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Radical anions and cations derived from ninhydrin and alloxan

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NINHYDRIN AND ALLOXAN.**

**Iowa State University of Science and Technology
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RADICAL ANIONS AND CATIONS DERIVED FROM NINHYDRIN AND ALLOXAN

by

Maria Chyang Young

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DOCTOR OF PHILOSOPHY

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Approved:

Signature was redacted for privacy.

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Dean of Graduate College

**Iowa State University
Of Science and Technology
Ames, Iowa**

1966

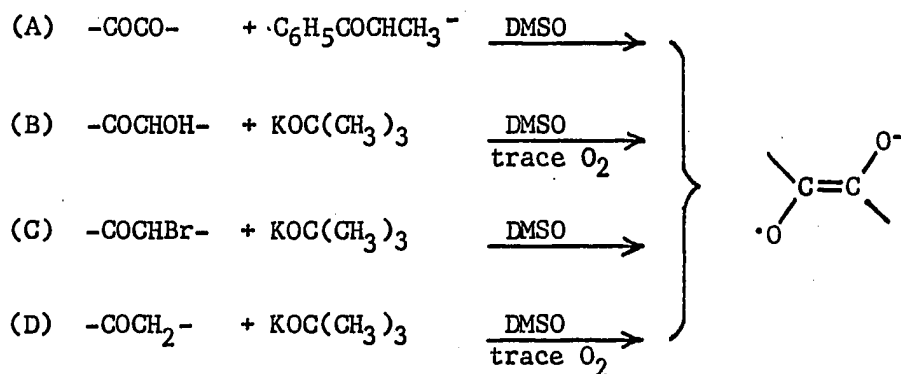
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INTRODUCTION

The formation of characteristic colors when compounds of the formula ArCHOHCOAr reacted with base and oxygen was noted as long ago as 1882 (1, 2). Michaelis and Fetcher (3) suggested that these species were semiquinones of the type $\text{ArC(O}\cdot\text{)}=\text{C(O}^-\text{)Ar}$. Many investigations of this system have been undertaken and the paramagnetic nature of these intermediates has since been demonstrated by a number of techniques (4, 5, 6, 7, 8). However not until recent work in this laboratory has an extensive and systematic study of the chemistry and application of these radical anions been performed.

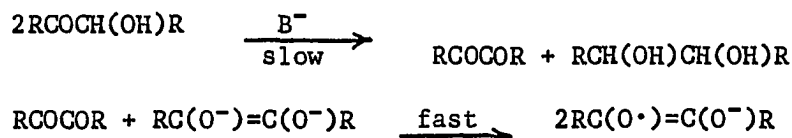
Semidiones, can be generated by the reduction of an α -diketone electrolytically, photochemically, or by alkali metals. In this laboratory semidiones have been prepared by a new route of electron transfer from mono-anions, dianions or other radical anions. Four major procedures are illustrated in the following equations:



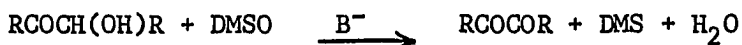
Reaction (A) illustrates that semidiones can be readily prepared by the reduction of α -diketones with certain electron donors, such as the enolate anion of propiophenone or 8,10-dihydroanthracene (9). Some

α -diketones even spontaneously form radicals in DMSO containing potassium *t*-butoxide in the absence of oxygen (10). Equation (B) demonstrates that oxidation of α -hydroxy ketone via the formation of α -diketones gives the same radicals.

Many α -hydroxy ketones also form radicals in the same medium without trace oxygen. This mechanism may involve the slow formation of α -diketones in the presence of a large excess of the dianion of the enediol.



Oxidation of the α -hydroxy ketone to the α -dicarbonyl compound by DMSO in the presence of base may be another possible route (11).



Formation of semidione radical anions from α -bromo ketones (12), reaction (C), apparently involves the formation of intermediate α -hydroxy ketones by reaction with traces of moisture. Thus, both phenacyl bromide and α -hydroxyacetophenone form the phenylglyoxal semidione in the DMSO-potassium *t*-butoxide system in the absence of oxygen. On the other hand, phenylglyoxal itself under the reaction conditions forms the semidione of 1-phenylpropane-1,2-dione (10).

Therefore it is thought that the major route to semidiones in the oxidation of monoketones, reaction (D), involves the α -diketone as an intermediate.

By the various methods described above and in combination with flow techniques, many semidione radical anions have been prepared in this laboratory and documented by electron spin resonance spectroscopy.

In the acyclic ketones $\text{CH}_3(\text{CH}_2)_n\text{CO}(\text{CH}_2)_n\text{CH}_3$, with $n=2-10$, the radical anions not only show α -splittings ($a_{\alpha}^{\text{H}}=4.68 \pm 0.05$ gauss) but also show the interaction of the four β - protons ($a_{\beta}^{\text{H}}=0.22$ gauss) (13). As the chain shortens, the cis-configuration gradually becomes recognized. For example, when the semidione of biacetyl was examined by e.s.r. spectroscopy under high signal amplification it was found that in addition to C^{13} satellites a minor radical was present. The minor and major radical anions have identical g -value and hyperfine structure, but have different hydrogen coupling constants. It was believed the minor radical to be cis (ca 4%) and the major radical to be trans from elementary considerations of electronic and steric repulsion.

Semidiones have been prepared from the C-4 to C-12 monocyclic ketones and their derivatives (14). All are quite stable. When the ring size is larger than six membered or when cyclohexanone is monosubstituted at the 4-position, the "axial" and "equatorial" hydrogens are no longer equivalent, and the spectra show two sets of splitting constant. If the hyperfine splitting constants of pure quasi-axial ($a_{\text{a}}^{\text{H}}=13.18$ gauss) and quasi-equatorial ($a_{\text{e}}^{\text{H}}=6.59$ gauss) are assumed from trans- Δ^2 -decalin semidione as a model, the relative concentrations of the two conformers can be calculated by use of the equations (11),

$$\underline{a}_{\text{axial}}^{\text{H}} = \underline{x} \underline{a}_{\text{a}}^{\text{H}} + (1-\underline{x}) \underline{a}_{\text{e}}^{\text{H}}$$

$$\underline{a}^{\text{H}} \text{ "equatorial"} = \underline{x} \underline{a}_e^{\text{H}} + (1-\underline{x}) \underline{a}_a^{\text{H}}$$

wherein \underline{x} is the mole fraction of the stable conformer (equatorial substituent) and $(1-\underline{x})$ is the mole fraction of the unstable conformer. The composition obtained from both the equations is very close. Furthermore the dihedral angles, $\theta_{\text{ax-H}}$, between the $\text{H-C}_\alpha\text{-C}_\pi$ and $\text{C}_\alpha\text{-C}_\pi\text{-p}$ orbital planes can be estimated by solving the two equations (15),

$$\underline{a}^{\text{H}} \text{ "axial"} = B' \text{Cos}^2 \theta_{\text{ax-H}}$$

$$\underline{a}^{\text{H}} \text{ "equatorial"} = B' \text{Cos}^2 (\theta_{\text{ax-H}} + 120^\circ) .$$

It is interesting that the value of $\theta_{\text{ax-H}}$ for cyclohexanedione radical anion (16) is exactly equal to that found by n.m.r. for cyclohexene by Smith and Kriloff (17).

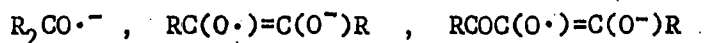
Followed by extensive and fruitful work concerning the semidiones of decalones, the study has been extended to the steroidal ketones (18). Often without reference to model compounds, cis or trans configurations can be assigned, and the positional isomers can be distinguished (19).

Recently long-range interactions in the semidiones of bicyclo compounds have been discovered. It was surprising to observe extremely strong splittings by certain β - and γ -hydrogen atoms in bicyclo semidiones with 1,3- and 1,4-ring fusions (20, 21). Experimental evidence was found to support the importance of the electronic interaction of bonds in a W-plan or zigzag arrangement with the carbonyl carbon P_z orbital. Such long range interactions are already recognized in p.m.r.

spectroscopy (22, 23, 24).

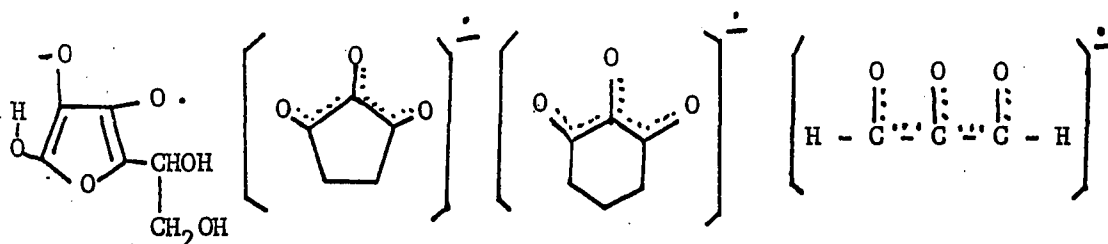
Ketyls, the radical anions of monoketones, have been recognized for a long time (25, 26, 27, 28, 29). However, the paramagnetic reduction products of vicinal triones have not been thoroughly investigated. Very little information could be found in a thorough literature search.

In the series of radical anions,



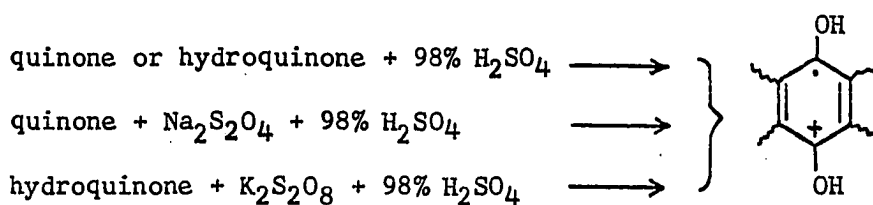
the stability increases from the ketyl to the semidione and presumably to the semitrione; in each group as R is altered from H to alkyl to aryl. Although diaryl ketyls are commonly encountered dialkyl ketyls have been reported only rarely and have low stability at room temperature. The parent compound (R=H) has been reported only for the trione $HOOC(O\cdot)C(O^-)H$ (30), although the semidione has now been prepared in this laboratory.

Several semitriones can be produced by the oxidation of ascorbic acid (31), oxidation of reductive acid, treatment of 2,6-dibromocyclohexanone with base in DMSO, and by the action of triose reductone with hydrogen peroxide at a pH of 4.8 (32).



There have been systematic studies of radical cations derived from aromatic hydrocarbons. The oxidizing agents so far employed include 98% H_2SO_4 (33), $\text{BF}_3\text{-CF}_3\text{COOH}$ (34), SbCl_3 (35), SbCl_5 (36, 37), AlCl_3 (38), I_2 (39), V_2O_5 (40), $\text{SiO}_2\text{-Al}_2\text{O}_3$ (41), VOCl_3 (42), $\text{K}_3\text{Fe}(\text{CN})_6\text{-HClO}_4$ (43), $\text{SO}_2\text{-BF}_3$ (44) and $\text{SbCl}_5\text{-CH}_2\text{Cl}_2$ (45).

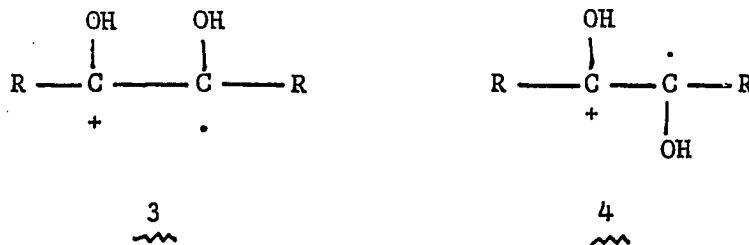
Radical cations derived from quinones have been obtained by the following methods (46, 47):



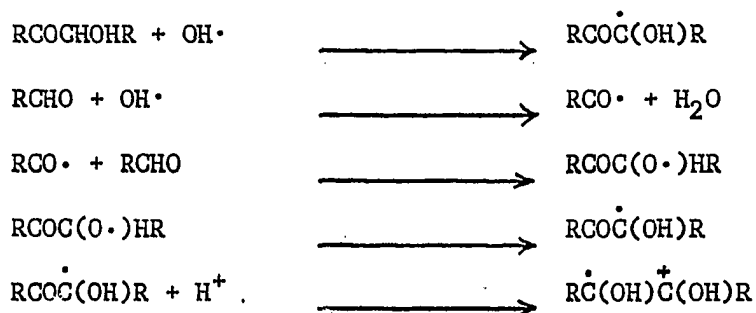
Recently this author applied the same technique to generate radical cations in the semidione series (48)



while Steven and Ward (49) have claimed to have prepared radical cations of the type 3 and 4



by the action of acidified aqueous titanous sulfate in the presence of hydrogen peroxide upon acetaldehyde or acetoin, presumably via



Hyperfine splittings by hydroxyl hydrogen atoms is found for the semiquinones but not for semidione radical cations. There must be rapid exchange of hydroxylic protons in the latter case.

Many problems in the area of radical cations of semidiones remain to be studied. Many things did not turn out as expected. Additional routes to prepare radical cations are desired. Benzil readily gives e.s.r. signal upon reduction in 98% H_2SO_4 with good resolution, but benzoin gives a very poorly resolved spectrum after oxidation in the same medium. Also there is the problem whether it is possible to detect both the cis-trans isomers of radical cation of semidiones. Steven and Ward (49) claimed they observed two sets of splitting constants with $\text{R}=\text{CH}_3$ but Russell and Talaty reported only one value (48).

Furthermore, side reactions probably occur under the conditions of generation of radical cations. Pivalil gives the radical anion without difficulty ($\underline{a}_\beta^{\text{H}} = 0.29$) (50), but only a very poor spectrum is obtained by reduction in 98% H_2SO_4 .

Usually deuteration is a good way to check upon the assignment of hyperfine splitting constants. However, in the case of radical cations of semidiones deuteration did not work satisfactorily. Thus cyclohexane-

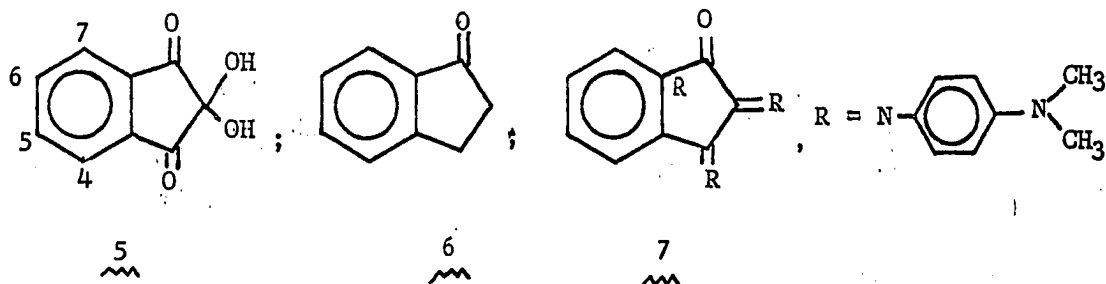
1,2-dione gave the expected quintet spectrum after reaction with $\text{Na}_2\text{S}_2\text{O}_4$ in H_2SO_4 , but an equally spaced triplet (the intensity ratio is 1:2:1) was observed when the reaction was carried out in D_2SO_4 . No good explanation is apparent.

The goals associated with this particular research were threefold. First, it was desired to ascertain whether we could prepare the radical anions and cations of semitriones of indan-1,2,3,-trione and alloxan. Second, we were drawn to examine whether there was any relationship between the radicals and the long reported brilliant blue coloration of barium salts of hydrinantin and alloxantin (51). Third, it is worthy to re-investigate the radical anions of ninhydrin and alloxan in the aqueous solution which were reported by several workers (52, 53, 54, 55, 56, 57).

Our studies are comprehensive and our results are fruitful.

HISTORICAL

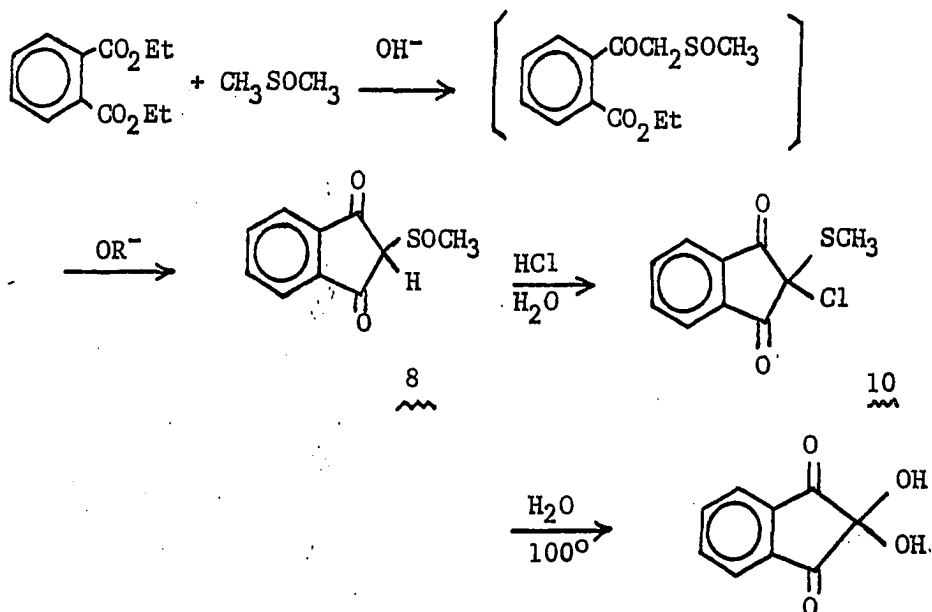
The discovery of ninhydrin by Siegfried Ruhemann in 1910 (58) is a well documented contribution made by a man whose name is almost unknown to chemists today. Most of Ruhemann's papers, though constituting solid and substantial bricks built into the masonry of chemistry, are not in themselves remarkable and so have been largely forgotten. His discovery of ninhydrin is a brilliant exception. He was the first to observe the characteristic color reaction of ninhydrin (1,2,3-triketohydrindan hydrate, 5) with amino acids and peptides, which makes it one



of the most valuable of all biochemical reagents. Since then numerous studies have been added to the field of chemistry and application of ninhydrin and related compounds.

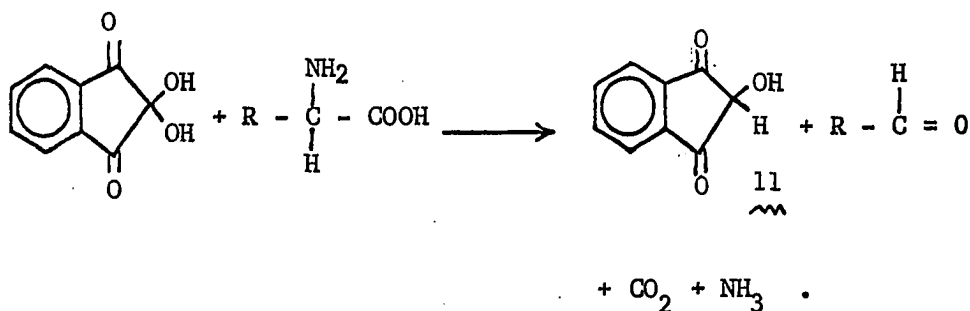
Ninhydrin was originally made by Ruhemann after the hydrolysis of the diimine (7) of α -indanone (6) and *p*-nitrosodimethylaniline, and later the monoimine of indan-1,3-dione. An instructive six-steps synthesis starting from esters of phthalic acid can be found in L. Fieser's laboratory manual for organic chemistry (59). However, recently a remarkable finding was made in this laboratory that ninhydrin can be readily prepared in two steps from ethyl phthalate (60). The intermediate 2-chloro-2-methylmercapto-1,3-indandione (10) is isolated after

reaction of hydrochloric acid and the salt (8) resulting from the condensation of the esters with dimethyl sulfoxide in the presence of alkali metal alkoxides. A subsequent hydrolysis of 10 leads to the final product in a total yield of 79%. The reaction mechanism has been approved to involve a Pummerer rearrangement of 8 \rightarrow 10 (61, 62).

