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Bromination of Phenylpropiolic Acid and Its Ethyl Ester[1]

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Abstract: The kinetics of the addition of bromine to phenylpropiolic acid, its anion, and its ethyl ester were studied in 75% aqueous acetic acid in the presence of varying amounts of sodium bromide, sodium acetate, and other salts. The reaction of the acid is characterized by the one-term rate equation, $-d[Br_2]_T/dt = k_2[A][Br_2]$, where A is the acetylenic substrate and $[Br_2]_T$ the total titratable bromine. The reaction affords small amounts of *cis*- and *trans*-α,β-dibromocinnamic acids and extensive decarboxylation products, as well as products derived from solvent incorporation. Analysis of the kinetic data and the products suggests that the reaction involves a bimolecular electrophilic attack of bromine on the phenylpropiolate anion and that it proceeds through an open vinyl cation intermediate. The bromination of ethyl phenylpropiolate has an additional third-order term, $k_3[A][Br_2][Br^-]$, which corresponds to a bromide ion catalyzed reaction. The bimolecular term also involves an open vinyl cation intermediate, because both ethyl *cis*- and *trans*-α,β-dibromocinnamates are formed, as well as solvent-incorporated products. By contrast, the termolecular, bromide ion assisted process yields only one product, ethyl *trans*-α,β-dibromocinnamate, and is best represented as an Ad_E-E3 reaction, as has been suggested for other halogenations of acetylenes. The activation paramaters for the reaction of the acid and the ester are consistent with the proposed reaction schemes.

An investigation of the kinetics and the products of the bromination of phenylpropiolic acid ($C_6H_5C{\equiv}CCOOH$), its sodium salt, and its ethyl ester in 75% by volume aqueous acetic acid has been carried out in order to elucidate further the nature of the mechanisms involved in acetylenic halogenation. An earlier study of the kinetics of the bromination of this acid

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Table I. Bromination of Phenylpropiolic Acid and Its Sodium Salt

NaBr, M	$NaClO_4$, M	NaCl, M	NaOAc, M	$HClO_4$, M	$k_{obsd} \times 10^2$, M^{-1} s^{-1}
		A. Phenylpropiolic Acid[a]			
0.02	0.48				71.1
0.03	0.47				53.3
0.04	0.46				41.7
0.05	0.45				35.2
0.07	0.43				27.3
0.10	0.40				21.1
0.10	0.40				21.8
0.13	0.37				16.5
0.15	0.35				14.2
0.20	0.30				10.6
0.30	0.20				7.04
0.40	0.10				5.17
0.50					4.44
0.10	0.10				14.2
0.10	0.20				16.0
0.10	0.30				18.9
0.10	0.40				21.8
0.10		0.10			14.4
0.10		0.20			15.6
0.10		0.30			17.8
0.10		0.40			19.9
0.45	0.05				4.52
0.45	0.04		0.01		7.79
0.45	0.03		0.02		9.82
0.45	0.02		0.03		13.2
0.45	0.01		0.04		15.6
0.45			0.05		17.7
0.10	0.39			0.01	12.0
0.10	0.38			0.02	8.73
0.10	0.37			0.03	6.13
0.10	0.36			0.04	4.13
0.10	0.35			0.05	2.45
		B. Sodium Phenylpropiolate[a]			
0.10	0.40				22.5
0.20	0.30				12.5
0.30	0.20				8.67
0.40	0.10				6.46
0.50					5.54
0.45	0.05				5.13
0.45	0.04		0.01		8.07
0.45	0.03		0.02		10.4
0.45	0.02		0.03		13.7
0.45	0.01		0.04		15.9
0.45			0.05		18.8

[a] The concentrations of the acetylenic substrates varied from (1.25 to 2.5) $\times 10^{-3}$ M and that of bromine from (0.5 to 1.0) $\times 10^{-3}$ M.

in 95% acetic acid indicated that the reaction was third order overall, second order in bromine concentration, when the reactants were kept at equal concentrations.[3]

Results

The Order of the Reaction. Reactions were carried out at an approximately 0.001 M concentration of bromine and 0.004 M of substrate in the presence of sodium bromide. Under these conditions the observed rate expression is $-d[Br_2]_T/dt = k_{obsd}[A][Br_2]_T$, where A is the acetylenic substrate and $[Br_2]_T$ is the total titratable bromine. The term which is of the second order in bromine is thus eliminated under these reaction conditions, as has been noted before.[4] The concentration of the substrate was varied by a factor of 3 and that of the bromine by a factor of 2, and the values of the rate constant k_{obsd} remained essentially constant at a constant bromide ion concentration. The addition of sodium perchlorate or sodium chloride (0.10–0.40 M) has an accelerating effect, and the rates increase linearly with the salt concentration by about 50% (Table I).

Effect of Bromide Ion. It has now been well established that many acetylenic brominations[5] (and iodinations)[6] follow the two-term rate expression

$$-d[Br_2]_T/dt = k_2[A][Br_2] + k_3[A][Br_2][Br^-] \quad (1)$$

in which the first term represents a bimolecular reaction between molecular bromine and the substrate and the second term represents a bromide ion catalyzed process. The two constants can be evaluated from the equation

$$k_{obsd}(K + [Br^-])/K = k_2 + k_3[Br^-] \quad (2)$$

by plotting the term on the left against the bromide ion concentration. In this equation K represents the dissociation constant of the tribromide ion. Reactions were consequently conducted at varying sodium bromide concentrations (0.02–0.50 M) at a constant ionic strength (0.50 M) maintained with sodium perchlorate. Results are reported in Table I. The data were collected in two sets of different bromine and substrate concentrations, because at low bromide ion concentrations the rates become very fast.

