Carbobenzyloxytyrosylproline was oxidized with NBS as previously described.[1] By ninhydrin assay, average cleavage yields were 85%.

N-2,4-Dinitrophenyl-S-carboxymethylcysteine Sulfone.— To a solution of S-carboxymethylcysteine sulfone[1] (0.63 g.) and sodium bicarbonate (1.1 g.) in water (25 ml.), fluorodinitrobenzene (1.1 g.) in ethanol (25 ml.) was added and the mixture stirred at room temperature for 4 hr. After dilution with water, the ethanol was removed *in vacuo* and the excess of reagent extracted with ether. Acidification with 6 N hydrochloric acid precipitated the crystalline derivative which was collected and washed well with water. The crude material (1.1 g.) was recrystallized twice from ethyl acetate–ligroin (65°) and once from aqueous ethanol to give yellow needles, sintering at 114–130°, resolidifying and melting again at 155–158°.

Anal. Calcd. for $C_{11}H_{11}O_{10}N_3S$: C, 35.02; H, 2.9 4; N, 11.14. Found: C, 35.11; H, 3.15; N, 11.21.

N-2,4-Dinitrophenyl-S-carboxymethylcysteine sulfoxide was prepared on the same scale and by the same method as above. It separated from water in prisms, m.p. 145–147°.

Anal. Calcd. for $C_{11}H_{11}O_9N_3S$: C, 36.57; H, 3.07; N, 11.63. Found: C, 36.49; H, 3.21; N, 11.35.

N-2,4-Dinitrophenyl-S-methylcysteine sulfone was prepared as above and was obtained as long needles from water; m.p. 176–178°.

Anal. Calcd. for $C_{10}H_{11}O_8N_3S$: C, 36.04; H, 3.33; N, 12.60. Found: C, 36.00; H, 3.62; N, 12.47.

Enzyme Oxidations.—Bovine pancreatic RNase (Sigma Chemical Co., chromatographic grade, Lot No. R60-B-069) was used without further purification. S-Carboxymethylribonuclease was prepared by mercaptoethanol reduction of the disulfide bonds in RNase, alkylation with iodoacetate and purification on Sephadex G-25 to a single, fairly symmetrical peak.[17]

To a solution of the protein (usually 0.5 μM) in 2 ml. of 50% acetic acid or pH 4.6 acetate buffer was added a solution of NBS in 2 ml. of acetic acid or acetate buffer–5% acetonitrile. The mixture was stirred for 4 hr. at 25° and the solvent removed by lyophilization.

Amino-Terminal Assay.—After lyophilization, the protein residue was taken up in 2 ml. of water to which was added 50 mg. of sodium bicarbonate followed by a solution of 50 mg. of fluorodinitrobenzene in 2 ml. of ethanol. After 4 hr. the mixture was carefully evaporated to dryness *in vacuo*. In early experiments, excess reagent was extracted with ether at this point; however,

it was found that some peptide material was also extractable by ether since the carboxyl terminals were present as lactones and not as carboxylate anions. In most runs, therefore, excess reagent was carried through subsequent steps. The mixture of DNP-polypeptide fragments was hydrolyzed with 6 N hydrochloric acid under N_2 at 105–110° for 16-18 hr., using 3–4 ml. of acid. A few drops of glacial acetic acid was often used to facilitate transfer and to ensure complete solution. Dinitrophenol was removed by repeated sublimation and the residual ether-soluble DNP-amino acids were resolved by two-dimensional chromatography on Whatman No. 1 paper using the solvent systems toluene–pyridine–2-chloroethanol–0.8 N ammonium hydroxide (50:15:30:30) and 1.5 M phosphate buffer, pH 6.5.[18] The DNP-amino acids were eluted with 1% sodium bicarbonate and assayed spectrophotometrically at 360 mμ. Individual DNP-amino acids were identified by running them with an authentic specimen in the *tert*-amyl alcohol–pH 6.0 phthalate system. The identification and determination of the water-soluble DNP-cysteic acid were carried out by evaporation of the aqueous phase and (1) two-dimensional chromatography in the usual systems or (2) adsorption on a column of talc and elution with ethanol–N hydrochloric acid (4:1), other DNP derivatives remaining on the column.[19] Paper electrophoresis at pH 1.9 was also used to separate and identify DNP-cysteic acid.[20] Proline was determined by the Edman procedure from independent runs.[18]

Determination of Correction Factors.—Authentic DNP-amino acids, at appropriate concentrations, were subjected to the usual acid treatment in the presence of oxidized ribonuclease. Recovery factors were averaged from several runs for each compound: lysine, 81; valine, 73; glutamic acid, 70; serine, 31. The phenylthiohydantoin of proline was recovered in 55% yield. DNP-S-carboxymethylcysteine sulfone was destroyed to a considerable extent by acid (12% recovery). The major product showed a peak in the ultraviolet at 330 mμ rather than 360 mμ, but could not be identified. It was demonstrated by paper chromatography that reduction to the sulfoxide did not occur, nor did the material decarboxylate to DNP-S-methylcysteine sulfone to any significant extent.

(17) C. B. Anfinsen and E. Haber, *J. Biol. Chem.*, **236**, 1361 (1961).

(18) H. Fraenkel-Conrat, J. I. Harris and A. L. Levy, "Methods of Biochemical Analysis," Vol. 2, Interscience Publishers, Inc., New York, N. Y., 1955, p. 360.

(19) G. Biserte, J. W. Holleman, J. Holleman-Dehove and P. Sautière, "Chromatographic Reviews," Vol. 2, Elsevier Publishing Co., Amsterdam, 1960, p. 59.

(20) K. Wallenfels and A. Arens, *Biochem. Z.*, **332**, 217 (1960).

Neighboring Carbon and Hydrogen. LI.[1] Dienones from Ar₁⊖-3 Participation. Isolation and Behavior of Spiro(2,5)octa-1,4-diene-3-one

BY RICHARD BAIRD[2] AND S. WINSTEIN

When the aryl group is *p*-hydroxyphenyl, Ar₁-3 participation in the phenoxide anion of 2-aryl-1-ethyl halides, designated by the symbol Ar₁⊖-3, leads to spiro(2,5)octa-1,4-diene-3-one. Kinetic investigation of the behavior of 2-*p*-hydroxyphenylethyl bromide in basic methanolic solution shows that conditions are very favorable for Ar₁⊖-3 participation; the intermediate spiro-dienone gives rise to monomeric methyl ether and higher molecular weight products in proportions dependent on the concentrations of methoxide and phenoxide ions. By spectroscopic methods it is possible to observe and study the kinetics of formation and decay of the intermediate spiro-dienone. Under specially designed conditions, it has been possible to isolate the unusually reactive spiro-dienone as a pure, crystalline solid and to study its behavior directly in solvolysis, hydrogenation, lithium aluminum hydride reduction and hydrogen bromide addition. The ultraviolet and n.m.r. spectra of the dienone are of some interest. Also, the acid-catalyzed rate of methanolysis of the spiro-dienone permits one to estimate the stationary state concentration of the ethylene phenonium ion intermediate in solvolysis of 2-*p*-anisylethyl toluenesulfonate. This is because the conjugate acid of the dienone may be taken as a model for the bridged-ion intermediate in anchimerically assisted ionization of a 2-*p*-anisylethyl derivative.

With suitable substrate structure and reaction conditions, it is possible to arrange for the formation of dienones through Ar₁⊖-participation of a neighboring

phenoxide-ion group.[1a,3] In the case of Ar₁⊖-assisted formation of dienones, it has been indicated already in preliminary communications[3,4] that 2-*p*-hydroxyphenylethyl bromide (I-Br) gives rise under alkaline conditions to the intermediate dienone IV which can be detected spectroscopically[3] and even isolated in pure form.[4] The results of this study of the formation and behavior of this interesting substance are presented and discussed in the present manuscript.

(1) (a) Paper XLVI: R. Baird and S. Winstein, *J. Am. Chem. Soc.*, **84**, 788 (1962); (b) Paper XLVII: E. Friedrich and S. Winstein, *Tetrahedron Letters*, No. 11, 475 (1962); (c) Paper XLVIII: E. Hedaya and S. Winstein, *ibid.*, No. 13, 563 (1962); (c) Paper XLIX: S. Winstein, E. Vogelfanger, K. C. Pande and H. F. Ebel, *J. Am. Chem. Soc.*, in press; (e) Paper L: S. Winstein, E. Vogelfanger and K. C. Pande, *Chem. Ind.* (London), 2061 (1962).

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(3) S. Winstein and R. Baird, *J. Am. Chem. Soc.*, **79**, 756 (1957).

(4) R. Baird and S. Winstein, *ibid.*, **79**, 4238 (1957).

TABLE I

REACTION OF 2-p-HYDROXYPHENYLETHYL BROMIDE IN METHANOLIC AND ETHANOLIC SODIUM ALKOXIDE AT 25.00°

Run	Solvent	(RBr) 10^2 M	(NaOR) 10^2 M	Excess (NaOR):(RBr)	Initial 10^3k, sec.$^{-1}$	$\%$ rn. at exp. ∞ [b]	Range of integ. 10^3k (20–80% rn.), sec.$^{-1}$
1	EtOH[a]	2.684	5.555	1:1	1.2	81.5	1.05–0.15
2	EtOH	3.502	17.54	4:1	1.4	85.3	1.27– .64
3	EtOH	3.494	17.63	4:1	1.2	84.9	1.57– .68
4	EtOH	3.019	33.10	10:1	1.4	88.7	1.23– .83
5	EtOH	3.284	72.34	20:1	1.32	95	1.18–1.03
6	EtOH	3.448	3.448	0:1	..	70	1.17 ± 0.04[c]
7	EtOH	3.448	3.448	0:1	..	70	1.16 ± 0.04[c]
8	MeOH[a]	3.004	13.03	3:1	0.86	91	0.893–0.739
9	MeOH[a]	3.000	13.03	3:1	0.87	89	0.796–0.665

[a] Followed by base consumption; the other rates were followed by bromide ion production.   [b] The experimental infinity was taken at 20 or more half-lives, based on the initial rate constant; the infinity values did not drift appreciably after this time.   [c] Calculated on the assumption that the rate of disappearance of RBr is twice the rate of production of bromide ion.

Kinetic Search for Ar$_1\ominus$-3 Participation.—Just as in the case of the Ar$_1\ominus$-5 investigation,[1a,3] the search for Ar$_1\ominus$-3 participation involved a combination of kinetic measurements and product examination. In the kinetic search for Ar$_1\ominus$-3 participation, a study was made of the solvolytic behavior of the phenoxide ion II-Br from 2-p-hydroxyphenylethyl bromide (I-Br) in methanolic and ethanolic sodium alkoxide solution.
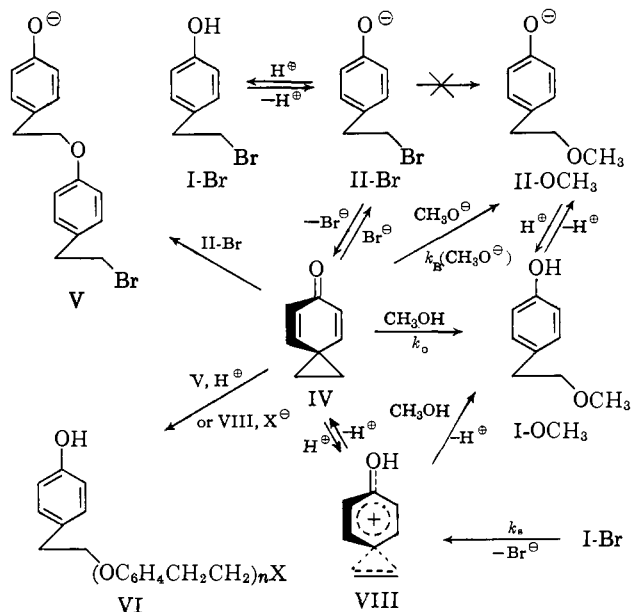

Fig. 1.—Reactions of 2-p-hydroxyphenylethyl bromide in anhydrous methanol at 25.0°.