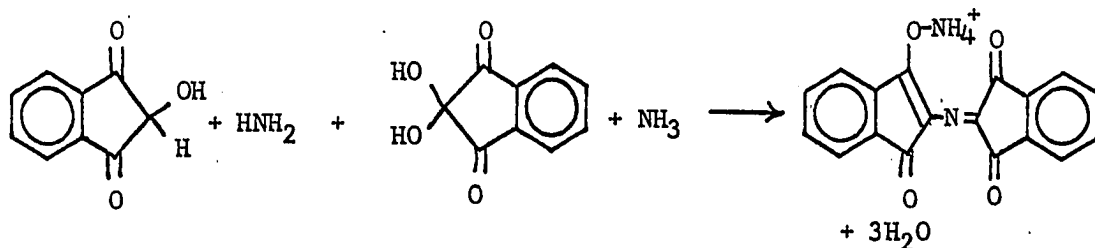


Many workers have studied the formation of "Ruhemann's purple" (12).

The reaction appears to involve the following (63):

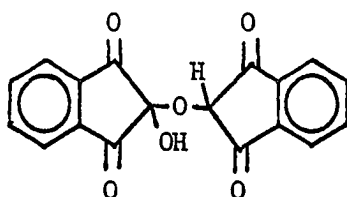
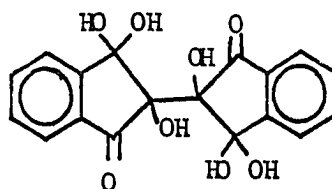


The blue-colored substance is formed by the reaction of some of the ninhydrin with its reduction product, diketohydrindol (11), and ammonia:

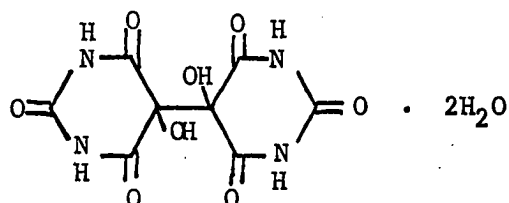


12

Bimolecular reduction of ninhydrin yields hydrindantin, which crystallizes with two molecules of water (64). Several aspects of hydrindantin have greatly interested chemists. Various structure formula have been introduced. Ruhemann believed the hemiacetal structure 13 (51) while Schönberg and Moubassher assigned the hydrated pinacol, 14 (65).

1314

Recently a crystallographic study on alloxantin, an analogue of hydrindantin, has shown that the triketopinacol structure is correct, except that the two molecules of water are not chemically bonded, 15 (66).

15

Colorless hydrindantin and alloxantin give blue barium salts. This is a most striking phenomenon. Hantzsch proposed that it must be related to a metal ketyl complex (67). Asmussen and Soling measured the mag-

netic susceptibility of the barium salts and found that these compounds have no unpaired electrons (68).

In addition to being able to distinguish among different amino acids (69), ninhydrin gives characteristic stains on paper strips with the ethylenediamine and ammonia complex of the metals, such as cobalt, nickel, and chromium (70). The detectability is up to 0.2-1.0 γ .

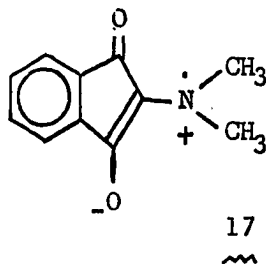
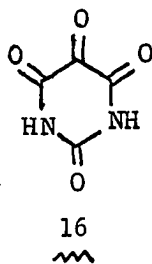
Ninhydrin is also used in the coating for a paper used in the thermographic process to generate a color compound between 50° and 150°C. The recipe of a coating mixture is trichlorethylene, 84 parts; ninhydrin, 8 parts; and Formoar 7/70, 8 parts (71).

Several workers have studied the radical anions of ninhydrin and alloxan (16). In the experiments on ninhydrin, Lagercrantz and Yhland reported the following results (52):

1. Identical e.s.r. spectra of the radicals were obtained in the reactions of ninhydrin with amino acids, sodium dithionite and glyoxal, respectively. The solutions exhibited a reddish-brown color. No radicals could be detected when the solutions contained only ninhydrin or the pH was lower than 7.0.
2. The spectra had a nine-line structure. A splitting of 1.0 gauss was assigned to the protons at the positions 4 and 7, 0.75 gauss to the protons at carbons 5 and 6. An identical spectrum was obtained when the reduction of ninhydrin by dithionite was performed in D₂O instead of H₂O.
3. There seems to be no correlation between the radical concentration and the intensity of "Ruhemann Purple" ¹² which is formed at a pH value much lower than that necessary for the production of radicals. However, the reddish-brown color seems in some way to be connected with the ninhydrin radicals, but it is not clear if the

colored substances are identical with the radicals or not. Evidently, both of them are destroyed by molecular oxygen.

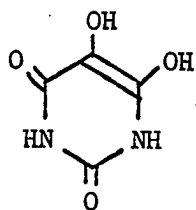
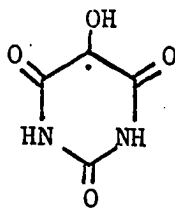
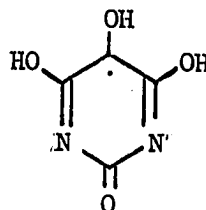
Orr reported as follows (54): 1. A similar spectrum can be produced directly by treating ninhydrin in methanol with 5 M aqueous sodium hydroxide. The values of two sets of equivalent protons are 0.94 and 0.74 gauss. In the presence of excess alkali the solution turns blue and the e.s.r. signal disappears. 2. When hydridantin is dissolved in a buffer at pH 9.0, the red solution obtained gives an intense e.s.r. signal with the same pattern. The blue solution obtained under more strongly alkaline conditions gives no signal. It seems probable that the free radical described above is the semitrione anion of indanone-ene-diol. 3. Radicals appear in the reaction of ninhydrin with amines. In the case of 2-(N, N,-dimethylamino)-1,3,-indanedione 17, a splitting of 8.8 gauss is assigned to the nitrogen atom and methyl protons. Two values of 0.7



and 0.47 gauss were attributed to the ring protons.

Adams, Blois and Sands reported that the ninhydrin radical anion was made by reduction in aqueous basic solution by metallic zinc. The paramagnetic intermediate had a splitting by two pairs of hydrogens, 1.95 and 1.59 gauss (52).

In the experiments on alloxan, Lagercrantz and Yhland reported the following results (55, 56). 1. Free radicals were obtained when alloxan reacts with sulphhydryl compounds or ascorbic acid in the pH range between 4.6 and 8.6. No radicals could be detected in the solution containing only alloxan. The radicals decayed more rapidly when the basicity increased. 2. The e.s.r. spectrum of the radical exhibited a hyperfine structure consisting of seven equally spaced lines with a splitting of about 0.4 gauss. The hyperfine structure is ascribed to the interaction of the odd electron with two nitrogen nuclei and two protons with equal coupling constants. When the reaction was performed in D_2O , a five-line spectrum was observed. 3. When dialuric acid 18 was oxidized by potassium ferricyanide free radicals were formed which exhibited a spectrum identical with the radicals obtained from alloxan.

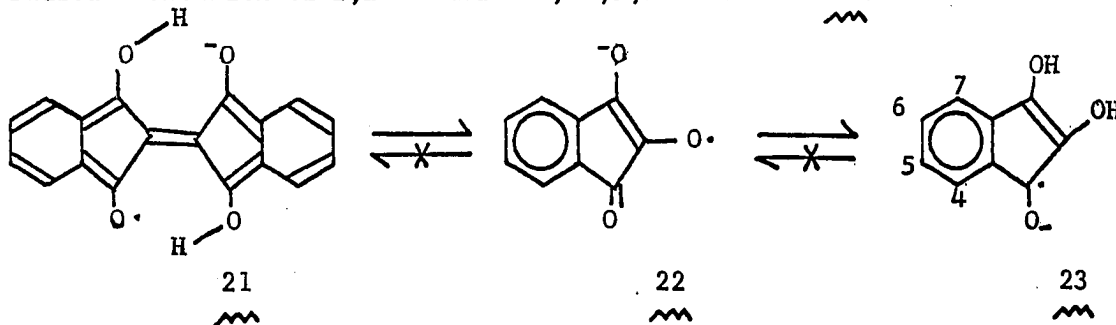
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Orr obtained an equally spaced (0.48 gauss) seven-line spectrum by treating alloxan with dithionite in a water-methanol solution. He assigned the radical structure (19). At high base concentrations, he reported a single splitting of 0.24 gauss (8M KOH) which was also obtained spontaneously by treating dialuric acid with 8M KOH. He assigned this second radical structure 20 (54).

RESULTS AND DISCUSSION

Radical Anions Derived from Ninhydrin

Three radical anions can be made in alkaline solutions: semitrione of indan-1,2,3-trione 22, radical monoanion of diketohydrindol 23, and radical monoanion of 2,2'-biindan-1,1',3,3'-tetraone 21. An irreversible



process can be depicted as above.

Radical anion 22 is easily prepared in high yield by a variety of techniques. Ninhydrin when dissolved in deoxygenated, anhydrous DMSO containing potassium t-butoxide forms 22 spontaneously with the development of little if any color. Reduction apparently involves the methylsulfinylcarbanion as an electron donor since in t-butyl alcohol ninhydrin is not converted to the radical anion by potassium t-butoxide. However 22 is formed spontaneously in methanol in the presence of potassium hydroxide. In t-butyl alcohol ninhydrin is reduced to 22 by the propiophenone enolate anion or by the anions derived from 9,10-dihydroanthracene and potassium t-butoxide. This simply indicates that ninhydrin semitrione is easily reduced by an easily oxidized anion. It is known that tertiary alkoxide ions are not oxidized easily.

The e.s.r. spectrum of 22 in DMSO solution is given in Figure 1

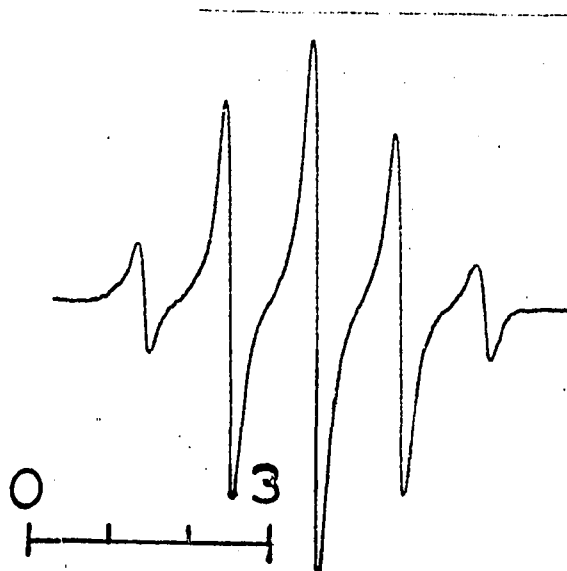


Figure 1. First derivative e.s.r. spectrum (9.5 gigacycle/s) of radical anion formed spontaneously from hydridantin or ninhydrin in dimethyl sulfoxide solutions of potassium t-butoxide at 25-28°.

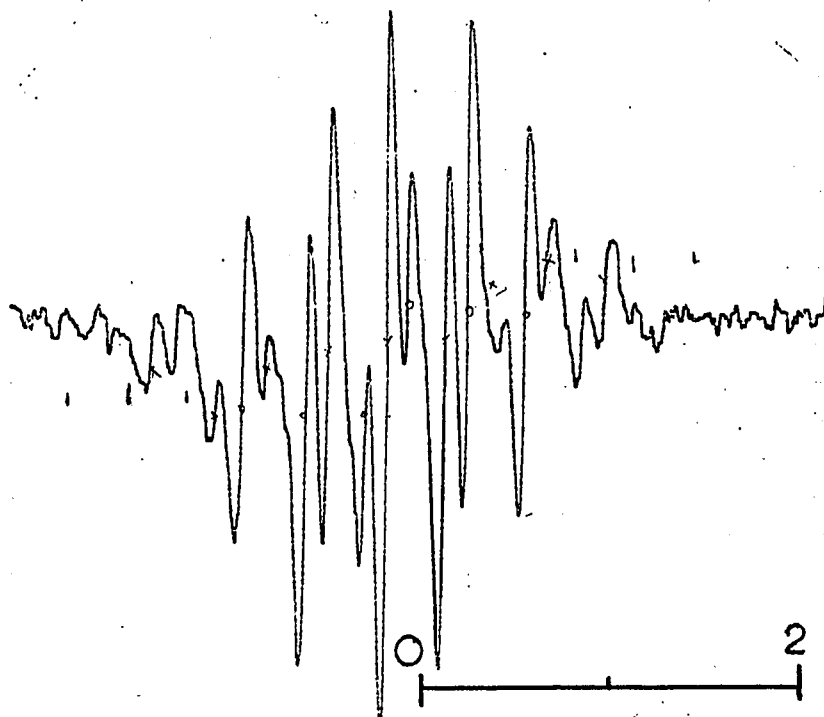


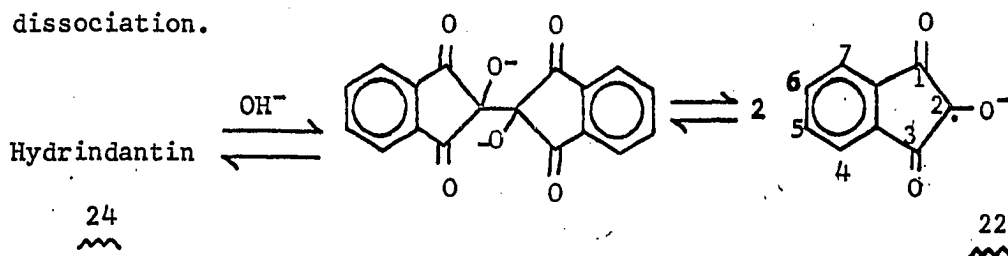
Figure 2. E.S.R. spectrum of radical anion formed from 2,2'-biindan-1,1',3,3'-tetraone (0.05 M) in dimethyl sulfoxide containing propiophenone (0.13 M) and potassium t-butoxide (0.05 M) at 25-28°.

and shows a 1:4:6:4:1 quintet, $a^H = 0.97$ gauss, attributed to the four aromatic hydrogen atoms which appear to be magnetically equivalent even though they exist in two chemically distinct sets. Other routes leading to ninhydrin semitrione in different solvents are tabulated in Table 1.

Table 1. Formation of ninhydrin semitrione from 1,3-indandione derivatives

Substrate (Structure number)	Electron donor	Base and (solvent)	Remarks
Ninhydrin (5)	Potassium	Potassium (Tetrahydrofuran)	Hyperfine splitting constants:
Ninhydrin (5)	Propiophenone or 9,10-dihydro- anthrance	Potassium <u>t</u> - butoxide (<u>t</u> -Butanol)	$a_6^H = a_7^H = 0.97$ gauss
Ninhydrin (5)	DMSO	Potassium <u>t</u> - butoxide (DMSO)	
Hydrindantin (24)	None	Potassium <u>t</u> - butoxide (DMSO)	
2-Bromo-1,3- indandione (25)	DMSO (with trace O ₂)	Potassium <u>t</u> - butoxide (DMSO)	A radical of 27 lines ($a_6^H = 0.423$ gauss, $a_{OH}^H =$ 0.292 gauss) followed by the 5-line spectrum
"Bishydroxy- indone" (26)	DMSO (with trace O ₂)	Potassium <u>t</u> - butoxide, 0.5 mole to 1 mole of substrate (DMSO)	
"Bishydroxy- indone" (26)	DMSO (with trace mois- ture and oxygen)	Iodine Potassium <u>t</u> - butoxide (DMSO)	
Ninhydrin (5)	Methanol	Potassium hy- droxide (Methanol)	Three triplet $a_7^H = 0.98$ and $a_6^H = 0.81$ gauss
Ninhydrin (5)	Zinc	Potassium hy- droxide (H ₂ O)	Three triplet $a_7^H = 1.00$ and
Hydrindantin (24)	None	KOH (H ₂ O)	$a_6^H = 0.68$ gauss

Hydrindantin in DMSO in the presence of an excess of potassium t-butoxide forms 22 in essentially a quantitative yield, possible via dissociation.



Radical anion 22 can also be prepared by the action of potassium t-butoxide and air upon 2-bromo-1,3-indandione or 26 in DMSO solution. In both cases an intermediate radical anion whose e.s.r. spectrum (Figure 2) shows a 9-line pattern (8 equivalent hydrogen atoms), $\underline{a}^{\text{H}} = 0.423$ gauss, further split into triplets, $\underline{a}^{\text{H}} = 0.292$ gauss, can be detected. The structure of this new intermediate is believed to be 21 and to involve hyperfine splitting by the hydroxyl hydrogen atoms.

Reduction of ninhydrin ($\sim 0.01 \text{ M}$) by zinc in basic aqueous solution forms paramagnetic products. When the ratio $[\text{OH}^-]/\text{ninhydrin}$ is < 3 , the spectrum shown in Figure 3 is found for the pale yellow-green (at very low base concentration) or red-orange (at higher base concentration) solutions. Hyperfine splitting by two pairs of hydrogen atoms, $\underline{a}^{\text{H}} = 1.00$ and 0.68 gauss is observed. Hydrindantin in the same base concentration also gives the same spectrum without zinc present.

Much consideration has been given to decide whether the three triplet radical is the same species as the semitrione in DMSO solution. Since ninhydrin in the hydrated form is more stable than the triketo form and also since the structure formally proposed (14) for hydrindantin (65) 22

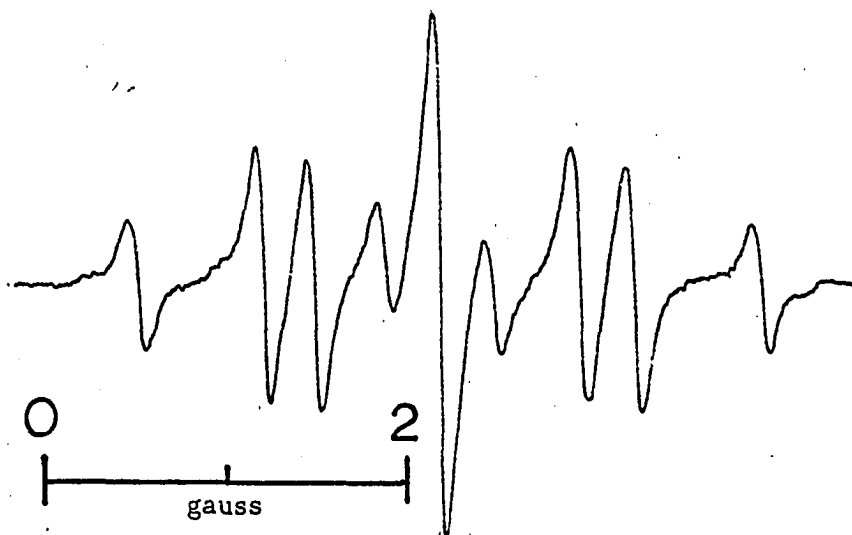


Figure 3. E.S.R. spectrum of radical anion formed from hydrindantin in dilute aqueous potassium hydroxide at 25-28° ($[\text{OH}^-] < 0.05 \text{ M}$). The same radical anion is formed by reduction of ninhydrin with zinc in dilute aqueous base.