The data indicate that the bromination of phenylpropiolic acid does not involve a k_3 term. If only the first term in eq 1

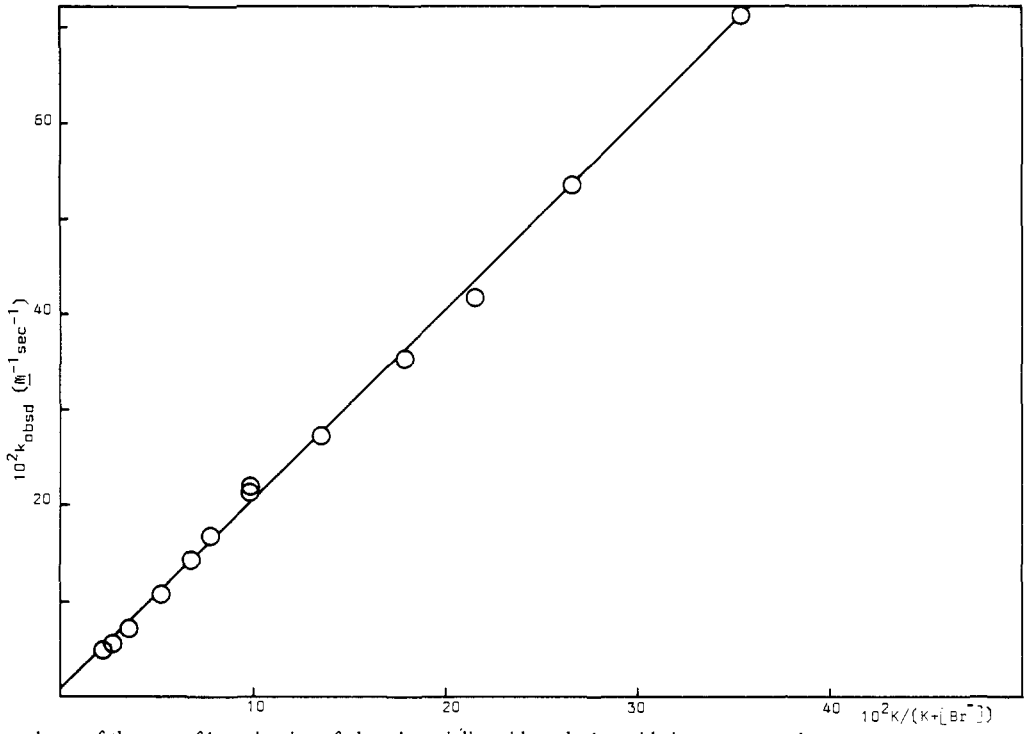


Figure 1. The dependence of the rate of bromination of phenylpropiolic acid on the bromide ion concentration.

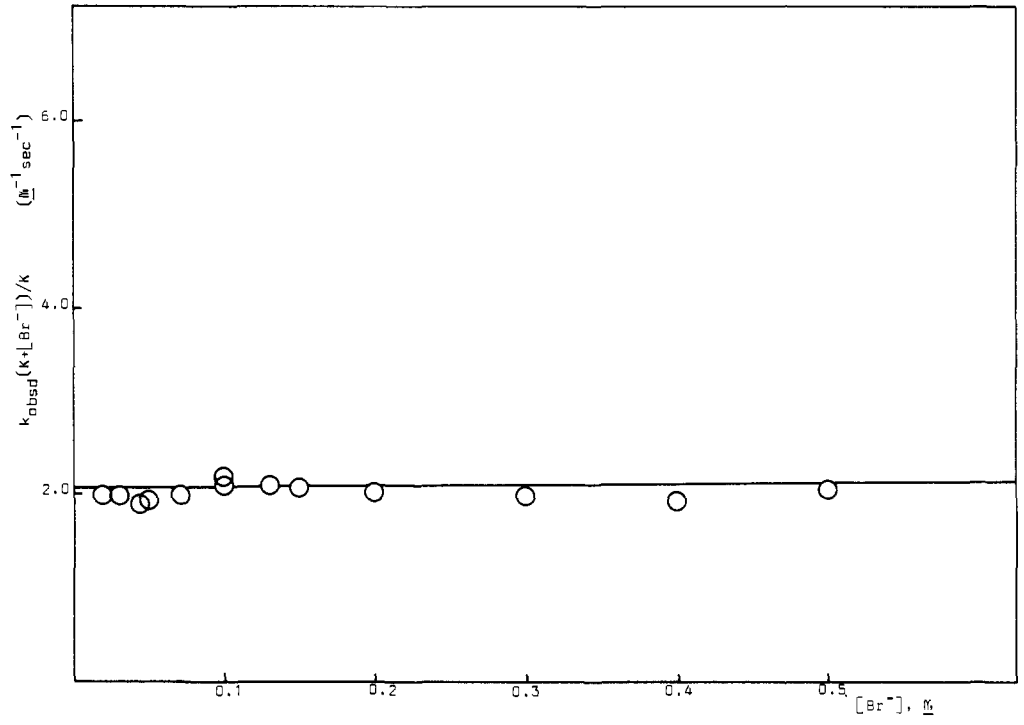


Figure 2. The dependence of the rate of bromination of phenylpropiolic acid on the bromide ion concentration.

contributes, the data can be plotted in the form

$$k_{obsd} = k_2K/(K + [Br^-]) \quad (3)$$

which should yield a straight line which goes through the origin. This plot is shown in Figure 1, which reveals a very small but finite intercept (k_2 = 1.97 ± 0.02 M^{-1} s^{-1}, intercept = (5.45 ± 2.55) × 10^{-3}).[7] However, when the data are plotted in the form of eq 2 (Figure 2), a line is obtained which is almost horizontal to the x axis, so that the slope is zero and the reaction does not appear to have a k_3 term. The intercept in this plot (k_2) is 2.04 ± 0.03 M^{-1} s^{-1}, which is in good agreement with the value obtained from Figure 1. Furthermore, a least-squares calculation of the data according to eq 2 affords, in fact, a negative slope of (−2.49 ± 11.03) × 10^{-2} M^{-1} s^{-1}, with a correlation coefficient of −0.04. On the other hand, the correlation coefficient for the plot in Figure 1 is 1.00. It is therefore safe to assume that this reaction does not have a k_3 term and that the bromination can be represented by only the first term in eq 1.

