The Reaction of Fenton's Reagent with Phenoxyacetic Acid and Some Halogen-Substituted Phenoxyacetic Acids[1]

RONALD F. BROWN, SAUNDERS E. JAMISON, UPENDRA K. PANDIT, JACK PINKUS, GEORGE R. WHITE, AND HANS P. BRAENDLIN

The Department of Chemistry, University of Southern California, Los Angeles 7, California

Received June 3, 1963

Phenoxyacetic acids have been shown to react readily with hydrogen peroxide in the presence of ferrous ion to give carbon dioxide, formaldehyde, phenols, and 1,2-diphenoxyethanes. Evidence in the form of the diphenoxyethanes as products, of formaldehyde-d_2 from phenoxy-d_2-acetic acid, and of monophenols as products favor attack by hydroxyl at the carboxyl group of the acids. Quantitative determination of the production or consumption of carbon dioxide, ferric ion, and diphenoxyethanes are reported. A slightly modified Merz-Waters type of mechanism has been employed as a basis for discussion.

Phenoxyacetic acids bearing halogen substituents in the *para* position exhibit activity as plant growth regulators. Additional substituents modify the activity in either direction, but phenoxyacetic acids lacking a *para* substituent show negligible activity.[2] The variations in biological activity of the variously substituted phenoxyacetic acids could not be correlated with variations in heterolytic reactivity as indicated by studies of ether hydrolysis rates,[3a] ester hydrolysis rates,[3b] or by comparison with acid dissociation constants.[4]

Therefore, it appeared to be of interest to study the homolytic reactivity of these compounds. The anaerobic treatment with hydrogen peroxide in the presence of ferrous ions, known as Fenton's reaction,[5] was chosen for study of the homolytic reactivity, since the work of Merz and Waters[6] suggested that quantitative reactivity data might be readily available in this system. The method also appeared attractive because it presented an analogy to biological oxidative processes.[7]

The effectiveness of Fenton's reagent in the oxidation of organic compounds is attributed to the action of a high energy intermediate formed by the interaction of the inorganic materials. Contrary views have been expressed as to the nature of the active intermediate. Both hydroxyl radical[8] and a tetravalent iron cation[9] have been proposed and are considered to arise, respectively, through reactions 1 and 2.

$$\mathrm{Fe(II)} + \mathrm{H_2O_2} \longrightarrow \mathrm{Fe(III)} + \mathrm{HO^-} + \mathrm{HO\cdot} \tag{1}$$

$$\mathrm{Fe(II)} + \mathrm{H_2O_2} \longrightarrow \mathrm{Fe(IV)} + 2\mathrm{HO^-} \tag{2}$$

Kolthoff and Medalia[10] showed that the radical hydroxylation of organic compounds and other homolytic reactions previously observed with this reagent could be explained equally well on the basis of initiation by either reaction 1 or 2, but suggested that their observation of the absence of a salt effect in the reaction of Fenton's reagent with ethanol favored reaction 1. In favor of reaction 2, Cahill and Taube[11] found evidence in isotope fractionation studies that the course of oxidation of ferrous ion by hydrogen peroxide resembled that of stannous ion and others in which two-electron transfer is structurally available rather than that of titanous ion in which it is not available. However, in common with most of the workers in the field, we shall employ the hydroxyl radical formulation.

Previous work[6] indicated that the wide variety of organic compounds susceptible to attack by Fenton's reagent comprised aliphatic ethers and acids along with a large number of aromatic compounds, including benzene itself. Thus all of the structural features of the phenoxyacetic acids appeared to offer vulnerable sites for attack, with different degrees of susceptibility. In the present work the phenoxyacetic acids were found to yield carbon dioxide, formaldehyde, and the related phenols and diaryloxyethanes as primary products of reaction with Fenton's reagent. The indidated stoichiometric relationships are summarized in eq. 3.

$$(2a)\mathrm{Fe}^{+2} + (2a)\mathrm{H}^{+} + (b + 2c)\mathrm{ArOCH_2COOH} + (a + b + c)\mathrm{H_2O_2} \longrightarrow (2a)\mathrm{Fe}^{+3} + (b)\mathrm{ArOH} + (b)\mathrm{HCHO} + (c)\mathrm{ArOCH_2CH_2OAr} + (b + 2c)\mathrm{CO_2} + (2a + b + 2c)\mathrm{H_2O} \tag{3}$$

The product recovery data are presented in Table I in terms of the relationships indicated in eq. 3. The tabulated data indicate the unlikelihood that other as yet unidentified primary products might be formed to any major extent.

Secondary attack on formaldehyde would reduce the yield not only of formaldehyde but also of carbon dioxide relative to hydrogen peroxide consumption. If eq. 4 be multiplied by the coefficient d and added to eq.

$$2\mathrm{H_2O_2} + \mathrm{HCHO} \longrightarrow 3\mathrm{H_2O} + \mathrm{CO_2} \tag{4}$$

$$(2a)\mathrm{Fe}^{+2} + (2a)\mathrm{H}^{+} + (b + 2c)\mathrm{ArOCH_2COOH} + (a + b + c + 2d)\mathrm{H_2O_2} \longrightarrow (2a)\mathrm{Fe}^{+3} + (b)\mathrm{ArOH} + (b - d)\mathrm{HCHO} + (c)\mathrm{ArOCH_2CH_2OAr} + (b + 2c + d)\mathrm{CO_2} + (2a + b + 2c + 3d)\mathrm{H_2O} \tag{5}$$

3, eq. 5 results; eq. 3 gives $(b + 2c)/(a + b + c)$ for the ratio of carbon dioxide formed to hydrogen peroxide consumed, and eq. 5 gives a ratio of $(b + 2c + d)/(a + b + c + 2d)$ obviously less than the former ratio if d has a finite value. After the first few runs the conversions (based on hydrogen peroxide added) were held to the range 5–20% in order to minimize secondary

---

[1] This work was supported by a contract with the U. S. Army Chemical Corps, Fort Detrick, Frederick, Md., and by a contract with the U. S. Atomic Energy Commission. It is based in part on a dissertation submitted by S. E. Jamison to the Graduate School of the University of Southern California in partial fulfillment of the requirements for the Degree of Doctor of Philosophy.

[2] R. L. Weintraub, J. W. Brown, and J. A. Thorne, *J. Agr. Food Chem.*, **2**, 996 (1954).

[3] (a) R. F. Brown and E. F. Claflin, *J. Am. Chem. Soc.*, **80**, 5960 (1958); (b) R. F. Brown and H. C. Newsom, *J. Org. Chem.*, **27**, 3010 (1962).

[4] N. V. Hayes and G. K. Branch, *J. Am. Chem. Soc.*, **65**, 1555 (1943).

[5] H. J. H. Fenton, *J. Chem. Soc.*, **65**, 899 (1894).

[6] (a) J. H. Merz and W. A. Waters, *Discussions Faraday Soc.*, **2**, 179 (1947); (b) *J. Chem. Soc.*, S15 (1949); (c) 2427 (1949).

[7] D. J. Mackinnon and W. A. Waters, *ibid.*, 323 (1953).

[8] F. Haber and J. Weiss, *Proc. Roy. Soc.* (London), **A147**, 332 (1934).

[9] W. C. Bray and M. Gorin, *J. Am. Chem. Soc.*, **54**, 2124 (1932).

[10] (a) I. M. Kolthoff and A. I. Medalia, *ibid.*, **71**, 3777 (1949); (b) **71**, 3784 (1949); (c) A. I. Medalia and I. M. Kolthoff, *J. Polymer Sci.*, **4**, 377 (1949).