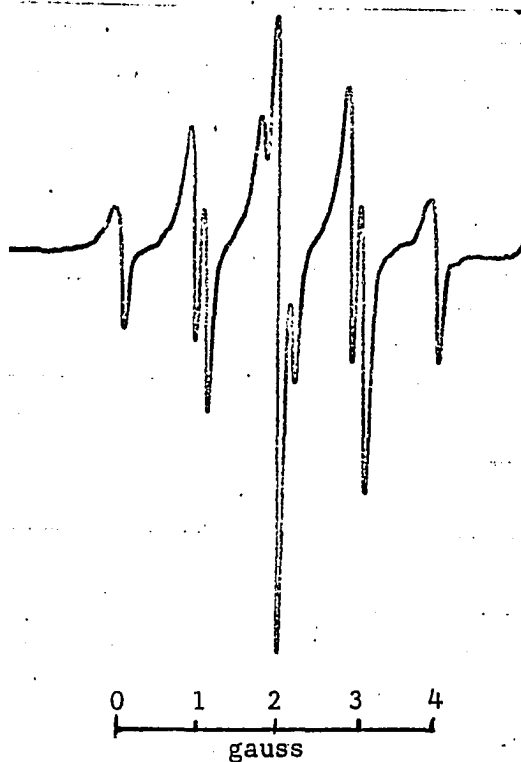
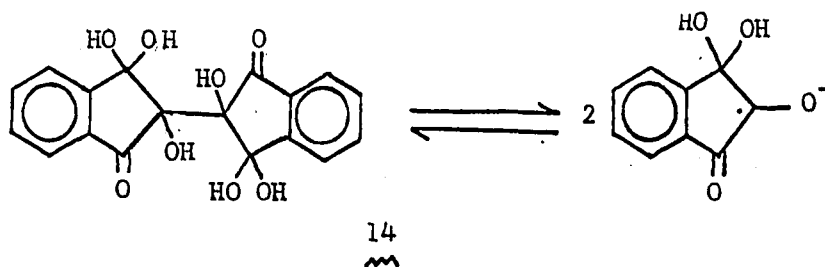
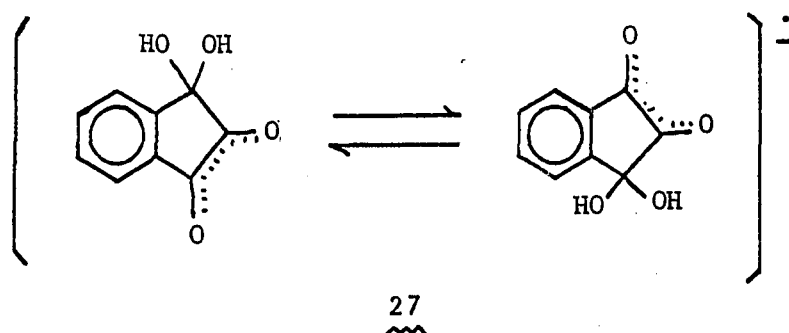


Figure 4. E.S.R. spectrum of radical anion formed spontaneously from ninhydrin in methanol solution of potassium hydroxide at 25-28°.

should undergo the following dissociation,



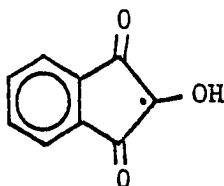
the structure of ninhydrin radical anion in low pH aqueous solution might possibly be the time averaged in structure 27.



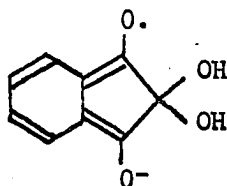
The radical anion in anhydrous THF with potassium metal (the most drastic dehydrate condition) has the same ratio of the two h.f.s.c. (ratio = 1) as the one in DMSO with *t*-butoxide (the fairly strong dehydrate condition). When the experiment shifts to anhydrous methanol, the ratio increases to 1.2 (Figure 4). Recently a crystallographic study on alloxantin, an analogue of hydrindantin, showed that the two molecules of water are not chemically bonded (66). Logically, it should be the same to hydrindantin. Thus, even though the ratio continues to increase, through methanol-water mixture (ratio = 1.3) (54) to water (ratio = 1.5), it is finally concluded that all these radicals are the same semitrione which illustrates a very good example of solvent effect upon radicals (72).

Other reasonable structures considered for the low pH radical are

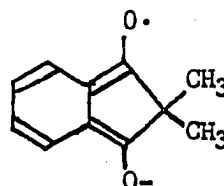
28, 29, 30.



28



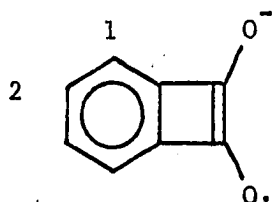
29



30

Structure 28 is discounted because of the expected acidity of 28 and of the stability observed for the radical anion. Structure 29 is discounted because 30 is difficult to produce and has little stability.

The equivalence of h.f.s.c. of H₆ and H₇ in 22 in DMSO



31

solution contrasts with the report of Geske and Balch that $a_2^H \gg a_1^H$ in 31 (73). A molecular-orbital calculation by Hückel and McLachlan treatments was performed to examine the predicted spin densities of the aromatic carbon atoms (f_c^π) in both radicals 22 and 31. Using $\alpha_0 = \alpha_c + \beta_c$, $\beta_0 = \beta_c$, $\lambda = -1.2$ and the equation $a^H = 22.5 f_c^\pi$ (74), leads to the values given in Table 2, where α is the Coulomb integral, β is the resonance integral, and λ is an adjustable parameter but it is always taken as 1.2 (75).

Table 2. Predicted and experimental hyperfine splitting constants (gauss) for $\underline{22}$ and $\underline{31}$

	$\underline{22}, \underline{a}_7^H$	$\underline{22}, \underline{a}_6^H$	$\underline{31}, \underline{a}_1^H$	$\underline{31}, \underline{a}_2^H$
Predicted, Hückel	0.42	0.50	1.52	1.06
Predicted, McLachlan	.22	.16	1.63	0.68
Found	.95 ^a	.95 ^a	3.74 ^{b,c}	1.87 ^{b,c}
		1.00, 0.68 ^d		

^aDMSO

^bAssignment from present calculations

^cCH₃CN

^dH₂O

Although the magnitudes of the spin densities calculated are in poor agreement with experimental values they do predict the near equivalence of h.f.s.c. for the aromatic hydrogen atoms of $\underline{22}$ and a ratio of close to 2 for the two sets of aromatic hydrogen atoms in $\underline{31}$. Thus it is concluded that in reality $\underline{a}_2^H < \underline{a}_1^H$ for $\underline{31}$ in contrast to the original assignment.

When hydroxyl deuterated ninhydrin is reduced in deuterium oxide by zinc and sodium deuterioxide at low base concentration the spectrum shown in Figure 3 is unaltered. Treatment of a solution giving the spectrum of Figure 3 with a large excess of base, or performing the zinc reduction at $[\text{OH}^-]/\text{ninhydrin} = 15-40$, gives rise to dark blue solution yielding a new e.s.r. spectrum (Figure 5). The hyperfine splittings required by Figure 5 are, \underline{a}^H (1:3:3:1 quartet) = 3.08 gauss, \underline{a}^H (doublet) =

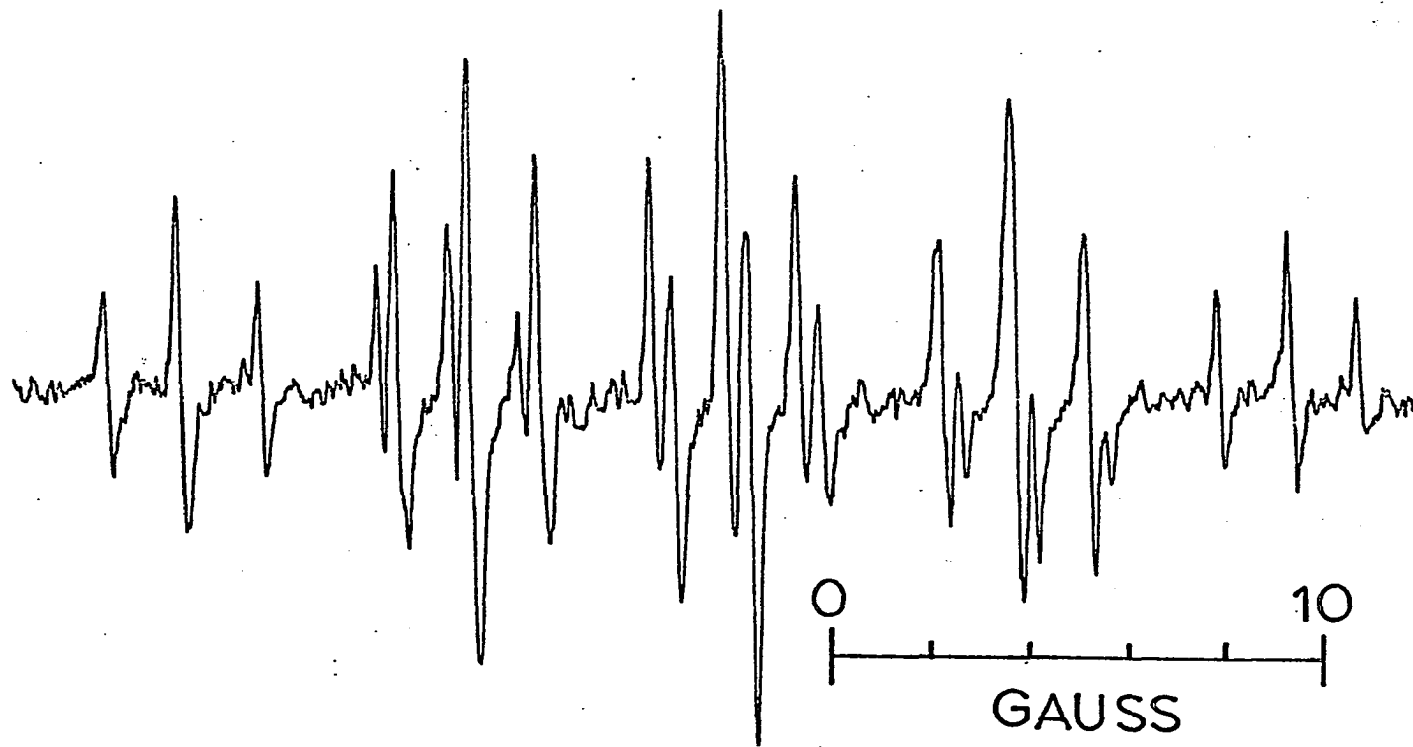


Figure 5. E.S.R. spectrum of radical anion formed by reduction of ninhydrin or hydrindantin with zinc at $[\text{OH}^-]$ 0.2 M. The same radical anion is formed by addition of hydroxide ion to a solution containing the radical anion whose spectrum is given in Figure 3.

2.66 gauss, and a^H (1:2:1 triplet) = 0.84 gauss. Ninhydrin in deuterium oxide, sodium deuterioxide solution gave a very complex spectrum (Figure 6) upon reduction in the presence of a large excess of base. Although the spectrum could not be analyzed by trial and error approaches, excellent agreement with the experimental spectrum was achieved by a computed spectrum (Figure 7) of Lorentzian absorption curves (0.05 gauss half-width) with a^H (doublet) = 2.80 gauss, a^H (doublet) = 2.50 gauss, a^H (triplet) = 0.75 gauss and a^D (1:2:3:2:1 quintet) = 0.446 gauss. Thus the radical anion at high pH has hyperfine splittings by two hydroxyl hydrogen atoms, $a_{OH}^H = 3.08$, $a_{OD}^D = 0.45$ gauss, $a^H/a^D = 6.85$ and the structure is assigned 23. At $[OH^-]/\text{ninhydrin}$ ratios of > 200 a colorless solution is produced but the e.s.r. spectrum of Figure 5 is still observed.

The high pH radical anion cannot be transformed to the low pH radical anion even though the reverse process can be routinely observed by adjustment of pH. Neutralization of excess base in a solution containing the high pH radical anion simply destroys all paramagnetic intermediates. Moreover, at intermediate pH stable mixtures of the two radical anions is never observed.

When a 0.05 M solution of ninhydrin was reduced with excess of zinc in the presence of hydroxide ion the following observations were made. At ratios of $[OH^-]/\text{ninhydrin}$ less than 4 the low pH radical anion is formed rapidly. After the maximum concentration is formed the low pH radical anion decays at a rate barely detectable over a five minute period. At $[OH^-]/\text{ninhydrin} = 8-15$ the low pH radical anion is initially

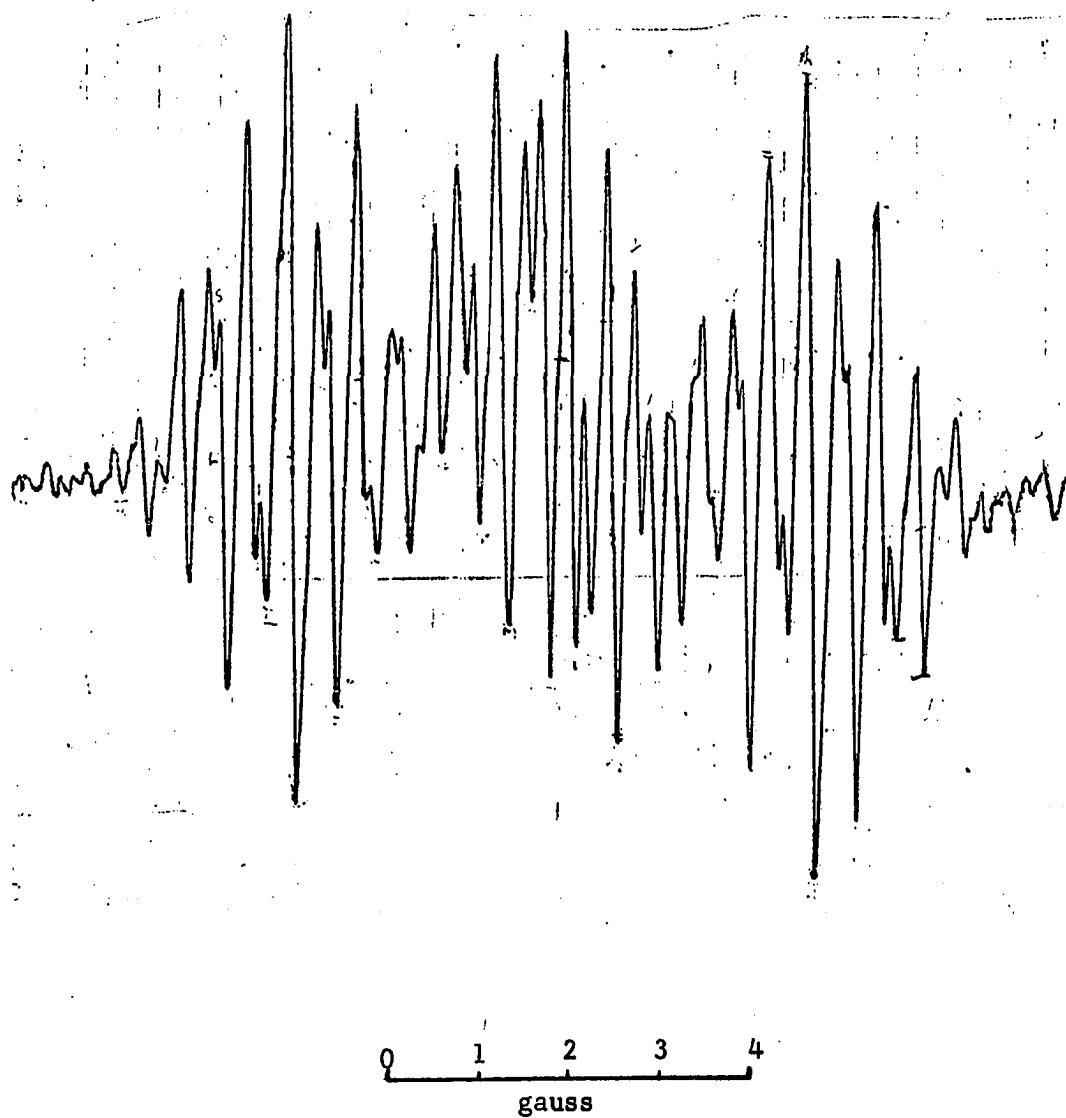


Figure 6. E.S.R. spectrum of radical anion formed by reduction of deuterioxyininhydrin with zinc at $[OD^-] > 0.2M$ in deuterium oxide at $25-28^\circ$.

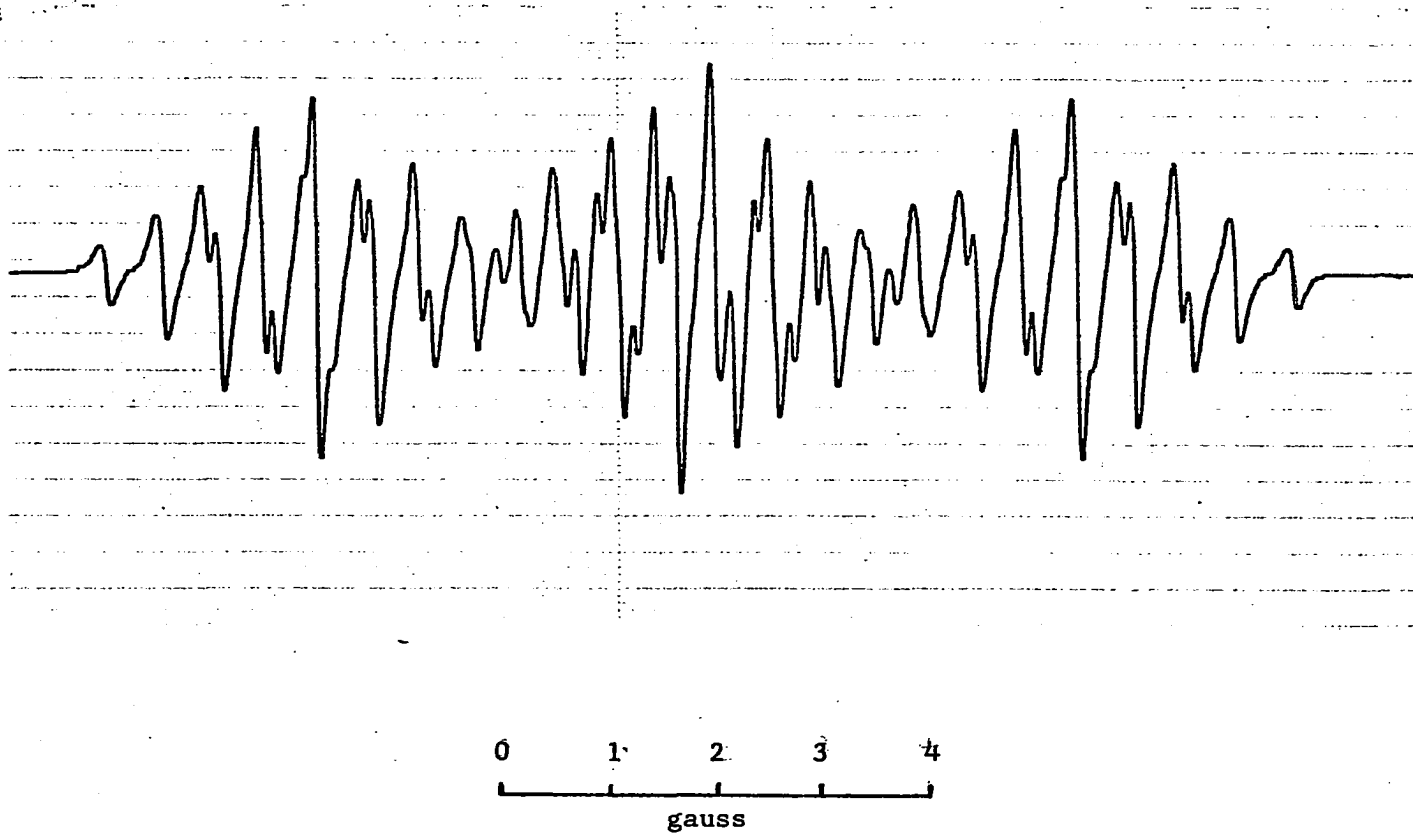
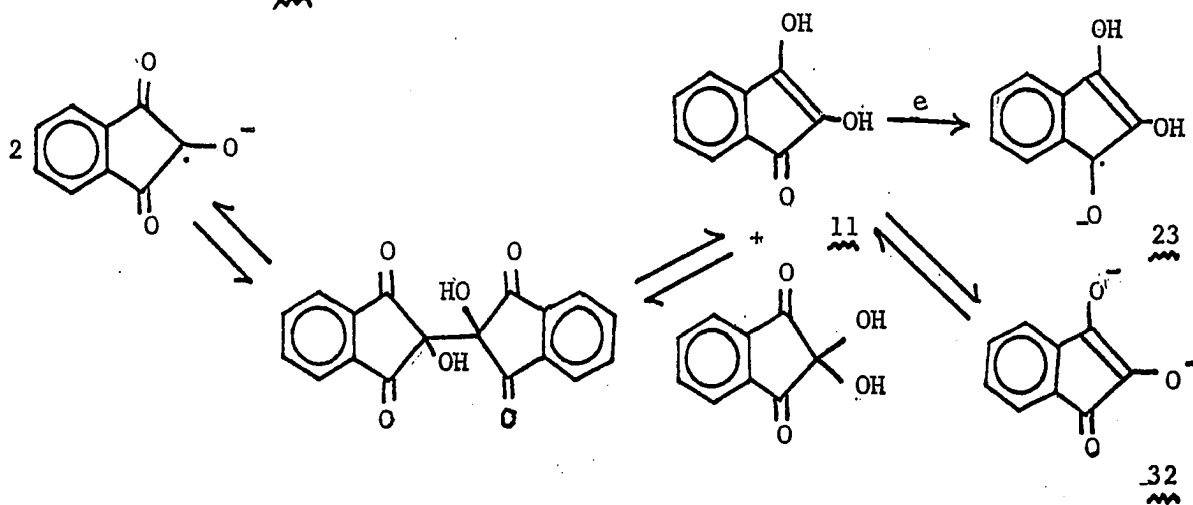


Figure 7. Computed e.s.r. spectrum of radical anion in Figure 6 by Lorentzian absorption curves (0.15 gauss half-width) with the h.f.s.c. given in the text.

formed but decays rapidly, particularly at the high concentrations of base. Following or concomitant with the decay of the low pH radical anion the high pH radical anion is formed at these base concentrations. The high pH radical is not particularly stable in 0.5 M sodium hydroxide solution and decays with loss of all paramagnetic character. Thus at $[\text{OH}^-]/\text{ninhydrin} = 10-12$ a low concentration of radical anions can be observed for only a few minutes at best. At $[\text{OH}^-]/\text{ninhydrin} = 15-40$ only the high pH radical anion has been detected although the possibility that the low pH radical anion is a precursor cannot be eliminated. The rate of formation of the high pH radical anion increases with hydroxide ion concentration. The net effect of these phenomena is that a high concentration of the low pH radical anion is achieved only at $[\text{OH}^-]/\text{ninhydrin} < 4$ while a high concentration of the high pH radical anion is found only when $[\text{OH}^-]/\text{ninhydrin} > 20$.

