized from absolute alcohol: $[\alpha]D$ −26.7°; c = 1 in water.

Anal. Calcd. for $C_{21}H_{26}O_2N_2 \cdot HCl$: N, 7.48; Cl, 9.36. Found: N, 7.59; Cl, 9.38.

Hydroxyethylapocupreicine.—The viscous hydroxyethylapocupreicine was very soluble in chloroform or alcohol and slightly soluble in ether or acetone. The dry monohydrochloride crystallized from absolute alcohol with one mole of alcohol of crystallization. This salt melted at 90° to a gum which would crystallize again if macerated with absolute alcohol. Because aqueous solutions of the salt clouded on dilution, the rotation was determined in normal sulfuric acid: $[\alpha]D$ −29° for the crystalline salt (c = 1). A crystalline dihydrochloride was precipitated from alcohol solution with ether. This gave a clear but somewhat colored solution.

Anal. Calcd. for $C_{21}H_{26}O_3N_2$: N, 7.92. Found: N, 7.72. Calcd. for $C_{21}H_{26}O_3N_2 \cdot HCl \cdot C_2H_5OH$: C_2H_5OH, 10.5; Cl, 8.25. Found: C_2H_5OH, 9.0; Cl, 8.31.

Summary

Some new apocupreicine ethers are described. Substituted sulfonamide compounds containing quinicine, apocupreicine and aminoquinoline nuclei have been prepared and tested experimentally. None of these compounds showed useful antipneumococcic power.

PITTSBURGH, PENNA. RECEIVED SEPTEMBER 27, 1940

[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Oxidation Potentials of Ketones and an Aldehyde

BY ROBERT H. BAKER[1] AND HOMER ADKINS

The relative strength as oxidizing agents of thirteen ketones was recently reported.[2] The values assigned to the various ketones were based upon the determinations with a polarograph of the concentrations at equilibrium of the ketones in systems of the type, $R_2CO + R_2'CHOH \underset{Al(OC_4H_9-t)_3}{\rightleftarrows} R_2CHOH + R_2'C{=}O$. The present paper describes the extension of this study so that it now includes twenty-three ketones, one aldehyde, and two anthraquinones. The inclusion of a quinone in the series makes it possible to assign to all the ketones and the aldehyde numerical values expressing in volts their oxidation potentials with respect to the hydrogen electrode, since the oxidation potentials of the quinones are known.[3]

Before describing the recent work it will be well to point out certain misconceptions expressed in the earlier paper. It was concluded that unsaturation was the most important structural factor bearing on the oxidation potential of a ketone.

(1) Assistant professor at the University of Kentucky and a fellow of the General Education Board at the University of Wisconsin during the year 1939–1940.

(2) Cox and Adkins, THIS JOURNAL, **61**, 3364 (1939).

(3) Conant and Fieser, *ibid.*, **46**, 1859 (1924); Fieser in Gilman's "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1938, pp. 105, 810.

It was supposed that any quinone would be a more powerful oxidizing agent than any simple ketone. These false conclusions were in part due to a lingering faith that there was "in general a parallelism between the depolarization potential as measured on a polarograph and the strength of a ketone as an oxidizing agent,"[1] even though it was stated in the same paper that the depolarization potential cannot "be safely used as a guide in predicting" oxidation potentials.

However, these misconceptions led to the choice of fluorenone as a cyclic unsaturated ketone that would probably have a high oxidation potential and might serve to bridge the gap supposed to exist between the oxidation potentials of the simple aryl ketones and the quinones. Fluorenone proved to have an even lower oxidation potential than benzophenone but its high rate of reaction under mild conditions has proven a great boon to this study.

In equilibrating most ketones against benzophenone a period of three or four days at 100° was required[1] while with fluorenone a few hours at 60° was sufficient. Certain pairs, such as fluorenone and cyclohexanone, required only an hour for reaction at 60°, while fluorenone and benzaldehyde reached equilibrium after three hours at room temperature. This high reactivity of fluorenone has made it possible to equilibrate ketones such as acetophenone and acetone which would undergo condensation under the more drastic conditions required for equilibration with benzophenone. The equilibrations reported in the present paper have been made in 0.05 *M* solutions rather than in the 1 *M* solutions previously used. Condensation of even the more reactive ketones is inconsequential at the lower concentration of reactants and temperatures used in this study.

The relative strengths of the ketones as oxidizing agents are expressed in Table I in four different ways, each of which has merit under certain circumstances. The column headed "% fluorenone at equilibrium" states the analytically determined mole % of that ketone, 100% representing the total amount of ketone present. For example, a representative reaction mixture contained 0.3085 millimole of fluorenone, *i. e.*, 61.7% of the total ketones, 0.3085 millimole of diphenylcarbinol, *i. e.*, 61.7% of the total alcohols, 0.1915 millimole of fluorenol, *i. e.*, 38.3% of the total alcohols, and 0.1915 millimole of benzophenone, *i. e.*, 38.3% of the total ketones. We believe that these experimentally determined values are reliable to within 1%. The figures in the second column of the table show clearly the extent to which the various carbonyl compounds varied from each other in their capacity to oxidize fluorenol to fluorenone.