[11] A. E. Cahill and H. Taube, *J. Am. Chem. Soc.*, **74**, 2312 (1952).

TABLE I

REACTION OF PHENOXYACETIC ACIDS WITH FENTON'S REAGENT[a]

Compound[b]	Mmoles × 10^2	Fe^{+2},[c] mmoles × 10^2	H_2O_2,[c,d] mmoles × 10^2	ΔFe^{+2}, mmoles × 10^2	CO_2, mmoles × 10^2	ArOH, mmoles × 10^2	HCHO, mmoles × 10^2	$(ArOCH_2)_2$,[e] mmoles × 10^4	$\frac{\Delta H_2O_2}{\Delta H_2O_2 - 0.5\Delta Fe^{+2}}$
POA	50	100	38.3	37.6	20		16.1		1.96
	150	100	13.0	11.7			6.2		1.82
	100	100	9.9	6.8	7.6				1.52
	100	100	13.3	9.3		8.8			1.54
	87	47	11.8	4.5				5.0	1.24
	181	47	11.8	3.8				16.6	1.19
2-FPOA	100	100	11.8	10.7	7.1				1.83
	100	100	9.8	9.0	6.3			130[f]	1.85
	17.5	46.4	1.57	1.2				6.4	1.62
	29.9	46.4	1.57	1.2				6.5	1.59
4-FPOA	100	100	11.0	12.5	4.7				2.31
	100	100	14.1	16.2	5.9			6.4[f]	2.34
	48.8	46.4	10.0	10.6				5.3	2.14
	73.8	46.4	10.0	10.6				8.1	2.12
	99.2	46.4	10.0	10.2				18.5	2.05
2,4-DiFPOA	100	100	9.9	11.0	4.3			2.4[f]	2.26
2-ClPOA	26	100	4.6	3.9		2.7			1.77
	7.5	46.4	2.72	3.8				8.6	3.26
	12.3	46.4	2.66	3.5				8.9	2.90
	13.6	46.4	2.76	3.1				12.3	2.28
4-ClPOA	26.7	100	4.7	4.3		3.0			1.81
	26.7	100	9.4	10.9		4.4			2.35
	9.3	46.4	3.76	4.5				2.3	2.53
	16.2	46.4	3.74	4.3				2.5	2.34
	18.7	46.4	3.71	4.1				1.1	2.24
	6.3	24.4	2.52	2.4				3.5	1.89
	9.0	24.4	2.49	2.9				4.0	2.35
	10.6	24.4	2.50	2.2				5.6	1.76
	13.3	24.4	2.48	2.2				8.8	1.81

[a] The volume of each solution before the hydrogen peroxide addition was 70 ml. The final volume was close to 75 ml. The sulfuric acid concentration varied from the initial 0.143 *N* to the final 0.133 *N* in each run. All runs made at room temperature, approximately 25°. [b] POA is the abbreviation for phenoxyacetic acid. [c] Initial amounts. [d] Also ΔH_2O_2, the amount consumed. [e] Determined by infrared spectrophotometry. [f] Determined by weighing of residues after extraction purification.

reactions. Even so, in those runs on 4-fluoro- and 2,4-difluorophenoxyacetic acid in which carbon dioxide was measured, $\Delta CO_2 - (\Delta H_2O_2 - \Delta Fe^{+2}/2)$ gave -0.0005, -0.001, and -0.001 mmole showing that the result represents $(c - d)$ from eq. 5 rather than c from eq. 3. This explanation also may apply to the value for c, 0.013 mmole, obtained by direct weighing of the residue on extraction of the reaction product of 2-fluorophenoxyacetic acid, which exceeds the value of 0.010 mmole, calculated from measurements of carbon dioxide and ferric ion formation. Moreover, in the experiments on the substrates from which the carbon dioxide yield indicated little or no dimer formation, slight if any turbidity was observed to develop in the course of the reaction, while those reactions yielding the appropriate high level of carbon dioxide also formed considerable precipitate. The precipitation reflects the formation of diaryloxyethanes, since they are the least soluble of the products in the reaction medium. Moreover, the identification was made positive by isolation and comparison in several instances with authentic materials. Infrared spectroscopy was employed subsequently to measure the concentration of these dimeric products in a series of runs which also are reported in Table I. It is interesting to note that, of the substances tested, the biologically active acids, which contain *para* substituents, formed in general a much smaller proportion of diaryloxyethanes than did the biologically inactive acids which lacked the *para* substituent. Although we have postulated four pathways for the disappearance of the phenoxymethyl radical so that, if applicable, the amount of diaryloxyethane formed would be inversely related to the concentrations of ferric ion, hydrogen peroxide, and hydroxyl radical, we found little variation in the fraction of total substrate reacted, which resulted in formation of the diether (except for 2,4-dichlorophenoxyacetic acid which varied widely and was interpreted as a solubility effect). Thus, for phenoxyacetic acid, 2 ± 1% of the amount which reacted became 1,2-diphenoxyethane; for the 2-fluoro acid, 13 ± 1%; 4-fluoro, 5 ± 3%; 2-chloro, 18 ± 2%; 4-chloro, 6 ± 3%; and for 2,4-dichlorophenoxyacetic acid, 22 ± 12%. This surprising difference between those compounds bearing an *ortho* substituent and the others may be ascribed, perhaps, to chelation with ferric ion by the *ortho*-substituted phenoxymethyl radicals following.

Such a complex could lead on the one hand to the reaction represented by k_6 or on the other hand to chelation of a second radical about the iron. Such accumulation of radicals about the iron could be thought of as a pseudocage effect, bringing the radicals together in

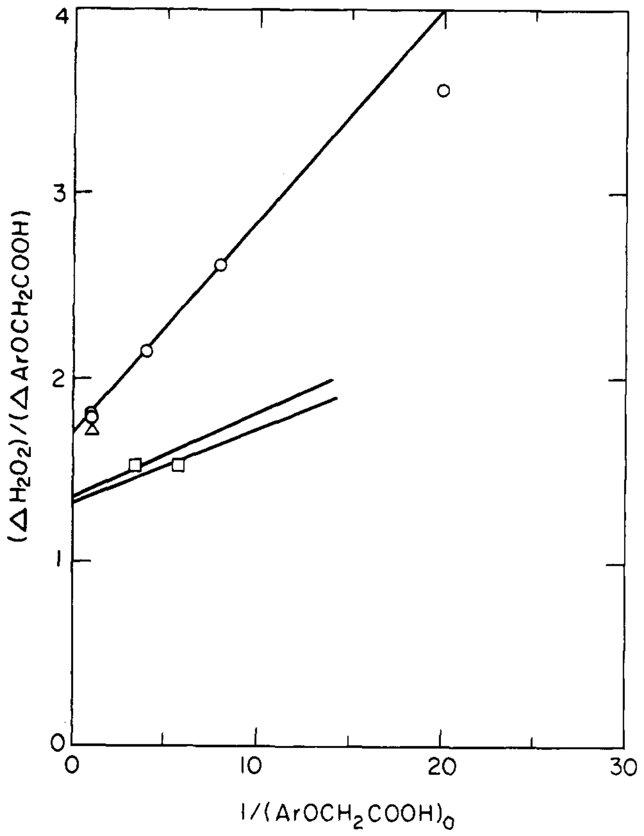


Fig. 1.—Plot of the ratio of hydrogen peroxide consumed to 2-fluorophenoxyacetic acid consumed against the reciprocal of the initial concentration (in mmoles per 75 ml.) of 2-fluorophenoxyacetic acid: ○, for initial concentration of ferrous ion, 1 mmole (in 75 ml.); △, 0.5 mmole; ⊡, 0.464 mmole. The lines are drawn for $k_2/k_3 = 0.068$, $k_5/k_4 = 52.5$ in eq. 6 with $k_2(Fe^{+2})_0 \gg k_9(ArOCH_2\cdot)$.

such a fashion as to facilitate the formation of diphenoxyethane.