The above mentioned qualitative observations can be explained in the following manner. The low pH radical anion is considered to be a one electron reduction product of ninhydrin. It thus can be considered to be in equilibrium with hydrindantin and further to be in equilibrium with ninhydrin and the two electron reduction product of ninhydrin, diketohydrindol 11 (76).

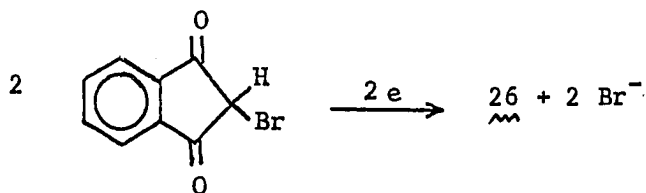


Hydrindantin has a weak center bond. In the low base concentration, the resonance stabilization of semitrione favors the center bond breaking and hydrindantin dissociating to the radical anion 22. In the high base concentration the stabilized dianion 32, which is blue, draws the reaction of hydrindantin to disproportionation rather than dissociation. Diketohydrindol has never been isolated, according to literature (64) and also attempts by the author, since it is extremely easily oxidized to hydrindantin. The whole interpretation above suggests that the high pH radical anion is derived from 11. In support of this reduced ninhydrin solutions that are blue, always give the e.s.r. spectrum of the high pH radical anion.

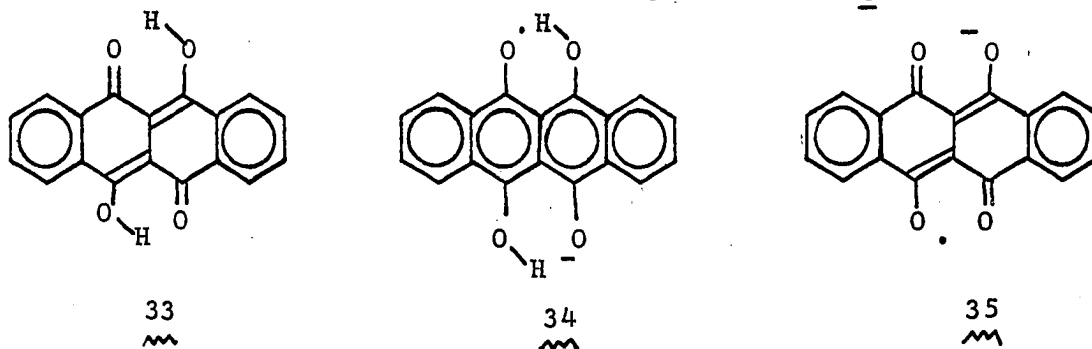
Apparently 11 does not spontaneously form 23. Evidence in regard to this point is available from experiments made with hydrindantin in basic aqueous solutions. At low pH hydrindantin forms 22 in high yield in the absence of any reducing agent. At high pH blue solutions are formed but radical anions are detected only when a reducing agent (zinc) is present. The high pH radical anion formed under these conditions is the same as found in the reduction of ninhydrin. The author used barium hydroxide as the base to run through all the experiments and found the same results. Perhaps this explains the long reported Ba-salt of hydrindantin which shows brilliant blue color but has no magnetic susceptibility (68). At very high base concentrations the dianion triketo ring has been ruptured and the solution becomes colorless but small amounts of 23 still can be detected.

The h.f.s.c. observed for the high pH radical anion are entirely

characteristic of 22. The formation of 21 from 2-bromo-1,3-indandione may involve 26 as an intermediate.



The rearranged structures 34 and 35 were eliminated for 21 as the intermediate since the parent hydroquinone 33, 6,11-dihydroxynaphthacenequinone, upon treatment in basic solution with propiophenone or oxygen produces a paramagnetic product, presumably 35, which shows no hyperfine splitting. For 35 the half-width of the 1st derivative spectrum between maximum and minimum is 0.35 gauss and the \underline{g} -value is 0.0022



greater than for 21 (Figure 8). Techniques for absolute measurement of \underline{g} -values are discussed in Ref. 78, 79, 80 and 81. The hydroquinone 33 produces the same singlet absorption when dissolved in dimethyl sulfoxide containing potassium t-butoxide, the same e.s.r. absorption is found in the presence or absence of oxygen or propiophenone, perhaps due to disproportionation of 36 and the easy oxidation of 34 to 35 by DMSO (82).

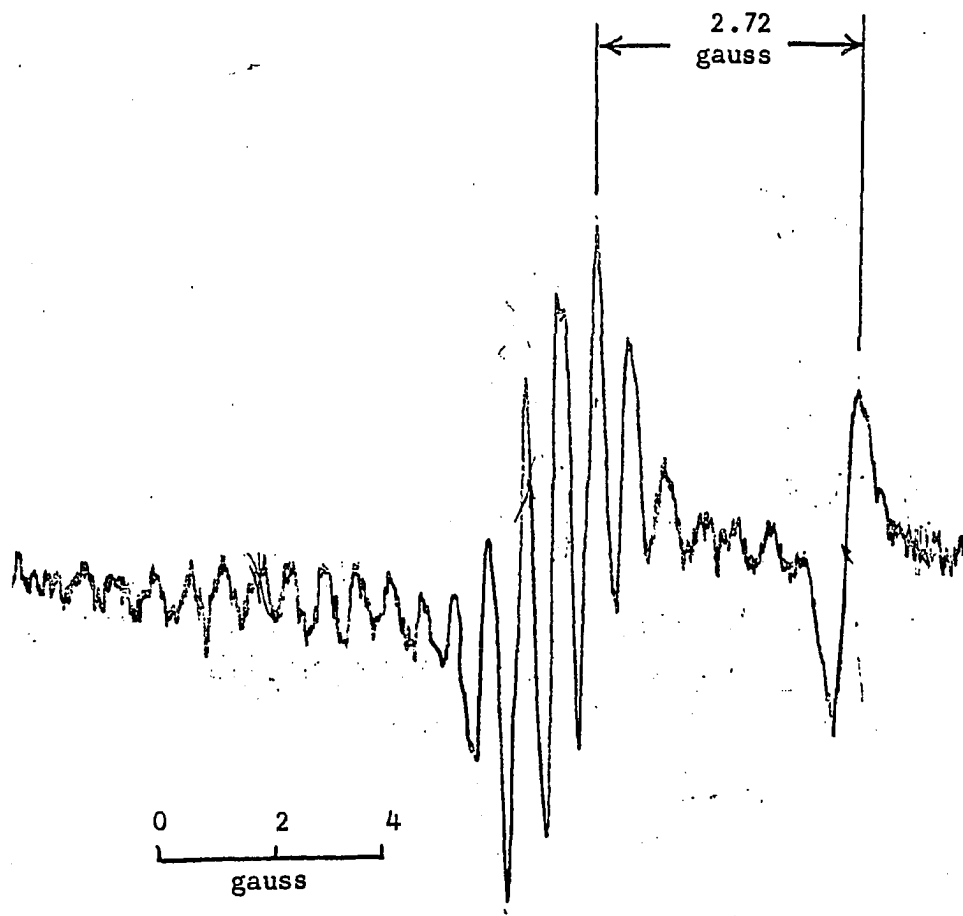
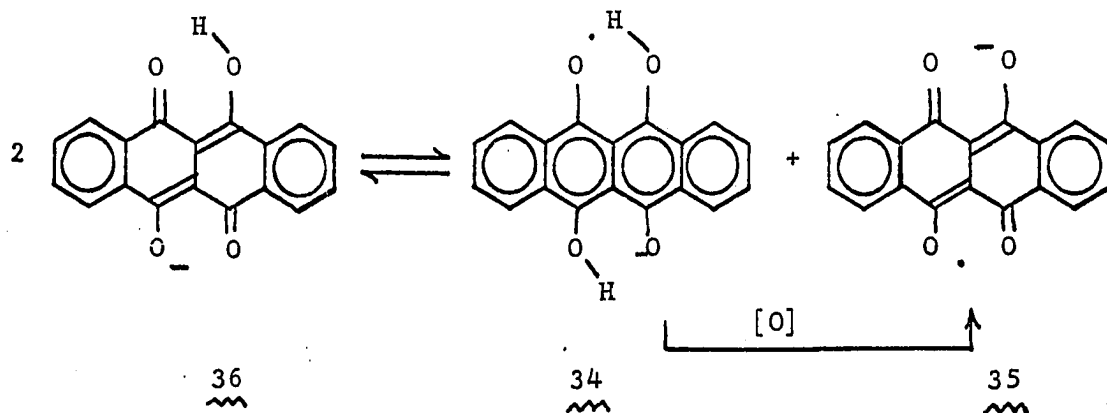
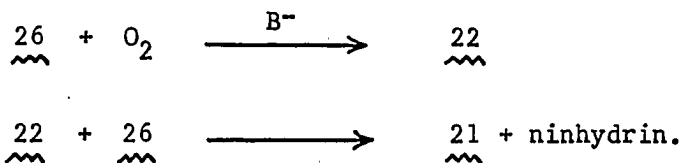


Figure 8. E.S.R. spectrum of radical anions produced from a mixture of 95% 6,11-dihydroxynaphthacenequinone (the singlet at low field) and 5% 2,2'-biindan-1,1',3,3'-tetranone in DMSO containing KOtBu .



The radical anion 21 can be observed in DMSO solution only when the base is deficient. The formation of 21 by reduction is a straight forward example of electron transfer. However, the oxidative result is surprising. A possible explanation is that the reaction involves oxygenation followed by electron transfer to unreacted 26.

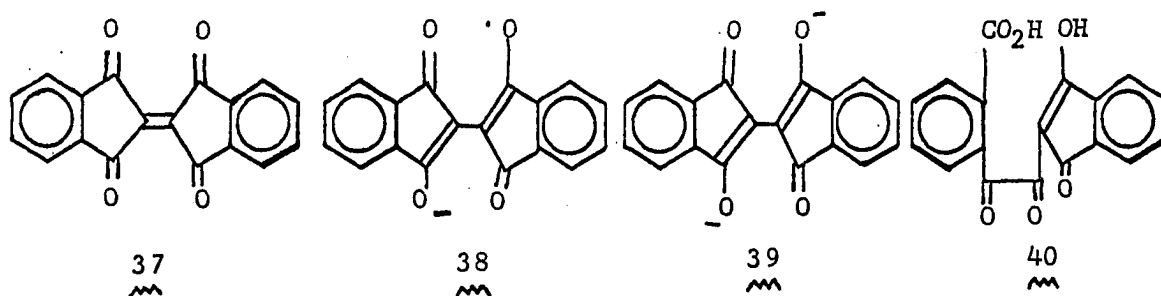


With small amounts of oxygen the formation of 21 might be favored by mass law effects. With higher extents of oxidation 22 is the observed product.

When the base is present in a large excess no paramagnetic products can be detected either in the presence of propiophenone or oxygen. This suggests that 39 is neither easily oxidized or reduced. This explains why Beringer and Galton obtained the rearrangement product (33) from 26 in a strongly basic solution rather than the desired product of electron transfer from 26 (83).

In independent experiments this author found that 26 absorbs little

oxygen in the presence of excess base in DMSO (80%)-t-butyl alcohol (20%) at 25°. One mmole substrate consumed 0.47 mmole of oxygen in a course of five hours, presumably via the formation of 22 by a minor extent. Theoretically at least two mmole of oxygen should be absorbed to give 22. However, at elevated temperatures the action of base and hydrogen peroxide converts 26 to 40 (65).

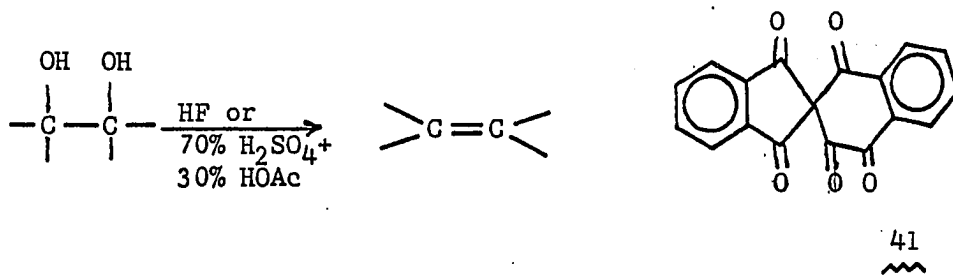


One other experiment gave further proof that the dianion 39 is not the source of the radicals. As was stated before compound 26 in DMSO solution with high base concentration did not give radicals either by oxidation or reduction. When a little iodine was added to such a mixture, no signal could be detected after thoroughly deoxygenation. However after the mixture was shaken with air, radical anion 21 was detected immediately. Apparently iodine had neutralized some of the base. The reaction of a dianion with iodine to yield an olefin is a recognized procedure (84). Apparently iodine does not convert 39 to 37.

In dilute aqueous base in the presence of zinc 26 gave appreciable amounts of a paramagnetic product which was expected to be 21. However, I was unable to obtain a resolved spectrum, possibly because the hydroxyl protons exchanges fast in water (85). At high concentration of base the sodium salt of 26 is insoluble.

Compound 37, a possible intermediate for radical anion 38, has been mentioned in the literature but I have been unable to repeat the preparations (86, 87). The latest report is made by Schonberg and Moubasher (88). They reported a good elementary analysis for 37 as well as several reactions. However when this author carefully repeated their procedure, their result could not be duplicated. I was unable to bring about the reductive coupling of 2,2-dichloro-1,3-indandione as reported in the synthesis. Different solvents (ether, benzene, toluene, xylene, DMF), temperatures (low, mild, high up to the b.p. of xylene), and coupling reagents (commercial copper bronze, copper powder, zinc powder, active zinc-copper alloy (89), molecular silver (90)) were used in these trials. Either no reaction occurred, or else a resinous material resulted. All the reactions were carried out under nitrogen.

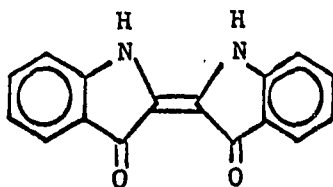
One other method (see equation) was also attempted (91, 92):



Hydridantin was the starting material in this reaction. However only the pinacol-pinacolone rearranged product 41 was found. N.M.R. did not show the symmetry expected for structure 37.

The difficulty of making this compound is not well understood. The strong polar repulsion of oxygen atoms and the rigid unrotatable center double bond might be the major troubles.

Recently Wyman and Zenhausern gave their view about the instability of cis-indigo 42 (93). The two carbonyl oxygens are so bulky, overlapping each other. A picture (Figure 9) is drawn to scale on the basis of crystallographic data on trans-indigo.(94). The circles show the



42

Van der Waals radii (1.40 Å) of the carbonyl oxygen atoms. If this is the true interpretation, then 37 may be even more serious, since it has a doubly cis-conformation.

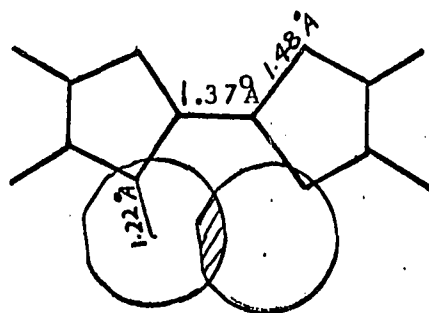


Figure 9. The picture, drawn to scale, of cis-indigo.

Radical Anions Derived from Alloxan

The semitrione of alloxan (43), an analog to 22, has been prepared by the different ways listed in Table 3.

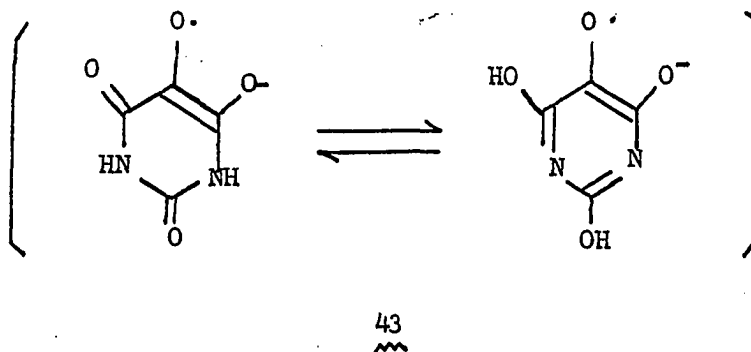


Table 3. Formation of alloxan semitrione

Substrate (structure number)	Electron donor	Base and (solvent)	Remarks
Alloxan (16)	Propiophenone or 9,10-dihydro- anthracene	Potassium <u>t</u> - butoxide (DMSO)	Five triplets $a^N = 0.587$
Dialuric acid (18) <u> </u>	None	Potassium <u>t</u> - butoxide (DMSO)	$a^H = 0.48$ gauss
Alloxantin (15) <u> </u>	None	Potassium <u>t</u> - butoxide (DMSO)	
Dialuric acid (18) <u> </u>	None	Potassium hydroxide (H ₂ O-CH ₃ OH)	Seven lines (spacings 0.51 gauss) followed by five-line spectra, a^N decreases with in- creasing base con- centration
Alloxan (16) <u> </u>	Sodium di- thionite	Potassium hydroxide (H ₂ O)	

Alloxantin in DMSO containing potassium t-butoxide produces a colorless solution containing a paramagnetic intermediate whose e.s.r. spectrum is a 15-line multiplet consistent with hyperfine splitting by two equivalent nitrogen atoms, $a^N = 0.587$ gauss and two equivalent hydrogen atoms, $a = 0.48$ gauss (Figure 10). Alloxantin- d_6 gave a broadened 5-line multiplet (approximately 1:2:3:2:1) consistent with the deuterated analog of $\overset{\sim}{43}$ with $a^N = 0.579$ gauss (Figure 11). The same radical anion at approximately the same concentration was formed from anhydrous alloxantin and from alloxantin dihydrate.

Radical anion $\overset{\sim}{43}$ was not formed spontaneously from alloxan in DMSO containing potassium t-butoxide. However, $\overset{\sim}{43}$ was formed from alloxan in the presence of the propiophenone anion or the anions derived from 9,10-dihydroanthracene. Radical anion $\overset{\sim}{43}$ was generated spontaneously from dialuric acid in DMSO containing excess potassium t-butoxide, following the same general mechanism already discussed on p. 2. The same radical was also produced in water-methanol solution in the presence of potassium hydroxide, except that the 15-line multiplet collapsed into 7-line spectrum. Since dialuric acid is barely soluble in water, methanol is essential.

The radical anion of alloxan is probably the rapidly time-averaged equilibrium mixture $\overset{\sim}{43}$ with only the protons in the imino-position giving observable splittings (95). This interpretation is strongly supported by experimental evidence.