Effect of Sodium Acetate and the Bromination of Sodium Phenylpropiolate. The rate constant for the bromination of phenylpropiolic acid increases linearly with the concentration

Table II. Bromination of Ethyl Phenylpropiolate

NaBr, M	$NaClO_4$, M	NaOAc, M	$k_{obsd} \times 10^3$, $M^{-1} s^{-1}$
Ethyl Phenylpropiolate $\simeq 2.0 \times 10^{-3}$ M, $Br_2 \simeq 5.0 \times 10^{-4}$ M			
0.01	0.49		8.81
0.02	0.48		7.76
0.05	0.45		7.02
0.10	0.40		6.82
0.20	0.30		6.62
0.30	0.20		6.61
0.40	0.10		6.58
0.10	0.39	0.01	6.85
0.10	0.38	0.02	6.86
0.10	0.30	0.10	6.90

of sodium acetate. The latter concentration was varied from 0.01 to 0.05 M ([NaBr] = 0.45 M, μ = 0.5 M), and the slope of the line, the catalytic constant k_{OAc^-}, is 2.64 ± 0.05 M^{-1} s^{-1} (Table I). The most reasonable assumption is that the acetate ion converts phenylpropiolic acid to its anion, because phenylpropiolic acid (in water) is a considerably stronger acid than acetic acid,[8] and the phenylpropiolate anion should react faster than the undissociated acid in electrophilic bromination. To test this possibility, the bromination of sodium phenylpropiolate was studied under the same conditions as the acid itself (Table I). The reaction of the salt shows the same bromide ion dependence as that of the acid, and from a plot similar to Figure 1, the rate constant for the bromination of sodium phenylpropiolate (k_2) was found to be 2.20 ± 0.02 $M^{-1} s^{-1}$. Surprisingly, it reacts only insignificantly faster than the acid itself. Furthermore, the bromination of the sodium salt is also significantly increased by the addition of sodium acetate, and by about the same extent as the reaction of the acid (k_{OAc^-} = 2.72 ± 0.04 $M^{-1} s^{-1}$).

These similarities in the rate constants are best explained by assuming that phenylpropiolic acid in 75% aqueous acetic acid is present both as the anion and the free acid, and that the same, or similar, proportions of acid and anion are also obtained if one starts with the anion. A solution of sodium acetate in acetic acid should have some buffer action, so that the amounts of acid and anion should be very similar whether the substrate is the acid or the anion. The further addition of sodium acetate will in both cases serve to convert more of the acid to its anion, which results in a greater rate. The assumption that the phenylpropiolate anion is the actual substrate involved in the bromination is strongly supported by two further observations. One is that added perchloric acid (0.01–0.05 M) has a strong decelerating effect on the bromination of the acid (k_{HClO_4} = −2.37 ± 0.13 $M^{-1} s^{-1}$), because it converts the anion to the less reactive acid. Furthermore, the bromination of ethyl phenylpropiolate (see later), which does not have an ionizable carboxyl group, is not affected by the addition of sodium acetate. It is therefore valid to assume that phenylpropiolic acid is brominated through its anion.

We have also investigated the possibility that acetate ion catalysis may be due to the formation of bromine acetate, formed according to eq 4, which should be a more powerful reagent than bromine.[9]

$$CH_3COOH + Br_2 \rightleftarrows CH_3COOBr + Br^- + H^+ \quad (4)$$

This should lead to a characteristic inverse linear bromide ion dependence on the rate, but runs conducted at a constant acetate and varying bromide ion concentration (μ = 0.5 M) did not lead to the anticipated dependence. The catalytic effect of acetate ion is therefore not due to the formation of bromine acetate.

Bromination of Ethyl Phenylpropiolate. The bromination of the ester is more straightforward than that of the free acid. The bromide ion dependence of the rate was investigated in runs in which the bromide ion concentration was varied from 0.01 to 0.4 M at a constant ionic strength (Table II). The data conform to eq 2 and afford a second-order rate constant, k_2, of (1.00 ± 0.02) × 10^{-2} $M^{-1} s^{-1}$ and a third-order rate constant, k_3, which is (5.89 ± 0.01) × 10^{-1} $M^{-2} s^{-1}$ (Figure 3). The existence of a two-term rate equation is thus well established. In Table III are listed the contributions to the total rate of the two terms at different bromide ion concentrations. At a bromide ion concentration higher than 0.20 M, the second term contributes well over 90% to the total reaction. Also, the

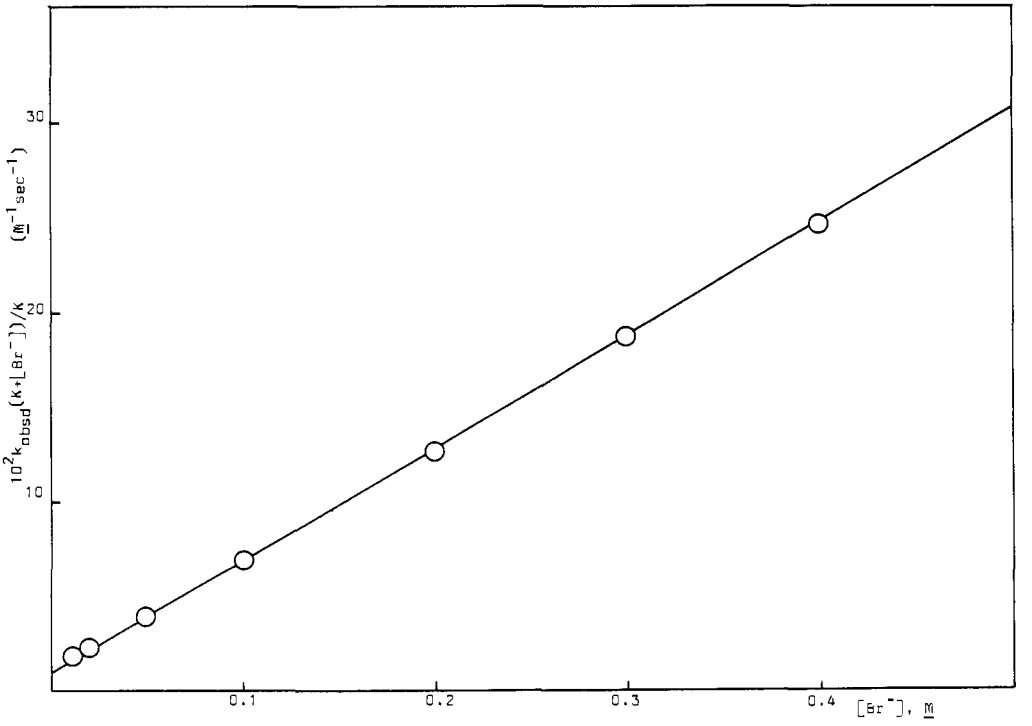


Figure 3. The dependence of the rate of bromination of ethyl phenylpropiolate on the bromide ion concentration.