The attempts at measurement of yields of phenol, identified as its tribromo derivative in the phenoxyacetic acid reaction product, appear to have given results that are distinctly high. The spectral procedure used was insufficiently precise, apparently because of inadequate removal of interfering substances (notably, unchanged phenoxyacetic acid). However, the results do correspond in order of magnitude to those obtained for the other products in more precise analyses and thus may be considered to provide additional confirmation of the applicability of eq. 3 or 5.

Following in the path of the already cited studies by Merz and Waters,[6] Mackinnon and Waters,[7] Kolthoff and Medalia,[10] and to which may be added the investigations by Baxendale and Magee[12] of the reaction of benzene with Fenton's reagent, the following scheme appears to indicate the reaction steps in the present system if the complicating secondary reactions are omitted. Despite the complications introduced by the inclusion of the steps indicated by k_5 and k_8, this mechanism satisfies the stoichiometry of eq. 3 and will serve as a basis for discussion.

$$Fe^{+2} + H_2O_2 + H^+ \xrightarrow{k_1'} Fe^{+3} + HO\cdot + H_2O \qquad k_1 = k_1'(H^+)$$

$$Fe^{+2} + HO\cdot + H^+ \xrightarrow{k_2'} Fe^{+3} + H_2O \qquad k_2 = k_2'(H^+)$$

$$ArOCH_2COOH + HO\cdot \xrightarrow{k_3} ArOCH_2COO\cdot + H_2O$$

$$ArOCH_2COO\cdot \xrightarrow{k_4} ArOCH_2\cdot + CO_2$$

$$ArOCH_2COO\cdot + Fe^{+2} + H^+ \xrightarrow{k_5'} ArOCH_2COOH + Fe^{+3} \qquad k_5 = k_5'(H^+)$$

$$ArOCH_2\cdot + Fe^{+3} + H_2O \xrightarrow{k_6'} ArOCH_2OH + Fe^{+2} + H^+ \qquad k_6 = k_6'(H_2O)$$

$$ArOCH_2\cdot + H_2O_2 \xrightarrow{k_7} ArOCH_2OH + HO\cdot$$

$$ArOCH_2\cdot + ArOCH_2\cdot \xrightarrow{k_8} ArOCH_2CH_2OAr$$

$$ArOCH_2\cdot + HO\cdot \xrightarrow{k_9} ArOCH_2OH$$

$$ArOCH_2OH + H^+ \xrightarrow{k_{10}} ArOH + HCHO + H^+$$

From the reactions given, there is readily derived, assuming that HO· and ArOCH₂COO· are steady states, eq. 6 as the correlation of the rates of disappearance of peroxide and organic substrate.

$$\frac{d(H_2O_2)}{d(ArOCH_2COOH)} = \left[1 + \frac{k_5(Fe^{+2})}{k_4}\right]\left[1 + \frac{k_2(Fe^{+2}) + k_9(ArOCH_2\cdot)}{k_3(ArOCH_2COOH)}\right] \qquad (6)$$

If the assumption be made that $k_2(Fe^{+2}) >> k_9(ArOCH_2\cdot)$—namely, that Fe^{+2} is superior to $ArOCH_2\cdot$ in competition for HO·— and that $k_4 >> k_5(Fe^{+2})$—namely, that the decarboxylation of $ArOCH_2COO\cdot$ predominates over the reaction with Fe^{+2}—then eq. 6 reduces to eq. 7,

$$\frac{\Delta(H_2O_2)}{\Delta(ArOCH_2COOH)} = 1 + \frac{k_2(Fe^{+2})_0}{k_3(ArOCH_2COOH)_0} \qquad (7)$$

the relationship originally introduced by Merz and Waters[6] for the action of Fenton's reagent on various substrates. This shows that, for reactions meeting the qualifications given, the ratios shown may be plotted to give a line with an intercept of unity and a slope which is the ratio of constants representing the relative affinities of ferrous ion and the substrate for the hydroxyl radical. None of our data fitted this limitation and eq. 7 failed to hold. If $ArOCH_2COO\cdot$ should be so stable that the lifetime before decarboxylation increases the relative rate of reaction with ferrous ion, k_5, then the intercept of a plot of the ratios will give a line with an intercept of $1 + k_5(Fe^{+2})/k_4$ and the slope will be increased by the same factor providing the ferrous ion concentration is held constant while the ratios are being varied. If, in addition, k_9 should be so large that $k_2(Fe^{+2})$ no longer is very much greater than $k_9(ArOCH_2\cdot)$ then the plot of ratios would become nonlinear and the slope and intercept would have a simple interpretation only if certain other requirements are met. Actually, most of our data give straight line plots as shown, for example, in Fig. 1 for 2-fluorophenoxyacetic acid. The graph also shows the effect of variation in the initial ferrous ion concentration, the point for 0.5 mmole being seriously out of place. The point at $1/(ArOCH_2COOH)_0 = 20$ also does not fit the plot, but in this instance the initial concentration of peroxide exceeded the initial concentration of substrate so that part of the peroxide must have been consumed in a secondary reaction with formaldehyde. Figure 2 illustrates the variation in slope and intercept for

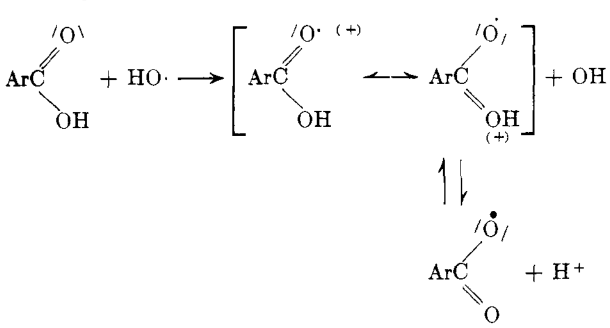
---

[12] J. H. Baxendale and J. Magee, *Discussions Faraday Soc.*, **14**, 160 (1953).

varying substrates at constant ferrous ion concentration.

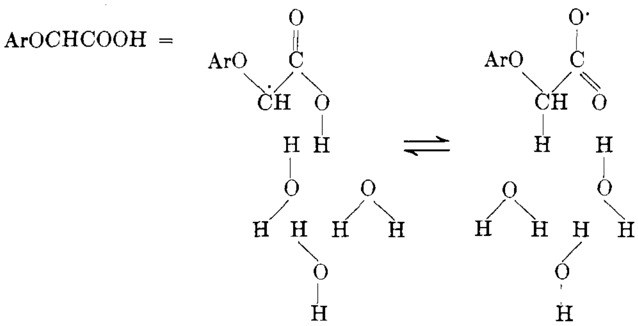
It may be recalled that Kolthoff and Medalia[10] explained the failure of acetic acid to undergo oxidation by Fenton's reagent on the basis of reduction by ferrous ion of acetoxy radical to acetate ion. In the absence of stabilizing substituents on the methyl group in acetoxy radical, ferrous ion apparently can suppress the tendency to decarboxylation. This suppression of acetoxy decarboxylation was complete at concentrations of ferrous ion considerably lower (0.51×10^{-3} *M*) than any used in the experiments described herein. Thus even the *para*-substituted phenoxy group appears to make an appreciable contribution to the ability of the carboxy radical to decarboxylate.