TABLE I

SUMMARY OF RESULTS

	Carbonyl compound	% Fluorenone at equilibrium	R. R.	E_0, v.	$-\Delta F$, kcal.
1	Camphor	20.4	2.03	0.115	5.3
2	Di-*i*-Pr ketone		(1.00)	.133	6.1
3	Di-*n*-Bu ketone		(0.97)	.134	6.2
4	Di-*n*-Pr ketone		(.95)	.134	6.2
5	Di-*i*-Bu ketone		(.93)	.135	6.2
6	Di-Et ketone		(.68)	.143	6.6
7	*n*-Pr Ph ketone		(.62)	.146	6.7
8	Me-cyclohexyl ketone	48.2	.56	.149	6.9
9	*n*-Bu Ph ketone		(.55)	.149	6.9
10	*n*-Am Ph ketone		(.52)	.150	6.9
11	Fluorenone		.52	.150	6.9
12	Me Ph ketone	50.3	.51	.151	7.0
13	Et Ph ketone		(.51)	.151	7.0
14	Me *t*-Bu ketone	53.4	.45	.154	7.1
15	Anthraquinone	53.1	.45	.154[a]	7.1
16	Me Et ketone	55.2	.42	.156	7.2
17	Me *i*-Pr ketone	55.0	.42	.156	7.2
18	Cyclopentanone	55.7	.41	.156	7.2
19	Xanthone	56.1	.40	.157	7.2
20	*i*-Pr Ph ketone		(.39)	.158	7.3
21	Di-Me ketone	61.3	.33	.162	7.5
22	Di-Ph ketone	61.7	.32	.163	7.5
23	1-Chloroanthraquinone	66.7	.26	.168 .174[a]	7.8
24	Cyclohexanone	84.9	.09	.195	9.0
25	Benzaldehyde	86.6	.08	.197	9.1
26	*t*-Bu Ph ketone	88.5	.07	.202	9.3
27	9,10-Phenanthrenequinone		3×10^{-6}	.460[a]	21.2
28	1,4-Naphthoquinone		1×10^{-6}	.484[a]	22.3
29	1,4-Benzoquinone		1×10^{-10}	.715[a]	33.0
30	Diphenoquinone		4×10^{-15}	.954[a]	44.0

[a] These values are the potentials as determined by electrochemical methods. The relative reactivities in parentheses were determined by Cox. The four given last in the table were calculated from the value of E_0.

The third column in the table headed "R. R." gives the relative reactivities of the various ketones in terms of diisopropyl ketone as unity expressed as in the previous paper. The relative reactivity in terms of any other ketone is readily calculated from these values as follows: The relative reactivity of cyclopentanone is 0.41 while that for cyclohexanone is 0.09. If equimolecular amounts of cyclopentanone and cyclohexanol were allowed to react there would be at equilibrium 0.41 mole of cyclopentanone for each 0.09 mole of cyclohexanone. The relative reactivity for cyclohexanone with cyclopentanone as unity would be 0.09/0.41 or 0.22. The equilibrium constant is the square of the value of the "relative reactivity" so that the value of K for the reaction

$(CH_2)_4CO + (CH_2)_5CHOH \rightleftarrows (CH_2)_4CHOH + (CH_2)_5CO$

would be 0.048.

The relative reactivities of *p*-benzoquinone, diphenoquinone, naphthoquinone and phenanthraquinone given in the table are calculated on the basis of their oxidation potentials as determined at the hydrogen electrode. The figures given in the third column of the table indicate the enormous difference in oxidizing power among carbonyl compounds. For example at equilibrium there would be about 10^{16} as many molecules of camphor as there would be of diphenoquinone, assuming that equimolecular amounts of the quinone and borneol were allowed to react.

There are given in the fourth column of the table the values in volts of the oxidation potential of the various carbonyl compounds with reference to the normal hydrogen electrode. These values have been calculated on the basis that 9,10-anthraquinone has a value for E_0 of 0.154 volt, as determined by Conant and Fieser.[3] The value of E_0' for any other ketone is ascertained as illustrated for cyclohexanone

$$E_0' = 0.0296 \log K + E_0$$

The equilibrium constant for anthraquinone in equilibrium with cyclohexanone is $(0.45/0.09)^2$ or 25, where 0.45 is the relative reactivity of anthraquinone and 0.09 that of cyclohexanone taken from column 3 of the table. $E_0' = 0.0296 \times 1.3979 + 0.154$ or 0.195 volt, where 1.3979 is the log of 25. For this calculation the equilibria are always so expressed that they are greater than 1.

The calculation of the free energy of reduction given in the fifth column of the table is based on the expression $-\Delta F = nFE_0 = 2 \times 23.06E_0$.

In many ways the values of E_0 are the most convenient ones to use in the discussion of the relation of structure to the oxidizing power of a compound. However, the fact that they are logarithmic functions of the equilibrium constant tends to obscure an easy visualization of the real difference in concentration at equilibrium, consequent upon a given difference in the oxidation potentials of two ketones. A few figures will therefore be given to illustrate this relationship.

If a mole each of ketone A and of the alcohol corresponding to ketone B are allowed to react and if ketone A has a potential 10 millivolts greater than ketone B, then at equilibrium there will be 0.595 mole of ketone B. If A has a potential greater than B by 20, 50, 75 or 100 millivolts then the moles of B at equilibrium will be 0.685, 0.875, 0.950 or 0.980, respectively. It is obvious that almost quantitative oxidation can be attained if the oxidizing agent has a potential 100 millivolts greater than the ketone to be produced.

These numerical relationships are of interest in evaluating the relative merits of the electrochemical and the equilibrium methods for the determination of oxidation potentials. The equilibrium method can only be accurately applied to the comparison of the potentials of ketones which do not differ from each other by more than perhaps 50 millivolts. If the analytical method is accurate to within 1% of the ketone measured and if the difference in potentials of the two ketones at equilibrium is 50 millivolts or less, then the uncertainty in analysis will only involve an uncertainty of 1 to 2 millivolts in the estimated potential. If however the difference in the potentials is 100 millivolts then the uncertainty in the estimated potential will be 16 millivolts. Thus the equilibrium method is almost useless for the comparison of ketones differing widely in potentials, but permits very accurate comparisons between ketones which show small differences in oxidation potentials. For example, there can be no question that cyclopentanone is a stronger oxidizing agent than pinacolone for the % of fluorenone at equilibrium with these ketones is 55.7 and 53.4%, respectively, a difference which is certainly real. Yet the calculated oxidation potentials differ by only 2 millivolts, a difference which could not be measured electrochemically with certainty, even if these ketones gave a potential (which they do not) at a hydrogen electrode.