Table III. Calculated Contributions of the k_2 and k_3 Processes in the Bromination of Ethyl Phenylpropiolate

NaBr, M	$k_2K/(K + [Br^-])$ $\times 10^3$	$k_3K[Br^-]/(K + [Br^-])$ $\times 10^3$	k_{obsd}, $\times 10^3$ L mol^{-1} s^{-1}	k_{calcd}, $\times 10^3$ L mol^{-1} s^{-1}	% $k_2K/(K + [Br^-])$	% $k_3K[Br^-]/(K + [Br^-])$
0.01	5.24	3.09	8.81	8.33	62.9	37.1
0.02	3.55	4.18	7.76	7.72	45.9	54.1
0.05	1.81	5.31	7.02	7.12	25.4	74.6
0.10	0.991	5.84	6.82	6.83	14.5	85.5
0.20	0.521	6.14	6.62	6.66	7.8	92.2
0.30	0.354	6.25	6.61	6.60	5.4	94.6
0.40	0.268	6.32	6.58	6.59	4.1	95.9
0.50	0.215	6.33	6.57	6.55	3.3	96.7

Table IV. Product Distribution

NaBr, M	$NaClO_4$, M	NaOAc, M	Product, %							
			A. Phenylpropiolic Acid							
			I[a]	II[b]	III[c]	IV[d]	V[e]	VI[f]	VII[g]	VIII[h]
0.50			17.7	45.0	18.1	17.0			0.7	1.5
0.10	0.40		16.6	42.6	19.0	18.4			1.2	2.2
	0.50		13.0	2.3	37.4	37.2	4.5	3.1	0.9	1.6
0.45		0.05	11.2	3.9	56.3	11.2	2.4	7.7	2.9	4.4
			B. Ethyl Phenylpropiolate							
			IX[i]	X[j]	XI[k]	XII[l]	XIII[m]			
0.50				100.0						
0.10	0.40			100.0						
	0.50		13.5	22.9	22.0	11.9	29.7			
0.45		0.05		100.0						
			C. Bromophenylacetylene							
			II[b]	III[c]	V[e]					
0.10			94	2	4					
			D. Phenylacetylene							
			I[a]	V[e]	VI[f]					
0.10			1	98	1					

[a] Bromophenylacetylene. [b] α,β,β-Tribromostyrene. [c] α,α-Dibromoacetophenone. [d] α-Acetoxy-β,β-dibromostyrene. [e] *trans*-α,β-Dibromostyrene. [f] Phenacyl bromide. [g] *cis*-α,β-Dibromocinnamic acid. [h] *trans*-α,β-Dibromocinnamic acid. [i] Ethyl *cis*-α,β-dibromocinnamate. [j] Ethyl *trans*-α,β-dibromocinnamate. [k] Ethyl bromobenzoylacetate. [l] Unidentified. [m] Unidentified.

values calculated for the two-term rate equation from the separate rate constants agree well with those observed. As noted earlier, the reaction of the ester is unaffected by acetate ion, and a tenfold variation of it does not affect the rate (Table II).

Reaction Products. The products of the reaction of phenylpropiolic acid were determined in runs paralleling the kinetic runs, at 25 °C and a constant ionic strength. Runs were conducted at high (0.5 M) and low (0.1 M) bromide ion concentrations, without initial bromide ion, and also in the presence and absence of sodium acetate. Results are listed in Table IV. The reaction yielded from six to eight products, depending on the conditions. The percentages are reported on the basis of 100%, excluding unreacted substrate, which was always used in excess. All runs afforded small amounts (less than 5%) of *cis*- and *trans*-α,β-dibromocinnamic acids and nonacidic products derived from extensive decarboxylation. In the presence of bromide ion, the nonacidic products were identified as bromophenylacetylene (I, $C_6H_5C{\equiv}CBr$), α,β,β-tribromostyrene (II, $C_6H_5CBr{=}CBr_2$), α,α-dibromoacetophenone (III, $C_6H_5COCHBr_2$), and α-acetoxy-β,β-dibromostyrene (IV, $C_6H_5C(OAc){=}CBr_2$). The first three were identified by comparison of their mass spectra and GLC retention times with those of authentic samples, while the last was identified only by its mass spectrum. Runs which were conducted in the absence of initially added bromide ion, or in the presence of sodium bromide and sodium acetate, yielded in addition *trans*-α,β-dibromostyrene (V, $C_6H_5CBr{=}CHBr$) and phenacyl bromide (VI, $C_6H_5COCH_2Br$), identified by comparison with authentic samples. The nonacidic products were derived from decarboxylation by routes which will be considered later. In considering these routes, it was necessary to study also the products of the bromination of bromophenylacetylene and of phenylacetylene under conditions similar to those of the kinetic runs. The results are also listed in Table IV. The bromophenylacetylene starting material contained about 5% phenylacetylene impurity by GLC, and the 4% of *trans*-α,β-dibromostyrene obtained in its bromination must result from the bromination of this impurity.

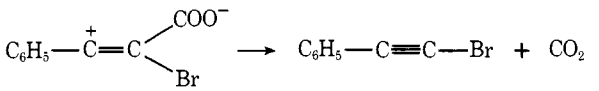
The products of the reaction of ethyl phenylpropiolate with bromine, also obtained under various reaction conditions, are listed in Table IV. Runs which were conducted in the presence of bromide ion (0.1 or 0.5 M), with or without sodium acetate present, afforded only one product, ethyl *trans*-α,β-dibromocinnamate. In the absence of bromide ion, the reaction afforded a mixture of ethyl *cis*- and *trans*-α,β-dibromocinnamates (13.5 and 22.9%), identified by comparison with authentic samples. The other three products were solvent-incorporated products, and all are ketonic, because they could be extracted with Girard's reagent. After this treatment, only the two ethyl cinnamates were recovered from the nonketonic fraction. Of the ketonic products, only one, ethyl bromobenzoylacetate (XI, $C_6H_5COCHBrCOOC_2H_5$), could be positively identified by comparison with authentic material. The other two did not pass through the mass spectrometer and could not be further identified, but it is clear that they derive

from solvent incorporation and are ketonic, or easily hydrolyzed to ketones in the workup procedure.

Activation Parameters. The activation energy, E_a, for the bromination of phenylpropiolic acid was determined by measuring the rates at six different temperatures in the range of 20.0–45.0 °C. It was found to be 11.9 ± 0.3 kcal/mol and the activation entropy[10] is −26.6 ± 0.7 eu at 25 °C. These values are composite in that they also contain small contributions from the enthalpy and entropy of tribromide ion formation,[4] as well as of the dissociation of the acid. Activation parameters for the bromination of the ester were similarly determined. The activation energy is 7.39 ± 0.11 kcal/mol and the entropy of activation at 25 °C is −45.7 ± 1.0 eu.