As is clear from the summary in Table I, the initial value of the instantaneous[5] first-order rate constant obtained in these runs was independent of excess alkoxide ion employed. This is shown by runs 1–5 in Table I where the ratio of excess alkoxide:II-Br varies from 1:1 to 20:1. However, first-order kinetics were not well obeyed throughout the runs, first-order rate constants drifting downward in all of them.

In contrast with the p-hydroxyphenylethyl bromide, the corresponding methyl ether III-Br reacted much more slowly in absolute methanol containing sodium methoxide. Good second-order kinetics were observed in this case, k_2 being $(1.49 \pm 0.03) \times 10^{-5}$ l. mole^{-1} sec.$^{-1}$ at 25°. This corresponds to a pseudo first-order rate constant of 1.9×10^{-6} sec.$^{-1}$ at 0.13 M sodium methoxide, much smaller than the value of 8.6×10^{-4} sec.$^{-1}$ observed with the hydroxyphenylethyl

bromide I-Br. The situation is similar in ethanol as solvent, since the second-order rates of reaction of III-Br with ethoxide ion reported by DePuy[6] correspond to pseudo first-order rate constants which are lower than the one observed with I-Br by a factor of ca. 20 at the highest base concentration and ca. 400 at the lowest practical alkoxide concentration.

In both methanol and ethanol as solvents it is evident that the reaction of the phenoxide ion II-Br is substantially accelerated over the reaction of the ether III-Br with alkoxide ion. The contrast becomes much greater if the comparison is made between the first-order rate of II-Br and the neutral solvolysis of III-Br. The bromide III-Br is exceedingly slow in ethanol at 25°, but a crude estimate of its neutral solvolysis rate can be obtained from that of 2-p-anisylethyl p-toluenesulfonate (III-OTs) at 75°. Extrapolation[7] leads to an estimated difference of ca. 10^6 between the rate of II-Br and either the anchimerically unassisted or anchimerically assisted rate of ethanolysis of III-Br at 25°.

The anchimeric acceleration and essentially first-order kinetics observed in the alkaline solvolysis of I-Br can be interpreted in terms of the rate-determining formation of the spiro-dienone intermediate IV as in Fig. 1. The fate of this intermediate can be inferred from the following evidence. First of all, the products from the reaction in methanol consisted primarily of 2-p-hydroxyphenylethyl methyl ether (I-OCH$_3$), plus an ill-defined higher molecular weight product which appeared to consist of a mixture of products of general structure VI. The proportion of I-OCH$_3$ isolated varied with the excess of alkoxide used in the reaction, ranging from 57% when a 3:1 excess was employed to 82% when the ratio was 30:1. It seems certain that these products were formed via dienone IV rather than directly from I-Br or II-Br since the methyl ether of I-Br gives a quantitative yield of p-methoxystyrene under very similar conditions.[6]

In agreement with the product analysis, the experimental infinity values in the kinetic runs varied with the excess of alkoxide ion employed in the reaction. As shown in Table I, the reaction stopped at 81.5% of completion when a 1:1 ratio of excess ethoxide to II-Br was used. This value rose to 95% when the ratio of ethoxide to II-Br was increased to 20:1.

(6) C. H. DePuy and D. H. Froemsdorf, J. Am. Chem. Soc., **79**, 3710 (1957).

(7) The anchimerically assisted and unassisted ethanolysis rate constants[8] for III-OTs are 6.6×10^{-8} sec.$^{-1}$ and 7.6×10^{-6} sec.$^{-1}$, respectively, at 75°. Applying a factor of 15 for the difference between a primary bromide and p-toluenesulfonate[9] and a factor of 15 for each 25° change in temperature gives an estimated rate constant of ca. 2×10^{-9} sec.$^{-1}$ for either anchimerically assisted or unassisted ethanolysis of III-Br at 25°.

(8) E. Jenny and S. Winstein, Helv. Chim. Acta, **41**, 807 (1958).

(9) A. Streitwieser, Jr., Chem. Rev., **56**, 654 (1956).

(5) The initial, instantaneous first-order rate constant was obtained by extrapolation of a plot of concentration vs. time to zero time, graphical determination of the slope (dx/dt) and division by the concentration at zero time. Zero time could be established accurately as described in the Experimental section.

Since the purity of I-Br was established by analysis and melting point, it seems reasonable to attribute this incomplete reaction to the formation of dimeric V, by reaction between IV and ion II-Br. The bromine in V should be comparable in reactivity to that in the methyl ether III-Br, so that it would be expected to be essentially inert under the reaction conditions. Accordingly, this process results in consumption of II-Br without production of bromide ion, which would lead to deviation from first-order kinetics. It also explains the dependence of the product ratio and experimental infinity value on the excess of alkoxide ion used, as the latter is competing with ion II-Br for intermediate IV.

In order to test the above scheme, the rate of reaction of II-Br was measured in ethanol containing no excess ethoxide.[10] Under these conditions it was expected that two moles of II-Br would be consumed for every mole of bromide ion produced and that the reaction would stop at 50% (as measured by bromide ion produced), all of II-Br being converted to dimeric V at this point. In spite of the possibility of additional reactions of IV and incomplete conversion[10] of phenol I-Br to phenoxide II-Br, the above expectation is essentially correct as shown by runs 6 and 7 in Table I. The reaction stops at 70% reaction and reasonably good, non-drifting first-order rate constants[12] were obtained. As shown in Table I, the values of these rate constants were comparable in magnitude to the initial, instantaneous rate constants in runs 1-5.

Although the above scheme affords a good qualitative explanation of the reactions of II-Br and IV, the multiplicity of reactions possible at titrimetric concentrations makes a quantitative interpretation difficult. Thus, it was not possible to fit the over-all kinetic behavior of II-Br with any precision on the basis of titrimetric measurements, nor was it possible to establish a simple relationship between the excess of alkoxide ion used and the experimental infinity value obtained.

It was possible, however, to eliminate many of the side reactions observed at titrimetric concentration (0.03 M) and to clarify many of the above points by studying the reactions in more dilute solutions (10^{-4} to 10^{-5} M) making use of the characteristic spectroscopic properties of I-Br, II-Br, IV and II-OCH$_3$.

Spectroscopic Study of Ar$_1^{\ominus}$-3 Participation.—Both the reactant phenol I-Br and the product phenol I-OCH$_3$ exhibited similar ultraviolet spectra in methanol solvent. Maxima occurred at 285 mμ (ϵ 1500), 278 mμ (ϵ 1900) and near 225 mμ for both compounds. The first two maxima, the so-called B-bands,[13] were reasonably insensitive to substitution at the 2-position in the aliphatic portion of the molecule, but the latter maximum proved to be somewhat more sensitive, occurring at 229.5 mμ with I-Br and 224 mμ for I-OCH$_3$.

Addition of sufficient base to convert the phenols to their salts caused a characteristic[14] bathochromic shift. Thus the maximum at 224 mμ for 2-p-hydroxyphenyl-
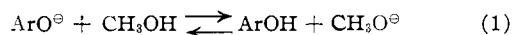
ethanol (I-OH), which is essentially identical spectroscopically with I-OCH$_3$, was shifted from 224 mμ (ϵ 8000) to 241 mμ (ϵ 11,300) and the two maxima at 277.5 and 285 mμ became a single maximum at 295 mμ (ϵ 2700). The effect of added base on I-Br was more complex due to concurrent reaction, but qualitatively similar behavior was observed.

When a $ca.$ 10^{-4} M solution of I-Br in methanol was treated with a two- or threefold excess of sodium methoxide at 25°, only a small fraction of the phenol was converted to its sodium salt because of the unfavorable equilibrium involved at these concentrations.[11] Over the course of about thirty minutes, however, the phenolic maximum at 229.5 mμ slowly disappeared and a new maximum appeared at 274 mμ much more intense than the original phenolic maximum at 277.5 mμ. After about thirty minutes, this new maximum began to decrease and a phenolic maximum began to reappear near 229 mμ. After a total of sixty minutes this entire process was complete and the spectrum was similar to that of the initial solution, except that the phenolic maximum was now at 224 mμ, corresponding to the maximum of I-OCH$_3$ rather than I-Br.

The maximum at 274 mμ could not be attributed to any of the known phenols or their salts, and it was extremely unlikely that it was due to dimeric or analogous products since the spectra of such compounds resemble those of the monomers. A sample of p-hydroxystyrene, prepared by decarboxylation of p-hydroxycinnamic acid, exhibited a maximum at 260.5 mμ (ϵ 15,000) in methanol, which was shifted to 285 mμ (ϵ 18,000) by base. Both the styrene and its salt were stable under conditions where the 274 mμ peak rapidly disappeared, so that a fortuitous mixture of the styrene and its salt could not have given this maximum. The latter possibility was completely eliminated by the observance of the 274 mμ peak at more than one base concentration.

By a process of elimination it was possible to associate the maximum at 274 mμ with the intermediate dienone IV. This wave length was not inconsistent with this structure, since the related spiro(4,5)deca-2,5-dien-3-one[1a] (VII) possessed a maximum at 242 mμ, and the added conjugation provided by a cyclopropane ring was expected to cause a bathochromic shift.[15] However, this shift of 32 mμ was much larger than had been previously observed for cyclopropane conjugation,[15] so that it could not be used as compelling evidence for the structure of IV.

Spectroscopic Kinetic Studies.—For further kinetic studies, it was necessary to estimate the equilibrium constant for the equilibrium in eq. 1, since, for simplicity of kinetic treatment, it was desirable to have the substrate I-Br either completely ionized or almost completely un-ionized. Using the method of Stenström,[16] the value of K_m defined by eq. 2 was determined in absolute methanol, for 2-p-hydroxyphenylethanol (I-OH), assuming the value for I-Br would be almost identical. The measurements were not cor-

$$\text{ArO}^{\ominus} + \text{CH}_3\text{OH} \underset{\longleftarrow}{\overset{\longrightarrow}{\rightleftharpoons}} \text{ArOH} + \text{CH}_3\text{O}^{\ominus} \qquad (1)$$

$$K_m = (\text{ArOH})(\text{MeO}^{\ominus})/(\text{ArO}^{\ominus}) \qquad (2)$$

rected for ionic strength effects, since only an estimate of the magnitude of K_m was necessary. The values determined are given in the Experimental section, the average value of K_m being taken as $(3.25 \pm 0.25) \times 10^{-3}$ M. This meant that concentrations of sodium methoxide of 0.05-0.1 M were necessary to ensure

(10) This situation could not in fact be achieved because of incomplete conversion of phenol to phenoxide ion.[11] Nevertheless, as a first approximation the major part of the substrate was present as II-Br. For further comment, see subsequent paragraphs.

(11) J. W. Baker and A. J. Neale, J. Chem. Soc., 3225 (1954).

(12) If two moles of substrate II-Br are consumed for every mole of bromide ion produced, $-d(\text{II-Br})/dt = 2k(\text{II-Br})$, where k is the rate constant for production of bromide ion. Integration gives $\ln (\text{II-Br})_0 - \ln (\text{II-Br}) = 2k(t - t_0)$. Setting $(\text{II-Br})_0 = a$, and $(\text{Br}^-) = x$, gives $(\text{II-Br}) = (a - 2x)$, and $\ln a - \ln (a - 2x) = 2k(t - t_0)$. Elimination of t_0 gives: $\ln (a - 2x_1) - \ln (a - 2x_2) = 2k(t_2 - t_1)$, which is the expression used to calculate k for runs 6 and 7.

(13) A. E. Gillam and E. S. Stern, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," Edward Arnold Ltd., London, 1955, p. 125.

(14) N. D. Coggeshall and A. S. Glessner, Jr., J. Am. Chem. Soc., 71, 3150 (1949).

(15) R. H. Eastman, ibid., 76, 4115 (1954).

(16) W. Stenström and N. Goldsmith, J. Phys. Chem., 30, 1683 (1926).

predominant conversion of I-Br to II-Br. Also, nothing could be gained by going in the other direction, since at 10^{-4} M sodium methoxide the equilibrium is still in the intermediate range and this is difficult to handle kinetically.[17] Both base and substrate are consumed at this concentration, and *ca.* 10% of the substrate is still present in the phenolic form I-Br. Lower concentrations were difficult to obtain because of reaction of the base with atmospheric carbon dioxide.