One criticism as to the validity of the equilibrium data might be that the apparent ketone concentration in the reaction mixture is in some cases modified by enolization. While none of the compounds studied are known to enolize extensively in inert solvents, the possibility remains that they might do so in the presence of aluminum alkoxides. This possibility cannot be eliminated directly, but if it be granted that the aluminum alkoxides are only weak bases, if indeed they are bases, and that strong bases increase the ratio of enol to keto form, a satisfactory answer is not lacking. Müller and Baumberger[4] have shown that in the case of pyruvic acid the enol–keto ratio can be measured polarographically and that the ratio is increased in alkaline solution.

(4) Müller and Baumberger, THIS JOURNAL, **61**, 590 (1939).

Then, since Cox has shown that benzophenone, which cannot enolize, has in alkaline solution the same ratio of wave height to concentration as do the alkyl phenyl ketones, we may deduce that even strong bases do not measurably bring about enolization of these compounds. It seems reasonable also to assume that the alkyl phenyl ketones would be more likely to enolize than the other types of compounds in Table I. Finally it should be noted that the comparison of the ketone to quinone series was made through fluorenone and benzophenone, neither of which can enolize.

The question may well be raised whether we are dealing with perfectly reversible systems and whether there is adequate justification for presenting the results in terms of E_0, since only two of the compounds which have been studied actually give a potential at the hydrogen electrode. With one exception equilibrium was approached from both sides so that there is experimental evidence that the equilibria were true and did not come to a constant value due simply to exhaustion of the condensing agent. However, with a few exceptions the reaction mixtures were made up so that the sum of the moles of a ketone and its alcohol was equal to the sum of the moles of the second ketone and its alcohol.

The reaction of benzophenone, diphenylcarbinol, fluorenenol and fluorenone was studied in more detail, in order to find if the values of K for different proportions of reactants were really constant. The data on experiments in which the ratio of reactants and of aluminum *t*-butoxide were varied are given in Table II. The values of the equilibrium constant varied from 2.23 to 2.77. This variation may seem to some rather large, but if the equilibrium constant is translated into "% of fluorenone at equilibrium in a reaction mixture originally containing equimolecular amounts of fluorenone and diphenyl carbinol" the actual variation is seen to be small. The average of these values given in the last column of the table is 61.4% fluorenone with the greatest deviation 1.5% in the third experiment recorded. The average deviation in the other five experiments is 0.5% with a maximum of 1%. The value used in Table I for the fluorenone–benzophenone ratio is 61.7% fluorenone, a value which is based upon the most reliable experiments, made after refinements in the analytical procedure had been put in practice.

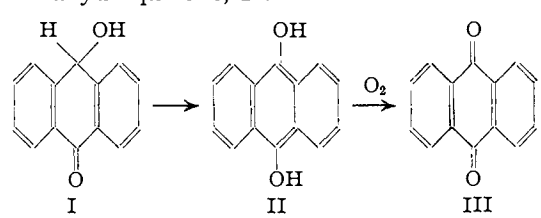
TABLE II

VARIATION IN THE VALUE OF THE EQUILIBRIUM CONSTANT WITH VARIATION IN CONCENTRATION OF REACTANTS

Moles × 10^{-3} in 11 ml. of toluene at beginning of reaction					Hr.	Ratio		
A	B	C	D	E	at 60°	C/A	K	% C[a]
0.43	0.43	0.57	0.57	0.7	25	1.66	2.77	62.4
0.43	0.43	.57	.57	4.2	25	1.57	2.46	61.1
1.50	1.00	.00	.00	0.7	113	0.90	2.23	59.9
2.00	1.00	.00	.00	1.4	20	0.67	2.69	62.2
1.00	1.00	.00	.00	0.7	21	1.65	2.72	62.3
1.00	1.00	.00	.00	3.5	88	1.45	2.10	59.3

[a] Calculated from the various values of K for the amount of fluorenone that would be present at equilibrium if the fluorenone and diphenylcarbinol (or fluorenol and benzophenone) were originally present in equivalent molecular amounts. A, B, C, D and E refer to benzophenone, fluorenol, fluorenone, diphenylcarbinol and aluminum *t*-butoxide, respectively.

The calculations of the values of the oxidation potentials of all the ketones depend upon the equilibrium between anthraquinone and fluorenone or benzophenone. The chief difficulty in this connection is the fact that the reduced form of anthraquinone, *i. e.*, anthrahydroquinone II, has never been obtained in a pure state because it is so rapidly oxidized by air. Recourse was had to oxanthrone, I, which under the influence of aluminum *t*-butoxide in toluene at 60° rearranges to anthrahydroquinone, II.



I II III

The reaction is practically quantitative. The rearrangement was followed with the polarograph as the "break" due to I decreases and the break corresponding to anthraquinone increases, since the phenol II was oxidized by air to the quinone III as rapidly as it was formed from oxanthrol.

The reactions between anthraquinone and fluorenol or diphenylcarbinol and between oxanthrone and fluorenone or benzophenone were carried out under anaerobic conditions so that the anthrahydroquinone formed would not be oxidized by air.

In calculating the values of E_0 given in the table it is assumed that the ratio of two ketones at equilibrium with their alcohols at 60, 80 and 100° would be the same as at 25°. The heats of reaction appear to be small and there is no apparent reason why the oxidation potential of other ketones should change more than does that of an-

thraquinone when an environment at 60° is changed to one at 25°. It was possible in the case of benzaldehyde and fluorenone to determine experimentally the concentration of the reactants at equilibrium at both 25° and 60°. The oxidation potentials calculated from the two sets of data were 0.197 and 0.200 volt, respectively.