When the experiment is performed in DMSO solution, a^H is independent of base concentration. This means that the imino hydrogen is always present. However the concentration of $\overset{\sim}{43}$ formed from alloxantin

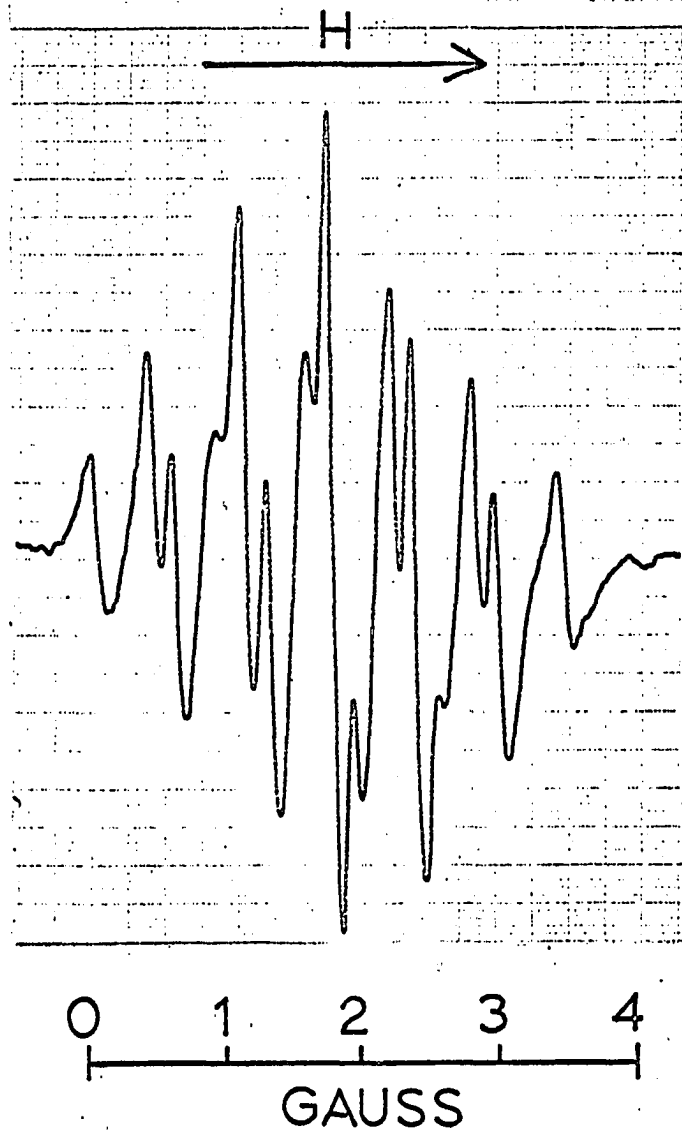


Figure 10. E.S.R. spectrum of radical anion formed by disproportionation of dialuric acid and alloxan in dimethyl sulfoxide containing an excess of potassium t-butoxide.

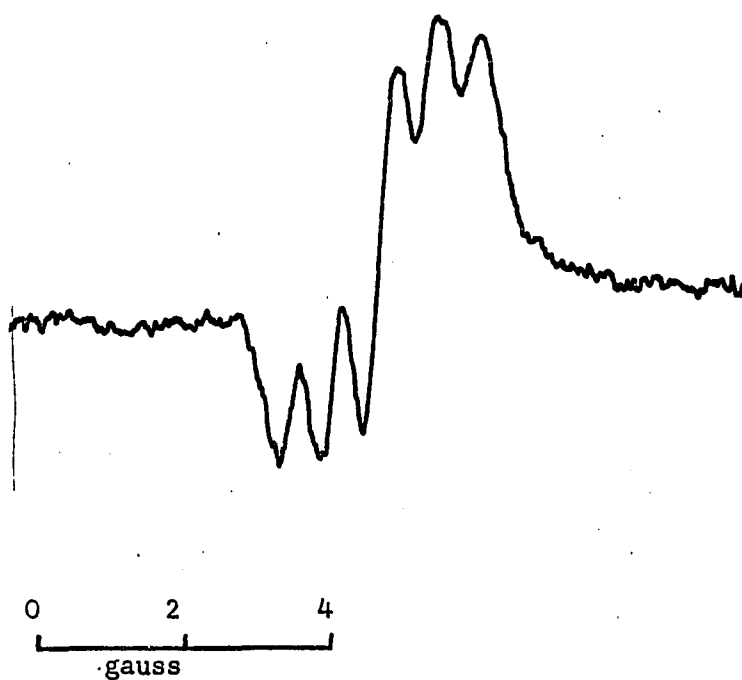


Figure 11. E.S.R. spectrum of radical anion formed spontaneously from alloxantin- \underline{d}_6 in DMSO- \underline{d}_6 containing an excess of potassium \underline{t} -butoxide.

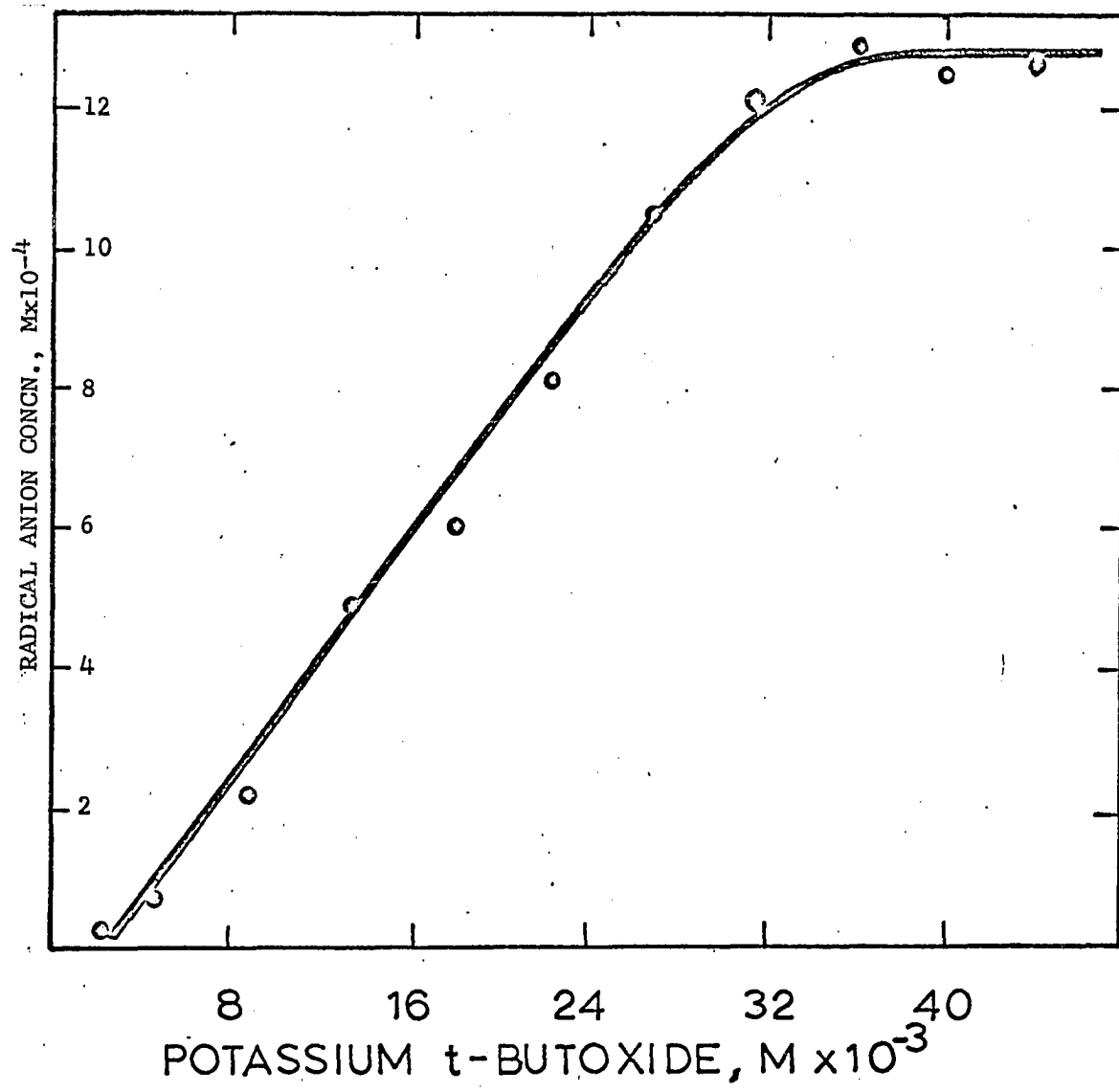


Figure 12. Radical anion formation from 7.8×10^{-3} M alloxantin in dimethylsulfoxide solution at 25-28°.

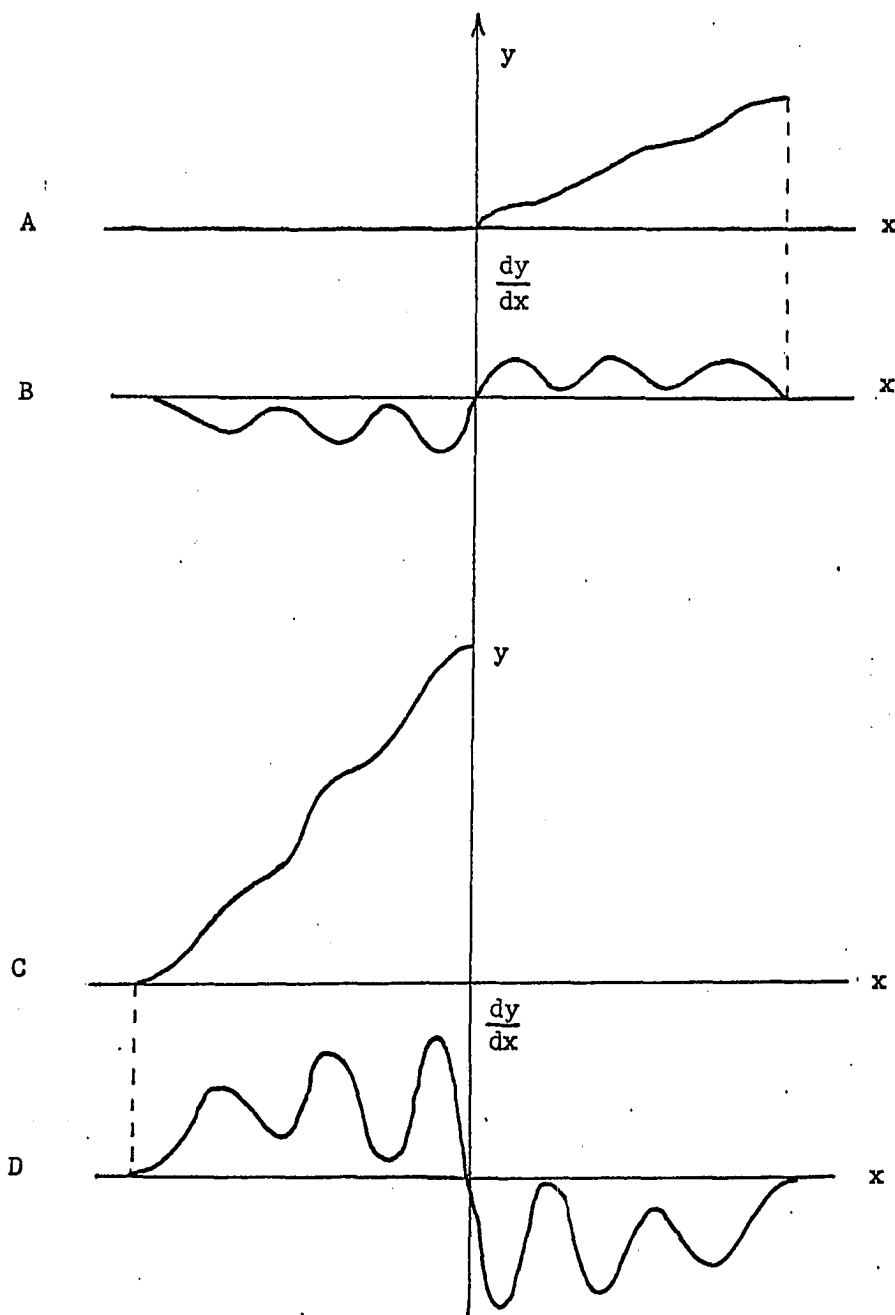
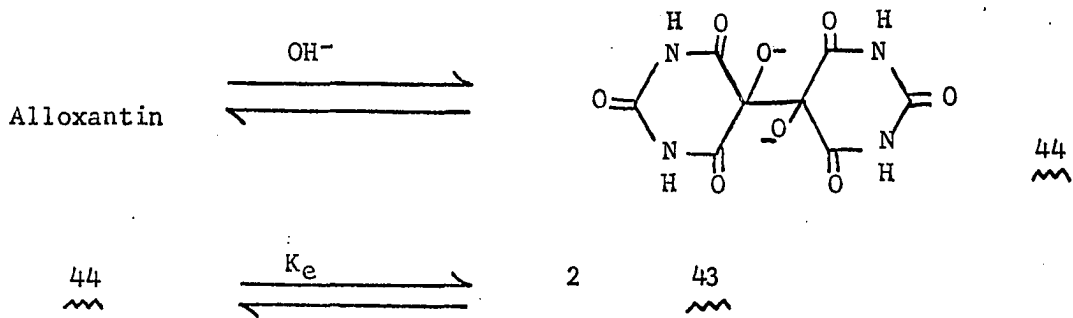


Figure 13. Curve B and D are the first derivative e.s.r. spectrum of DPPH (slight overmodulation) at signal level 1 (curve B) and 2.5 (curve D) under exactly the same conditions. Curve A and C are the integrations made by hand such that B and D are their first derivatives, respectively. The ratio of peak heights of D to B is 2.5. The areas under D and B as well as under C and A are in the same ratio.

was dependent upon the concentration of base, suggesting that an acid-base equilibrium is involved in a reversible process leading to the formation of 43 from alloxantin. Figure 12 shows the effect of base concentration on the yield of 43 in DMSO solutions and indicates that at high base concentrations the yield of 43 becomes independent of the concentration of base. The maximum yield of 43 from alloxantin is 8.2 percent. Such behavior is consistent with the following formulation.



I have measured K_e (96) using a variety of different initial alloxantin concentrations by increasing the concentration of base until the concentration of 43 becomes constant. Table 4 summarizes results that lead to a value of K_e of 2.3×10^{-4} moles/l. Values of K_e in Table 4 were calculated on the basis that

$$[\text{Alloxantin}]_{\text{initial}} = 2 \frac{\text{43}}{\text{44}}$$

The radical concentration was obtained by comparison of the height of the slightly overmodulated signal of 43 with the central peak of diphenylpicrylhydrazyl (DPPH) whose intensity was equated to 1/3 of the concentration of DPPH. DPPH has been recrystallized from a benzene-ligroin mixture (97). Justification for the use of peak heights is illustrated in Figure 13 in which the radical concentration in one experiment was

Table 4. Dissociation of alloxantin in dimethyl sulfoxide solution in the presence of potassium t-butoxide at 25°

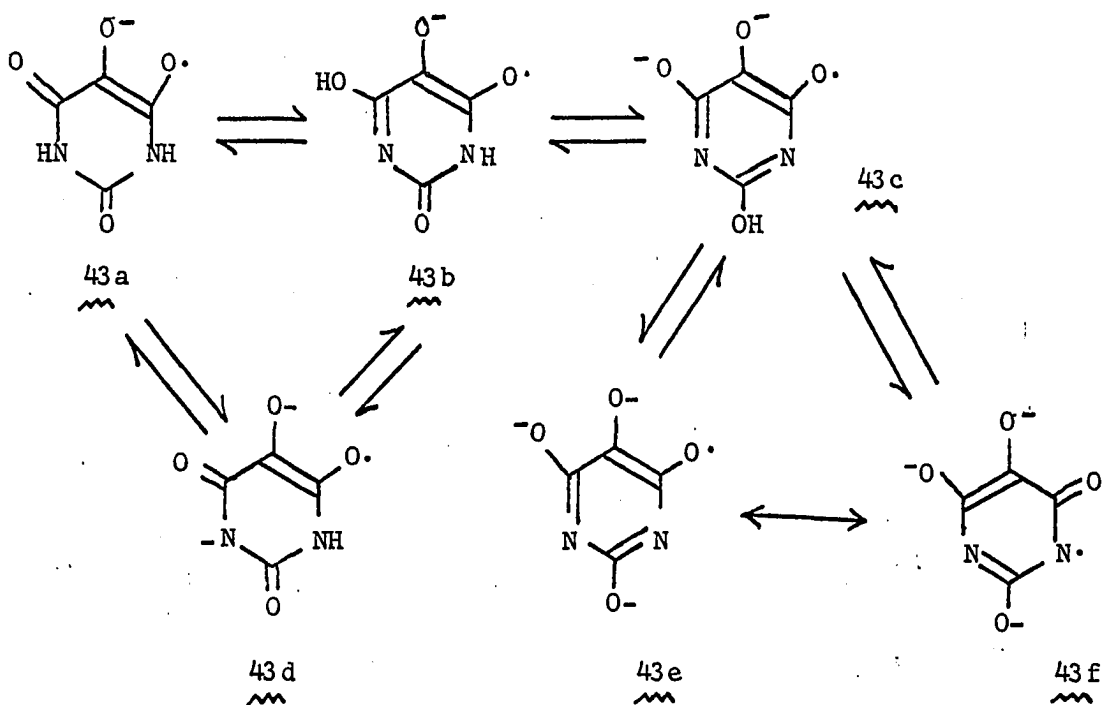
Initial alloxantin concn., Mmoles/liter	KOC(CH ₃) ₃ concn., ^a Mmoles/liter	Concn. of <u>43</u> Mmoles/liter	10 ⁴ <u>K_e</u>
7.8	45	1.28	2.27
8.8	45	1.60	3.20
7.0	22	1.34	2.84
3.9	22	0.87	2.18
3.9	12	0.67	1.85

^aConcentration at which a further increase in base concentration did not give rise to an increase in the concentration of 43

found the same by the comparison of the peak heights of the derivative signals or the areas doubly integrated by hand. Radical anion 43 had a line width approximately equal to one of the five lines (1:2:3:2:1 intensity ratio) in the DPPH spectrum.

The second experimental point in regard to the structure of 43 concerns observations of radical anions of alloxan in aqueous solution. Alloxan in aqueous basic solution did not give an e.s.r. signal upon reduction with zinc. However, in aqueous basic solution alloxan (0.1 M) is readily reduced by sodium dithionite (Na₂S₂O₄). At ratios of [OH⁻]/alloxan of < 2.5 a 7-line multiplet was observed that was superimposable upon the low resolution multiplet observed for 43 in DMSO solution (i.e. seven lines with an intensity ratio of approximately 1:4:8:10:8:4:1 separated by about 0.51 gauss). However, in DMSO the multiplet could be

completely resolved to give 15-lines while in water the spectrum could not be further resolved. At a ratio of $[\text{OH}^-]/\text{alloxan}$ of 3-40 only a 5-line pattern with intensity ratios of approximately 1:2:3:2:1 was observed. The value of a^{N} decreased with increasing $[\text{OH}^-]$ up to a ratio of 20:1 after which it remained constant at $a^{\text{N}} = 0.276$ gauss. At $[\text{OH}^-]/\text{alloxan} = 4$ the value of a^{N} was 0.374 gauss. The value of a^{N} decreases with increasing $[\text{OH}^-]$ again suggesting that there is an acid-base ionization or isomerization process.



The radical anion of dialuric acid, an analog of 23, has been investigated. Dialuric acid is not soluble in water. In DMSO or methanol, even in the presence of reducing agents, the best resolved spectrum still is the same as observed for 43. However, dialuric acid gives intense and lasting blue color which seems associated with the dianion structure,

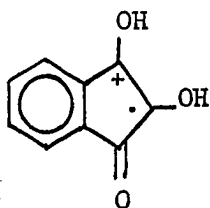
analogous to 32.

Amalic acid (tetramethylalloxantin), or dimethylalloxan with propiophenone in DMSO containing potassium t-butoxide gave a spectrum (Figure 14) consistent with two nitrogen atoms, $a^N = 0.500$ gauss, and two methyl groups, $a_{CH_3}^H = 0.300$ gauss (linewidth 0.15 gauss). N,N'-dimethylalloxantin and methylalloxan also have been made. However, the e.s.r. spectra could not have been resolved either in water or DMSO.

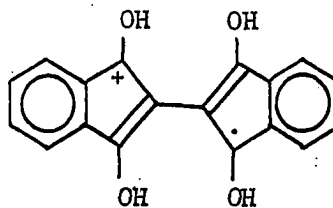
In aqueous solution, the dimer compounds of alloxan (alloxantin, tetramethylalloxantin) seem to favor disproportionation more than dissociation. No signal could be detected unless sodium dithionite was added. The radical anions of methylated alloxan do not give a resolved spectrum in aqueous solution.