When preliminary kinetic measurements were made at base concentrations of 0.05 and 0.1 M, it was found that the intermediate IV was destroyed at a rate comparable to that at which it was formed. Since the base concentration was high compared to that of the substrate, any process leading to destruction of the intermediate could be treated as pseudo first order. This made both formation and destruction of IV first order so that the system resembles a radioactive parent-daughter series as in eq. 3. In this formulation k_2 is a complex rate constant, but it does not vary in any one run since base concentration is essentially constant.

$$\text{II-Br} \xrightarrow{k_1} \text{IV} \xrightarrow{k_2} \text{product (II-OCH}_3) \quad (3)$$
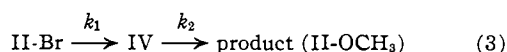
$$[B] = \frac{[A]_0 k_1}{k_2 - k_1} (e^{-k_1 t} - e^{-k_2 t}) \quad (4)$$

$$(k_2 - k_1)t_m = \ln (k_2/k_1) \quad (5)$$

Because the reactant II-Br and product II-OCH$_3$ had similar ultraviolet spectra, the reaction was followed at the maximum of the intermediate (274 mμ). However, in order to evaluate the rate constants for the reaction by the usual kinetic method,[18] it was necessary to relate the concentration of IV to either that of II-Br or II-OCH$_3$. Since the molar extinction coefficient of IV was not available at the time these experiments were carried out, it was necessary to devise a method which did not require this information. The following method not only provided an estimate of the rate constants, but also proved convenient for the calculation of better values after more information about IV became available.

Provided that the rate constant for the second step in a series first-order sequence is enough smaller than that for the first step, the reaction will reach a point where only the second step is important and the value of this rate constant can be obtained from the slope of a plot of log (optical density) *vs.* time. This condition could not be obtained with the bromide II-Br, but with the corresponding iodide II-I the rate of the second step could just be measured at 0.01 M sodium methoxide concentration.

Once a method for evaluating k_2 was derived, the value of k_1 could be determined as follows: The integrated rate expression for a series first-order reaction is given in eq.[18] 4 where [B] represents the concentration of IV and [A]$_0$ the initial concentration of II-Br. As was stated above, this equation could not be evaluated without a way of relating [B] and [A]$_0$. However, on differentiation of expression 4 with respect to t, eq. 5 is obtained,[18] giving the value of t at which the concentration of IV is a maximum (t_m). By the use of a special rapid mixing flask[19] it was possible to determine t_m quite accurately, and eq. 5 could be solved by successive approximations. This value of t_m could be obtained without complication at 274 mμ since only the intermediate absorbed strongly at this wave length,

both substrate II-Br and product II-OCH$_3$ having minima here. The sensitivity of the value of k_1 to small errors in t_m was low, so that small errors in the latter were unimportant.

The value of k_1 obtained from this method is shown in run 2 in Table II. This value is known to be low because at the base concentration employed, the highest one at which k_2 could be evaluated, the substrate II-Br is less than 90% in the ionized form. Nevertheless, the value is of the same order of magnitude as the values for k_1 obtained titrimetrically (Table I). When another method, described later in this article, was derived for determining k_2 at base concentrations higher than 0.05 M, it was possible to determine k_1 under conditions where most of the substrate was in the phenoxide ion form (runs 3 and 4 in Table II). The values of k_1 in runs 3 and 4 are self consistent, but are larger than the titrimetric values of k_1 by a factor of *ca.* 2.3. As will be shown later, these values are believed to be correct, the titrimetric rate constants being low due to return by bromide ion.

TABLE II

SPECTROSCOPIC BEHAVIOR OF 2-p-HYDROXYPHENYLETHYL HALIDES (RX) AT 274 mμ IN ABSOLUTE METHANOL AT 25°

X	(RX), 10^5 M	(NaOMe), 10^2 M	$10^3 k_1$, sec.$^{-1}$	$10^4 k_2$, sec.$^{-1}$
I	5.08	0.994	5.1	9.2
Br	6.03	0.994	1.1	9.2^a
Br	6.14	4.88	1.9	30.4^b
Br	6.03	12.9	2.2	80.6^b

^{a} Assumed to be the same as in run above. ^{b} Calculated from decay rates of the intermediate.

The reaction of I-Br became much simpler in *t*-butyl alcohol as solvent. In this solvent, phenols are converted to their salts at much lower base concentrations than were required in methyl and ethyl alcohols, so that attack on IV by base could be made less serious. Both the bromide I-Br and the iodide I-I rapidly gave rise to an intense maximum at 271 mμ on addition of potassium *t*-butoxide, the reaction half-lives being less than 30 seconds at 30°. No species other than that absorbing at 271 mμ remained in the region 220 to 350 mμ after the treatment (except for iodide ion end absorption with I-I), and both the bromide I-Br and the iodide I-I gave the same optical density at 271 mμ when equivalent concentrations were used. The molar extinction coefficient (ϵ 22,200) calculated on the basis of complete conversion of I-Br or I-I was taken to be that of IV in *t*-butyl alcohol.

The chloride I-Cl reacted enough less rapidly than I-Br and I-I that it could be used for kinetic studies. However, competing reactions of II-Cl, etc., with IV were more significant with this derivative and the maximum absorption at 271 mμ was never as great as that obtained with I-Br and I-I. From the summary in Table III, it is evident that competing processes still cause a drift in the observed first-order rate constants, but this is much less serious than in methanol.

TABLE III

SPECTROSCOPIC BEHAVIOR OF 2-p-HYDROXYPHENYLETHYL CHLORIDE AT 271 mμ IN ABSOLUTE *t*-BUTYL ALCOHOL AT 30°

Run	(RX), 10^5 M	KOBu-*t*, 10^4 M	$10^4 k$ inst., sec.$^{-1}$	$10^4 k$ integ.,^{a} sec.$^{-1}$	$\dfrac{\text{O.D.}_{max}{}^b}{\text{O.D.}_\infty}$
1	3.21	3.60	3.00	3.03–2.49	0.90
2	3.21	1.01	3.01	3.05–2.58	.94
3	6.42	5.04	2.10	2.21–1.49	.88
4	3.21	35.3	1.41	1.38–0.93	.57

^{a} This is the range of the integrated first-order rate constant from *ca.* 20–80% reaction. ^{b} O.D.$_\infty$ is the optical density of the intermediate obtained from the same concentration of the bromide or iodide.

(17) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," second edition, John Wiley and Sons, Inc., New York, N. Y., 1961, p. 195.

(18) Reference 17, p. 166.

(19) L. O. Winstrom and J. C. Warner, *J. Am. Chem. Soc.*, 61, 1205 (1939).

Isolation of the Intermediate Dienone.—In view of the apparent stability of IV in *t*-butyl alcohol, attempts were made to concentrate solutions prepared from I-Br and potassium *t*-butoxide in this solvent. All such attempts, carried out at as low temperatures as possible by evaporation under reduced pressure, led to loss of the maximum at 271 mμ and the eventual isolation of a high-melting insoluble product which appeared to be polymeric.

When the preparation of IV was attempted in anhydrous ether, sodium hydride being used to convert I-Br to its salt, no reaction was observed. The sodium salt regenerated starting material on acidification and reacted normally on addition to a large excess of *t*-butyl alcohol. The use of a two-phase system was also attempted. Shaking solutions of I-Br in ether or pentane with aqueous sodium hydroxide yielded only high melting, ill-defined products.

A variation of the last method led to the successful isolation of the intermediate IV. When a strong aqueous potassium hydroxide solution was adsorbed on alumina,[20] and 2-*p*-hydroxyphenylethyl bromide dissolved in ether was passed through a chromatographic column of this alumina, effluent solutions were obtained which possessed a new maximum at 261 mμ in addition to the phenolic absorption at *ca.* 230 mμ.

By careful adjustment of column height and volume, flow rate and substrate concentration, solutions could be obtained which possessed only the maximum at 261 mμ. Estimation using the molar extinction coefficient obtained in *t*-butyl alcohol (ϵ 22,200) indicated an average concentration of IV in the vicinity of 10^{-3} M in a series of experiments run under essentially identical conditions. Dilution of samples of this solution with 99 volumes of *t*-butyl alcohol or methanol produced solutions exhibiting the previously observed ultraviolet absorption maxima for the intermediate at 271 and 274 mμ, respectively. In methanol containing 0.01 M sodium methoxide, the rate constant for disappearance of the absorption maximum, k_2, was within 1% of that previously observed (run 2 in Table II).

When carefully neutralized glassware was employed, the above ether solutions could be evaporated to give a white crystalline solid, which was soluble in ether, alcohols and in halogenated solvents. This substance could be recrystallized from ether–pentane at low temperatures in carefully neutralized apparatus, to give a low melting solid which possessed the correct carbon-hydrogen analysis for C_8H_8O. The spectral and chemical properties of the isolated compound were consistent with the dienone structure IV.

The infrared spectrum of the compound possessed strong absorption maxima for a highly conjugated carbonyl at 1650 cm.$^{-1}$ in carbon disulfide and 1640 cm.$^{-1}$ in chloroform, and in general was quite similar to that of spiro(4,5)deca-1,4-diene-3-one.[1a] The ultraviolet absorption maxima were also indicative of a highly conjugated carbonyl system, both in the position at which they occurred and in their intensity.[21,22] In addition, the positions of these maxima were unusually sensitive to the nature of the solvent,[23] λ_{max} being shifted from 261 mμ in ether to 271 mμ in *t*-butyl alcohol, 274 mμ in methanol and *ca.* 282 mμ in water.

The nuclear magnetic resonance spectrum of dienone IV in CDCl$_3$ consisted of two sharp singlets of equal intensity at 8.31 and 3.56[24] p.p.m. on the τ-scale of

Tiers.[25] The positions of these peaks correspond closely with those observed for the cyclopropyl and vinyl hydrogens of dienone IVa at $\tau = 8.42$ and 3.66 p.p.m., respectively.[24,26]

The lack of splitting of the vinyl hydrogens of IV is surprising but real, the resolution obtained being more than sufficient to show the characteristic triplet and quartet of diethyl ether under these conditions.

(6)

IVa
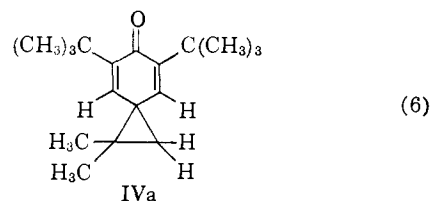
Some Reactions of the Intermediate.—In addition to the above-mentioned reaction with methoxide ion, the intermediate in dilute solution reacted with a variety of reagents to produce phenolic products. Thus, catalytic hydrogenation with reduced platinum oxide in ether required *ca.* one mole of hydrogen and the product, *p*-ethylphenol, was isolated in over 50% yield. The ultraviolet spectrum of the product indicated that it was actually formed in near quantitative yield, the difference being attributed to losses in the isolation of small quantities from very dilute solution. The same product was obtained in over 50% yield by dilute lithium aluminum hydride reduction. Addition of an ether solution of the intermediate to a large excess of hydrogen bromide in ether resulted in the formation of 2-*p*-hydroxyphenylethyl bromide, isolated in 50% yield with an 80% yield being observed spectroscopically. In dilute "neutral" or acidified methanol the ultraviolet maximum of the intermediate disappeared and the resulting spectrum was identical with that of 2-*p*-hydroxyphenylethyl methyl ether (I-OCH$_3$).

Addition of more concentrated solutions of the intermediate to neutral or acidified solutions of sodium bromide in methanol caused the disappearance of up to one equivalent of bromide ion, the resulting solution exhibiting the solvolytic behavior of 2-*p*-hydroxyphenylethyl bromide in methanol. This behavior is reminiscent of the opening of ethylene oxide by chloride ion.[27]

When the precautions mentioned above concerning neutrality of the glassware were not taken, the solid isolated on evaporation of the ether solution was insoluble in all of the common organic solvents and melted above 160°. The intermediate itself, on standing, or more rapidly on heating to above its melting point, was converted to this material. The infrared spectrum of this solid was quite different from that of the intermediate, resembling that of *p*-anisylethyl bromide in most respects. A substance quite similar to the above solid was also obtained on treatment of fairly concentrated solutions of the intermediate in ether with stannic chloride etherate. The spectrum of the solid in the infrared was nearly identical with that of the solid previously obtained by treatment of 2-*p*-hydroxyphenylethyl bromide with potassium *t*-butoxide in moderately concentrated solution in *t*-butyl alcohol. All of these were presumed to be linear

(20) J. Castells and G. A. Fletcher, *J. Chem. Soc.*, 3245 (1956).