The similarity of reactivity of the various substrates may imply a similarity in process involved such as electron abstraction by the hydroxyl radical from either ferrous ion or the substrate phenoxyacetic acid rather than hydrogen atom abstraction from the hydration shell of the ferrous ion or from the substrate. Thus we envisage the process indicated by k_3 as proceeding as follows.



Although the concept of initial attack by electron abstraction at the carboxyl group offers the simplest explanation of the product distribution, the C–H bond α to an ether oxygen or to a carbonyl group is typically quite susceptible to free-radical attack.[13] Such attack can be formulated to give the observed products if it is assumed that initial removal of an α-hydrogen is followed by proton migration from the carboxyl group, possibly facilitated by bridging through solvent water, or conversely, that α-hydrogen is lost after initial electron removal. That neither occurs was demonstrated as follows.

$$ArOCH_2COOH + HO\cdot \longrightarrow ArO\dot{C}HCOOH + H_2O$$



If the acid in which the two α-hydrogens had been replaced by deuteriums were used, the product formaldehyde would retain both deuterium atoms if α-hydrogen were not involved. The product formaldehyde would have one deuterium replaced by hydrogen if α-hydrogen involvement occurred. Dideuterated phenyoxyacetic acid was prepared and the formaldehyde produced was isolated as the dimedone derivative, which was burned. The resulting water was reduced to furnish a gaseous sample for analysis in a mass spectrometer,[14] but the results were not decisive. The experiment was repeated when a Beckman IR-7 spectrophotometer became available.[15]

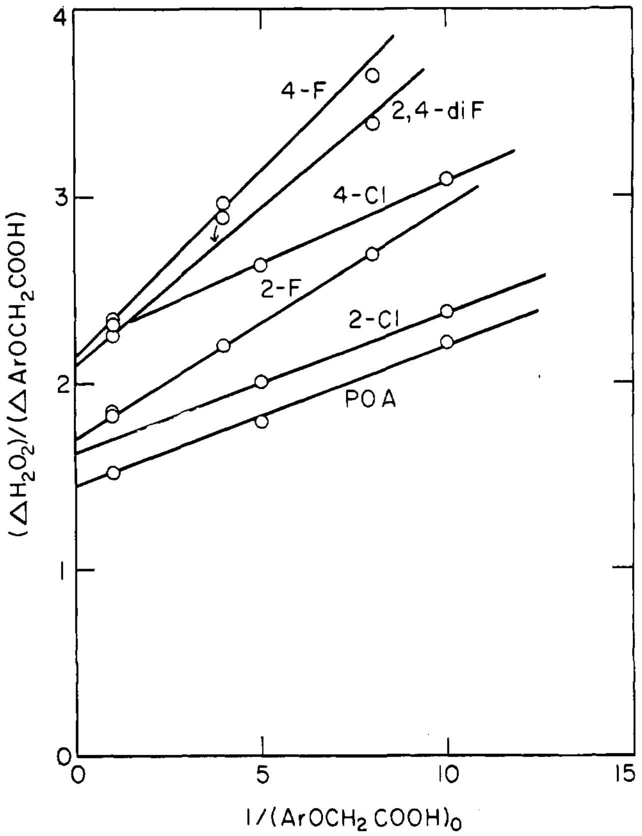


Fig. 2.—Plot of the ratio of hydrogen peroxide consumed to various substituted phenoxyacetic acids consumed against the reciprocal of the initial concentrations (in mmoles per 75 ml.) of the various substrates. All were at ferrous ion concentration of 1 mmole (in 75 ml.). The lines are merely graphical straight lines drawn for identification.

The infrared absorption spectra of chloroform solutions of the dimedone derivatives of formaldehyde, formaldehyde-d_2, and of the formaldehyde product from reaction of deuterated phenoxyacetic acid were compared in the 950–2300-cm.$^{-1}$ region. Three bands were chosen for quantitative examination. The HCHO derivative absorbed at 976 cm.$^{-1}$ (ϵ 10.3), 1085 (160), and had no band at 2117 while the DCDO derivative absorbed at 952 cm.$^{-1}$ (ϵ 24), 1064 (130), and 2117 (3.3). The product derivative spectrum was identical with that from DCDO with ϵ 23.2, 127, and 3.3 for the three bands. The identity of the absorption at 2117 cm.$^{-1}$ may be regarded as critical, representing a C–D vibration assignment[16] whereas the bands at 952 and 1064 are in the "fingerprint" region without specific

---

[13] W. E. Cass, *J. Am. Chem. Soc.*, **69**, 500 (1947).

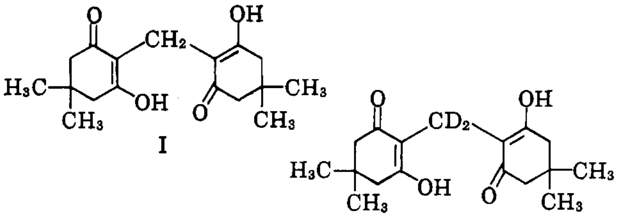
[14] R. B. Alfin-Slater, S. M. Rock, and M. Swislocki, *Anal. Chem.*, **22**, 421 (1950).

[15] Made possible by Grant G14665 of the National Science Foundation, which we are happy to acknowledge.

[16] B. Nolin and R. N. Jones, *J. Am. Chem. Soc.*, **75**, 5626 (1953); *Can. J. Chem.*, **34**, 1382 (1956). See also E. S. Ebers and H. H. Nielsen, *J. Chem. Phys.*, **6**, 311 (1938); R. N. Jones and F. Herling, *J. Org. Chem.*, **19**, 1252 (1954).

assignment.[17] The possible objection that the latter two bands may be due to an interaction between the six-membered rings of the bismethone which may be altered by the introduction of only one deuterium on the linking carbon is ruled out by the 2117-cm.$^{-1}$ band datum. Thus the evidence for the lack of attack at the α-position was strengthened, but the low intensities of the bands chosen left a residual doubt.

Turning to n.m.r., it was reasoned that the formaldehyde bismethone (I), but not the formaldehyde-d_2 bismethone (II), should exhibit distinct absorption for the bridged methylenic protons. This was verified; substance I gave three peaks: A at -2.14, B at -4.61, and C at -6.36 p.p.m. relative to tetramethylsilane. The relative area ratios[18] were A:B:C = 6.00:3.89:0.91. Substance II gave a spectrum identical with I but without the C peak, which was assigned to the bridged methylenic protons. The product, isolated from the reaction of phenoxy-d_2-acetic acid with Fenton's reagent as the bismethone, gave a spectrum identical with that from II. The accumulation of evidence points conclusively to the strange resistance by phenoxyacetic acid to attack on the α-protons by Fenton's reagent.