Radical Cations Derived from 26

When ninhydrin is dissolved in concentrated sulfuric acid containing sodium dithionite or when indan-1,3-dione is dissolved in sulfuric acid containing potassium persulfate, the expected radical cation 45 is not



45



46

formed. Instead a complicated spectrum soon develops, which also can be obtained by dissolving 26 in 98% H_2SO_4 . This radical cation is assigned structure 46 with a^H (eight equivalent hydrogen atoms) = 0.912 and a^H (four equivalent hydrogen atoms) 0.228 gauss. The e.s.r. spectrum is

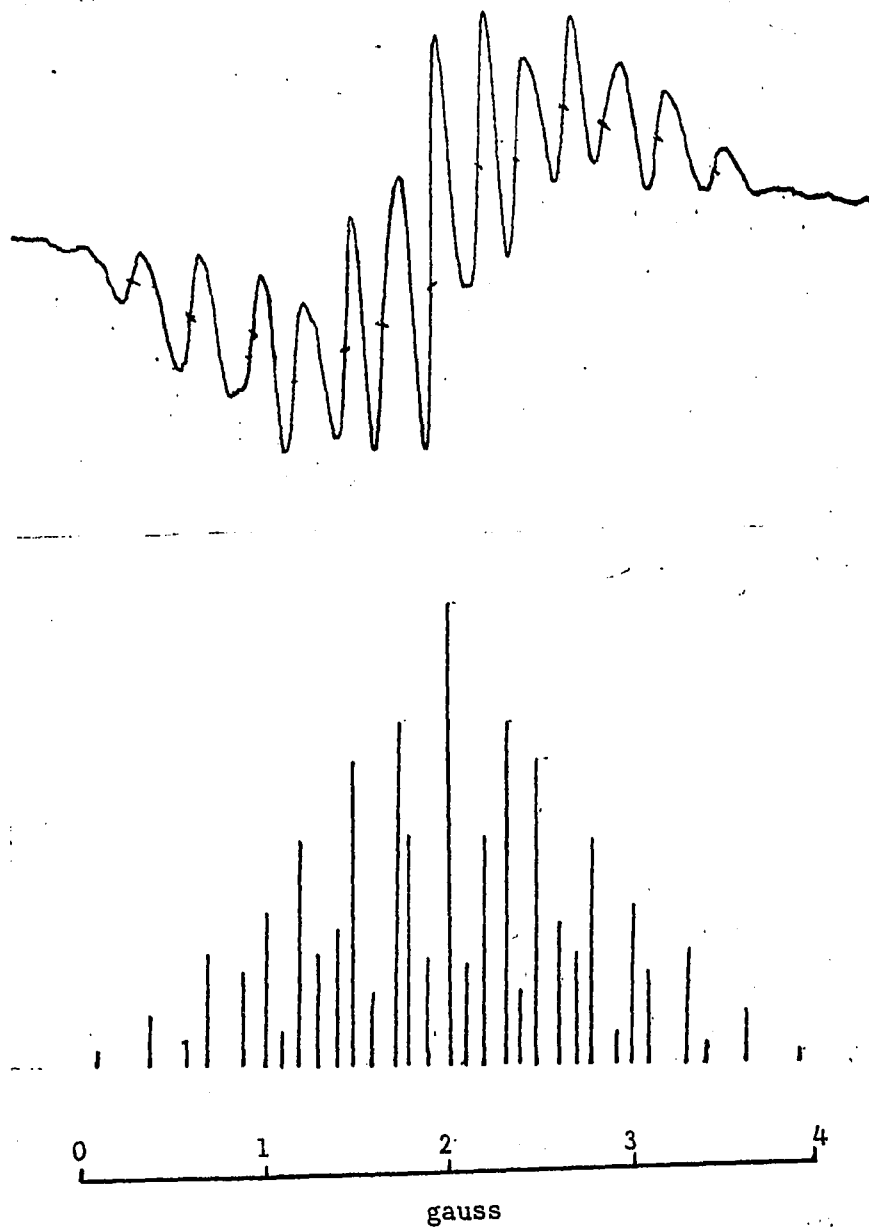


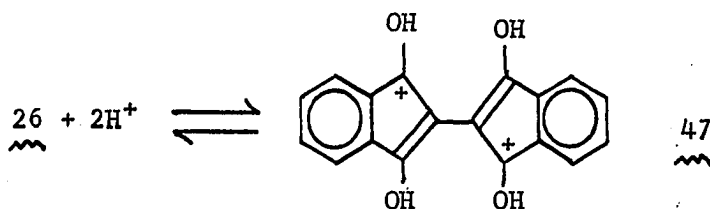
Figure 14. E.S.R. spectrum of radical anion formed from dissociation of tetramethylalloxantin in dimethyl sulfoxide containing an excess of potassium *t*-butoxide. The correlation diagram was derived from the h.f.s.c. given in the text.

shown in Figure 15. Table 5 lists all the methods by which 46 has been formed.

Table 5. Formation of radical cations from 1,3-indandione derivatives

Substrate	Reagents		
	98% H ₂ SO ₄	98% H ₂ SO ₄ + Na ₂ S ₂ O ₄	98% H ₂ SO ₄ + K ₂ S ₂ O ₈
Ninhydrin	<u>46</u> , slowly formed	<u>46</u>	poor spectrum
1,3-Indandione	no signal	no signal	<u>46</u>
2-bromo-1,3-indandione	<u>46</u>	<u>46</u>	poor spectrum
Hydrindantin	<u>46</u> , slowly formed	<u>46</u>	poor spectrum
"Bishydroxyindone" (<u>26</u>)	<u>46</u>	<u>46</u>	poor spectrum

The formation of 46 instantly from 26 in 98% sulfuric acid in the absence of sodium dithionite is not easily explained. The reaction formally involves the addition of two protons and a one electron reduction. The solvent system (98% sulfuric acid) is not usually considered to be a reducing agent. Moreover, upon dilution with water 26 can be recovered in nearly quantitative yield. The best explanation that can be put forth is a series of oxidation and reduction steps.



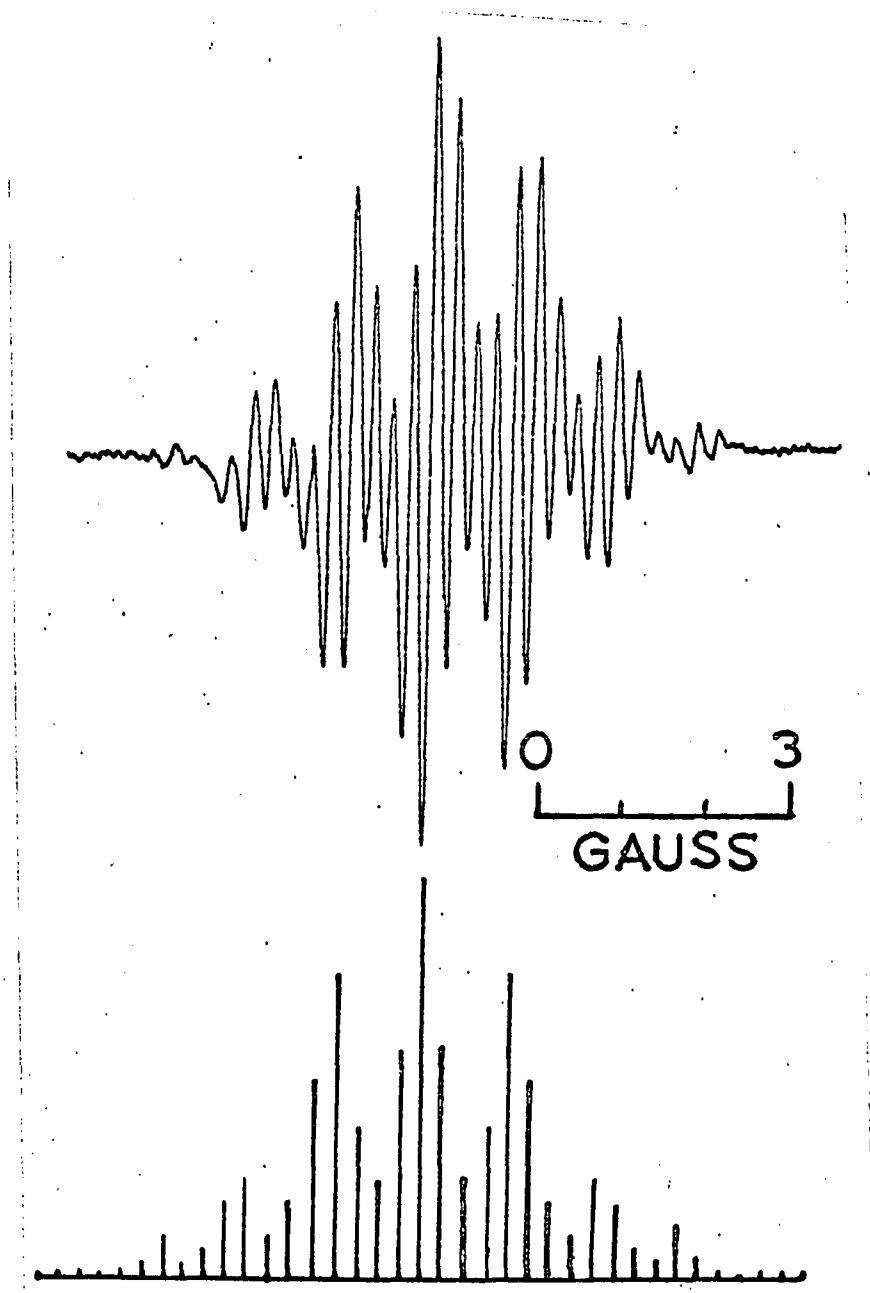
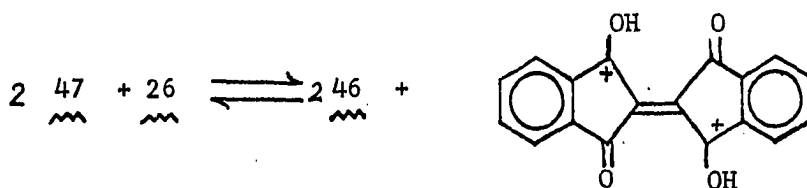
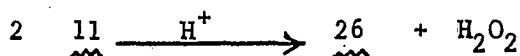
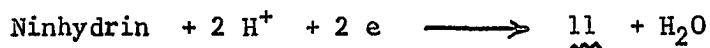


Figure 15. First derivative e.s.r. spectrum of radical cation formed from reduction of ninhydrin by sodium dithionite in 98% sulfuric acid. The same radical cation is formed by the oxidation of 1,3-indandione by potassium persulfate in sulfuric acid solution. The correlation diagram was derived from the h.f.s.c. given in the text.

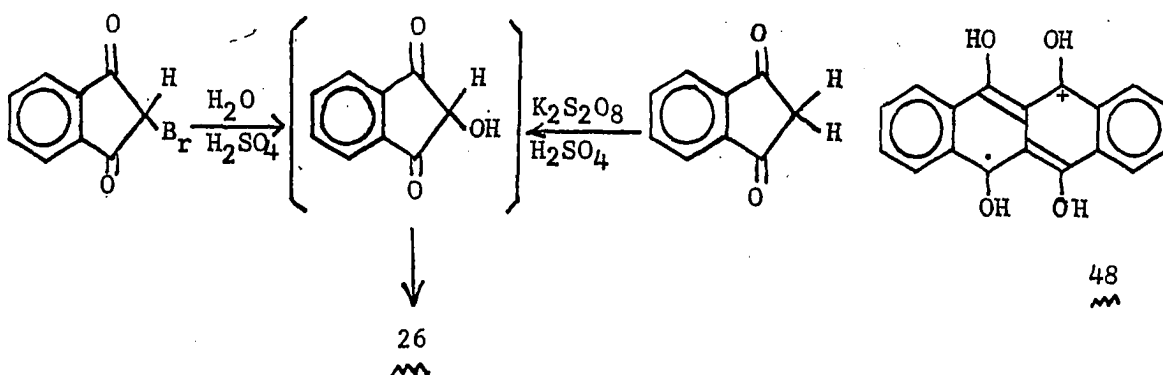


The reaction sequence could proceed by a series of bimolecular electron transfer reactions which could be reversed by the addition of water.

The formation of 46 from the other indone derivatives (Table 5) is very suggestive of reactions involving 26 as an intermediate. By treatment with concentrated sulfuric acid other vicinal triketones undergo fast decarbonylation to α -diketones (98), but ninhydrin is converted to 26 (99, 100), possibly involving 11 as an intermediate.



The reaction should be greatly facilitated at the first step by a reducing agent ($\text{Na}_2\text{S}_2\text{O}_4$). The formation of 46 from 2-bromo-1,3-indandione in 98% sulfuric acid follows logically.



Oxidation of 1,3-indandione 26 by persulfate can be formulated to involve similar intermediates. The formation of 46 from hydrindantin in the

presence of sodium dithionite undoubtedly involves 26 since 26 is commonly prepared by the reduction of hydrindantin by hydrogen sulfide.

Although the observed spectrum (Figure 14) is consistent with 46, it can also be easily rationalized with the rearranged cation 48. In fact, in sulfuric acid 33 with a purity estimated at > 95% gave rise to a radical cation whose e.s.r. spectrum was identical to that of Figure 14. However, on the basis of additional experimental results, I am forced to conclude that 26 yields radical cation 46 and not 48, and that 26 is not isomerized to 33 under the reaction conditions.

Compound 26 (m.p. 315-17^o, dark purple) is readily distinguished from 33 (m.p. 345-347^o) by ultraviolet spectroscopy. In ethanol 26 gives λ_{\max} . at 220 and 288 m μ whereas 33 has a λ_{\max} at 261 m μ . In sulfuric acid solution, wherein radical cations can be detected at higher substrate concentrations, compound 26 gives a purple solution, λ_{\max} . 216, 309 m μ while 33 gives a pink solution, λ_{\max} = 298 m μ . The sulfuric acid solution of 33 shows no change in the ultraviolet spectrum during a two week period whereas a solution of 26 deteriorates in a few hours with a shift in the 309 m μ peak to longer wavelength opposite to the direction of 33. (It was reported (82) 26 rearranges to 33 in acidic condition.) On the other hand the e.s.r. spectrum of the radical cation generated from 26 shows no change in two weeks at 25^o while the e.s.r. spectrum of the radical cations generated from 33 decays in a few hours.

Examination of mixtures of 26 and 33 by ultraviolet absorption led to the conclusion that 5% of 26 could be detected in 33. Samples of 26 and 33 were treated with 98% sulfuric acid and the buildup of radical

cations followed. In two hours, a maximum concentration of radical cations had been formed. The signal from 26 grew very rapidly until about 50% of the starting material had been converted to a radical cation.

Compound 33 formed radical cations more slowly and about 2% of the starting material was converted to a radical cation. In the case of radical anion, compound 33 only 0.6% was converted. After the two hour reaction period the samples were diluted with water and a quantitative recovery (from weight of filtrate) of material obtained. The infrared and ultra-violet spectra of the crude filtrates showed them to be identical with the respective starting compound. These observations exclude the rearrangement of 26 to 33 or 48 under the reaction conditions.

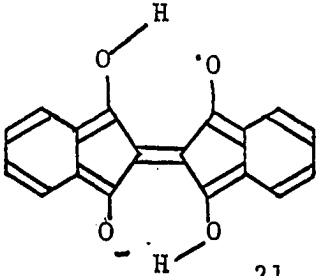
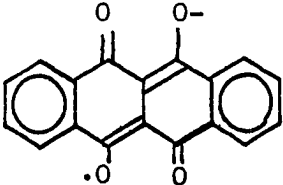
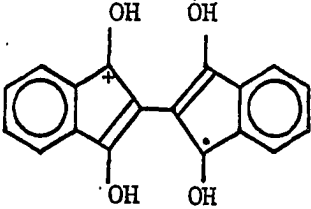
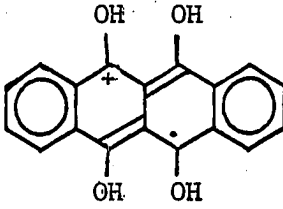
Oxidation of 33 in DMSO solutions containing potassium t-butoxide gave rise to a singlet e.s.r. absorption that is ascribed to 35. There was no indication of the formation of 21 or 22. Oxidation of basic solutions of 33 to which 5% of 26 had been purposefully added gave mainly 21 which is readily distinguished from 35 by hyperfine structure and g -value. Thus it is concluded that 33, whose oxidation gave no indication of the presence of 26, must have contained $< 0.5\%$ of 26, and that radical cations of the two compounds probably have exactly the same spectra.

The above statements were summarized in Table 6.

For compound 26, Eck and Marvel presented the evidence for the dienolic structure (101), a bis-dihydroxyindone.

The radical cation prepared from 26 in deuteriosulfuric acid did not give a well resolved spectrum, presumably due to the small value of a^D and line broadening due to the quadrapole of the deuterium nucleus.

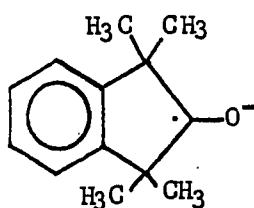
Table 6. Physical properties of compounds 26 and 33

Substrate	<u>26</u>	<u>33</u>
Name	2,2'-Biindan-1,1',3,3'-tetraone	6,11-Dihydroxynaphthacene-quinone
M.P.	315 - 317°C	345 - 347°C
Color	dark purple	brown orange
Sulfuric acid Solution	Purple, $\lambda_{\max} = 216, 309\text{m}\mu$ $\epsilon_{216} = 1.82 \times 10^3$ $\epsilon_{309} = 2.8 \times 10^3$	pink orange, $\lambda_{\max} = 298\text{m}\mu$ $\epsilon_{298} = 6.7 \times 10^3$
Alcoholic Solution	Purple, $\lambda_{\max} = 220, 288\text{m}\mu$ $\epsilon_{220} = 4.65 \times 10^4$ $\epsilon_{288} = 1.95 \times 10^4$	yellow orange, $\lambda_{\max} = 261\text{m}\mu$ $\epsilon_{261} = 3.9 \times 10^4$
KBr Pellet (IR, μ)	2.9, 6.45, 6.8, 7.2 9.05, 10.25, 12, 13.1, 14.2, 14.8	2.9, 6.3, 6.6, 7.1, 7.95 9.6, 11.65, 13.85
Radical anion	 21	 35
Radical cation (both might have the same spectrum)	 46	 48

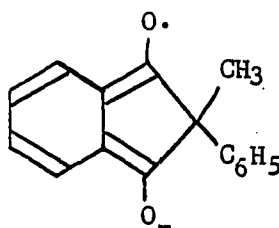
Attempts to prepare radical cations from alloxantin and tetramethylalloxantin in sulfuric acid gave only unresolved e.s.r. signals.

Attempted Synthesis of Other Radical Anions in the Indan System

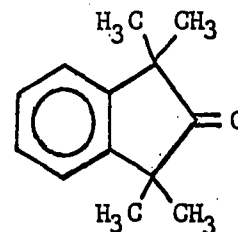
2,2-Dimethyl-1,3-indandione, 2-methyl-2-phenyl-1,3-indandione, and 1,1,3,3-tetramethyl-2-indanone were synthesized. None of these compounds were reduced to give detectable amounts of radical anions by the propiophenone enolate anion in DMSO solution. Reduction by potassium in tetrahydrofuran gave e.s.r. signals which were short-lived at room temperature and showed poor resolution. Therefore it is concluded that structures 49, 30 and 50 are not unusually stable.



49



50

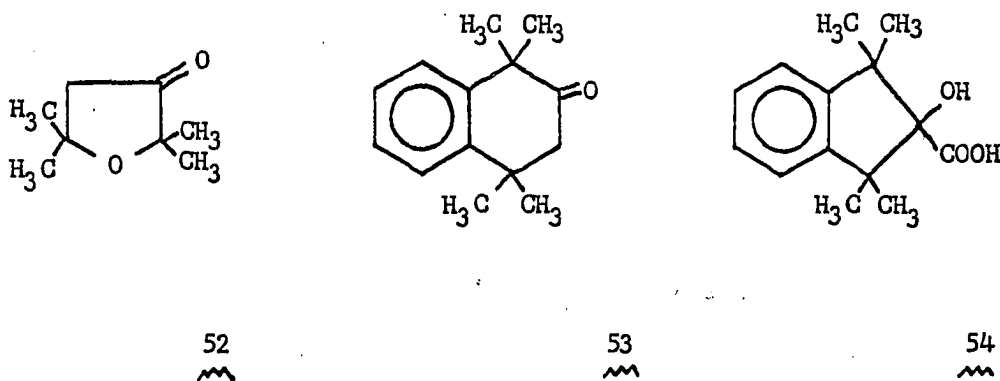


51

The instability of the semidione structures of 30 and 50 is probably because of the deterioration of the conjugated aromatic system.