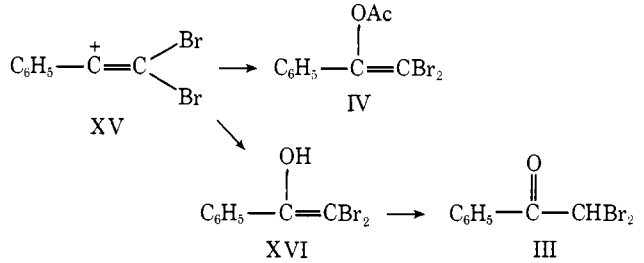
Discussion

Phenylpropiolic Acid. The rate of bromination of phenylpropiolic acid can be expressed by $-d[Br_2]_T/dt = k_2[A][Br_2]$, where $[Br_2]$ is the free bromine concentration, and the second kinetic term, so prevalent in acetylenic halogenations, is absent. Because the anion reacts faster than the acid itself, the reaction can best be considered to involve an electrophilic attack of bromine on the anion. The reaction involves an intermediate which must be an open vinyl cation formed in the rate-determining step, rather than a bridged or a weakly bridged one. Open cations are known to be favored when adjacent to a phenyl group. The main evidence for an open vinyl cation, rather than a bridged one, comes from the nature of the products of the reaction. Bridged ions are known to lead to exclusive trans addition and, in the case of the hexynes, to no solvent incorporation,[5] whereas in the present case, a mixture of cis and trans addition products results in the presence and absence of external bromide ion. About twice as much *trans*-α,β-dibromocinnamic acid is formed as cis acid, but the total amounts of acidic products are only a few percent. The remainder are decarboxylation products. The first product of the decarboxylation reaction is probably bromophenylacetylene (I) which is formed from the cationic intermediate XIV as shown.



XIV I

Bromophenylacetylene is formed in considerable amounts. In principle, bromophenylacetylene can be the precursor for most of the reaction products. Its further bromination yields α,β,β-tribromostyrene (II), analogously to the triiodostyrene formed in iodination.[6] The bromination of bromophenylacetylene which leads to tribromostyrene may involve a cationic intermediate (XV), which on reaction with the solvent can form either α-acetoxy-β,β-dibromostyrene (IV) or the enol (XVI), and subsequently the ketone (III). It is not possible to



XV IV XVI III

say if all of the solvent-incorporated product is first the enol acetate, which on workup partially produces the ketone, or if both the enol acetate and the enol are original reaction products.

While the main products of the decarboxylation reaction can be qualitatively accounted for by assuming them to be derived from initially formed bromophenylacetylene, there are difficulties when their quantitative relationships are considered. In the bromination of bromophenylacetylene in the presence of 0.10 M NaBr, the main product (94%) is the tribromide, and only 2% of α,α-dibromoacetophenone (III) is produced (Table IV), whereas in the bromination of phenylpropiolic acid, the proportion of solvent-incorporated products is much greater (36%). Also, the bromination of bromophenylacetylene does not account for the formation of small amounts of *trans*-α,β-dibromostyrene (V) and phenacyl bromide (VI), which are only formed in the absence of bromide ion or in the presence of sodium acetate and bromide ion. The latter two compounds can be expected to be formed from the bromination of phenylacetylene. However, the bromination of phenylacetylene (0.10 M NaBr) leads to 98% of *trans*-α,β-dibromostyrene (V) and 1% each of phenacyl bromide (VI) and bromophenylacetylene (I) (Table IV). This is in agreement with the results of Pincock and Yates,[5] who showed that the reaction is an Ad-E3 process, but again it produces much less of the solvent-incorporated products than is found among the decarboxylation products.

The formation of the solvent-incorporated products can be accounted for by an additional route which involves the formation of benzoylacetic acids. Intermediate XIV can react with the solvent to form the enol $C_6H_5C(OH)=CBrCOOH$, which, after ketonization to form $C_6H_5COCHBrCOOH$, decarboxylates to $C_6H_5COCH_2Br$ (VI). This will account for the formation of the ketone VI, without involving phenylacetylene. It was shown that under the conditions of the reaction, phenacyl bromide is not further brominated to form dibromoacetophenone (III), and ketone VI is therefore not the precursor for III. A possible route, however, for the formation of additional III is the further bromination of bromobenzoylacetic acid to form the dibromo acid, $C_6H_5COCBr_2COOH$, which will yield III on decarboxylation.

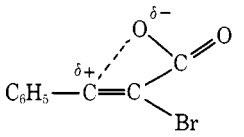
The only product among the decarboxylation products which is not easily accounted for is α,β-dibromostyrene (V), which is only formed in small amounts. It can only be formed from phenylacetylene, but no reasonable scheme could be devised by which this compound can arise in the reaction mixture. Phenylpropiolic acid decarboxylates at higher temperatures in water,[11] but no phenylacetylene could be detected under the reaction conditions in the absence of bromine over a 4-day period at room temperature. Phenylacetylene can also be produced from bromophenylacetylene, but only in the presence of strong bases. It is reported not to react with iodide ion,[12] which is a stronger nucleophile than either the bromide or acetate ions here used. Another possibility is that the dibromostyrene is formed by hydration of bromophenylacetylene and capture of bromide ion, but the medium is probably not sufficiently acidic to allow for this reaction. However, about 5% of phenylacetylene must have been present to account for the dibromostyrene. Under the reaction conditions, both *cis*- and *trans*-α,β-dibromocinnamic acids are stable and do not decarboxylate. These products can therefore not be precursors of any further products.

It is difficult to account quantitatively for each of the products obtained. In the presence of bromide ion, however, the total amount of solvent-incorporated products averages 36%. In the absence of bromide ion, this increases to 78% and in the presence af acetate and bromide ion, it averages 75%. These increases are reasonable and are caused by increased solvent incorporation when bromide ion is absent or acetate ion is present. The increase in the amounts of dibromocinnamic acids in the presence of acetate ion, however, remains unexplained, but the fact that larger amounts of trans than cis acids are invariably formed is probably due to steric effects.