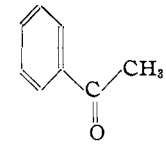
Even the values of the oxidation potential assigned to the various quinones, based upon the potential set up at a hydrogen electrode, are not above suspicion, for they vary somewhat depending upon the solvent which must be used in making the measurements. The relative oxidizing power of the carbonyl compounds studied during this investigation was made in an anhydrous toluene solution while oxidation potentials determined at the hydrogen electrode have been made in aqueous solutions containing widely varying amounts of alcohol, etc. When Kvalnes determined by an equilibrium method the oxidation potentials of six quinones, he found that there was a discrepancy of 2 to 39 millivolts between the potentials measured electrochemically and those by the chemical method.[5]

Similarly we found that there was a small discrepancy between the value of the potential previously reported for 1-chloroanthraquinone and that based upon equilibration of the quinone against fluorenone and the equilibrium of the latter with anthraquinone. If anthraquinone is assumed to have a value of 0.154 then the equilibration studies indicate a value of 0.168 for 1-chloroanthraquinone instead of 0.174 reported previously.[3] However, these are minor differences and while it is presumptive to say that the absolute values of the oxidation potentials have been determined either for the quinones or the ketones, yet it seems safe to assume that the relative values of the potentials have been measured with sufficient accuracy to make them significant.

The figures listed in Table I for the oxidation potentials of thirty carbonyl compounds, speak for themselves and require no extended exposition. Perhaps one of the most striking facts is the diversity in structure among ketones which have similar oxidation potentials. The potentials of seventeen of the ketones listed lie within a range of 20 millivolts. The potentials of benzophenone and acetone are almost identical. In fact anthraquinone, xanthone, cyclopentanone, and dimethyl, diphenyl and *i*-propyl phenyl ketones are all within the range 159 ± 5 millivolts, yet the list includes a quinone and diaryl, dialkyl, alkyl aryl, cyclic, unsaturated and saturated monoketones. However, cyclohexanone and *t*-butyl phenyl ketone are very much more powerful oxidizing agents than are the other ketones investigated. These two ketones do not resemble each other in structure but have similar oxidation potentials. The greater strength of cyclohexanone as an oxidizing agent as compared with an open chain ketone of similar molecular weight is brought out by the figures that if an equilibrium were set up between cyclohexanone and dipropyl ketone there would be 8% of the total ketones present as cyclohexanone and 92% as dipropyl ketone.

At the lower end of the series of ketones is camphor, which despite the fact that it may be regarded as a substituted cyclohexanone is 39 millivolts weaker than anthraquinone as an oxidizing agent, while cyclohexanone is 41 millivolts stronger than the quinone.

The ineffectiveness of unsaturation in modifying the oxidation potential of a ketone is indicated by many facts given in the table. Perhaps the most striking is that acetophenone IV and methyl cyclohexyl ketone V have almost identical oxidation potentials, 151 as compared with 149 milli-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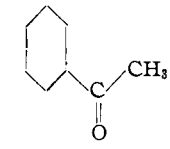
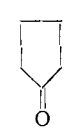
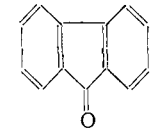

V

volts. Another interesting comparison is between cyclopentanone VI and fluorenone VII which show a difference of only 6 millivolts in potentials. The fusion of unsaturated rings has made little difference in the behavior of the carbonyl group.


VI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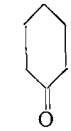
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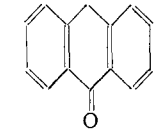
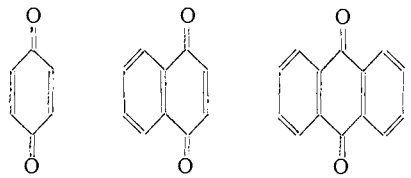

IX

A similar comparison between cyclohexanone, VIII, and anthrone, IX, would be interesting but unfortunately anthrone isomerizes to the corresponding phenol under the influence of aluminum *t*-butoxide and so does not act as an oxidizing agent.

Unsaturation is a distinguishing characteristic of the quinones and the effect of fused unsaturated

(5) Kvalnes, THIS JOURNAL, **56**, 2487 (1934).

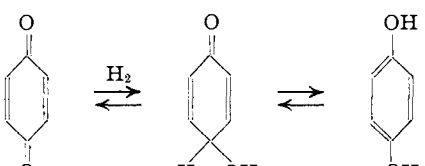
rings upon the oxidation potential is very marked. This is brought out by a comparison of the values for *p*-benzoquinone, 1,4-naphthoquinone and 9,10-anthraquinone. The oxidation potentials of these



X XI XII

three quinones are very different from each other, being 0.715, 0.484 and 0.154 volt, respectively.

A reaction is involved when a quinone accepts hydrogen from another compound which is not involved when a monoketone accepts hydrogen. The first reaction of XIII to XIV may be similar



XIII XIV XV

for the quinone and the ketone but the second step of isomerization, XIV to XV, is characteristic of the quinones. In view of the unimportance of unsaturation in determining the oxidation potential of the monoketones, it seems reasonable to conclude that the very high oxidation potential of diphenoquinone and benzoquinone is not due to the effect of unsaturation upon the strength of the carbonyl group as an oxidizing agent, but rather to the possibility it gives for the second stage, *i. e.*, isomerization of the reduced form to a benzenoid system, in which the equilibrium concentrations are far to the right. Thus by effectively removing the product of the reduction of the quinone, the latter continues to be reduced, *i. e.*, to act as an oxidizing agent. It is of course immaterial for our present purpose, as to whether the reduced form of the quinone undergoing rearrangement is an ion, a complex or of the structure formulated in XIV. As noted above, naphthoquinone is a much less powerful oxidizing agent than benzoquinone while anthraquinone has an oxidation potential of the same order of magnitude as many monoketones. In naphthoquinone and particularly in anthraquinone the position of the double bonds in the oxygenated ring is stabilized by the benzenoid rings. These facts are in harmony with the concept that the effectiveness of unsaturation in determining the oxidation potential of quinones is concerned with a tautomerization of the reduction product of the quinone.