I

II

In contrast, Garrison, *et al.*,[19] present evidence that aqueous hydroxyl radical attack is directed preponderantly to the methyl rather than the carboxyl group in acetic acid. This has been confirmed by Coffman, Jenner, and Lipscomb[20] who also observed both α- and β-attack by Fenton's Reagent on propionic and isobutyric acids leading to dimeric products. The yields of coupled products fell off drastically as the concentrations of substrate or of hydrogen peroxide decreased so that our observation of the formation of any diaryloxyethanes was a surprise to us. There is no cage effect operating here to cause dimerization so one recourse is to postulate relative stability to the phenoxymethyl radicals. Russell[21] points out that ". . . hydrogen atoms alpha to ether linkages are often attacked by peroxy radicals . . . " while Walling[22] in a discussion of relative stability of radicals points out that an adjacent carbonyl group is better than an adjacent alkoxy group in stabilizing a radical, or (>C–COOR) > (>Ċ–OR). The point of attack by a radical on a substrate molecule is difficult to predict because of the lack of understanding of the effects of various factors (electronic, structural, steric, etc.) on the activation energy and the pre-exponential factor. The stabilization of the resulting new radical will have an effect in lowering the expected activation energy. Thus, since we found the aryloxymethyl radical to be relatively stable, one might predict that anisole should be somewhat susceptible to attack by radicals on the methyl group to form the phenoxymethyl radical even though benzene ring attack would produce a methoxyphenyl radical. Frazer-Reid and co-workers[23] using an excess of Fenton's reagent on anisole at 0° and high concentrations identified guaiacol and hydroquinone as products, the latter probably arising by a demethylation *via* attack on the methyl group preceded by or followed by ring attack. On the other hand Norman and Radda[24] employed the "model peroxidase" conditions (ferrous ion with hydrogen peroxide under nitrogen with added phosphate buffer, ascorbic acid, and ethylenediaminetetracetic acid in aqueous acetone) on anisole and also with various deletions such as omission of acetone or ascorbic acid, etc., and up to 4% reaction. They detected no dihydroxy products and found only ring attack. This system has been discussed by Grinstead[25] who pointed out the relative oxidation–reduction potential changes involved in chelation and who found both salicyclic and benzoic acids to be subject to attack. Recently, Hamilton and Friedman[26] investigated the reaction of anisole with hydrogen peroxide using Fenton conditions as well as the model peroxidase system and the use of catechol and hydroquinone as intermediate carriers instead of ascorbic acid. They found the yield of ring hydroxylated products under Fenton conditions to be only 20% which was 86% *ortho.* Here again no mention is made of phenol, formaldehyde, or of 1,2-diphenoxyethane as products to be expected from attack on the methyl group.

Of interest also is the report of Friess and co-workers[27] who studied the reaction of perbenzoic acid in chloroform with anisole and a series of polymethoxybenzenes. Unfortunately for our purpose, they used an excess of perbenzoic acid in nearly every instance so that primary products could not be identified and in particular did not identify any products from demethylation along with oxidation to quinones. Again, no effort was made to isolate neutral products; thus if any diphenoxyethane were formed it remained undetected in the recovered anisole fraction.

That an adjacent amino group does not shift attack away from the α-position was shown by Maxwell and Peterson[28] in an extensive study of the aerobic reaction of Fenton's reagent with glycine. They concluded that the initial attack was at the α-hydrogen and that the

---

[17] S. C. Burkett and R. M. Badger, *J. Am. Chem. Soc.*, **72**, 4397 (1950); R. N. Jones, B. Nolin, and G. Roberts, *ibid.*, **77**, 6331 (1955).

[18] Although not of immediate importance, the n.m.r. spectra were of general interest. The absence of any splitting pattern (A had a tiny, almost questionable, shoulder) may be attributed to the absence of any adjacent protons in either I or II. Peak A was assigned to the twelve methyl protons, supported by the 6:1 relationship to the two bridged methylenic protons (peak C). The surprise came in the collapse of the nominally ten ring protons into a single peak (B) of eight methylenic protons. The averaging effect of the enolic double bond position would explain the identical absorptions, but the enolic hydrogens could not be found even though the down-scale limit of the instrument was reached.

[19] W. M. Garrison, W. Bennett, S. Cole, H. R. Haymond, and B. M. Weeks, *J. Am. Chem. Soc.*, **77**, 2720 (1955).

[20] D. D. Coffman, E. L. Jenner, and R. D. Lipscomb, *ibid.*, **80**, 2864 (1958).

[21] G. A. Russell, "Peroxide Reaction Mechanisms," J. O. Edwards, Ed., John Wiley and Sons, Inc., New York, N. Y., 1962, p. 117.

[22] C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 122.

[23] B. Frazer-Reid, J. K. N. Jones, and M. B. Perry, *Can. J. Chem.*, **39**, 555 (1961).

[24] R. O. C. Norman and G. K. Radda, *Proc. Chem. Soc.*, 138 (1962).

[25] R. R. Grinstead, *J. Am. Chem. Soc.*, **82**, 3464, 3472 (1960).

[26] G. A. Hamilton and J. P. Friedman, *ibid.*, **85**, 1008 (1963).

[27] S. L. Friess, A. H. Soloway, B. K. Morse, and W. C. Ingersoll, *ibid.*, **74**, 1305 (1952).

[28] C. R. Maxwell and D. C. Peterson, *ibid.*, **79**, 5110 (1957).

ratio of rate constants for the competition between ferrous ion and glycine for the hydroxyl radical was 80.

The susceptibility to attack at various sites on a substrate molecule by radicals remains a question for exploration. The sensitivity of the phenoxyacetic acids to attack at the carboxyl group followed by extensive decomposition offers a new probe for the study of free-radical reactions. In subsequent papers we will report in more detail our results pertinent to the mechanism and to other substrates and other radical systems.

Experimental[29]

The phenols and phenoxyacetic acids were prepared by standards methods.[3] Authentic samples of the 1,2-diphenoxyethanes were prepared in low yield (15–25%) from ethylene bromide and the phenol as described by Cope.[30] Five of the ethers do not seem to have been described previously.

1,2-Bis(2-fluorophenoxy)ethane had m.p. 116.5–117°.

Anal. Calcd. for $C_{14}H_{12}O_2F_2$: C, 67.20; H, 4.80; mol. wt., 250. Found: C, 67.09; H, 5.12; mol. wt., 247 (Rast).

1,2-Bis(4-fluorophenoxy)ethane had m.p. 85–86.5°.

Anal. Calcd. for $C_{14}H_{12}O_2F_2$; C, 67.20; H, 4.80; mol. wt., 250. Found: C, 67.28; H, 4.96; mol. wt., 250 (Rast).

1,2-Bis(2-chlorophenoxy)ethane had m.p. 103–105°.

Anal. Calcd. for $C_{14}H_{12}O_2Cl_2$: C, 59.38; H, 4.27; Cl, 25.04. Found: C, 58.39, 60.05; H, 4.52, 4.64; Cl, 25.24.

1,2-Bis(4-chlorophenoxy)ethane had m.p. 130–131.5°.

Anal. Calcd. for $C_{14}H_{12}O_2Cl_2$: C, 59.38; H, 4.27; Cl, 25.04. Found: C, 59.18; H, 4.17; Cl, 25.28.

1,2-Bis(2,4-dichlorophenoxy)ethane had m.p. 131–133°.

Anal. Calcd. for $C_{14}H_{10}O_2Cl_4$: C, 47.76; H, 2.86; Cl, 40.29. Found: C, 47.78; H, 3.12; Cl, 40.50.