It is very likely that, in the medium, various ion pairs are involved,[5] but no advantage was gained by invoking them to account for the variety of products formed. It suffices to say

that all of the data can be reasonably well accounted for by postulating an open vinyl cation as the first intermediate in the reaction.

The absence of a bromide ion catalyzed term, when the reaction is conducted in the presence of bromide ions, appears to be unusual in acetylenic halogenation and needs consideration. It may be accounted for by assuming the intervention of an internal ion pair (XVII) similar to the β-lactones isolated

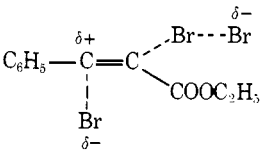


XVII

in the halogenation of sodium dimethyl fumarate or maleate.[13] The carboxylate ion is a better bridging group than is bromine.[14] The usual occurrence of the bromide ion catalyzed term can be interpreted as a means of avoiding the formation of a high-energy intermediate vinyl cation. The formation of the internal ion pair (XVII) should stabilize the intermediate by dissipating the charge, thereby obviating the need for participation by bromide ion. The bridging in XVII is likely to be sufficiently weak so as not to have any stereochemical consequences for the subsequent reaction.

Ethyl Phenylpropiolate. The rate of bromination of ethyl phenylpropiolate follows the two-term rate equation 1, and the reaction therefore consists of a bimolecular attack of bromine on the substrate, as well as a bromide ion catalyzed attack. The first term has the same mechanistic significance as the corresponding term in the reaction of the acid. It represents an electrophilic attack by bromine and involves the formation of an intermediate open vinyl cation. The observation that phenylpropiolic acid reacts about 200 times faster than ethyl phenylpropiolate is in accord with an electrophilic attack, since the anion of the acid should react faster than the ester. So is the further observation that *ethyl* phenylpropiolate reacts about two to three times faster than *methyl* phenylpropiolate,[15] which is in accord with the greater electron-releasing effect of the ethyl as compared to the methyl group. The conclusion that an open vinyl cation is involved is again based on the products of the reaction. When the reaction was conducted in the absence of initially added bromide ion, when only the first term in eq 1 is significant, a mixture of ethyl *cis*- and *trans*-α,β-dibromocinnamates was formed to the extent of 13.5 and 22.9%, respectively. The remainder are ketonic esters, or esters easily hydrolyzed to ketones because they were completely extracted with Girard's reagent. These ketonic products are formed by a nucleophilic attack of the solvent on the vinyl cation. One of the three products was identified as ethyl bromobenzoylacetate (22%), but the other two could not be further identified (see Results). They could conceivably be the cis and trans enol acetates of ethyl bromobenzoylacetate, or one could also be the dibromo ester. The formation of both cis and trans isomers, and of esters derived from solvent incorporation, are typical of open vinyl cations, rather than bridged ones. The large amount of solvent-incorporated products in the bromination of both the acid and the ester must be related to the high energy of the intermediate vinyl cation, which is more likely to react indiscriminately with the solvent, rather than the more nucleophilic but less plentiful bromide ion.

The situation is strikingly different when reactions were conducted in the presence of bromide ion (the second term in eq 1). The product of the reaction at both 0.10 and 0.50 M sodium bromide was exclusively ethyl *trans*-α,β-dibromocinnamate, even in the presence of sodium acetate. No other products were detected, and test runs indicated that the presence of the cis ester in an amount greater than 1% would have been detected. The most reasonable mechanism for this bromide ion catalyzed term is one involving a transition state resembling XVIII in which the bromine and the bromide ion



XVIII

attach themselves almost simultaneously to the ends of the triple bond. Such a transition state should lead exclusively to trans products and preclude the formation of solvent-incorporated products. This is the mechanism first documented by Pincock and Yates for bromination,[5] and described also for hydrochlorination[16] and iodination[6] of alkynes. Because of the electrophilic nature of the attack,[15] bond making with bromine may have progressed further than that with bromide ion in the transition state. A fast and reversible formation of a bromine-acetylene complex, followed by a slow attack by bromide ion, is another possibility compatible with the kinetics.[17] Although this avoids the difficulty of invoking a termolecular reaction,[17] it is less attractive, because such a complex might be expected to be susceptible to attack by the solvent.

The activation parameters for the bromination of the ester were determined at 0.50 M bromide ion concentration, when over 95% of the reaction proceeds by the Ad_E3 mechanism. The activation entropy has the very negative value of −45.7 eu, which would be expected of the highly ordered and restrained transition state. Characteristically, the entropy of activation for the reaction of the acid, also obtained at 0.50 M NaBr concentration, but involving only the k_2 term, is −26.6 eu. Furthermore, the activation energy for the reaction of the acid (11.9 kcal/mol) is larger than that of the ester (7.39 kcal/mol). That is, the termolecular transition state, once it has reached the proper geometry, is energetically more favorable than the one involving the vinyl cation. This is perhaps the reason why the second term in the halogenation of acetylenes corresponds to a termolecular attack rather than to a kinetically equivalent bimolecular attack by the tribromide ion, which is involved in olefinic halogenations.[1,18] There is no evidence that the tribromide ion is involved in this or in previously studied halogenations of acetylenes.

Experimental Section

Materials. All melting points were taken with a Hershberg melting point apparatus and are corrected. All inorganic salts were reagent grade chemicals, and those used in the kinetic runs were dried at 120 °C before use. Mass spectra were taken on a Hitachi Perkin-Elmer RMS-4 mass spectrometer with a Perkin-Elmer 990 gas chromatograph.