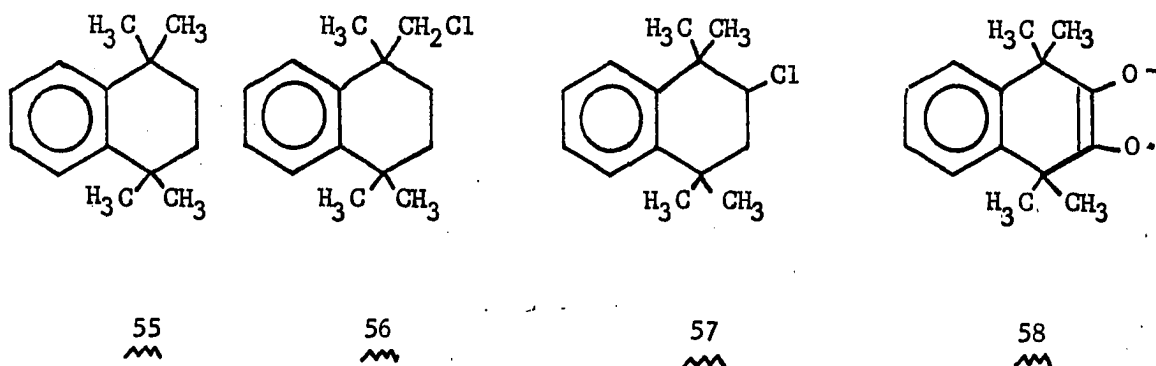
In the course of making compound 51, three intermediates, tetramethyltetrahydrofuranone 52, 1,1,4,4-tetramethyltetrahydronaphthalenone

53, and 1,1,3,3-tetramethyl-2-carboxylindanol 54 were isolated. Compounds 52 and 53 show paramagnetic species upon oxidation in DMSO con-



taining excess potassium *t*-butoxide. The spectra are singlet and decay very rapidly, probably due to the fast benzilic acid rearrangement.

In order to further examine whether the sec-H in compound 55, 1,1,4,4-tetramethyltetraline, is activated by benzene ring, the hydrocarbon was synthesized and a chlorination experiment was performed.

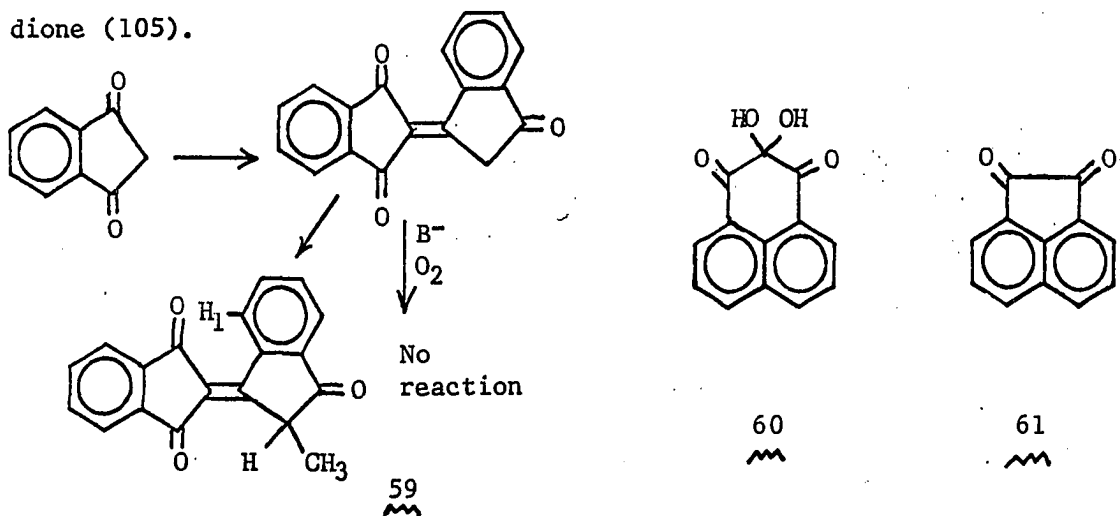


The reaction was carried out in carbon tetrachloride by adding deficient quantities of chlorine in the presence of light. By VPC measurement (Golaya column, polypropylene glycol, 110°C; and column R, polypropylene glycol UCON. oil LB-550-X, 195°C), the ratio of the two products 56 and

57 was 1.27. An attempted preparation of 57 involved hydrogenation of 53 with LiAlH_4 , followed by chlorination with SOCl_2 . However, the hydrogenation produced two isomers. The results from chlorination are consistent with e.s.r. experiments that the β -carbon atoms are not activated by the aromatic ring in structures 55 and 58.

In the original procedure 51 was made in two steps from 53 (102). This author found if excess base was added, the alkaline-potassium permanganate oxidation gave the end product almost quantitatively, while the reported acidic-chromic trioxide oxidation (the second step) gave very poor yield. Furthermore the reported benzilic acid rearrangement only gave a yield of 65%. This author found if the reaction was carried out in *t*-butanol containing excess potassium *t*-butoxide through molecular oxygen oxidation the yield went up to 84%, and the process was much neater.

Exposure of 1,3-indandione to oxygen in basic solution failed to give an e.s.r. signal. Presumably the carbanion is stable to oxygen (103). In addition condensation to bindone occurs readily (104). I have been unable to alkylate 1,3-indandione with methyl iodide in basic solution prior to condensation. The situation is analogous to cyclopentane-1,4-dione (105).



Methylated bindone 59 shows unusual diamagnetic shielding of H_1 which absorbs (60 Mc.p.s.) 9.62 p.p.m. downfield from tetramethylsilane. The other seven aromatic hydrogen atoms absorb at the expected ~ 7.0 p.p.m. shift from tetramethylsilane.

Perinaphthindantrione, compound 60, was synthesized for the comparison with ninhydrin. It spontaneously formed radical anion in DMSO containing excess potassium t-butoxide, but the e.s.r. spectrum (Figure 16) is identical with the one derived from acenaphthenequinone (4), compound 61, probably due to a decarbonylation reaction. In UV absorptions, both compounds and ninhydrin all have a sharp peak at 207 $m\mu$ in 95% ethanol, but the rest of spectra are entirely different.

Radical Cations from Some Semiquinones and α -Diketones

During the course of extending the preparation of radical cations of semiquinones to α -diketones, this author found some new stable radical cations.

Structure 62 has been reported (47) from both the reduction of p-benzoquinone and oxidation of p-hydroxyquinone. By the oxidation route, this author made the paramagnetic species which was identical to the one reported ($a_{OH}^H = 3.44$, $a_H^H = 2.36$ gauss). However, when p-benzoquinone is dissolved in 98% sulfuric acid in the presence of zinc or sodium dithionite, a triplet is always present. The intensity ratio is close to 1:2:1, and the spacing is 1.92 gauss. This situation is perhaps analogous to the p-benzosemiquinones reported by Higas (106). Structure

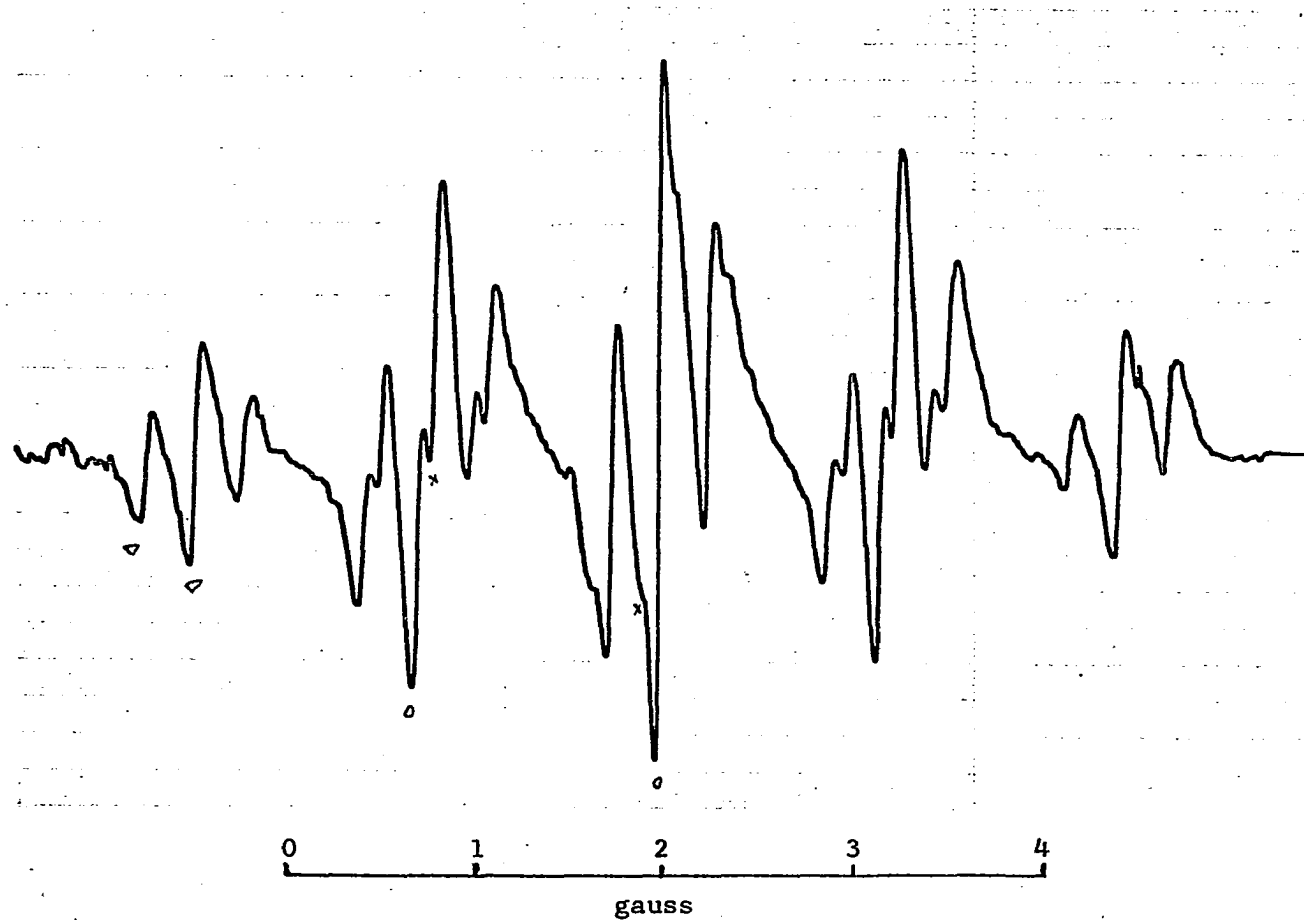
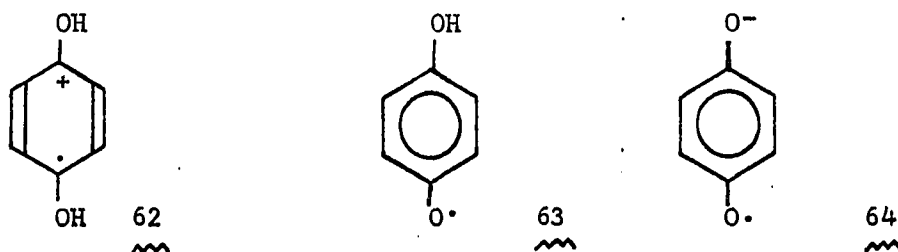


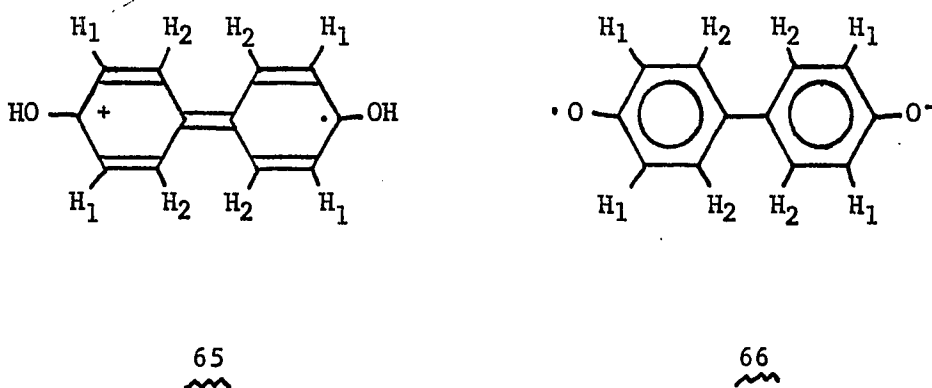
Figure 16. E.S.R. spectrum of radical anion formed spontaneously from acenaphthene quinone in dimethyl sulfoxide containing an excess of potassium t-butoxide at 25 - 28°.



63 gave a 3-line spectrum and 64 a 5-line spectrum. A method was used to explain the fact that spin density was very low in the m-position.

When p-benzoquinone is dissolved in D_2SO_4 containing $Na_2S_2O_4$, the triplet of 1.94 gauss is unaltered.

p-Biphenol gave a radical cation 65 whose e.s.r. spectrum (Figure 17)



corresponds to the h.f.s.c. $a_{OH}^H = 2.56$, $a_{H1}^H = 1.97$, $a_{H2}^H = 0.68$

gauss. The radical anion was also made by this author. Figure 18 shows the spectrum which has the h.f.s.c. $a_{H1} = 2.09$, $a_{H2} = 0.546$ gauss. The aromatic protons have about the same splittings in both the positive and negative radicals. This agrees with other reported semiquinone radical anions and cations (47).

Structure of 67 could be obtained both from quinone and hydroquinone, but reduction always gave better resolution in this case. Figure 19

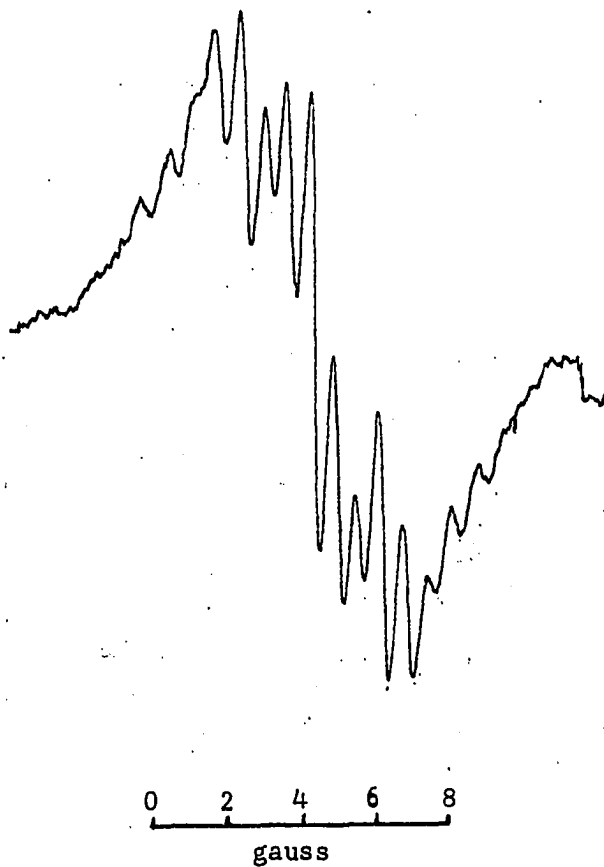


Figure 17. E.S.R. spectrum of radical cation formed from oxidation of p-biphenol by potassium persulfate in 98% sulfuric acid at 25 - 28°.

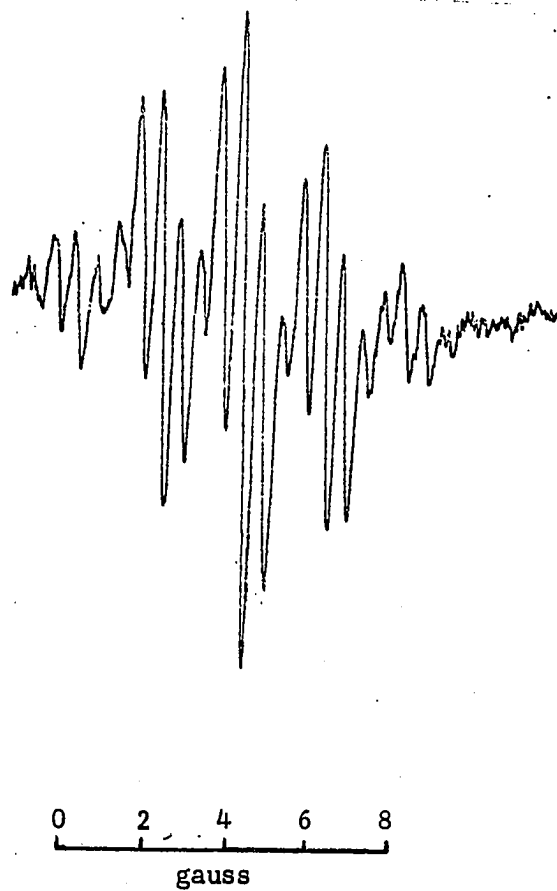
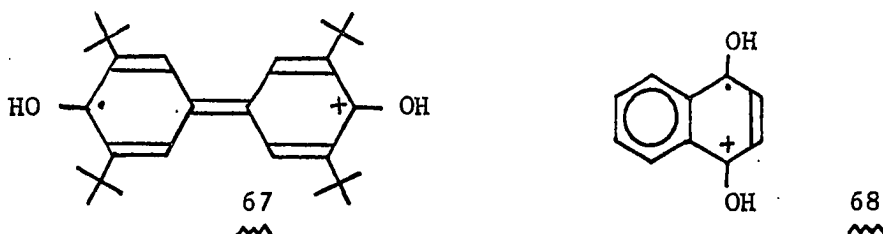


Figure 18. E.S.R. spectrum of radical anion formed spontaneously from p-biphenol in dimethyl sulfoxide containing an excess of potassium t-butoxide.



Figure 19. E.S.R. spectrum of radical cation formed from reduction of 2,2',6,6'-tetra-*t*-butyl-4,4'-diphenquinone by sodium dithionite in 98% sulfuric acid at 25 - 28°.

shows the e.s.r. spectrum which has five triplets with $a_{OH}^H = 1.76$, $a_H^H = 1.31$ gauss. The splitting of ring protons in radical anion is reported from 0.6 (107) to 0.78 (108) gauss.



A spectrum of 68 was made by reduction of the quinone and identical with the one from oxidation of the hydroquinone (47). Anthraquinone gave a poorly resolved spectrum by reduction with sodium dithionite but a well resolved spectrum by zinc. The h.f.s.c. is the same as given by Bolton (47) who used the oxidation method.