All of the diethers absorbed at 8.00 ± .01 μ (1250 ± 2 cm.$^{-1}$). The molecular extinction coefficients were determined from the data at three concentrations in carbon tetrachloride, which gave linear plots through the origin. Because of uncertainty in path length, nominally 0.01 cm., the coefficients probably are in error as to absolute values, but the relative values and their use in determining unknown concentrations were not affected since the same cell was used throughout. The molecular extinction coefficients used were 729.6 ± 2.2 for 1,2-diphenoxyethane, 812.6 ± 1.5 for 1,2-bis(2-fluorophenoxy)ethane, and 800.2 ± 6.6 for the 4-fluoro, 478.1 ± 7.5 for the 2-chloro, 794.3 ± 9.2 for the 4-chloro, and 378.7 ± 3.7 for the 2,4-dichloro analogs.

Phenoxy-d_2-acetic acid was prepared from a solution of potassium phenoxyacetate (6.68 g., 0.033 mole) and sodium hydroxide (1.05 g., 0.026 mole) in 98% deuterium oxide (8.5 ml.) which was refluxed for 24 hr., transferred to another flask, and concentrated *in vacuo* to a solid so that 5 ml. of deuterium oxide were removed. More deuterium oxide (6.5 ml.) was added to the residue which was then refluxed for 26 hr. The 6.5 ml. of deuterium oxide was recovered by evaporation as before.

A portion (*ca.* 1 g.) was removed from this residue (50 hr. total refluxing) and worked up in a manner similar to that described subsequently for the main product formed after 70 hr. refluxing.

The main residue was diluted with deuterium oxide (5 ml.) and refluxed for 20 hr. (70 hr. total reflux time) during which a solid deposited. The reaction mixture was dissolved in 0.1 *N* hydrochloric acid (310 ml.) and the acid solution extracted with six 50-ml. portions of ether. After drying over sodium sulfate, filtration, and evaporation under reduced pressure, the combined ethereal extracts gave an oil which crystallized on trituration with benzene. Recrystallization from benzene gave phenoxy-d_2-acetic acid, m.p. 99–100°; ν_{max} 2100 cm.$^{-1}$ (ϵ 11.6), 2169 (2.7), 10% in chloroform. The infrared absorption spectrum of phenoxyacetic acid (10% in chloroform) showed no absorption in the region 2000–2300 cm.$^{-1}$.

Anal. Calcd. for $C_8H_8D_2O_3$: C, 62.33; H + D, 6.54. Found: C, 62.92; H + D, 6.54.

The phenoxy-d_2-acetic acid isolated after 50 hr. refluxing had ν_{max} 2100 cm.$^{-1}$ (ϵ 11.0), 2169 (2.0), showing no further exchange to have occurred (within experimental error) during the extra 20 hr. refluxing undergone by the main product; combined yield, 1.37 g., 25%.

A mass spectrometric determination[31] showed that material which had undergone a 17-hr. period of exchange contained at least 96% of the theoretical two deuterium atoms per molecule.

Distilled water which had been boiled for 15–30 min. and cooled under nitrogen was used throughout in the preparation and dilution of all solutions. More elaborate treatment did not improve reproducibility of results.

Procedure.—In general, 10 ml. of a standardized solution of ferrous sulfate or of ferrous ammonium sulfate (usually 0.05 to 0.10 *N*) in 0.1 *N* sulfuric acid as solvent was added to 60 ml. of a solution of a known weight of a phenoxyacetic acid (kept in storage over phosphorus pentoxide in the dark) in 0.1 *N* sulfuric acid contained in a 250-ml. filter flask mounted on a magnetic stirrer. The flask was fitted with a two-hole rubber stopper. One of the holes carried a glass tube connected to a nitrogen source and which delivered nitrogen below the surface of the solution in the flask. The other hole carried a glass plug which could be interchanged with the tip of a buret which had been elongated to reach close to the surface of the solution. The outlet arm of the flask was connected to a three-way stopcock so that the exit gases could be vented to an aspirator (or to the room) or passed through an absorption train consisting of bubble counter, water absorber, and two carbon dioxide absorbers as used in a semi-micro carbon–hydrogen combustion train. The nitrogen was purified according to Fieser[32] and was passed through 0.1 *N* sulfuric acid before entering the reaction flask.

If carbon dioxide was not to be measured, with the plug in place, the flask was evacuated through the aspirator while nitrogen was shut off and the contents were stirred. When bubbles of dissolved gas ceased to appear, the stopcock was turned to isolate the flask and nitrogen introduced to atmospheric pressure. The evacuation and restoration of pressure by nitrogen was repeated. Then with a small excess pressure maintained in the flask, the plug was replaced by the buret tip. With nitrogen flow maintained through the flask, and with the stirrer in operation, a standardized solution of hydrogen peroxide was added from the buret as rapidly as possible without exceeding a dropwise rate. The flow of nitrogen and the stirring was continued for about 5 min. after the hydrogen peroxide addition was complete. In every instance an insoluble product was formed ranging from a faint turbidity to an actual precipitate depending upon the reactant and concentrations used.

The standardized hydrogen peroxide was prepared fresh every day from a 30% solution by dilution of 1 ml. to 500 ml. with 0.1 *N* sulfuric acid which had been previously boiled and then cooled with soda lime protection. The diluted solution (about 0.05 *N*) was standardized against potassium permanganate or potassium iodide and sodium thiosulfate. No variation in concentration was noted during the day. The bottle of 30% solution was stored in a refrigerator after opening. When first opened, the solution was acidified with 1 ml. of 10 *N* sulfuric acid per 200 ml. Before each use, nitrogen was bubbled through the solution at 0° for 30 min.

Analytical and Identification.—If carbon dioxide was to be determined, the procedure was the same until the two evacuations had been completed. The nitrogen flow through the absorption train was begun and continued for 30 min. The absorption tubes were disconnected, weighed, and replaced in position. The buret replaced the plug and the hydrogen peroxide solution was added as before. The flow of nitrogen and stirring was continued for 30 min. when it was interrupted and the absorption tubes were removed and weighed. As a check, a further 30-min. period of flow was carried out. Results are given in Table I. The method was checked and the details worked out in runs in which standardized sodium carbonate solutions replaced the hydrogen peroxide. For about 10 mg. of carbon dioxide evolved recovery averaged 99 ± 2%.

If ferric ion was to be determined, the reaction mixture was diluted to 100 ml. and a suitable aliquot transferred to a 50-ml. volumetric flask. Sulfuric acid, 5 ml. of 10 *N*, and 5 ml. of 10%

---

[29] Melting points are corrected. Analyses by W. Schenck and R. S. Walpole, Department of Chemistry, University of Southern California; Elek Micro Analytical Laboratories, Los Angeles, Calif.; and by Dr. Joseph Alicino, Metuchen, N. J.

[30] A. C. Cope, *J. Am. Chem. Soc.*, **57**, 572 (1935).

[31] Analysis by Mr. V. Skipski, Department of Biochemistry, University of Southern California.

[32] L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed., D. C. Heath and Co., Boston, Mass., 1955, p. 299.

potassium thiocyanate were added[33] and the contents diluted to the mark with water. The red solution was measured within 5 to 10 min. in a Klett-Summerson photoelectric colorimeter with a no. 54 filter. Readings were calibrated against suitable standards freshly prepared by the treatment of excess ferrous sulfate solutions with varying quantities of standardized hydrogen peroxide. The ferric ion concentration in the diluted reaction mixture remained constant up to 5 hr. after completion of the reaction. Results are given in Table I.