Phenylpropiolic acid (Aldrich Chemical Co.) was recrystallized twice from CCl_4 and melted at 137.8–138.4 °C (lit.[6] 137.6–138.4 °C). Sodium phenylpropiolate was prepared as earlier described.[6] Ethyl phenylpropiolate had bp 94–95 °C (2 mm) (lit.[19] 124 °C (6 mm)). All compounds needed for comparison purposes were prepared according to literature procedures. *trans*-α,β-Dibromocinnamic acid had mp 136.0–136.6 °C (lit.[20] 134 °C) and the yellow cis acid 99.8–100.4 °C (lit.[20] 98 °C). A 74% yield of a mixture of the two was obtained by bromination of phenylpropiolic acid in $CHCl_3$. The methyl esters of the two acids were prepared by esterification of the acids with 1-methyl-3-*p*-tolyltriazene (Willow Brook Laboratories) in 50–60% yields. Methyl *trans*-α,β-dibromocinnamate had bp 124–125 °C (1 mm) (lit.[20] 167 °C (15 mm)) and the cis ester 122.5–123.5 °C (1 mm) (lit.[20] 171–172 °C (18 mm)). Ethyl *trans*-α,β-dibromocinnamate was similarly prepared with 1-ethyl-3-*p*-tolyltriazene (Willow Brook Laboratories) in 61% yield and boiled at 130–131 °C (1 mm) (lit.[20] 174 °C (12 mm)). The mass spectrum showed peaks at *m/e* 332, 334, and 336 for M^+ in a 1:2:1 ratio of intensities which is indicative of the presence of two bromine atoms; *m/e* 287, 289, and 291 for $M^+ - OC_2H_5$; *m/e* 253 and 255 $M^+ - Br$; *m/e* 174 for $M^+ - 2Br$; *m/e* 77 for $(C_6H_5)^+$. Ethyl *cis*-α,β-dibromocin-

namate does not seem to have been described before. It was synthesized as was the trans isomer and is a yellow oil of bp 127.5–128 °C (1 mm). Anal.[21] Calcd for $C_{11}H_{10}Br_2O_2$: C, 39.56; H, 3.02; Br, 47.85. Found: C, 39.71; H, 3.04; Br, 47.74. Its mass spectrum has the same parent peak and fragmentation pattern as the trans isomer. *trans*-α,β-Dibromostyrene was prepared from phenylacetylene (Aldrich Chemical Co.).[22] The reaction yielded a single compound, a yellow oil of bp 85–87 °C (1 mm) (lit.[22] 132–135 °C (15 mm)) which is the trans isomer, because any cis product isomerizes to the trans on distillation.[23] The ice-cold reaction mixture prior to distillation contained 78% of the trans and 17% of the cis isomer (as well as 3% of bromophenylacetylene and 2% of unreacted starting material). A selective debromination[23] of the trans isomer with zinc dust and $ZnCl_2$ in absolute ethanol changed the ratio of *trans*- to *cis*-α,β-dibromostyrene from 4.56 to 0.79. This analysis showed that the compound obtained in the Nef procedure (and also among our isolated products) was the trans isomer. α,β,β-Tribromostyrene, prepared from phenylacetylene (Aldrich Chemical Co.), was distilled under argon as a yellowish oil of bp 112–113 °C (4 mm) (lit.[24] 102 °C (0.3 mm)). α,α-Dibromoacetophenone had mp 33.7–34.1 °C (lit.[25] 36 °C) and phenacyl bromide had mp 50.5–51.0 °C (lit.[26] 51 °C) after recrystallizations from 95% and from 75:25 v/v aqueous ethanol, respectively. The sample of bromophenylacetylene[27] contained about 5% of the phenylacetylene starting material. Ethyl bromobenzoylacetate was obtained as a yellowish oil of bp 132–133 °C (1 mm) (lit.[28] 135–137 °C (1 mm)). α-Acetoxy-β,β-dibromostyrene was identified only on the basis of its mass spectrum, which showed peaks at *m/e* 318, 320, and 322 in a 1:2:1 ratio showing the presence of 2 Br atoms in the parent ion; *m/e* 239 and 241 for $M^+ - Br$; *m/e* 198, 200, and 202 for $(O{=}C{=}CBr_2)^+$; *m/e* 77 for $(C_6H_5)^+$.

Product Isolation. Solutions for isolation runs were made up at 25 °C under the same conditions as the kinetic runs except that the total volume was 1 L. An initial 10-mL aliquot was used to determine the Br_2 concentration. Reaction mixtures of the acid were allowed to stand overnight. The reaction period for the ester was 2 weeks. When all of the bromine color had disappeared, the solvent was removed below 40 °C with a rotary evaporator attached to a vacuum pump. The residue was dissolved in 200 mL of ether, and the ether was washed with several portions of H_2O to remove the inorganic salts and residual HOAc. The acidic products were then extracted with 50-mL portions of 5% sodium bicarbonate solution. This extract was acidified and reextracted into ether. The ether layers of both the acid and neutral products were dried with anhydrous Na_2SO_4 and the ether was removed with a rotary evaporator under reduced pressure. Reaction products of phenylpropiolic acid and the ethyl ester were worked up in the same way, but no acidic products were isolated in the case of the ester. For purposes of analysis, the mixture of cinnamic acids and starting material was esterified with 1-methyl-3-*p*-tolyltriazene and the subsequent analysis was carried out on the methyl esters. Acetone solutions of products were analyzed by GLC on an F & M Model 720 gas chromatograph. The columns used were a 2-ft, 5% LAC-728 (diethylene glycol succinate) on 80–100 S. Up. at 175 °C and a flow rate of 125 mL/min of the helium carrier gas, and a 2-ft Carbowax 20M column on 80–100 S. Up. and a flow rate of 65 mL/min at 175 °C. Products were identified on the basis of their retention times, which were compared to those of the authentic samples. Relative amounts were calculated from relative areas. The validity of the procedure was confirmed with known mixtures containing different ratios of methyl phenylpropiolate and methyl *trans*- and *cis*-α,β-dibromocinnamates. The reliability of the esterification procedure was tested on mixtures of the above three acids in the ratios 40:30:30 and 20:40:40. The ratio of the esters obtained on GLC was the same as that of the starting acids within 1–2%.

The workup procedure and the stability of the products under the workup conditions were also checked by working up reaction mixtures of known composition in 75% acetic acid in the presence of NaBr (0.1 or 0.5 M). Several known mixtures of the products, which were esterified by the above procedure, and of the esters in different ratios were analyzed. No new compounds were found by GLC. There were no significant changes in the ratio of products due to workup conditions. In six such test runs the resulting ratios agreed within 2–5% with the original ones. Samples of α,α-dibromoacetophenone and of α,β,β-tribromostyrene were passed through the same procedure and recovered unchanged, with no other products having been formed. The sensitivity of the GLC measurements was determined by analyzing known mixtures of methyl *trans*- and *cis*-α,β-dibromocinnamates. Two peaks were detected when they were in the ratio of 100:1, and only one if the ratio was 200:1. The limit of detection of our procedure for these two compounds was therefore 1%. All isolation runs were conducted in duplicate.