(21) E. A. Braude and E. R. H. Jones, *ibid.*, 498 (1945).

(22) L. Dorfman, *Chem. Rev.*, **53**, 47 (1953).

(23) For normal shifts see: R. B. Woodward, *J. Am. Chem. Soc.*, **63**, 1123 (1941).

(24) The nuclear magnetic resonance spectrum was determined with a Varian 60-megacycle high resolution spectrometer. Tetramethylsilane was used as an internal standard and the τ-values were obtained by imposing 200-cycle side-bands with a variable frequency audio-oscillator. The values obtained were not extrapolated to infinite dilution.

(25) G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

(26) R. Baird, unpublished work.

(27) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd edition, John Wiley and Sons, Inc., New York, N. Y., 1961, p. 292.

polymers of the type $HOC_6H_4(CH_2CH_2OC_6H_4)_nCH_2\text{-}CH_2X$ (VI).

Solvolytic Reactions of the Intermediate.—Solvolytic reactions of the intermediate were studied kinetically in absolute methanol as a function of pH by measurement of the rates of disappearance of the ultraviolet absorption maximum at 274 mμ. These rates were measured on solutions prepared by addition of 1 ml. of an appropriately concentrated ether solution of the intermediate to 99 ml. of the requisite methanol solution.

The reaction was accelerated by both acid and base, acid being much more effective than base. The reactions in the presence of base could be measured directly, using sodium methoxide solutions of known concentration. Because the concentration of the intermediate was so low, pseudo-first-order rate constants were obtained at each concentration. At low concentrations ($<3 \times 10^{-4}$ M) the reaction was essentially independent of base concentration, the first-order rate constant reaching a minimum value of 3.1×10^{-4} sec.$^{-1}$. This was taken to be the rate constant, k_0, of the "uncatalyzed" rate.

In contrast to the behavior observed in basic solution, the decay rates of the intermediate in acid solution were so rapid that concentrations of acid lower than 10^{-7} M were required in order to obtain rates slow enough to be measurable. Dilution of solutions of perchloric acid in methanol failed to provide reproducible concentrations below 10^{-5} M, so that it was necessary to use buffer solutions in order to attain the requisite acid concentrations.

Buffer solutions were prepared from mixtures of carboxylic acids and their sodium salts in methanol, the pH values being estimated from the pK values of Kilpatrick.[28] The use of buffers introduced two problems, that of general acid catalysis[29] and that of the so-called second-order salt effect.[30]

Correction for the small effect of general acid catalysis on the rate was made by extrapolation of a plot of the rate constant vs. acid concentration at constant ratio of buffer salt to buffer acid.[29] In these experiments the ionic strength was maintained constant by the addition of sodium perchlorate as indicated in Table IV. At the ionic strength used, 0.01 M, the rate constant for acetic acid was 1.2×10^{-2} l. mole^{-1} sec.$^{-1}$.

TABLE IV

ACID CATALYZED METHANOLYSIS OF THE INTERMEDIATE[a] WITH ACETIC ACID–SODIUM ACETATE BUFFERS AT 25°

Run	(NaOAc), 10^4 M	$\dfrac{\text{(NaOAc)}}{\text{(HOAc)}}$	Ionic strength,[b] 10^4 M	$10^4 k_2$, sec.$^{-1}$
1	97.1	1.0	97.1	9.93 ± 0.11
2	38.9	1.0	97.1	9.27 ± .12
3	9.72	1.0	97.1	8.97 ± .08
4	9.72	1.0	9.72	6.69 ± .17
5	97.1	0.5	97.1	16.7 ± .12
6	48.6	.5	97.1	15.15 ± .06
7	48.6	.5	97.1	15.35 ± .2
8	9.71	.5	97.1	14.73 ± .1
9	9.71	.5	9.71	10.04 ± .1

[a] Concentration of IV 3.8×10^{-5} M; all rates were followed spectroscopically at 274 mμ. [b] Sodium perchlorate was used to maintain ionic strength.

Correction for the second-order salt effect, primarily an effect of ionic strength upon the apparent ionization constant of the buffer acid, was accomplished as

(28) L. J. Minnick and M. Kilpatrick, J. Phys. Chem., **43**, 259 (1939).

(29) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 215.

(30) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 84.

follows. The hydrogen-ion concentration of a buffer system is given by eq. 7 and 8, where K_c is the concentration-dependent equilibrium constant of the buffer acid BH at a given ionic strength and K is the thermodynamic equilibrium constant.[31] Assuming that the normal salt effect on k_0 is negligible (as can be veri-

$$[H]^\oplus = K_c([BH]/[B^\ominus]) \tag{7}$$

$$\log K_c = \log K + C\sqrt{\mu} \tag{8}$$

$$k_2 = k_A(H^\oplus) + k_0 \tag{9}$$

$$\log (k_2 - k_0) = \log k_A + \log [K([BH]/[B^\ominus])] + C\sqrt{\mu} \tag{10}$$

$$\log (k_2 - k_0)_{\mu=0} = \log k_A + \log [K([BH]/[B^\ominus])] \tag{11}$$

fied from measurements in basic solution), one can correct for the significant second-order salt effect on K_c by extrapolating the pseudo-first-order rate constant for the acid-catalyzed portion of the rate, $k_A(H^\oplus)$, to zero ionic strength. This procedure has the advantage that it also corrects (approximately) for the normal salt effect on k_A. In acid solution, the rate constant $k_A(H^\oplus)$ is related to the pseudo-first-order rate constant for solvolysis of the intermediate, k_2, as in eq. 9, so that k_A is given by eq. 10. Consequently, the intercept of a plot of log $(k_2 - k_0)$ vs. $\sqrt{\mu}$ at $\mu = 0$ is given by eq. 11 and k_A at zero ionic strength can be obtained. The values of k_2 determined for acetic acid–sodium acetate buffers (runs 3 and 4 in Table V) were corrected in this way. The magnitude of the ionic strength effect can be seen by comparing runs 3 and 4 and runs 8 and 9 in Table IV.

With glycolic and chloroacetic acids as catalysts, concurrent esterification of the acids by methanol rendered the data less precise than those with acetic acid, so that no corrections for ionic strength or general acid catalysis were attempted. The data listed in Table V were obtained from measurements at low ionic strength (0.011 M) and 1:1 buffer ratios, the pH values being taken as the pK values of the acids.

TABLE V

FIRST-ORDER RATE CONSTANTS FOR SOLVOLYSIS OF THE INTERMEDIATE[a] IN ABSOLUTE METHANOL AT 25.0°

Run	Added solutes	Concn., 10^3 M	pH[b]	$10^4 k_2$, sec.$^{-1}$ Obsd.	Calcd.[d]
1	ClCH$_2$COOH ClCH$_2$COONa	1.05 1.05	7.9 ± 0.1	ca. 200	244
2	HOCH$_2$COOH HOCH$_2$COONa	1.0 1.0	8.85 ± 0.05	30	27.1
3	CH$_3$COOH CH$_3$COONa	..[c] ..[c]	9.46	8.47	8.37
4	CH$_3$COOH CH$_3$COONa	..[c] ..[c]	9.76	5.71	5.75
5	NaOCH$_3$	0.097	12.64	3.17 ± 0.07	3.16
6	NaOCH$_3$	0.307	13.13	3.29 ± .04	3.28
7	NaOCH$_3$	0.95	14.64	9.19 ± .05	8.87
8	NaOCH$_3$	51.4	15.35	31.8 ± .4	32.6

[a] Concentration of intermediate 3.8×10^{-5} M in 99% methanol–1% ether; rates were followed spectroscopically at 274 mμ. [b] In this work pH refers to $-$ log $[CH_3OH_2^\oplus]$. For the buffered solutions, the pH was determined from the pK values of the buffer acids as described in the text. For the basic solutions the pH was taken as the difference between the log of the base concentration and the log of the autoprotolysis constant of methanol. [c] See Table IV. [d] Calculated using eq. 13.

The solvolysis rates of the intermediate dienone IV under all of the conditions are summarized in Table V and also presented in Fig. 2 in the form of a catalytic catenary. From Fig. 2 it is apparent that the rate reaches a rather broad minimum at intermediate pH values (11–13), where the rate is effectively due to the "uncatalyzed" reaction with solvent. Over the whole pH range, the over-all first-order decay constant, k_2, may be expressed as in eq. 12, where k_H and k_B are rate constants for the methoxonium and methoxide ion-

(31) S. Glasstone, "Textbook of Physical Chemistry," second edition, D. van Nostrand Co., Inc., New York, N. Y., 1946, p. 970.

catalyzed reactions, respectively. They are listed in Table VI. Using the autoprotolysis constant[32] of

$$k_2 = k_0 + k_A(H^\oplus) + k_B(MeO^\ominus) \qquad (12)$$

$$k_2 = \left[3.10 \times 10^{-4} + 1.52 \times 10^6[H^\oplus] + \frac{1.32 \times 10^{-18}}{[H^+]} \right] sec.^{-1} \quad (13)$$

methanol at 25°, 2.27×10^{-17}, eq. 12 may be written in the form of 13. The ability of this equation to reproduce the values of k_2 in Table V is illustrated by the last column in that table.

TABLE VI

RATE CONSTANTS FOR CATALYZED AND "UNCATALYZED" SOLVOLYSIS OF INTERMEDIATE IV IN ABSOLUTE METHANOL AT 25°

Catalysis	Symbol	Value
"Uncatalyzed"	k_0	3.10×10^{-4} sec.$^{-1}$
Acid	k_A	$(1.52 \pm 0.03) \times 10^{-8}$ l.-mole^{-1}-sec.$^{-1}$
Base	k_B	$(5.84 \pm 0.24) \times 10^{-2}$ l.-mole^{-1}-sec.$^{-1}$

Over-all Reaction Scheme.—The over-all solvolytic scheme for the 2-p-hydroxyphenylethyl system in anhydrous methanol can be summarized as in Fig. 1. From the available evidence, it appears that all of the reactions of 2-p-hydroxyphenylethyl bromide I-Br in basic solution proceed by way of dienone IV. As indicated, this intermediate can react with a variety of nucleophilic species, the actual ratios of products depending on the relative concentrations of the various nucleophiles. This explains the published observations that 2-p-hydroxyphenylethyl halides react normally with amines[33] and sodium acetate,[34] but abnormally with hydroxide ion.[34] With the first two reagents, the primary fate of IV is reaction with amines or acetate ion. With the more strongly basic hydroxide ion, the concentration of phenoxide ions is much greater and a bigger spectrum of possible reactions of IV is available. Formation of IV also explains the fact that no styrene is formed when I-Br is treated with ethoxide ion, while the corresponding methyl ether III-Br gives quantitative conversion to olefin.[6]

Reaction of IV with bromide ion affords an explanation of the difficulties observed in fitting the kinetics of the titrimetric runs with I-Br. Return by bromide ion becomes more serious as reaction proceeds since more bromide ion is becoming available, and the kinetic situation becomes more complicated. It also explains the discrepancy between titrimetric and spectrophotometric rate constants, return being serious in 0.01 M solution but negligible in the 10^{-5} M spectrophotometric solutions. For this reason the rate constants obtained in runs 3 and 4 in Table III are believed to represent more accurately the true value of k_1 in the reaction of II-Br in methanol. The failure of the experiments in t-butyl alcohol directed toward isolation of IV can be attributed in part to the fact that concentration of such solutions increased the bromide ion concentration, with return by bromide ion eventually leading to polymerization.