Formaldehyde was identified first from a reaction involving 0.2 g. (1.3 mmoles) of phenoxyacetic acid, 1.0 g. (2.5 mmoles) of ferrous ammonium sulfate in 200 ml. of 0.1 N sulfuric acid, and 10 ml. of 0.1 N (1.0 mmole) hydrogen peroxide. To the reaction mixture, 50 ml. of a solution of 1.2 g. of 2,4-dinitrophenylhydrazine in 300 ml. of 2 N hydrochloric acid was added. After standing overnight in the refrigerator, the product was collected and dried, m.p. 157–160°. Recrystallization from aqueous acetic acid gave a material of m.p. 161–162°. Admixture of authentic formaldehyde 2,4-dinitrophenylhydrazone of m.p. 164–165°, lit.[34] m.p. 167°, gave m.p. 157–160°. With 2- and 4-chlorophenoxyacetic acids it became necessary to modify the isolation by extracting the reaction mixture with ether, followed by addition to the aqueous phase of 5 g. of sodium hydroxide in 10 ml. of water. The mixture was centrifuged and the supernatant liquid acidified with 6 N hydrochloric acid. Addition of 50 ml. of the 2,4-dinitrophenylhydrazine solution yielded a crude precipitate, m.p. 155–158°, in both instances. Recrystallization from aqueous acetic acid gave material, m.p. 159–161°, with no lowering upon mixture with the pure substance.

Formaldehyde was determined, for example, by removal of 35 ml. of the 100 ml. of the diluted reaction mixture from 1.00 mmole of ferrous ion, 1.50 mmoles of phenoxyacetic acid, and 0.13 mmole of hydrogen peroxide in approximately 0.05 N sulfuric acid. The aliquot was made basic with two pellets of sodium hydroxide, filtered, and 25 ml. taken for analysis. The pH was adjusted to 4.6 with 1.0 N sulfuric acid and 0.04 N sodium hydroxide[35] and a solution of 10 mg. of dimedone (5,5-dimethyl-1,3-cyclohexanedione) in 10 ml. of water was added. After standing for 3 days, the product was collected in a weighed filtering crucible, dried, and weighed, m.p. 186–187°. Mixed with an authentic substance of m.p. 186–187°, lit.[36] m.p. 187°, it had m.p. 186–187°. The weight, 4.48 mg., was equivalent to 1.84 mg. (0.0613 mmole) of formaldehyde in the total reaction mixture. Neglecting the formation of any diether, the theoretical amount of formaldehyde formed was equivalent to 0.13 mmole of hydrogen peroxide consumed less one-half of the amount of ferric ion formed. A 5-ml. aliquot of the diluted reaction mixture was analyzed as already described and showed 0.117 mmole of ferric ion to be present, hence 0.0715 mmole (2.145 mg.) of formaldehyde. This gave a yield of 86%.

An independent determination was made on a 25-ml. portion of the diluted reaction mixture by extraction with four 25-ml. portions of ether, each of which was backwashed with 2 ml. of water which was added to the aqueous phase. The aqueous solution was diluted to 50 ml. and analyzed for formaldehyde by the chromotropic acid method[37] standardized with reference to formaldehyde solutions standardized by dimedone. The formaldehyde concentration in the 50-ml. solution was 0.0094 mg. per ml. which corresponded with 1.88 mg. (0.00627 mmole) total for a yield of 88%.

Formaldehyde-d_2 was purchased as a 20% solution in deuterium oxide from Isotope Specialities Company, Burbank, California. Formaldehyde bismethone and formaldehyde-d_2 bismethone were prepared by the method of Shriner, Fuson, and Curtin.[38] Solutions in chloroform, 10%, showed the following differences in infrared absorption spectra as determined on a Beckman IR-7 spectrophotometer[15]: formaldehyde bismethone, m.p. 190–191°, $\nu_{\max}$ 976 cm.$^{-1}$ (ϵ 10.3), 1085 (160); formaldehyde-d_2 bismethone, m.p. 187–188°, $\nu_{\max}$ 952 cm.$^{-1}$ (ϵ 24), 1064 (130), 2117 (3.3). A mixture of the two had m.p. 186–187°.

Formaldehyde-d_2 was identified by three methods after isolation of the bismethone. From a reaction of 0.1034 g. (0.67 mmole) of phenoxy-d_2-acetic acid, 1.02 mmoles of ferrous ion, and 0.363 mmole of hydrogen peroxide run in the usual fashion, the reaction mixture was extracted with four 25-ml. portions of ether. The combined ethereal extract was backwashed with three portions of water (2, 10, and 2 ml.) which were combined with the previous aqueous mixture. Sodium hydroxide (0.3 g.) was added and the mixture centrifuged, the residue washed with 10 ml. water which was centrifuged, and the supernatant liquids combined. Ether was removed from the aqueous mixture by evaporation at room temperature for 1 hr. at the water pump. The pH of the solution was adjusted as described previously and the bismethone precipitated and dried, 0.044 g. (0.15 mmole), m.p. 185–186°; $\nu_{\max}$ 952 cm.$^{-1}$ (ϵ 23.2), 1064 (127), 2117 (3.3), 10% in chloroform, identical with formaldehyde-d_2 bismethone.

For deuterium analysis in the mass spectrometer, the isolated bismethone was diluted with undeuterated formaldehyde bismethone to an anticipated deuterium content of 0.1 to 1.0%. After combustion of the mixture in a stream of dry oxygen, the recovered water was reduced over zinc[14] at about 400° and the gas submitted for analysis in a Westinghouse modified type LV mass spectrometer.[39] Three water samples of known deuterium content were reduced and submitted for analysis at the same time to give correction factors of 0.99, 1.21, and 1.30. Using 1.30 gave 70–93% deuterium in the bismethone. The n.m.r. spectra were obtained on a Varian A-60.[40]

Phenol was identified in a typical reaction mixture from phenoxyacetic acid by extraction with three 50-ml. portions of ether which were combined and washed with two 10-ml. portions of water and with ten 10-ml. portions of 5% sodium bicarbonate solution. The ether layer then was extracted once with 10 ml. of 5% sodium hydroxide, which was acidified with hydrochloric acid and extracted with 25 ml. of ether. The ether was evaporated and the residue treated with 100 ml. of 0.1 N potassium bromate–potassium bromide solution. The precipitate was collected, washed with 50 ml. of 1% sodium bisulfite solution, dried, and recrystallized three times from ethanol to give 2,4,6-tribromophenol, m.p. 92–93°; mixture with pure material of m.p. 94–95° gave m.p. 92–93°, lit.[41] m.p. 95°.

Phenols were determined by extraction of an aliquot of a diluted reaction mixture with five 10-ml. portions of ether each of which was washed with 2 ml. of water. The combined ethereal layer was extracted with five 5-ml. portions of 1.0 N sodium hydroxide which were combined and evaporated for 1 hr. at the filter pump. The residual alkaline liquid was diluted to 50 ml., clarified by centrifugation, and used directly for examination by ultraviolet absorption according to Brown and Claflin.[3a] Results are given in Table I. In addition, such a solution from a reaction with 2-chlorophenoxyacetic acid was examined over the range 235 to 320 mμ. For every 5-mμ interval the absorbance was calculated as the sum of the absorbances of 2-chlorophenoxide ion and of 2-chlorophenoxyacetate ion of concentrations as determined at the absorption maximum. The calculated and observed curves agreed very well except for a discrepancy of about 20% in absorbances at 250–255 mμ. This agreement was taken as evidence that no other phenoxides were present.