All products were analyzed by mass spectrometry. The products were first separated on a gas chromatograph (Perkin-Elmer 990) with a 6-ft OV-1 (dimethyl silicone gum) on a Chromosorb W AW DMCS HP, 80/100 mesh column before entering the mass spectrometer. Mass spectra were compared with those of authentic samples.

One reaction mixture of ethyl phenylpropiolate was treated with Girard's "T" reagent (Fisher Chemical Co.) according to the procedure of Fieser.[29]

Kinetic Determinations. Glacial acetic acid was purified by a modification of the method of Orton and Bradfield.[4] All acid was 99.98% pure and this was taken to be 100%. The temperature of the kinetic runs was 25.00 ± 0.05 °C. Reactions were conducted as described before for other bromination reactions.[4] Kinetic runs were carried out usually to well over 50% of reaction.

Second-order rate constants were calculated with a least-squares program. In addition, graphs were prepared for each run, and if only one point deviated markedly, it was discarded and the calculation repeated with the remaining points. If more than one point deviated, the run was repeated. The least-squares probable errors in the slopes and intercepts were never greater than 1%. Rate constants for all runs were determined at least in duplicate with different sets of stock solutions. If duplicate runs did not agree within 2%, an additional determination was made. All errors in rate constants and activation parameters are probable errors obtained from the least-squares calculations. The equilibrium constant K was taken as 0.0110 M.[30]

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Two-Photon Spectroscopy of the Visual Chromophores. Evidence for a Lowest Excited $^1A_g^-$-Like $\pi\pi^*$ State in *all-trans*-Retinol (Vitamin A)

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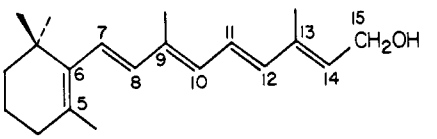
Abstract: A two-photon excitation maximum of *all-trans*-retinol (vitamin A) is observed approximately 1600 cm^{-1} to the red of the one-photon absorption maximum in EPA at 77 K. The observed state is "strongly allowed" in two-photon spectroscopy exhibiting a cross section at the 704-nm two-photon maximum of approximately 2×10^{-49} cm^4 s $molecule^{-1}$ $photon^{-1}$. The two-photon maximum is assigned to the lowest $\pi^* \leftarrow \pi$, "$^1A_g{}^{*-}$" $\leftarrow$ "$^1A_g{}^-$" transition on the basis of two-photon cross-section calculations using PPP-SCF-MO-CI wave functions including full single and double excitation configuration interaction. Torsional distortion and substituent effects associated with the β-ionylidene ring, while not altering the level ordering of the lowest energy "$^1B_u{}^*$" and "$^1A_g{}^{*-}$" $\pi\pi^*$ states, decrease the energetic separation of these two states relative to that observed in the analogous linear polyene, 2,10-dimethylundecapentaene.

The initial step in vertebrate vision involves the photochemical isomerization of the polyene aldehyde, 11-*cis*-retinal, which is bound to the opsin protein of rhodopsin via a protonated Schiff base linkage.[3] Characteristics of the visual chromophore that are important to its biophysical function include a high probability for photon absorption and a high quantum efficiency of cis → trans photoisomerization. Investigators have long recognized that these properties are characteristic of polyenes, but the photochemical origins of these properties are still not fully understood.[4]

The recent discovery of a lowest excited $^1A_g{}^{*-}$ $\pi\pi^*$ singlet state in linear polyenes[5-7] has prompted important revisions in our understanding of polyene electronic structure.[4-10] Prior to this discovery investigators had assigned the strongly allowed $^1B_u{}^* \leftarrow {}^1A_g$ transition as having the lowest energy. A lowest excited $^1A_g{}^{*-}$ $\pi\pi^*$ state has been reported in the high-resolution electronic absorption spectra of 1,8-diphenyloctatetraene[5,6] and 2,10-dimethylundecapentaene[7] and in the two-photon excitation spectra of diphenylpolyenes.[11,12] An identical level ordering in the visual chromophores, however, cannot automatically be assumed on the basis of these model compounds since little is known experimentally about the sensitivity of the $^1A_g{}^{*-}$-like ("$^1A_g{}^{*-}$")[13] state to conformational and electrostatic perturbations. In fact recent calculations predict that the ordering of the "$^1A_g{}^{*-}$" and "$^1B_u{}^*$" states in the visual chromophores is highly sensitive to conformation.[8] Since the photochemical behavior of the two states is predicted to be significantly different[8,14] an experimental determination of the level ordering is important to our understanding of polyene photochemistry both in solution and in the visual pigment.

In this paper we present a two-photon excitation spectrum which provides evidence that the "$^1A_g{}^{*-}$" state is 1600 cm^{-1} lower in energy than the "$^1B_u{}^*$" state in *all-trans*-retinol



ALL-TRANS RETINOL

(vitamin A). Our assignment is based on a theoretical analysis indicating that only "$^1A_g{}^{*-}$" $\pi\pi^*$ states have significant two-photon cross sections in nonpolar polyenes at long wavelength (non-resonance-enhanced) regions of the spectrum. The out-of-plane distortion and substituent interaction associated with the β-ionylidene ring do not alter the level ordering of the lowest energy "$^1B_u{}^*$" and "$^1A_g{}^{*-}$" $\pi\pi^*$ states in *all-trans*-retinol. However, these substituent effects reduce the energy separation of these two states relative to that observed in the analogous linear polyene, 2,10-dimethylundecapentaene.[7]

Experimental Section

all-trans-Retinol was prepared by the sodium borohydride reduction of twice-recrystallized *all-trans*-retinal (Eastman Organic Chemicals) following the procedures of Hubbard.[15] The reduction was followed spectrophotometrically and the solute taken up in petroleum ether following reduced-pressure rotary evaporation of the ethanol. The petroleum ether was washed three times with distilled water and then removed under reduced pressure. The oil was then taken up in *n*-hexane and purified using thin layer chromatography on silica gel G using a solvent mixture of *n*-hexane and ethyl acetate (90:10 v/v). TLC purification was carried out in the dark under a nitrogen atmosphere. The solute was eluted with ethanol, filtered, and stored at liquid nitrogen temperature until used. Commercial preparations of *all-trans*-retinol contained a significant amount of luminescent impurities which produced spurious emission bands. Furthermore the nonanhydrous commercial preparations consistently proved more difficult to purify using TLC than were the synthesized samples.

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