Relationship to Other Systems.—It is interesting to inquire whether $Ar_1^\ominus$-3-assisted solvolysis would contribute seriously to the methanolysis of 2-p-hydroxyphenylethyl bromide (I-Br) under initially neutral conditions. From the estimated value[35] of 7.2×10^{-15} for K_A of I-Br, the concentration of phenoxide ion II-Br would be ca. 8×10^{-9} M in a 0.01 M solution
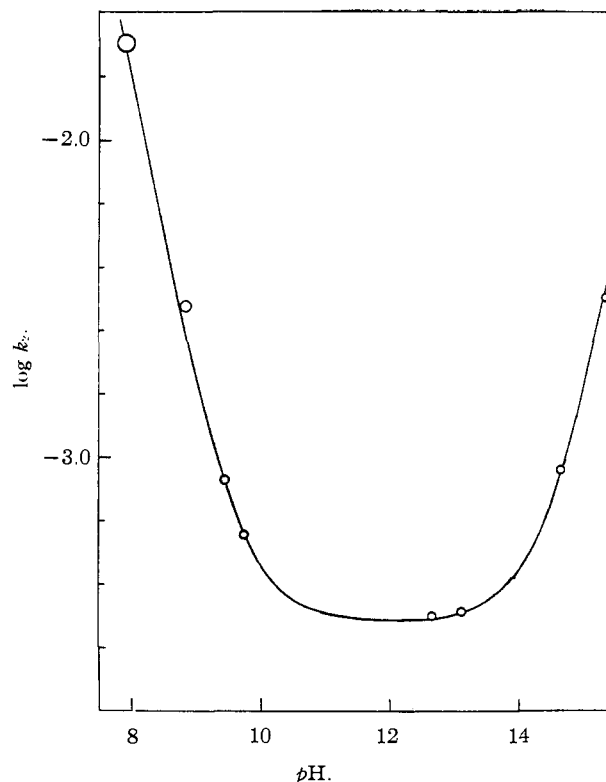

Fig. 2.—Catalytic catenary for solvolysis of dienone IV in absolute methanol at 25.0°. The circles represent experimental points; the solid line is calculated using eq. 13.

of I-Br. This would give rise to a rate of formation of dienone IV of ca. 2×10^{-11} mole per liter per second at 25° and thus contribute a value of ca. 2×10^{-9} sec.$^{-1}$ to the instantaneous first-order rate constant for 0.01 M I-Br. This is as large as the rate constant for either Ar_1-3-assisted or unassisted ethanolysis of 2-p-anisylethyl bromide (III-Br) estimated earlier in this manuscript, so it is certainly competitive with the rate of Ar_1-3-assisted or unassisted methanolysis of 2-p-hydroxyphenylethyl bromide (I-Br). As reaction proceeds, however, acid is generated, and $Ar_1^\ominus$-3-assisted solvolysis will soon become negligible.

The rate of acid-catalyzed methanolysis of dienone IV to the methyl ether I-OCH$_3$ can lead to an estimate of the first-order rate constant for the dienone conjugate acid VIII, provided some measure of the basicity of IV is available. A very rough pK value for VIII can be based on Stewart's correlation[36] between the basicity of ketones and their infrared carbonyl stretching frequencies.[37] The frequency 1650 cm.$^{-1}$ (in CS$_2$) for IV leads to a value of $+2$ for the pK of VIII in water, suggesting that IV is considerably more basic than simple ketones, the pK values of which range from -4 to -8.[36] This is consistent with the high basicity reported[38] for the structurally similar 4-methylene-1,2,3,5,6-hexamethylcyclohexadiene-2,5.

On the basis of results obtained for bases of similar charge-type[39,40] the value of pK for VIII would be expected to increase by ca. 1.5 pK units on going from water to methanol as solvent, suggesting a value of 3.5

(32) H. Goldschmidt and F. Aas, Z. physik. Chem., 112, 423 (1924).

(33) (a) E. Späth and P. Sobel, Monatsh., 41, 87 (1920); (b) C. S. Cheng, C. Ferber, R. T. Bashford, Jr., and G. F. Grillot, J. Am. Chem. Soc., 73, 4081 (1951).

(34) J. V. Braun, Ber., 45, 1282 (1912).

(35) This is based on K_m for the equilibrium in eq. 2 and the autoprotolysis constant for methanol.[32]

(36) R. Stewart and K. Yates, J. Am. Chem. Soc., 80, 6355 (1958).

(37) It must be emphasized that Stewart's correlation was developed only for substituted acetophenones over a limited range of pK values (-4.5 to -8), so that such an extrapolation cannot be given much weight.

(38) W. von E. Doering, M. Saunders, H. G. Boyton, H. W. Earhart, E. F. Wadley, W. R. Edwards and G. Laber, Tetrahedron, 4, 179 (1958).

(39) H. Goldschmidt and E. Mathiesen, Z. physik. Chem., 119A, 439 (1926).

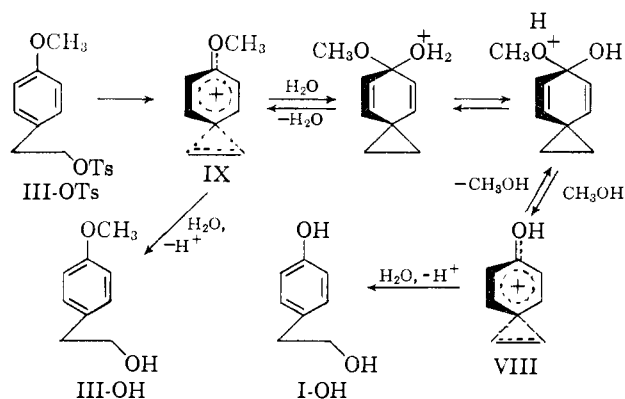(40) A. L. Bacarella, E. Grunwald, H. P. Marshall and E. Lee Purlee, J. Org. Chem., 20, 747 (1955).

Fig. 3.—Possible interconversion of bridged ions.

for pK of VIII in the latter solvent. The use of the corresponding K-value (3×10^{-4}), together with the k_A value for acid-catalyzed methanolysis of IV, leads to a value of $ca.$ 5×10^2 sec.$^{-1}$ for k_s, the first-order methanolysis rate constant for VIII (eq. 14). This corresponds to a half-life of $ca.$ 10^{-3} second for VIII.

$$\text{IV} + \text{H}^+ \overset{K}{=\!=\!=} \text{VIII} \overset{k_s}{\longrightarrow} \text{I-OCH}_3 \qquad (14)$$
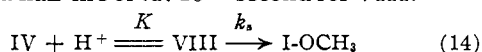
If we use VIII as a model for the p-methoxyethylene phenonium ion IX, we can obtain a rough estimate of the stationary state concentration of the latter intermediate in the Ar$_1$-3-assisted solvolysis of 2-p-anisylethyl toluenesulfonate (III-OTs) shown in Fig. 3. For the latter substrate in ethanol, the estimated Ar$_1$-3-assisted ethanolysis[8,41] rate constant is $ca.$ 3×10^{-8} sec.$^{-1}$ at 25°. This is the rate constant for formation of IX from III-OTs; using a rate constant for ethanolysis of intermediate IX the same as that of methanolysis of VIII leads to a stationary state concentration of IX equal to 4×10^{-11} times that of III-OTs. For 0.025 M III-OTs the estimated stationary state concentration of IX becomes 10^{-12} M.

The relatively long life of VIII, and by analogy the intermediate IX, as well as other considerations, suggested the possibility that intermediate IX might be converted to VIII in an aqueous solvent by a route involving nucleophile solvent attack on the aromatic ring as depicted in Fig. 3. Such an interconversion would give rise to some p-hydroxyphenylethyl alcohol (I-OH) from hydrolysis of the p-anisylethyl ester III-OTs. However, when III-OTs was solvolyzed in buffered aqueous dioxane (NaHCO$_3$), the proportion of I-OH formed was shown to be less than 0.3%. Thus, reaction at the "cyclopropane ring" of IX predominates by a large factor over reaction at the methoxyl-bearing carbon atom of the "benzene ring."

Spectroscopic Considerations.—Formation of spiro-octa-1,4-diene-3-one (IV) represents the first reported synthesis of such a system by a reaction involving neighboring group participation, although Barton and Hendrickson[42] have observed the conversion of fucsin (X) into homofucsin (XI) on treatment with diazomethane, and Mustafa[43] reported a similar conversion of methylene-anthrone to XII. In both of these compounds, however, the presence of other functional groups mask the properties of the system found in IV. This is particularly true for the spectroscopic properties, so that only in the case of IV is it possible to make a direct comparison of the effects of various ring sizes and a methylene group on the ultraviolet spectrum of cyclohexadienones. In Table VII are given the ultraviolet

(41) (a) S. Winstein, C. R. Lindegren, H. Marshall and L. L. Ingraham, *J. Am. Chem. Soc.*, **75**, 147 (1953); (b) A. H. Fainberg and S. Winstein, *ibid.*, **78**, 2767 (1956).

(42) D. H. R. Barton and J. B. Hendrickson, *J. Chem. Soc.*, 1028 (1956).

(43) A. Mustafa and M. K. Hilmy, *ibid.*, 1434 (1952).

TABLE VII

ULTRAVIOLET MAXIMA (K-BANDS) OF CYCLOHEXADIENONES IN METHANOL SOLUTION

R$_1$, R$_2$	$\lambda_{max}^{(CH_3OH)a}$		$\Delta\lambda$, mμ
	mμ	log ϵ	
CH$_3$-, CH$_3$-	227[b]	4.1[c]	
-(CH$_2$)$_5$-	242.5[d]	4.17	15
-(CH$_2$)$_4$-	242	4.20	~0
-(CH$_2$)$_3$-	274	4.34	32
CH$_2$=	280[e]	4.40[f]	6

[a] Except for the last two cases no correction is needed between methanol and ethanol; those two were both run in methanol. [b] Calculated by application of Woodward's rules (á la Dorfman[22]). The same value was obtained by subtracting 10 mμ for an α-substituent from the value for the known 2-methyl derivative[44] which has λ_{max} 237 mμ. This correction works very well in the cases cited by Dorfman.[22] [c] The epsilon is that of the 2-methyl derivative.[44] [d] The value given is that of Dreiding.[45] Burnell and Taylor[46] report λ_{max} 235 mμ for the same compound, but they do not specify the solvent. [e] Corrected for α-substituents by subtracting 10 mμ from the value for the dimethyl derivative reported by Filar and Winstein[47] for which λ_{max} 290 mμ. [f] This is the value observed in isoöctane; the compound is too reactive in methanol.

absorption maxima and intensities of several 4,4-disubstituted cyclohexadienones of this type. Unless otherwise noted, these data are for the compounds substituted only in the 4-position, appropriate corrections being made in two cases where α-methyl substituents are also present.

The position of the cyclopropane ring in IV is such that it must be at right angles to the plane of the 6-ring. In this position it appears to be almost as effective as a double bond in extending the conjugation
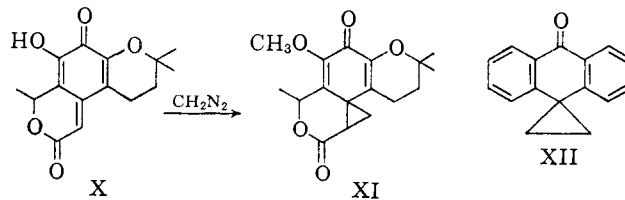
of the dienone system. Thus, the bathochromic shift, measured from the dimethyl compound, is +47 mμ for cyclopropane and $ca.$ +53 for methylene. Other factors are no doubt involved, as witnessed by the shift (+15 mμ) introduced by 5- and 6-rings, but these should not greatly affect the above comparison.

Experimental

2-p-Hydroxyphenylethanol.—A solution of 23.5 g. of p-hydroxyphenylacetic acid in 250 ml. of anhydrous ether was added to a slurry of 11.7 g. of lithium aluminum hydride in 400 ml. of ether. The mixture was heated under reflux for 48 hours to complete reduction of the slightly soluble salt. The product was isolated by the addition of the minimum amount of dilute aqueous hydrochloric acid and extraction with ether; yield 9.2 g. (43%) of material, m.p. 89–91.5° (reported[34] m.p. 93°).

2-p-Anisylethanol was prepared by the method of La Forge.[48] This alcohol, b.p. 144–145° (11 mm.), n^{25}D 1.5345, was obtained in 73% yield (reported[48] b.p. 130–132° (6.5 mm.).