The isolation of 1,2-diphenoxyethane as a reaction product was accomplished by filtration of a reaction mixture from, 8 g. of ferrous ammonium sulfate, 3 g. of phenoxyacetic acid, and 50 ml. of 0.25 N hydrogen peroxide (total volume, about 300 ml.). The precipitate was washed with two 14-ml. portions of warm (about 70°) water and dried. The products from eleven such reactions were combined by solution in 25 ml. of peroxide-free ether which was evaporated. The residue was digested with 25 ml. of 5% sodium bicarbonate solution at 50°, filtered, washed with 25 ml. of 5% sodium bicarbonate solution, and washed copiously with water. After drying, the material was dissolved in 25 ml. of petroleum hexane, decolorized, filtered, and evaporated. The colorless residue was crystallized from 0.1 ml. of methanol to give 5 mg. of product, m.p. and m.m.p. 95–96°,

---

[33] T. C. J. Ovenston and C. A. Parker, *Anal. Chim. Acta*, **3**, 277 (1949).

[34] C. D. Hodgman, Ed., "Tables for Identification of Organic Compounds," Chemical Rubber Publishing Co., Cleveland, Ohio, 1960, p. 68.

[35] J. H. Yoe and L. C. Reid, *Ind. Eng. Chem., Anal. Ed.*, **13**, 238 (1941).

[36] W. Weinberger, *ibid.*, **3**, 365 (1931).

[37] C. E. Bricker and H. R. Johnson, *ibid.*, **17**, 400 (1945).

[38] R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1959, p. 220.

[39] We wish to acknowledge the help of Mr. R. Vanselow who performed the analysis on the instrument at the Department of Chemistry, University of California, Los Angeles 24, Calif.

[40] The purchase of this instrument was made possible by a generous grant from the National Science Foundation, which we are happy to acknowledge.

[41] See ref. 34, p. 41.

lit.[30] m.p. 98–98.5°. An infrared spectrum of a Nujol mull was superposable on a similar spectrum of authentic 1,2-diphenoxyethane.

The estimation of diphenoxyethanes was carried out by a single extraction of a 75-ml. aliquot of the diluted reaction mixture with 100 ml. of ether. The ethereal extract was washed with three 10-ml. portions of water, with three 10-ml. portions of 2% sodium hydroxide solution, and then with five 5-ml. portions of water or until the water wash was neutral to Universal Indicator paper. The ethereal solution was dried over anhydrous magnesium or calcium sulfate, filtered, and the residue washed with fresh portions of ether. The combined filtrates were evaporated under a stream of dried air, and the residue was taken up in 5 ml. of Spectro Grade carbon tetrachloride. This was evaporated to dryness and repeated once more. Finally the residue was dissolved in 0.5 ml. of the solvent for infrared examination. The extinction coefficients were determined on synthetic materials.

Polyfunctional Aliphatic Compounds. V. The Cyclization of Dinitriles by Halogen Acids. A New Synthesis of Imidazoles

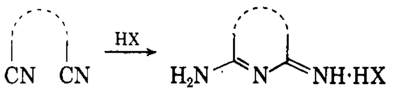
Francis Johnson and W. A. Nasutavicus

The Dow Chemical Company, Eastern Research Laboratory, Framingham, Massachusetts

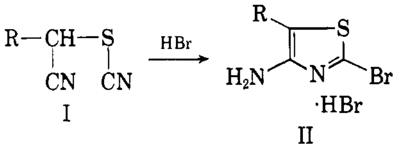
Received July 8, 1963

Dinitriles having the general structure, RN(CN)CH(CN)R, undergo cyclization to 2-bromo-4(5)-aminoimidazoles when treated with anhydrous hydrogen bromide. Where R and R′ are aryl groups these amino compounds are generally stable enough to be isolated as the free bases. Otherwise, the imidazoles can be obtained as their acetamino derivatives. A convenient method for the synthesis of the previously unavailable starting dinitriles utilizes the reaction of a monosubstituted cyanamide with an α-haloalkyl, or an α-[4-toluenesulfonyloxyl]alkyl cyanide in anhydrous dimethylformamide using triethylamine as an acid acceptor.

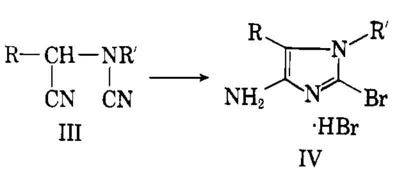
In previous publications[1–3] we have demonstrated that the halogen acid (X = Br or I) cyclization of dinitriles, *viz.*,



can be used for the synthesis of heterocyclic compounds in the pyridine,[1] isoquinoline,[2] and thiazole[3] series. The successful cyclization of α-cyanoalkyl thiocyanates (I) to 4-amino-2-bromothiazoles (II) suggested that

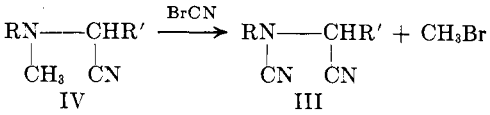


the analogous α-cyanoalkyl cyanamides (III) might lead to the corresponding imidazoles (IV).



Our findings, presented in this paper, now confirm this prediction and demonstrate, as anticipated, that the cyclization occurs in one specific direction, affording only derivatives of 4(5)-aminoimidazole.

α-Cyanoalkyl Cyanamides.—The chief difficulty in broadening the scope of the dinitrile cyclization to include imidazoles, lay in the unavailability of the precursors, namely α-cyanoalkyl cyanamides. For these aliphatic systems, only one recorded method of synthesis could be found in the literature. This, due to v. Braun,[4] involves the action of cyanogen bromide on N-alkyl-N-methylaminoacetonitriles (IV).



Where R is a simple alkyl group, selective cleavage of the methyl group occurs. Although this method proved suitable for the preparation of III, where R = alkyl and R′ = H, it was severely limited by the lack of easy methods of preparation of IV, where R = aryl or hydrogen and R′ = aryl, alkyl, or hydrogen. Therefore, a number of other approaches to III were tried, most with little success.

N-Phenyl-α-(4-methoxyphenyl)aminoacetonitrile did not react at room temperature with cyanogen bromide, and N-phenylaminoacetonitrile could only be induced to react with this reagent at temperatures above 90°. The sole product was N-(4-cyanophenyl)aminoacetonitrile.[5]

When α-phenylaminoacetonitrile (V) was treated with half an equivalent of cyanogen bromide in anhydrous ether the hydrobromide salt of V was rapidly precipitated, and from solution a sirup was obtained which could not be distilled or crystallized. Attempted chromatography only caused decomposition, and no α-cyanobenzyl cyanamide could be obtained.

A number of reactions using cyanamide (VI) itself were tried to no avail. A combination of benzaldehyde, hydrogen cyanide, and VI in the presence of anhydrous calcium sulfate did not lead to any α-cyanobenzyl cyanamide. On the other hand the reaction of α-cyano-2-chlorobenzyl 4-toluenesulfonate (VII) in the presence of triethylamine and VI afforded only the sulfone (VIII).

---

[1] F. Johnson, J. P. Panella, A. A. Carlson, and D. H. Hunneman, *J. Org. Chem.*, **27**, 2473 (1962).

[2] F. Johnson and W. A. Nasutavicus, *ibid.*, **27**, 3953 (1962).

[3] Part IV: F. Johnson and W. A. Nasutavicus, *ibid.*, **28**, 1877 (1963).

[4] J. v. Braun, *Ber.*, **40**, 3933 (1907).

[5] Contrast N-methyl-N-phenylaminoacetonitrile which reacts with cyanogen bromide to give the bromo compound, N-methyl-N-(4-bromophenyl)aminoacetonitrile [J. v. Braun, *ibid.*, **41**, 2113 (1908)].