Cyclohexane-1,2-dione and 4-*t*-butylcyclohexane-1,2-dione (48) readily give radical cations upon the reduction of the corresponding α -diketones in 98% H_2SO_4 . The spectra can be compared with the respective radical anions. It is obvious that (a) both radical ions of cyclohexane-1,2-dione do not have conformational stability since axial and equatorial hydrogen atoms have the same hyperfine splitting constant (9.82 gauss in the anion, 3.02 gauss in the cation); (b) the 4-*t*-butyl group confers conformational preference (due to unequally populated conformations) to both the radical cation and anion and hydrogens that spend most of their time in axial positions ($a^H = 4.04$, 13.02 gauss for the cation and anion, respectively) and equatorial positions ($a^H = 2.02$, 6.64 gauss for the cation and anion, respectively) are easily distinguished. Figure 20 shows the e.s.r. spectrum of the radical cation from cyclo-

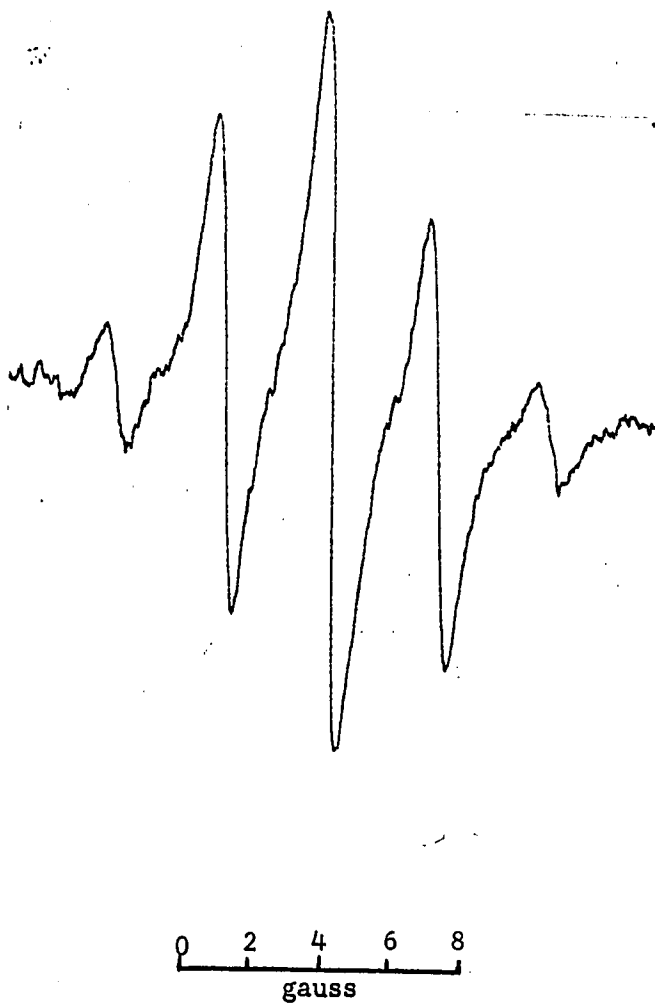
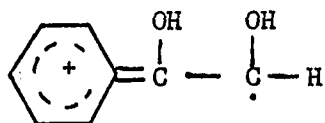


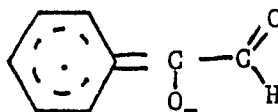
Figure 20. E.S.R. spectrum of radical cation formed from reduction of cyclohexane-1,2-dione by sodium dithionite in 98% sulfuric acid at 25 - 28°.

hexane-1,2-dione.

Dissolving of monomeric or polymeric phenylglyoxal in concentrated sulfuric acid containing dithionite, produces a radical cation (69). The e.s.r. spectrum consisted of an equal intensity doublet whose spacing is 3.12 gauss. Phenylglyoxal radical anion (70) has been made only recently



69



70

from phenacyl bromide (10), and the e.s.r. spectrum is entirely different from the radical cation. The h.f.s.c. for radical anion are $\underline{a}_{\text{CHO}^{\text{H}}} = 6.88$, $\underline{a}_{\text{p}}^{\text{H}} = 1.70$, $\underline{a}_{\text{o}}^{\text{H}} = 1.50$, and $\underline{a}_{\text{m}}^{\text{H}} = 0.52$ gauss.

The benzil radical cation shows a very beautiful and complicated spectrum (Figure 21), but the pattern is easily analyzed with the splittings $\underline{a}_{\text{p}}^{\text{H}} = 3.24$, $\underline{a}_{\text{o}} = 0.96$, $\underline{a}_{\text{m}} = 0.48$ gauss. The h.f.s.c. for radical anion have been reported (4), $\underline{a}_{\text{p}} = 1.12$, $\underline{a}_{\text{o}} = 0.99$, $\underline{a}_{\text{m}} = 0.36$ gauss. Obviously the two phenyl rings accumulate more electron density in benzil radical cation than in the anion.

Compounds 71 - 79 give very poor e.s.r. spectra in sulfuric acid solution.

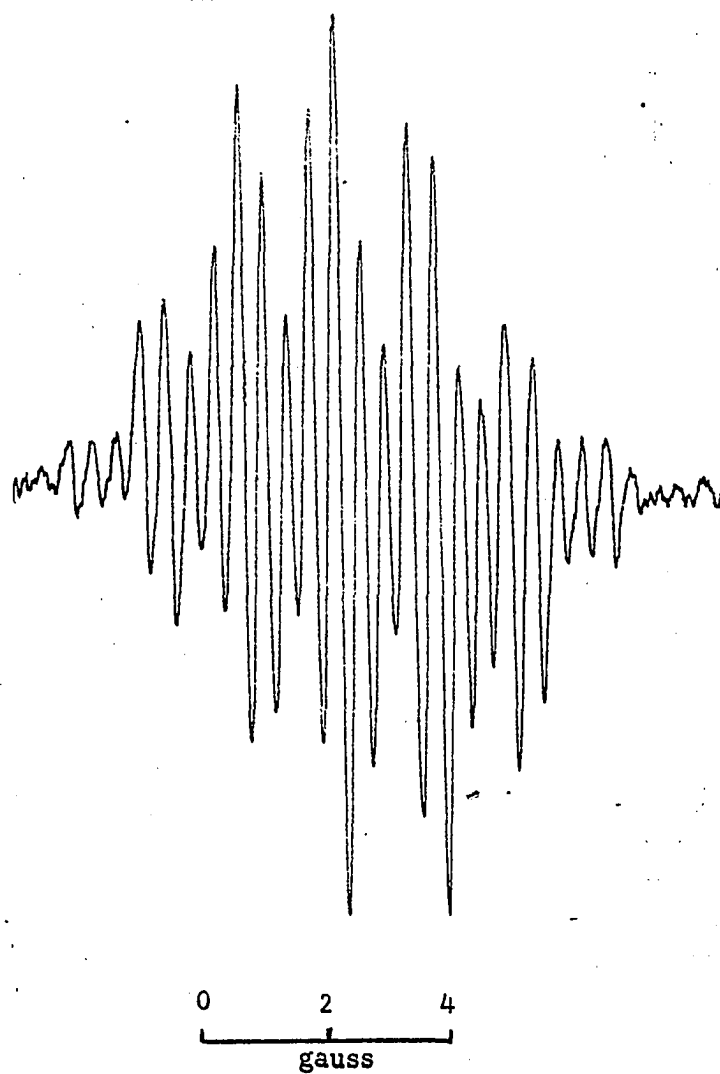
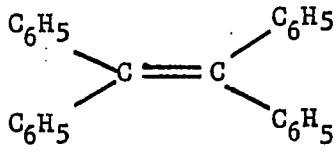
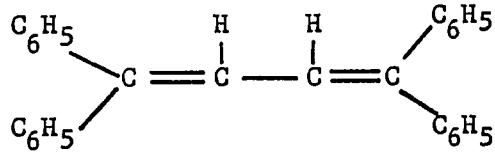


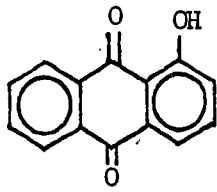
Figure 21. E.S.R. spectrum of radical cation formed from reduction of benzil by sodium dithionite in 98% sulfuric acid at 25 - 28°.



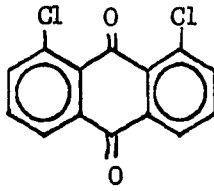
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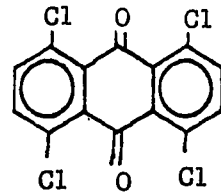
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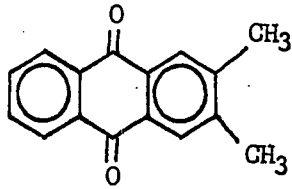
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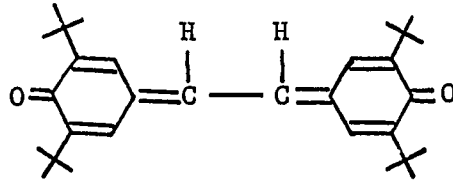
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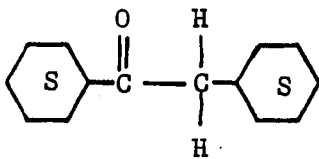
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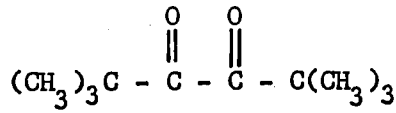
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79



EXPERIMENTAL

Reagents

Dimethyl sulfoxide was distilled under reduced pressure at 100° from calcium hydride.

The potassium t-butoxide used generally was commercial material from Mine Safety Appliance Corporation. The portion used in the study of equilibrium constant had been sublimed under reduced pressure at 170°.

Ninhydrin was commercial material.

Deuterated ninhydrin was recrystallized from deuterium oxide until hydroxyl protons could not be detected by p.m.r.

Hydrindantin (W. R. Grace and Company) was recrystallized from water, m.p. 235 - 236° (dec.).

Commercial 2,2'-biindan-1,1',3,3'-tetraone, m.p. 295-315°, was sublimed at 292° under reduced pressure to give material melting sharply at 315-317°. Anal. Calcd. for C₁₈H₁₀O₄: C, 74.48; H, 3.47. Found (crude) C, 74.2; H, 3.55. Found (sublimed) C, 74.4; H, 3.47. In sulfuric acid λ_{\max} occurred at 309 m μ ($\epsilon = 2.8 \times 10^3$) and 216 m μ ($\epsilon = 1.82 \times 10^3$). In ethanol λ_{\max} occurred at 288 m μ ($\epsilon = 1.95 \times 10^4$) and 220 m μ ($\epsilon = 4.65 \times 10^4$). The mass spectrum contained peaks at mass no. 273, 262, 256, 233, 228, 216, 205, 187, 178, 150, and 145.

Dideutero-2,2'-biindan-1,1',3,3'-tetraone was prepared by refluxing the ketone in a dilute solution of sodium deuterioxide in deuterium oxide for two days. Upon cooling 6,11-dideuterioxynaphthacenequinone was removed by filtration. The solid solution was neutralized with deuteriosulfuric acid to yield the deuterated tetraone.

6-11-Dihydroxynaphthacenequinone was prepared from 2,2-biindan-1,1',3,3'-tetraone by refluxing an ammonical solution according to the procedure of Vanag (109), m.p. 347-349°. In sulfuric acid the quinone gave λ_{\max} at 298 m μ ($\epsilon = 6.7 \times 10^3$). In ethanol λ_{\max} occurred at 261 m μ ($\epsilon = 3.9 \times 10^4$). The mass spectrum gave peaks at mass no. 262, 233, 205, 187, 178, 150, and 145. At high sensitivity mass no. 273, 272, 256, 228, and 216 could be detected but these peaks were no more than 7.5% as intense as the corresponding peaks observed for 2,2'-biindan-1,1',3,3'-tetraone.

2,2-Dimethyl-1,3-indandione was prepared from ethyl phthalate and ethyl propionate by the method of Koelsch (110), m.p. 106-107°, p.m.r. (60 Mc./s) sharp singlet at 1.07 p.p.m. The intermediate 2-methyl-1,3-indandione gave a p.m.r. of a sharp singlet at 1.39 p.p.m. and a quartet at 3.06 p.p.m.

2-Methyl-2-phenyl-1,3-indandione (m.p. 155-157°) was prepared from 2-phenyl-1,3-indandione (111), p.m.r. sharp singlet at 1.71 p.p.m.

1,1,3,3-tetramethyl-2-indanone was prepared (102), m.p. 76-77°, p.m.r. sharp singlet at 1.37 p.p.m. The intermediates were: 2,2,5,5-tetramethyltetrahydrofuranone (b.p. 80-82°/93-96 Hg mm., p.m.r. singlets at 1.3 p.p.m., 1.18 p.p.m., 2.4 p.p.m. with intensity ratio 3:3:1); 1,1,4,4-tetramethyltetrahydronaphthaceneone (m.p. 75°, p.m.r. sharp singlets at 1.42, 1.3, 2.64 p.p.m. with an intensity ratio 3:3:1); 1,1,3,3-tetramethyl-2-carboxylindanol (m.p. 188-189°, p.m.r. a sharp singlet at 1.34 p.p.m. and a broad singlet at 5.83 p.p.m. with an intensity ratio of 6:1).

2-Bromo-1,3-indandione was prepared by the reaction of 5 g. of pyridinium perbromide (0.0156 mole) with 3 g. of 1,3-indandione (0.0206 mole) in 25 ml. of acetic acid. Since the dibromo compound was also formed, the reaction product was extracted with 10% aqueous sodium hydroxide and acidified to obtain the monobromo product. The crude product was recrystallized from ether, m.p. 119-120°, lit. (112) m.p. 119°.

2,2-Dichloro-1,3-indandione was prepared from ninhydrin by reaction with phosphorous pentachloride in phosphorous oxychloride solution (88). The material melted at 123-125°, lit. (88) m.p. 125°.

2-Methyl- $\Delta^{1,2}$ -biindan-1,3,3-trione was prepared by adding an excess of methyl iodide to 1,3-indandione in methanolic potassium hydroxide solution. The material, m.p. 175-176° (lit. (113) m.p. 176°) gave a p.m.r. showing a doublet (intensity 3.0) at 1.48 p.p.m. ($J = 6.96$ c.p.s.), a quartet (intensity 1.0) at 4.42 p.p.m. ($J = 6.96$ c.p.s.), a single deshielded aromatic proton at 9.62 p.p.m. and 7 aromatic protons at approximately 7.8 p.p.m. Bindane ($\Delta^{1,2}$ -biindan-1',3,3-trione) also showed a single low field proton at 9.62 p.p.m. in deuteriochloroform.

Perinaphthindantrione was made from naphthalene-1,8-dicarboxylic anhydride by the method of Errera (114) through the intermediates; 3-hydroxyphenalone (dec. at 350°) and 2-amino-3-hydroxyphenalone (dec. at 260°). The triketone decomposed at 273°.

Alloxan was commercial material.

Commercial alloxantin hydrate was pyrolyzed under vacuum at 75° for 12 hours and recrystallized from dry DMSO until the p.m.r. did not show any hydroxyl peak at about 3.5 p.p.m. to give alloxantin, m.p. 226-228°.

d_6 -Alloxantin was prepared by refluxing the hydrate in deuterium oxide for two days. The product gave no proton peaks in p.m.r., m.p. 248° (dec.).

N,N,N',N'-Tetramethylalloxantin was prepared from caffeine by the method of Cope et al. (115), m.p. $215-217^\circ$.

N,N-Dimethylalloxan was prepared from caffeine as an intermediate in the preparation of N,N,N',N'-tetramethylalloxantin. The aqueous solution containing N,N-dimethylalloxan was evaporated to dryness at 50° . The residue was repeatedly extracted by ether to give material m.p. 267° (dec.) upon recrystallization from ether, lit. (116) m.p. $270-272^\circ$.

Methylalloxan was prepared in the same way from theobromine. The pure compound decomposed at 156° (116).

E.S.R. Studies

The e.s.r. spectra were obtained using a Varian V-4500 spectrometer equipped with a 9" magnet with 100 kc./sec. field modulation. Flat fused silica cells and a temperature of $25-28^\circ$ were used for all experiments. An inverted U-type reaction cell (117) was used. All reactants were thoroughly deoxygenated by purging with prepurified nitrogen before mixing even though the radical cations were stable to oxygen.

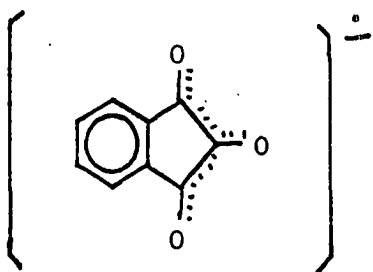
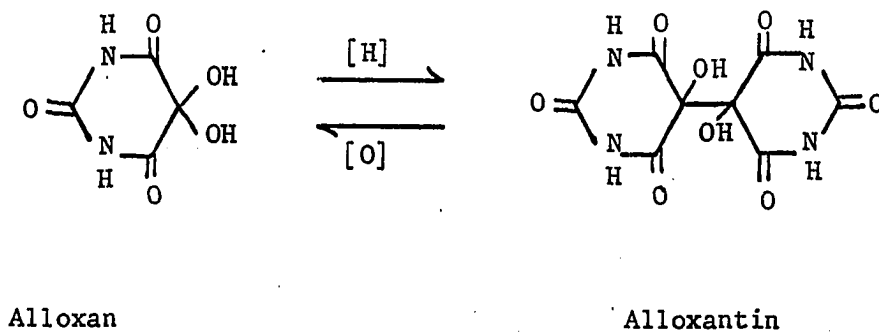
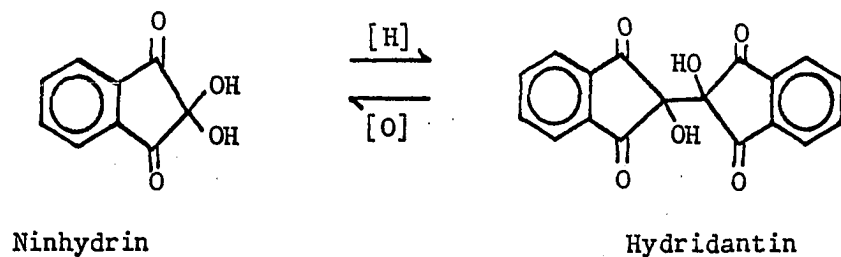
Reactions involving reduction by zinc were performed by adding aqueous potassium hydroxide to a mixture of the compound and powdered zinc in one leg of the inverted U-type cell. For the preparation of radical cations sulfuric acid was added from one leg of the U-type cell to a mixture of the compound and sodium dithionite or potassium persulfate in the other leg of the cell.

Concentration measurements were obtained by comparison of a slightly over-modulated signal with the central peak of standard solutions of diphenylpicrylhydrazyl under the same instrumental conditions.

SUMMARY

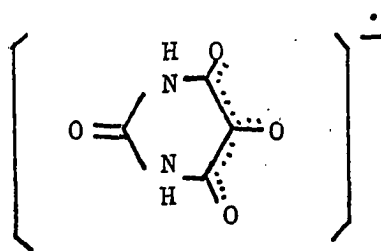
The facile and reversible reductive dimerization of ninhydrin and alloxan suggested a possible existence of intermediate semitrions 22 and 43.

43.



22

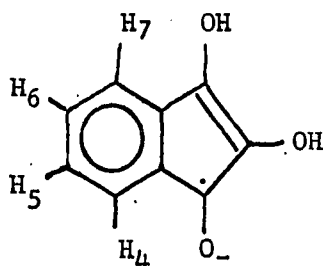
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43

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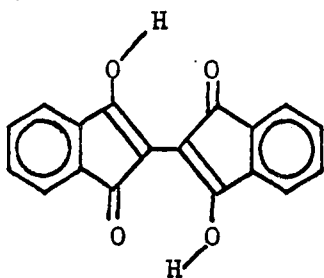
Semitriones 22 and 43 can be detected by e.s.r. spectroscopy in dimethyl sulfoxide (DMSO) under a variety of conditions. In aqueous solution 43 can be detected but the reduction of ninhydrin gives rise to two radical anions. At high pH an unsymmetrical radical anion containing two hydroxyl groups is detected. The observed e.s.r. spectrum is attributed to 23.



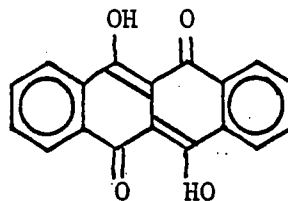
23

At low pH the reduction of ninhydrin in aqueous solution yields a symmetrical radical anion assigned structure 22. The hyperfine splitting constants of 22 show an appreciable solvent effect.

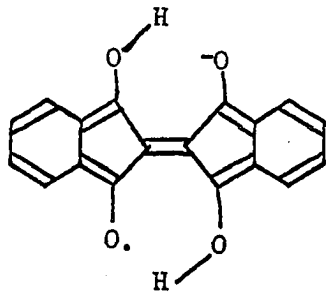
In the course of this investigation the radical anions and cations derived from 2,2'-biindan-1,1',3,3'-tetraone (26) and the isomeric 6,11-dihydroxynaphthacenequinone (33) were considered. Radical ions 21, 35, 46, and 48 have been observed.



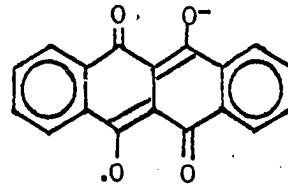
26



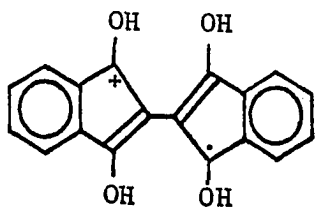
33



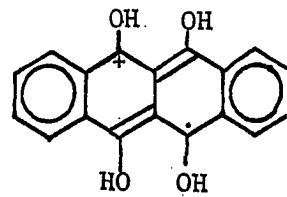
21



35



46



48

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