The chain length and the extent of branching play a role in determining the oxidation potential of a ketone. Acetone, for example, is a more powerful oxidizing agent than any of its homologs. There is very little difference between the methyl ketones irrespective of whether the second group is ethyl, *i*-propyl, *t*-butyl, phenyl, or cyclohexyl. Similarly there is no great difference with the phenyl ketones irrespective of whether the other group is phenyl, methyl, ethyl, *n*-propyl, *i*-propyl, or *n*-butyl. However phenyl *t*-butyl ketone has the highest oxidation potential of any ketone determined. As noted above it is very similar to cyclohexanone and the two are quite anomalous with respect to the other ketones measured.

It has been possible so far to determine the oxidation potential of only one aldehyde, benzaldehyde. Other aldehydes studied underwent the aldol or Tischtschenko reaction to some extent even under the mildest conditions which it was possible to use in equilibrating them against fluorenone. The potential of benzaldehyde is much higher than any of the ketones measured except cyclohexanone and phenyl *t*-butyl ketone to which it is very similar.

The foregoing discussion has been concerned primarily with the concentration of reactants at equilibrium. No precise study has been made of the relative rates of reaction of various types of ketones. Wide variations in rates of reaction have been noted. The rate of reaction of a ketone is of course a function of the particular alcohol which is being oxidized so that the figures given below can only give a very rough estimate of the relation of structure to rate of reaction. Fluorenone, benzaldehyde and cyclohexanone react several times as rapidly as do ketones of intermediate reaction rates such as acetophenone, acetone and cyclopentanone. Approximately one to two hours would be required for the more reactive ketones to reach equilibrium, while five to ten hours would be needed for the ketones of intermediate rate of reaction. The branched chain ketones such as camphor, di-*i*-propyl ketone, pinacolone and phenyl *t*-butyl ketone react very slowly indeed. Time intervals of the order of one hundred hours would be required to reach equilibrium. It is interesting that the two ke-

tones, camphor and phenyl *t*-butyl ketone, which represent the extremes in oxidation potentials of the ketones measured, are both included in the group of the ketones reacting the most slowly.

In our opinion, there is no correlation between the oxidation potential of the ketones and their depolarization potential at the dropping mercury cathode. Only the unsaturated ketones show a break on the polarograph, *i. e.*, a depolarization potential. Saturated ketones such as cyclohexanone, acetone, and cyclopentanone do not show a depolarization potential, yet they are more powerful oxidizing agents than anthraquinone, which shows a low depolarization potential at -0.6 volt. There is no reason to expect that such a correlation should exist for the reaction occurring at a droplet of mercury falling through a solution of a ketone is an irreversible reaction even though it may well have a reversible step. There may be as suggested by Müller,[4] a correlation between the depolarization potential and Conant's "apparent reduction potential" for both are concerned with irreversible reactions.

Equilibration and Analysis.—In order to minimize the time of reaction and extent of side reactions, mixtures were usually made up which contained two ketones and two alcohols in concentrations somewhat to the "right" and somewhat to the "left" of those which had been previously tentatively established as the concentrations at equilibrium. The reaction mixtures were usually 0.05 *M* in total ketones, and in total alcohols, and 0.07 *M* in aluminum *t*-butoxide. Due to the insolubility of anthraquinone the reaction mixtures for determinations involving this substance were 20% as concentrated as indicated above for the other carbonyl compounds. The exact procedure for the equilibration of two ketones is described below.

Acetophenone *vs.* Fluorenone.—Solution "A" was made 0.05 *M* in acetophenone and in fluorenol by diluting to 50 ml. with toluene 0.3001 g. of the former and 0.4551 g. of the latter. Solution "F" was similarly made 0.05 *M* in each of methylphenylcarbinol and fluorenone by diluting 0.3052 g. of the carbinol and 0.4501 g. of the ketone to 50 ml. with dry toluene. The catalyst was a toluene solution which analyzed 0.70 *M* in aluminum *t*-butoxide. It was preserved without deterioration in sealed bottles for a period up to a year, small quantities being transferred to tightly stoppered bottles about once each ten days to give what is referred to as fresh catalyst.

Reaction mixtures were made to contain a total of 10 ml. of A and F in addition to 1 ml. of fresh catalyst. Such mixtures then contained 0.0005 mole of ketones and an equivalent quantity of carbinols along with 0.0007 mole of aluminum *t*-butoxide. Immediately after adding the catalyst and mixing, 2-ml. aliquots were removed. The first of these was pipetted into 10 ml. of 92% isopropyl alcohol to hydrolyze the catalyst and give a sample at zero time which was used for the polarographic standard. The other aliquots were pipetted into previously constricted, nitrogen-filled, soft glass test-tubes which were loosely re-stoppered, sealed, and placed in the thermostat at 60°. At the specified times these tubes were cooled, opened, and their contents quantitatively diluted with 10 ml. of 92% isopropyl alcohol.