2-p-Anisylethyl Bromide.—The p-toluenesulfonate ester of 2-p-anisylethanol was prepared from the alcohol by the low temperature method of Heck.[49] This ester (29 g.) was treated overnight at room temperature with 17.4 g. of Mallinckrodt NF lithium bromide in 200 ml. of Braun ACS acetone. The bulk of the solvent was then removed on the steam-bath, the solution diluted with 600 ml. of water and the product extracted with ether. Distillation at reduced pressure provided the bromide, b.p. 94.0–95.7° (2 mm.), n^{25}D 1.5570, in 53% yield (reported b.p. 130–131° (11 mm.)[50]; b.p. 63° (0.15 mm.), n^{25}D 1.5595).[51]

(44) M. Yanigita and S. Inayama, *J. Org. Chem.*, **19**, 1724 (1954).

(45) A. S. Dreiding, *Helv. Chim. Acta*, **40**, 1812 (1957).

(46) R. H. Burnell and W. I. Taylor, *J. Chem. Soc.*, 3486 (1954).

(47) L. J. Filar and S. Winstein, *Tetrahedron Letters*, No. **25**, 9 (1960).

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Anal. Calcd. for $C_9H_{11}OBr$: C, 50.25; H, 5.16. Found: C, 50.19; H, 5.20.

2-*p*-Hydroxyphenylethyl bromide was prepared from 2-*p*-anisylethanol by the method of Späth and Sobel.[33a] After three recrystallizations from hexane, the bromide, m.p. 89.6–90.8°, was obtained in 46% yield (reported[33a] m.p. 89–91°).

Anal. Calcd. for C_8H_9OBr: C, 47.79; H, 4.51; Br, 39.74. Found: C, 47.89; H, 4.45; Br, 40.02.

This compound was further analyzed by treatment of two 0.0500-g. samples with 10-ml. portions of 1.2 *M* NaOH overnight, acidification with 6 *N* nitric acid and titration of the bromide ion by the Volhard procedure. Both samples gave 99.6% of the theoretical bromide ion.

2-*p*-Hydroxyphenylethyl iodide was synthesized from 2-*p*-anisylethanol by the procedure of Cheng.[33b] The iodide, m.p. 112–113.5°, was obtained in 68% yield (reported[33b] m.p. 113°).

2-*p*-Hydroxyphenylethyl Chloride.—A solution of 40 g. of 2 *p*-hydroxyphenylethyl iodide in 800 ml. of Braun ACS acetone was treated with 70 g. of anhydrous lithium chloride under reflux for 29 hours. The product was isolated as described for 2-*p*-anisylethyl bromide; yield 54% of the chloride, b.p. 97–99° (1.2 mm.), m.p. 55.3–57.0° (from hexane) (reported[34] as a viscous liquid).

2-*p*-Hydroxyphenylethyl Methyl Ether.—To a mixture of 3 g. of reagent grade silver nitrate and 300 ml. of anhydrous methanol containing just enough brom phenol blue to give a detectable color was added a solution of 3 g. of 2-*p*-hydroxyphenylethyl bromide in 100 ml. of anhydrous methanol. Silver bromide began to precipitate at once, and 0.18 *M* sodium methoxide in methanol was added at such a rate as to keep the solution just slightly acidic (as measured by the color of the brom phenol blue). The solution was heated on the steam-bath to complete the reaction and the silver bromide removed by filtration through Celite. This solution was heated with solid sodium chloride to remove the unreacted silver nitrate and refiltered through Celite. Evaporation of the solvent and extraction of the salts with water led to the crude ether, which was converted to a 3,5-dinitrobenzoate with 3,5-dinitrobenzoyl chloride in pyridine. The 3,5-dinitrobenzoate, m.p. 102.2–103.1° from hexane, was obtained in a yield of 1.2 g.

Anal. Calcd. for $C_{16}H_{14}O_7N_2$: C, 55.49; H, 4.08. Found: C, 55.25; H, 3.98.

Saponification of this ester with potassium hydroxide in methanol, followed by recrystallization from methylene chloride-pentane and then ether-pentane, provided 2-*p*-hydroxyphenylethyl methyl ether as prisms, m.p. 41.7–42.5°.

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.81; H, 8.24.

p-Hydroxycinnamic acid was prepared according to the procedure in reference 52 for 2,4-dihydroxycinnamic acid. The acid, m.p. 215–216° dec., was obtained in 70% yield from *p*-hydroxybenzaldehyde [reported[53] m.p. 206° dec.].

p-Hydroxystyrene was prepared in poor yield by the method used by Reichstein for 3-methoxy-4-hydroxystyrene.[54] A mixture of 5 g. of *p*-hydroxycinnamic acid, 10 g. of redistilled quinoline and 1 g. of copper-bronze, heated at 220° for 5 minutes, led on extraction, sublimation at 0.9 mm. and recrystallization from pentane to *ca.* 20 mg. of styrene, m.p. 61–64.5° (reported[55] m.p. 73.5°).

Kinetic Procedures. Solvents.—Anhydrous methanol and *t*-butyl alcohol were prepared as described previously.[1a] Anhydrous ethanol was prepared in the same manner as anhydrous methanol and tested for water with Karl Fischer reagent. Methanol purified over magnesium always tested very slightly basic to neutralized brom phenol blue, and by dilution of known concentrations of standard perchloric acid was estimated to contain 10^{-5} to 10^{-6} *M* basic or buffering species. In the experiments in which especially neutral methanol was desired, the solvent was further purified by the method of Evers and Knox,[56] by distillation over potassium acid·phthalate–phthalic anhydride, followed by distillation over sodium, or by distillation over sulfanilic acid.[32] The second and third methods above gave methanol that was slightly less basic than that prepared by the method of Evers and Knox.

Standard alkoxide solutions were prepared as described previously.[1a] The sodium ethoxide solutions were prepared and standardized immediately before use.

Mixing.—The rates measured in basic solution were rapid enough that mixing of reactants constituted a serious problem. In the earlier runs an alkoxide solution was quickly pipetted into

a phenol solution in a volumetric flask, the mixture diluted to the mark and aliquots taken. Both solutions were pre-equilibrated at 0.8° lower than the temperature of the bath to compensate for the heat of neutralization. Aliquots could then be pipetted as little as 90 seconds after the start of mixing.

For the reactions in methanol the two-chamber rapid mixing flask of Winstrom and Warner[19] was used for both the titrimetric and spectroscopic runs. This provided more thorough mixing and more rapid equilibration with the thermostat.

Methods of Following Rates.—Rates at concentrations of 0.01 *M* or greater were followed by titration. In methanol the procedures were identical with those described previously,[1a] acid–base titrations being used. In all but one of the measurements in ethanol the extraction procedure of Fainberg[57] was used, and the bromide ion produced was titrated by the Volhard procedure. For a quench, aliquots were pipetted into a mixture of pentane and dilute, halide-free, nitric acid in a small separatory funnel, and the mixture shaken vigorously, *ca.* forty times to ensure rapid neutralization of the base.

Rates at concentrations lower than 10^{-4} *M* were followed spectrophotometrically. These measurements were made in a Beckman DU spectrophotometer, thermostated by double thermospacers connected to a constant temperature circulating bath. The temperature of the cell compartment did not differ by more than 0.1° from that of the bath. Optical density measurements were made at a wave length which had been shown by qualitative measurements with a Cary (model 11PMS) recording spectrophotometer to represent the region of maximum absorption for the species being studied. Both cells in the Beckman DU were filled with the solvent used in the rate, excluding only the substrate, and the sample cell calibrated against the reference cell at the desired wave length. The kinetic solution was prepared and mixed as described previously and the kinetic sample cell washed several times with this solution and replaced in the thermostated compartment. The remainder of the solution was replaced in the thermostat and used to check the infinity value at the end of the rate. The sample cell, once filled, was left in the spectrophotometer during the entire run, and the optical density was measured as a function of time.

Buffer Solutions.—Buffer solutions in absolute methanol were prepared by treatment of a *ca.* 0.2 *M* solution of the appropriate acid with sufficient standard sodium methoxide in absolute methanol to give the desired buffer ratio, and then diluted to the appropriate concentration. The 0.2 *M* acid solutions were standardized by titration with sodium hydroxide in a predominantly aqueous medium, phenolphthalein being used as the indicator. The more concentrated buffer solutions were also titrated in this way, and agreed in all cases to within a few per cent of the expected titer. The ionic strengths of the buffer solutions were increased in some cases by the addition of the appropriate amount of anhydrous sodium perchlorate in methanol to the buffer mixture before dilution.

Freshly prepared buffer solutions were used in all runs with acetic acid buffers since esterification of the acid by methanol was a serious problem on prolonged standing. A 0.1927 *M* solution of acetic acid in methanol titrated 0.1780 *M* after *ca.* 36 hours at room temperature. With the stronger acids, glycolic and chloroacetic acids, this problem was more serious and only approximate *p*H values are given for these solutions.

Equilibrium Constants.—The equilibrium constant, K_m, for *p*-hydroxyphenylethanol was determined spectroscopically in absolute methanol at approximately 25°. The molar extinction coefficients of the phenolic and phenoxide forms of the phenol were determined from the spectra in 0.09 *M* methanolic sulfuric acid and 0.16 *M* methanolic sodium methoxide, respectively. The wave length of 241 mμ was used for this work because it afforded the largest difference in molar extinction coefficients between the phenolic and phenoxide forms. The optical density of solutions of the diluted phenol (1.08×10^{-4} *M*) containing varying amounts of base was determined at this wave length, and the concentrations of the phenol and phenoxide ion were calculated by the usual method.[16]

The value of K_m is not strictly constant, but decreases with increasing base concentration so that the extent of ionization increases slightly more rapidly with increasing base concentration than expected. This most likely is due to a salt effect.[18]

The equilibrium constant for the analogous reaction in *t*-butyl alcohol was also investigated spectrophotometrically. Qualitative measurements with a series of solutions indicated that at concentrations above 10^{-4} *M*, the phenol was completely converted to its salt, but at lower concentrations conversion dropped off sharply, presumably due to the action of atmospheric carbon dioxide on the lower base concentrations. Consequently, no exact value was determined for the equilibrium constant in this solvent.

Product Runs in Absolute Methanol. With 0.13 *M* Sodium Methoxide.—To a solution of 6.03 g. (0.030 mole) of 2-*p*-

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hydroxyphenylethyl bromide in 500 ml. of anhydrous methanol in a one-liter volumetric flask was added 500 ml. of 0.258 M sodium methoxide in absolute methanol. Both solutions were pre-equilibrated at 25.0° before mixing. The flask was then placed in a 25.0° bath for 3 hours, and subsequently cooled in an ice-bath and neutralized to brom phenol blue with p-toluene-sulfonic acid in methanol. The methanol was then distilled at reduced pressure so as to keep the pot temperature below 25° until ca. 100 ml. of solution remained. This solution was poured into water and the mixture extracted six times with ether. The extracts were washed with a small amount of water, with saturated salt solution and then dried over magnesium sulfate. The solution was filtered and the bulk of the ether removed on the steam-bath through a 12-inch Vigreux column. The residue was distilled at reduced pressure to give three fractions: 1, b.p. 126.5–128° (3.3 mm.), m.p. 39.5–42.5°, weighing 2.35 g.; 2, b.p. 128–135° (3.3 mm.), weighing 0.17 g.; 3, b.p. 215–220° (0.8 mm.), weighing 0.89 g.

Fraction 1, which amounted to 57% of the theoretical, was recrystallized from ether–pentane to give 1.3 g. of material, m.p. 42–44°, which did not depress when mixed with authentic 2-p-hydroxyphenylethyl methyl ether.

With 1 M Sodium Methoxide.—This run was carried out exactly as the one above except that the solution was neutralized with sulfuric acid in methanol and was filtered to remove most of the salts. The salt-paste obtained on filtration was dissolved in water and washed six times with ether. The combined extracts were added to the bulk of the methanol and the reaction worked up as for the lower base concentration above.

TABLE VIII

EQUILIBRIUM CONSTANT MEASUREMENT FOR 2-p-HYDROXY-PHENYLETHANOL[a] IN ABSOLUTE METHANOL AT 25°

Optical density 241 mμ	$\dfrac{\text{(HOAr)}}{\text{(ArO}^-\text{)}}$	Total (NaOMe) × 10^4 M	$10^3 K_{m}$, M
0.013	100	..[b]	..
.031	100	..[c]	..
.230	4.005	9.007	3.53
.357	2.157	15.25	3.22
.543	1.049	29.90	3.08
.733	0.5083	59.79	3.01
1.099	0.01	1600	

[a] Concentration, 1.018 × 10^{-4} M. [b] Contains 0.090 N sulfuric acid. [c] Contains no added base or acid.

On distillation, a main fraction, b.p. 127–128° (3.4 mm.), m.p. 38–42° (without recrystallization), weighing 3.74 g., was obtained in 82.4% yield. The melting point of a mixture of this compound with authentic 2-p-hydroxyphenylethyl methyl ether was undepressed. On treatment with 3,5-dinitrobenzoyl chloride in pyridine, a 3,5-dinitrobenzoate ester, m.p. 101.8–103.9°, weighing 6.92 g., was obtained in a 66.5% over-all yield (from 2-p-hydroxyphenylethyl bromide).

Experiments Directed toward Isolation of Dienone Intermediate. 2-p-Hydroxyphenylethyl Bromide with Sodium Hydride in Ether.—A solution of 1.0 g. of 2-p-hydroxyphenyl bromide in 50 ml. of Mallinckrodt anhydrous ether was stirred with an excess of sodium hydride with protection from moisture until the evolution of hydrogen had ceased. The solution was then filtered through sintered glass under nitrogen pressure into a dry 125-ml. flask, and was allowed to stand tightly stoppered in this flask for 24 hours at room temperature. At the end of this time a portion of this solution was diluted 100-fold and the ultraviolet spectrum run in a 1-mm. cell. Intense maxima were observed at 257–258 mμ, and at 301 mμ, similar to those exhibited by the sodium salts of other phenols in absolute alcoholic solvents. No strong absorption in excess of the above was observed at 261 mμ. Dilution of the ether solution further, e.g., to run the spectrum in a 1-cm. cell, gave the spectrum of the parent 2-p-hydroxyphenylethyl bromide.

Addition of a small sample of the above solution to dilute aqueous sulfuric acid, extraction with ether and drying over magnesium sulfate led to an oil which crystallized immediately when seeded with the parent compound, 2-p-hydroxyphenylethyl bromide, to give a solid, m.p. 83–87°, without recrystallization.

A portion of the above ether solution, when poured into a large excess of t-butyl alcohol, gave at once a strong maximum at 271 mμ for the dienone, and a weaker maximum at 230 mμ. The maximum at 271 mμ had increased about 5% on rerunning the spectrum after about 5 minutes, indicating that the formation of this maximum was actually occurring in t-butyl alcohol and not in the ether.

Reaction with Potassium t-Butoxide in t-Butyl Alcohol.—A solution of 0.025 mole of 2-p-hydroxyphenylethyl bromide in 50 ml. of absolute t-butyl alcohol and a second solution of 0.026

mole of potassium t-butoxide in an equal volume of t-butyl alcohol were added simultaneously through two separate addition funnels to a well-stirred 100-ml. portion of anhydrous t-butyl alcohol in a 500-ml. three-necked flask. This addition was carried out over the course of an hour at room temperature. At the end of this time, two 5-ml. aliquots of this solution were taken and one was filtered through Celite to remove the colloidal solid, the other being diluted with two volumes of pentane and washed four times with water, and dried over potassium carbonate. The ultraviolet spectra of both solutions thus treated were determined over the range 250–300 mμ, but neither solution exhibited maxima other than those attributable to phenolic species.

The bulk of the solution was diluted with two volumes of pentane and the solid precipitate filtered with suction. This residue was washed thoroughly with water and then recrystallized from benzene to give a white solid, m.p. 137–145°. The infrared spectrum was quite similar to that of 2-anisylethyl bromide, especially with respect to aromatic substitution patterns and the strong aromatic–aliphatic ether band at 1235 cm.$^{-1}$.

Anal. Calcd. for $HOC_6H_6(OC_6H_8)_4Br$: C, 72.8; H, 6.19. Found: C, 72.88; H, 6.11.

In another experiment, a mixture of 0.0045 mole of 2-p-hydroxyphenylethyl bromide and 100 ml. of 0.045 M potassium t-butoxide in t-butyl alcohol was shaken for 3 minutes and then diluted with 600 ml. of pentane and washed with 300-ml. portions of ice-water. The pentane solution was then dried over potassium carbonate and the solvent removed under reduced pressure. A small amount of solid remained which exhibited only characteristic phenolic spectral maxima in t-butyl alcohol in the ultraviolet.

To a solution of 0.0036 mole of 2-p-hydroxyphenylethyl iodide in 100 ml. of t-butyl alcohol was added, in small portions, 100 ml. of a solution of 0.036 M potassium t-butoxide in t-butyl alcohol over a period of 60 seconds. After 2 minutes, solid sodium bicarbonate was added and the mixture shaken vigorously for 60 seconds more and then diluted with 3 volumes of pentane and poured into water. The pentane phase was separated and washed twice with water, dried over potassium carbonate, and the ultraviolet absorption spectrum determined. Again, no maxima other than those attributable to phenolic species were observed.

Isolation of Dienone.—A basic alumina was prepared by shaking 1 kg. of alumina (Harshaw, activated powder, catalyst grade, 90% Al_2O_3, #A1–0101–P) with a solution of 100 g. of reagent grade potassium hydroxide in 75 ml. of water until a homogeneous mixture was obtained.[20] Passage of solutions of 2-p-hydroxyphenylethyl bromide in anhydrous ether through columns made of this alumina resulted in effluent solutions possessing absorption maxima at 261 and ca. 230 mμ in the ultraviolet. The absolute and relative intensities of the two maxima varied with the ratio of alumina to the bromide, the flow rate, the amount of ether passed through the column, and the length of time the effluent solution was kept. On standing for varying periods of time, solutions possessing both maxima exhibited an increase in the maximum at 230 mμ at the expense of that at 261 mμ.

A variety of conditions and times were investigated and the following set of conditions was found to lead consistently to ether solutions containing only the maximum at 261 mμ: A solution of 3.25 g. of 2-p-hydroxyphenylethyl bromide (free from non-phenolic species such as 2-p-anisylethyl bromide) in 150 ml. of Mallinckrodt anhydrous reagent grade ether was forced with gentle air pressure onto a column made from a slurry of 325 g. of the basic alumina in a 66-mm. (inside diameter) chromatography column. The column was then eluted with anhydrous ether at a flow rate of 40–50 ml. per minute. The first 100 ml. of the ether passing through the column was discarded, and the next 700 ml. was collected in a 1-liter erlenmeyer flask.

All glassware used from this point on (including the flask above) was thoroughly cleaned in hot detergent solution and the surface neutralized by successive rinses with water, dilute acetic acid, distilled water, dilute ammonium hydroxide, and distilled water, and then dried in an oven.

The above 700 ml. of solution was shaken with a mixture of sodium bicarbonate and anhydrous potassium carbonate, and then filtered. Aliquots (2.00 ml.) of this solution were diluted to 25 ml. with ether and the ultraviolet spectrum determined in the range 220–300 mμ. From the homogeneity of this spectrum (absence of maxima at 230 mμ) the purity of the product could be verified. Solutions with a visible maximum at 230 mμ were not used. From the optical density of the above solution at 261 mμ, assuming the same molar extinction coefficient as in t-butyl alcohol (22,200), the concentration of the intermediate could be estimated to be ca. 10^{-3} M and from the known volume of the original ether solution the yield of the intermediate could be estimated to be about 2%, or ca. 84 mg.

The above solution could be concentrated at reduced pressure to ca. 4 × 10^{-3} M where it was stable for about a week. Evaporation of the solution to dryness at reduced pressure and room temperature led to a white solid. This compound could be recrystallized from ether–pentane at low temperatures to give

white needles, m.p. 40–43° (one run), m.p. 43–46° (different preparation).

This solid, immediately after preparation, was soluble in alcoholic solvents, ether, chloroform, carbon disulfide and acetone, but difficultly soluble in pentane. After standing for some time, or after drying under vacuum, or heating to above its melting point, the substance was no longer soluble in the above, or any common solvents, and possessed a melting point in the range 160–200°. One sample, after drying under vacuum, was analyzed and possessed the correct carbon–hydrogen analysis for spiro-(2,5)octa-1,4-diene-3-one, although it had changed to the high-melting solid before the analysis was performed.

Anal. Calcd. for C_8H_8O: C, 79.97; H, 6.71. Found: C, 79.66; H, 6.81.

Isolation of the solid was required only for carbon–hydrogen analyses and for infrared spectra. Other experiments and reactions were performed in ether solution or in solvents containing 1% ether obtained by dilution of one volume of the partially concentrated ether solution of the intermediate with 99 volumes of the appropriate solvent. Thus, for the kinetic studies of the decay rate of the intermediate, a solution of *ca.* 4×10^{-3} M intermediate in anhydrous ether, which could be stored for about a week, was diluted 1 to 99 with the appropriate kinetic solvent, to give a solution which for all practical purposes was not affected by the presence of 1% ether. The spectrum of the stock solutions was checked periodically and when phenolic absorption was detected a new stock solution was prepared.

Reactions of the Dienone. Reaction with Lithium Aluminum Hydride.—A freshly prepared solution of the intermediate in 700 ml. of anhydrous ether, prepared as described previously, was added to a slurry of 5 g. of lithium aluminum hydride in 800 ml. of dry ether over a 70-min. period, and the mixture was stirred for 15 additional minutes. The excess hydride was discharged with 50 ml. of water and then 500 ml. of 20% hydrochloric acid was added and the ether phase separated. The aqueous phase was separated and extracted twice more with ether. The combined ether extracts were washed with water, saturated sodium bicarbonate solution, saturated sodium chloride solution and then dried over magnesium sulfate. The volume of this solution, after filtration, was measured, and the ultraviolet spectrum of this solution, appropriately diluted, was measured with a Cary recording spectrophotometer. At this time, a sample of the original ether solution of the intermediate was diluted 2 to 25 ml. and its ultraviolet spectrum determined. From the optical density of this control, which indicated that only the intermediate was present in the original ether solution, the concentration of the intermediate was obtained (assuming ε 22,200). On this basis, 5.56×10^{-4} mole of the intermediate had been added to the lithium aluminum hydride, and from the spectrum of the product solution the spectroscopic yield of *p*-ethylphenol was 4.35×10^{-4} mole, or 78.5% of the theoretical. The spectrum was identical with that of *p*-ethylphenol.

The ether was distilled through a bubble-plate column, and the residue treated with 0.7 g. of 3,5-dinitrobenzoyl chloride in pyridine, yielding a 3,5-dinitrobenzoate, m.p. 130–131.5°. The melting point of a mixture of this compound with authentic *p*-ethylphenol 3,5-dinitrobenzoate showed no depression. The derivative was obtained in the amount of 0.088 g., representing a 55% over-all yield (64% of the amount observed spectroscopically).

With Hydrogen Bromide in Ether.—A freshly prepared solution of the intermediate in 650–700 ml. of ether was rapidly added to 1 liter of a 0.06 M solution of anhydrous hydrogen bromide in ether. The excess acid was removed by extraction with saturated sodium bicarbonate solution and the solvent evaporated on the steam-bath. This procedure provided a solid, m.p. 84.5–88.5° without recrystallization, weighing 0.069 g. Recrystallization from hexane yielded 0.064 g., m.p. 88.5–90.5°. The melting point of a mixture of this substance with 2-*p*-hydroxyphenylethyl bromide was undepressed.

The ultraviolet spectra of the original solution of the intermediate before treatment with hydrogen bromide, of the hydrogen bromide in ether solution, and of the solution resulting on their admixture, were determined. The first solution exhibited only a maximum at 261 mμ for the intermediate, with no phenolic maxima. The hydrogen bromide solution exhibited a gradual increase in absorption toward the lower wave length range, but no maxima whatsoever. The product solution exhibited a phenolic maximum, which when corrected for the small underlying contribution from the hydrogen bromide was identical with that of 2-*p*-hydroxyphenylethyl bromide in ether. Using the previously derived value of 22,200 for the ε of the intermediate at 261 mμ, and the known ε for the bromide at 229.5 mμ of 11,800, the yield of the 2-*p*-hydroxyphenylethyl bromide observed spectroscopically could be estimated to be 79–82%, and that actually isolated was 47–50% over-all yield from the intermediate.