After allowing the aluminum hydroxide to settle, polarographic cells were made of standard and test samples alike by diluting 2 ml. of the supernatant liquid with an equal volume of isopropyl alcohol and 1 ml. of an aqueous solution 0.84 *N* in tetramethylammonium hydroxide. In some cases ammonium chloride or tetramethylammonium bromide have been preferred to the alkaline supporting electrolyte. Polarograms were run at 25° and at an appropriate sensitivity to give as high a wave as practicable on the Leeds and Northrup Polarograph. This method obviates the necessity of preparing the standards separately and at the same time gives a check on the accuracy of making up of the reaction mixtures. The ratio of ketones was determined from wave heights by methods adequately described.[2]

This general procedure was followed except for the quinones. In order to avoid oxidation of the reduction products of the quinones by air one or the other of two modified procedures was followed. In the first the reaction was carried out in a three-necked 125-ml. flask which was fitted with a reflux condenser, a gas inlet tube, and a siphon tube of 2-mm. bore for removal of samples of the solution for analysis. The oxanthrone, ketone, anthraquinone, and carbinol dissolved in 48 ml. of benzene was added to the flask. A boiling chip was added and gentle refluxing was maintained by means of an electrically heated oil-bath. Dry, oxygen-free nitrogen was bubbled through benzene at room temperature and then was led into the reaction flask about two centimeters above the refluxing liquid. The gas escaped through the condenser and a drying tube. After refluxing for fifteen to twenty minutes under the above conditions two milliliters of the catalyst solution was added through the top of the condenser. At the specified time intervals 3–4 ml. of the liquid was drawn into a cooled 50-ml. side-arm flask by applying slight suction. After cooling to room temperature 2 ml. of this solution was pipetted into 10 ml. of 92% isopropyl alcohol to give an hydrolyzate upon which polarograms were run. Samples taken at zero time and quickly hydrolyzed were used as standards for the polarographic analyses.

The second technique, used in equilibrating fluorenol with 1-chloroanthraquinone was similar to that used with ordinary ketones except that further precautions were taken to remove air. The 2-ml. aliquots of the reaction mixture were pipetted as usual into nitrogen-filled, constricted, soft-glass test-tubes the necks of which were immediately shrunk further and pulled to heavy-walled capillaries. The tubes were then evacuated at the water pump until the toluene began to boil and were then sealed by heating the capillary in the flame from a wing-top burner.

In the case of 1-chloroanthraquinone the hydroquinone was not available so that equilibrium could be approached from only one side. In order to be sure that equilibrium

had actually been attained different ratios of the quinone and fluorenol were made up in the ratios 5/3.9, 5/5 and 7/5. After three to four days the equilibrium constants were 0.261, 0.246 and 0.244, respectively. The constant was considered to have the value 0.25 and the relative reactivities calculated on that basis.

Polarograms were usually made in an ammonium chloride solution as described above. However, for mixtures containing the anthraquinones anomalous results were obtained in using this electrolyte so that tetramethylammonium hydroxide was used. Oxidation by air of any anthrahydroquinone present in a solution occurred during the process of carrying out the preparation of the reaction mixture for analysis, so that the height of the anthraquinone wave was not significant.

A summary of the analytical data is given in Table III. In general the figures given in Table I represent the average of the analyses given in Table III. However, in certain cases the concentration of the ketones at equilibrium was found by extrapolating to the point of intersection of the curves which represented the approach to equilibrium from opposite sides. In no case was the last analysis actually made more than 1.4% from the % stated in Table I to represent the concentration at equilibrium.

TABLE III

SUMMARY OF ANALYTICAL DATA

Ketone	Hrs. at 60°	% Fluorenone Begin.	% Fluorenone Equi.
Acetophenone	44	20	50.2
	44	40	50.5
	2.8	60	50.2
	44	60	50.2
Benzaldehyde	0.5	40	86.0
	0.5	60	86.8
	3(25°)	60	87.6
	0.5	80	86.6
Cyclopentanone	1	50	55.7
	4	50	55.7
	1	70	61.4
	4	70	58.5
Acetone	0.5	55	56.9
	1.5	55	59.9
	0.5	65	64.5
	1.5	65	62.7
Methyl ethyl ketone	2	60	56.4
	3	60	55.8
	2	50	52.9
	3	50	54.0
Methyl *i*-propyl ketone	4	60	55.6
	5	60	55.4
	4	40	54.8
	5	40	54.3
Pinacolone	3	60	58.8
	16	60	54.6
	3	40	49.8
	16	40	52.0
Methyl cyclohexyl ketone	3	60	48.2
	16	60	48.2
	3	40	48.0
	16	40	48.5
Phenyl *t*-butyl ketone	23	80	86.4
	107	80	88.4
	23	100	89.4
	45	100	88.6
Camphor	75	50	20.4
	120	50	22.7
	75	20	20.4
	120	20	21.5
Xanthone	21	40	55.2
	45	40	57.8
	23	70	58.1
	95	30	56.3
Benzophenone	25	43	62.4
	89	43	62.8
	21	100	62.3
	47	100	62.0
Anthraquinone	3	60	54.2
	3.2	50	51.8
	4.5	60	55.6
	4.5	40[a]	40.4[a]
1-Chloro-anthraquinone	72	0	66.2
	87	0	66.9
	96	0	67.0
Cyclohexanone	1	100	84.6
	2.5	100	84.8
	1	80	85.3
	1	60	85.0
Cyclohexanone	21	63[a]	78.2[a]
	21	65[a]	77.7[a]
	21	80[a]	79.1[a]
	21	90[a]	81.7[a]

[a] % Benzophenone.

Improvements in the procedure for equilibration and repetition of the experiments have made it necessary to change the values of the relative reactivity for cyclohexanone and pinacolone given in the preceding paper.[2] There is a typographical error in Table II in that paper where "*t*-BuCOPh" is printed where "*t*-BuCOMe" was intended.

Preparation of Compounds.—9-Bromoanthrone-10 was prepared by a modification of the procedure of Goldmann.[6] To a mechanically stirred suspension of 3.0 g. of anthrone in 70 ml. of dry carbon bisulfide was slowly added a solution of 2.5 g. of bromine in 5 ml. of carbon bisulfide, the temperature being maintained at 8–10°. No color of the bromine remained when addition was complete, but a precipitate was obtained and this was filtered off. The mother liquor served as solvent for an additional 2 g. of anthrone which was then brominated until the color of bromine just persisted. The two crops of crystals were washed with cold carbon bisulfide, then with ice water until free of acid, and dried in vacuum overnight. The dry product, 7 g., was added to 25 ml. of boiling toluene which, as soon as solution was complete, was cooled quickly to 10°. This yielded 5.8 g., 83%, of slightly yellow crystals, m. p. 145–150° with extensive decomposition.