Catalytic Hydrogenation.—A freshly prepared solution of 5.9 $\times 10^{-4}$ mole of the intermediate in 750 ml. of ether was concentrated to *ca.* 23–25 ml., with precautions being taken to neutralize the surface of the glassware and to avoid overheating of the

product. This solution was added to a slurry of reduced platinum oxide (obtained from 14 mg. of PtO₂) in ether, and the volume of hydrogen consumed was measured. Because of the high partial pressure of ether and the method of introduction of the sample, the uptake of hydrogen could only be roughly estimated as 1 ± 0.2 mole of hydrogen per mole of intermediate.

The resultant solution was filtered to remove the catalyst and the ultraviolet spectrum determined. The spectrum was identical with that of *p*-ethylphenol and corresponded to *ca.* 5.6 $\times 10^{-4}$ mole (*ca.* 95% yield). The ultraviolet spectrum of the concentrated solution of the intermediate, a portion of which had been kept aside and run at the same time as that of the product, indicated that the intermediate at this concentration was stable for the time required for hydrogenation in the absence of hydrogen and the catalyst.

Evaporation of the ether from the above product and treatment of the residue with 3,5-dinitrobenzoyl chloride in pyridine gave a 3,5-dinitrobenzoate, m.p. 129.5–131.5° (from hexane), weighing 0.106 g. (52% over-all yield). The melting point of a mixture of this compound with the 3,5-dinitrobenzoate of *p*-ethylphenol was undepressed.

Reactions with *p*-Toluenesulfonic Acid and Sodium Bromide.—A solution of the intermediate in ether, prepared by the usual chromatographic procedure, was concentrated to 50 ml. and the concentration determined from the ultraviolet absorption maximum. The remainder of the solution (49 ml.) was added to 0.083 g. of sodium bromide in methanol and the total volume brought up to 100 ml. with anhydrous methanol, making the solution 0.081 M in sodium bromide and 0.00359 M in the intermediate, the solvent being *ca.* 50% methanolic ether.

From the above solution, 5.021-ml. aliquots were quickly pipetted into 5.021-ml. portions of 0.02713 M *p*-toluenesulfonic acid in methanol. These solutions were titrated to neutrality as in the kinetic runs with standard sodium methoxide in methanol, using brom phenol blue as the indicator. These solutions required 4.015 ml. of 0.002929 M sodium methoxide per aliquot as compared to the blank measurements which required 4.630 ml. per aliquot. The difference of 0.615 ml. between the solution of the intermediate and the blank amounted to *ca.* 100% of the intermediate present in an aliquot. Pipetting larger amounts of the intermediate into the above amount of acid or adding the same amount of intermediate solution to larger amounts of acid led to consumption of 91–94% of the acid theoretically possible.

The only reaction in the above procedure which consumes acid is one in which bromide ion or *p*-toluenesulfonate ion is incorporated into the products; the incorporation of methoxide ion on methanol does not consume acid. The fact that bromide ion was incorporated was demonstrated by the fact that solutions of the intermediate plus sodium bromide tested basic to neutralized brom phenol blue. After such solutions had stood for 7 hours, only 0.205 ml. of 0.03863 M *p*-toluenesulfonic acid in methanol was consumed by an aliquot. After 12 hours this dropped to 0.160 ml., corresponding to 26% of the intermediate originally present. Titration for bromide ion by the procedure of Fainberg[57] accounted for the other 74% of the original intermediate.

A new solution of the intermediate was prepared and concentrated to 21 ml. The concentration was determined as before, and 20 ml. of this was diluted to 100 ml. with anhydrous methanol, giving a solution 0.00360 M in the intermediate and containing no sodium bromide. Aliquots of this solution were pipetted into equal volumes of 0.0271 M *p*-toluenesulfonic acid in methanol and also into equal volumes of the acid containing 0.0069 M sodium bromide.

Of the above solutions, those containing sodium bromide decreased in titer by about 0.00387 millimole, corresponding to the trapping of 21.5% of the possible acid by the intermediate. Those with no added bromide ion showed no measurable decrease.

Addition of the sodium bromide solution (0.0416 M) to the solution of the intermediate in *ca.* 20% methanolic ether caused the mixture to become strongly basic (toward brom phenol blue), the color intensifying as more sodium bromide was added. Neither the sodium bromide solution nor that of the intermediate tested basic before admixture.

Search for Methoxyl Cleavage of 2-*p*-Anisylethyl *p*-Toluenesulfonate.—A solution of 2-*p*-anisylethyl *p*-toluenesulfonate (0.001 M) in 40% aqueous dioxane, buffered with 0.005 M sodium bicarbonate, was prepared. Its ultraviolet absorption was then determined in the region 240–250 mμ; 100 ml. of this solution was then treated with one ml. of 4 M sodium hydroxide and its ultraviolet spectrum again determined in the 240–250 mμ region. Both solutions were run against the appropriate reference solutions minus the substrate. The differences between these two solutions were then determined (corrected for the 1% dilution caused by the sodium hydroxide). These values are tabulated in column 2 in Table IX.

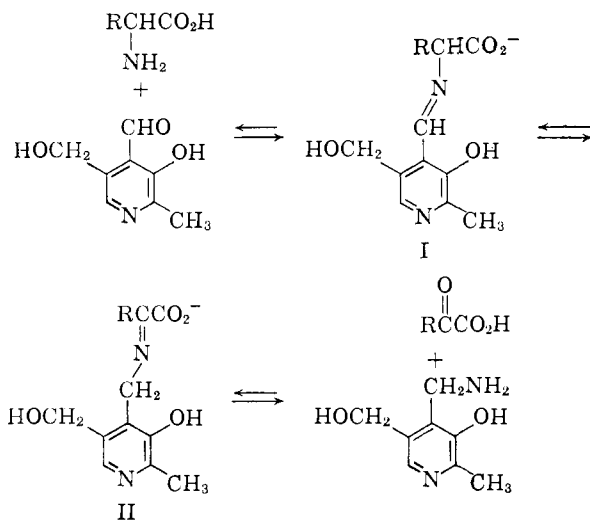The original solution of 2-*p*-anisylethyl *p*-toluenesulfonate was then solvolyzed for 20 hours at 75°. This represented more

Azomethine Chemistry. II. Formation of Peptides from Oxazolidine-5-ones[1,2]

BY RICHARD G. HISKEY AND JAMES M. JUNG[3-5]

Treatment of N-arylidene salts of α-amino acids with phthaloylglycyl chloride has provided 65–85% yields of 2-aryl-3-phthaloylglycyl-4-alkyloxazolidine-5-ones. These oxazolidine-5-ones afford tripeptides in 30–50% yield when treated with α-amino acid esters. Acylation of the azomethines with the p-nitrophenyl ester of N-carbobenzoxyglycine or the mixed carbonic anhydride of phthaloyl glycine also proceeds but in lower yield.

In an earlier report[1] model compounds resembling the azomethine intermediate II in the pyridoxal-catalyzed transamination reaction were generated and catalytically hydrogenated. The addition of hydrogen was shown to proceed stereospecifically and afford optically active α-amino acids from the corresponding α-keto acid. In order to obtain a more complete understand-

ing of the possible reactions of pyridoxal in biological systems, model compounds related to the azomethine intermediate I have also been studied.

The condensation of α-amino acids, in the form of carboxylate salts, with aryl aldehydes is well known.[6,7] Using a modification of the earlier method[7] of preparation, azomethine salts of a number of α-amino acids could be obtained in good yield (Table I). The salts

(1) Part I of this series, R. G. Hiskey and R. C. Northrop, *J. Am. Chem. Soc.*, **83**, 4798 (1961).

(2) This work was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgement is hereby made to the donors of this fund.

(3) Abstracted in part from a dissertation by J. M. Jung submitted to the University of North Carolina in partial fulfillment of the requirements for the Ph.D. degree, June, 1962.

(4) Petroleum Research Fund Fellow, 1959–1961.

(5) Tennessee Eastman Corporation Fellow, 1961–1962.

(6) O. Gerngross, *Biochem. Z.*, **108**, 84 (1920); O. Gerngross and E. Zuhlke, *Ber.*, **57**, 1482 (1924).

(7) M. Bergman, H. Ensslin and L. Zervas, *ibid.*, **58**, 1034 (1925).

TABLE IX

OPTICAL DENSITY DIFFERENCES BETWEEN NEUTRAL AND BASIC SOLUTIONS OF 2-p-ANISYLETHYL p-TOLUENESULFONATE

Wave length, mμ	O.D. differences before solvolysis	O.D. differences after solvolysis	Net change in differences
242	0.000	0.008	0.008
243	− .002	.004	.006
244	.012	.003	.008
245	.009	.004	− .005
246	.017	.007	− .010

than 20 half-lives for this compound as estimated from known rates in other solvents using the Winstein–Grunwald equation.[58]

The neutral and basic solutions obtained after solvolysis were examined spectroscopically and the optical density differences are tabulated in column 3 of Table IX.

Subtraction of the difference in column 2 from those in column 3 gives column 4. The net differences in column 4 represent the spectral contributions of any phenolic species present after solvolysis which were not present before, *i.e.*, any cleavage product. These net differences are very small (within experimental error of zero), and since 2-p-hydroxyphenylethanol has a maximum at 241 mμ (ε 10,150) in basic solution, it can be estimated from these differences that less than 0.2% of the 2-p-anisylethyl p-toluenesulfonate undergoes cleavage during solvolysis.

(58) S. Winstein, E. Grunwald and H. W. Jones, *J. Am. Chem. Soc.*, **73**, 2700 (1951).

TABLE I

SCHIFF BASE SALTS OF AMINO ACIDS

X	R	Yield, %	X	R	Yield, %
H–	–H	95.7	CH₃O–	–CH₃	84.0
H–	–CH₂OH	96.5	CH₃O–	–CH(CH₃)₂	71.2
H–	–CH₂C₆H₅	74.5	CH₃O–	–CH₂CH(CH₃)₂	89.3
CH₃O–	–H	90.0	CH₃O–	–CH₂SCH₂C₆H₄	80.0
CH₃O–	–CH₂C₆H₅	96.0	HO	–H	98.0

are sensitive to moisture and evolve the aldehyde on exposure to air. Consequently the salts were usually generated immediately prior to use. The Schiff base salts decomposed rather than melted. The criterion of purity used was the complete disappearance of the carboxyl OH band and the appearance of azomethine and carboxylate peaks in the 1640 and 1625 cm.⁻¹ regions, respectively.

Of interest was an earlier experiment[7] in which barium N-benzylideneglycinate (IIIa, Ar = C₆H₅, R = H) was reported[8] to yield 2-phenyl-3-acetyloxazolidine-5-one (IVa, Ar = C₆H₅, R = H, R′ = CH₃) with either acetyl chloride or acetic anhydride in refluxing carbon tetrachloride. More recently a similar reaction
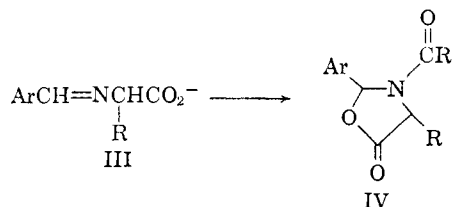
using trifluoroacetic anhydride[9] provided 2-phenyl-3-trifluoroacetyloxazolidine-5-one (IVb, Ar = C₆H₅, R = H, R′ = CF₃). In view of the close relationship between I and III and the fact that a number of biological processes involve acylation (usually by "active esters") it seemed possible that oxazolidine-5-

(8) H. Scheibler and P. Baumgarten, *ibid.*, **55**, 1358 (1922), prepared IVa by the action of acetic anhydride on sodium N-benzylideneglycinate. The proposed betain structure was subsequently revised.

(9) F. Weygand and E. Leising, *ibid.*, **87**, 248 (1954).