Oxanthrone was obtained from 5.8 g. of bromoanthrone according to Meyer.[7] Not all of the material dissolved in the 50% acetone, but the suspension was refluxed one minute, filtered hot, and the residue discarded. After addition of 30 ml. of water to the filtrate it was cooled to

(6) Goldmann, *Ber.*, **20**, 2437 (1887).

(7) Meyer, *Ann.*, **379**, 37 (1911).

10° and filtered. The crystals were washed well with water and dried at the pump, then crystallized from 30 ml. of benzene. The yield was 1.7 g., m. p. 160° with slight reddening. Polarograms on the product in ammonium chloride–isopropyl alcohol solution showed no break other than for oxanthrone.

Fluorenone, m. p. 82–82.5°, was prepared in 64% yield by oxidizing 1.2 moles of fluorene.[8] Fluorenol was prepared from fluorenone as follows: To 100 ml. of absolute isopropyl alcohol contained in a 250-ml. flask was added 27 g. (0.05 mole) of fluorenone and 20.4 g. (0.1 mole) of aluminum isopropoxide. The flask was fitted with a modified Widmer column and a receiver which was protected from moisture of the air. The mixture was heated with an oil-bath so as to maintain slow distillation during eight hours of each of three days and was allowed to stand over the intervening nights at room temperature. An additional 50 ml. of absolute isopropyl alcohol was added after the second day, and after the third day no acetone could be detected by the dinitrophenylhydrazine test in successive 1-ml. portions of the distillate.

The cooled yellow solution was poured into a rapidly stirred solution of 10 ml. of concentrated sulfuric acid in 600 ml. of cold water. After stirring for ten minutes longer the product was collected on a filter and washed with water until free of acid. The solid was extracted for two hours with 225 ml. of benzene, filtered, and when cooled to 10° the yield of air-dried crystals was 18 g. A reëxtraction of the undissolved solid with the mother liquor yielded, when cooled as before, an additional 6 g. of crystals.

These crystals from benzene hold some of the solvent which however is lost by storage in a vacuum desiccator for a week if the pressure is daily brought down to 30 mm. The yield of white crystals was 23 g. (85%), m. p. 155–156°. Polarographic analysis failed to detect any fluorenone in the product. Fluorenol is said to be easily oxidized by the air, but this product gave no evidence of such reaction either by polarographic analysis or by change in appearance, despite the fact that the container was opened over a period of ten months.

Xanthone, m. p. 174–175°, anthrone, m. p. 154–155°, xanthydrol, methyl *i*-propyl ketone, benzophenone, and pinacolone were prepared by the methods described in "Organic Syntheses." Methyl-*i*-propylcarbinol was prepared by a Grignard synthesis in 65% yield from *i*-butyraldehyde and methylmagnesium iodide in preference to the method given in "Organic Syntheses." Methyl-*i*-propylcarbinol and phenyl-*t*-butylcarbinol were oxidized to the corresponding ketones with dichromate as described in "Organic Syntheses" for the preparation of α-γ-dichloroacetone.

Methyl-*t*-butylcarbinol, methyl-*i*-propylcarbinol and diphenylcarbinol, m. p. 68°, were prepared by the catalytic hydrogenation over Raney nickel of methyl *i*-propyl ketone, pinacolone and benzophenone, respectively. Anthraquinone, m. p. 286°, and 1-chloroanthraquinone, m. p. 159.5–160°, were recrystallized from the technical products using benzene as the solvent.

The ketones and alcohols which could not be recrystallized were purified by careful fractionations through a modified Widmer or a Stedman column. The spiral in the modified Widmer was 15 cm. in length with 1 cm. distance between the turns of the helices. At a distillation rate of six drops per minute the column showed a value of 3.2 plates. The Stedman column was 14 × 400 mm. and was equipped with a vapor partition-partial take-off head. It was found to have a value of 16 plates at total reflux when benzene–carbon tetrachloride was the test liquid.

Table IV gives data on the physical properties of various compounds purified in these columns.

The depolarization potentials at the dropping mercury cathode have been determined for fluorenone as −0.99 (doublet in Me_4NOH), and −1.06 (NH_4Cl), xanthone −1.34 (Me_4NOH), oxanthrone −1.14 (NH_4Cl) and phenyl *t*-butyl ketone −1.73 volts (Me_4NOH). 1-Chloroanthraquinone, like anthraquinone, shows a doublet break at −0.60 volt (Me_4NOH) and in addition a break at −1.85 volt (Me_4NOH). The electrolyte used has been indicated in parentheses; the procedure and method of measurement was the same as for the values previously reported from this Laboratory.[9]

TABLE IV

Compound	Column	B. p. range, (mm.)	O/D[a]	$n^{25}D$
Acetone	W	56 (740)		1.3561
Benzaldehyde	S	50 (7)	10	
Benzyl alcohol	W	204 (740)		1.5382
t-Butylphenylcarbinol	S	97 (7)	10	M. p. 43–43.5°
t-Butylphenyl ketone	S	88 (8)	10	1.5060
Cyclohexanol	S	158 (740)	8	1.4637
Cyclohexanone	W	152.5–153		1.4490
Cyclopentanol	W	140 (740)		1.4458
Cyclopentanone	S	128 (740)	7	1.4348
Methyl-*t*-butylcarbinol	S	120 (746)	12	1.4132
Methyl *t*-butyl ketone	S	105 (740)	8	1.3944
Methylcyclohexylcarbinol	W	73 (8)		1.4631
Methyl cyclohexyl ketone	W	58 (8)		1.4493
Methyl ethyl ketone	W	78.8 (740)		1.3761
Methyl-*i*-propylcarbinol	S	111 (740)	10	1.4071
Methyl *i*-propyl ketone	S	93 (740)	10	1.3858
Methylphenylcarbinol	S	81 (7)	15	1.5260
Methyl phenyl ketone	W	200 (740)		1.5321
i-Propyl alcohol	W	81.8 (740)		1.3750

[a] Refers to the ratio of the reflux at the top of the column to the distillate.

Summary

The oxidation potentials of representative ketones and one aldehyde have been evaluated in relation to the potential of the normal hydrogen electrode by the device of comparing the oxidizing power of these carbonyl compounds with quinones in a strictly reversible process. The range of the normal potentials of the compounds measured is from 115 millivolts for camphor to about 200 millivolts for cyclohexanone or benzaldehyde. 9,10-Anthraquinone lies about mid-way in this range. The data are summarized in Table I.

The relative unimportance of unsaturation as a structural factor in determining the oxidation potential of a ketone has led to the suggestion that

(8) Huntress, Hershberg and Cliff, THIS JOURNAL, **53**, 2720 (1931).

(9) Adkins and Cox, *ibid.*, **60**, 1153 (1938).

p-benzoquinone, for example, owes its strength as an oxidizing agent not so much to a particularly active carbonyl group, but rather to the tendency of its reduction product to rearrange to a benzenoid system.

Additional evidence has been given to support the supposition that the alcohol–ketone–aluminum *t*-butoxide systems come to a true equilibrium. The technique and procedures for equilibration and analysis of these reaction mixtures have been improved.

The lack of correlation between the depolarization potential of a carbonyl compound at a dropping mercury cathode and its true oxidation potential has been demonstrated.

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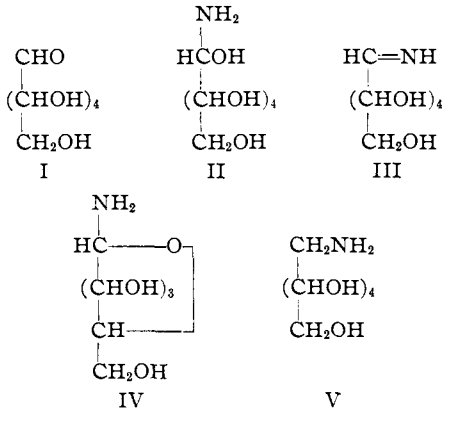
[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

d-Glucamine from *d*-Glucose

BY WINSTON WAYNE[1] AND HOMER ADKINS

The success realized in this Laboratory three years ago in the direct preparation of primary amines by the hydrogenation over Raney nickel of an aldehyde or ketone in an ammonia–methanol solvent, prompted an extension of the method into the sugar series.[2] The present paper is concerned with the preparation of glucamine from glucose.

The aldehyde form of *d*-glucose, I, may add ammonia to give *d*-glucoseammonia, II, which may then lose water to give *d*-glucoseimine for which both an imine, III, and a pyranose, IV, structure have been proposed. The hydrogenation of glucoseimine or the hydrogenolysis of glucoseammonia would give *d*-glucamine, V.



Glucamine was first prepared by the sodium amalgam reduction of glucoseoxime.[3] Later Neuberg and Marx[4] used calcium turnings instead of sodium amalgam. Roux in an excellent review paper[5] has described the purification of the compound and its physical and chemical properties. Ling and Nanji[6] reported the hydrogenation over nickel of glucose-ammonia to glucamine. They also used electrolytic reduction and aluminum amalgam. A patent was issued to Flint and Salzberg covering the hydrogenation over nickel of monosaccharides in the presence of ammonia.[7] It is difficult to evaluate these various processes for data are lacking as to the purity of the product. In fact our experiments soon showed that the difficulty in obtaining glucamine was not in the hydrogenation stage but in the isolation of the compound.

It seemed desirable therefore to start with pure glucoseimine (III or IV) and thus perhaps avoid some of the reactions and products possible with a mixture of glucose and ammonia. Attempts were therefore made to repeat the preparation according to Muskat,[8] who obtained glucoseimine by dissolving glucose in liquid ammonia, evaporating the excess ammonia, washing the product with alcohol and drying. The material obtained differed greatly in physical characteristics from the *d*-glucoseimine prepared in the usual manner and from the material reported by Muskat.[9]

(1) Research assistant on funds from the Wisconsin Alumni Research Foundation.

(2) This method was apparently first used by C. F. Winans for the preparation of furfurylamines from furfural. His U. S. Patent 2,109,159 (1938) was issued after the completion of the experimental work described by Schwoegler and Adkins, THIS JOURNAL, **61**, 3499 (1939).

(3) Maquenne and Roux, *Compt. rend.*, **132**, 980 (1901).

(4) Neuberg and Marx, *Biochem. Z.*, **3**, 539 (1907).

(5) Roux, *Ann. chim. phys.*, [8] **1**, 77 (1904).

(6) Ling and Nanji, *J. Chem. Soc.*, **121**, 1682 (1922).

(7) Flint and Salzberg, U. S. Patent 2,016,962, Oct. 8, 1935.

(8) Muskat, THIS JOURNAL, **56**, 693 (1934).

(9) *d*-Glucoseimine prepared by the method of Lobry de Bruyn was very slightly hygroscopic and had a m. p. of 130–131°; $[\alpha]^{25}D$ +21.0 after 15 min.; +22.6 after 24 hr. (*c*, 4; H_2O). The material obtained by Muskat's procedure was very hygroscopic and had a m. p. of 49–51°; $[\alpha]^{25}D$ +26.1 after 20 min.; + 20.1 after 24 hr. (C, 5.5; H_2O). It will be observed that the specific rotations of the