The Preparation and Characterization of Phenylhydroxycyclopropenone[1]

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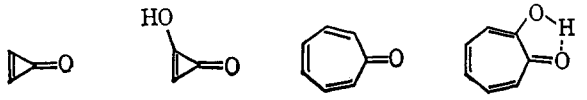
Abstract: Phenylhydroxycyclopropenone is prepared by two routes: the reactions of 2-phenyltetrachloropropene or 1-phenyl-2,3,3-trichlorocyclopropene with potassium *t*-butoxide. The compound is characterized by its physical properties, those of several transformation products, including a methyl ether, and conversion to known compounds. It is a strong acid (pK = 2) and undergoes fairly facile ring opening.

The curious combination of large strain energy, aromatic character, and reactive functional groups present in the cyclopropenones (**1**) continues to attract the attention of organic chemists challenged by the synthetic problem and anticipating the exposure of unusual reactions.[5] There is ample evidence, both empirical[5,6] and theoretical,[7] to suggest that the introduction of a hydroxyl functional group to give hydroxycyclopropenones (**2**), or cyclopropenolones, should compound both the problems and rewards. Thus, for example, the substitution of a hydroxyl group onto the aromatic tropone (**3**) to give tropolone (**4**) introduced chemists to a wealth of new reactions and substances.[6a]



1 **2** **3** **4**

The acidity of the enolic hydroxyl in cyclic α- and β-diketones and the increase of this acidity with decreasing ring size are well-documented phenomena illustrated once again in Table I. The empirical conclusion suggested by the trend evident in Table I, *i.e.*, that cyclopropenolone should be a strong acid with a pK_a near 2, is also in accord with the results of detailed theoretical calculations by Roberts[7a] and by West.[7b] The failure of one previous well-conceived attempt to synthesize phenylhydroxycyclopropenone (**5**)[6c] provided yet another goad to incite us to attempt the synthesis of this particular compound.

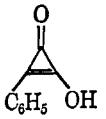


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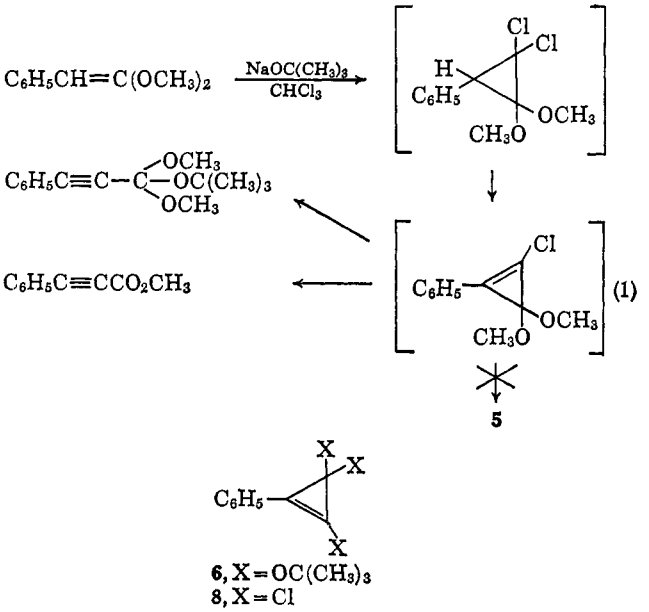
Table I. Acidities of Some Cyclic α- and β-Hydroxyenones

Compound	pK_a	Ref	Compound	pK_a	Ref
3-Hydroxycyclohex-2-enone	5.25	*a*	2-Hydroxycyclohex-2-enone	10.3	*d*
3-Hydroxycyclopent-2-enone	4.5	*b*	2-Hydroxycyclopent-2-enone	9.1	*e*
3-Hydroxycyclobut-2-enone	3	*c*	2-Hydroxy-3-phenylcyclobut-2-enone	6.3	*f*

[a] G. Schwarzenbach and K. Lutz, *Helv. Chim. Acta*, **23**, 1162 (1940). [b] J. H. Both, R. G. Wilkinson, S. Kurshner, and J. H. Williams, *J. Am. Chem. Soc.*, **75**, 1782 (1953). [c] H. H. Wasserman and E. V. Dehmlow, *ibid.*, **84**, 3786 (1962). [d] G. Schwarzenbach and C. H. Wittwer, *Helv. Chim. Acta*, **30**, 663 (1947). [e] L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1961, p 410. [f] See ref 7a.

The known ease of base-catalyzed ring opening of cyclopropenones[5a] and the failure of the McElvain synthetic sequence[6c] (1) (which gave only ring-opened products) as well as some of our own early failures brought us to a consideration of phenyltri-*t*-butoxycyclopropene (**6**) as a potentially useful synthetic intermediate. In this compound, facile cleavage of the *t*-butyl groups by anhydrous acid at low temperatures could be imagined as a mild method for conversion to **5**.



6, X = $OC(CH_3)_3$
8, X = Cl

(1) A preliminary account of a portion of this work has been published by D. G. Farnum and Paul E. Thurston, *J. Am. Chem. Soc.*, **86**, 4206 (1964).

(2) Fellow of the Alfred P. Sloan Foundation, 1962–1965.

(3) Fellow of the National Institutes of Health, 1965–1966.

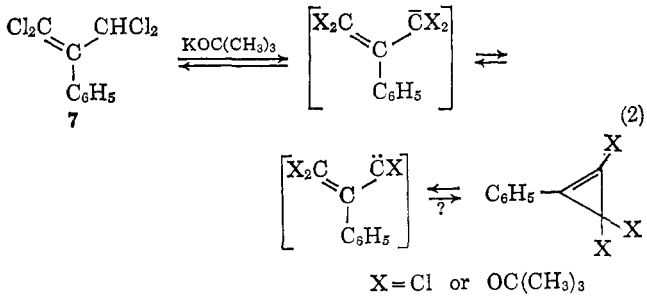
(4) Woodrow Wilson Fellow, 1960–1961; Danforth Fellow, 1960–1964.

(5) (a) R. Breslow, T. Eicker, A. Krebs, R. A. Peterson, and J. Posner, *J. Am. Chem. Soc.*, **87**, 1320 (1965); (b) M. Battiste, *ibid.*, **86**, 942 (1964); (c) B. E. Zaitsev, Yu. D. Koreshkov, M. E. Vol'pin, and Y. N. Sheinker, *Dokl. Akad. Nauk SSSR*, **139**, 1107 (1961); for a review see (d) A. Krebs. *Angew. Chem., Intern. Ed. Engl.*, **4**, 10 (1965).

(6) (a) T. Nozoe in "Non-Benzenoid Aromatic Compounds," D. Ginsburg, Ed., Interscience Publishers Inc., New York, N. Y., 1959, p 339; (b) C. H. DePuy and E. F. Zaweski, *J. Am. Chem. Soc.*, **81**, 4920 (1959); (c) S. M. McElvain and P. L. Weyna, *ibid.*, **81**, 2579 (1959).

(7) (a) E. J. Smutny, M. C. Caserio, and J. D. Roberts, *ibid.*, **82**, 1793 (1960); (b) R. West and D. L. Powell, *ibid.*, **85**, 2577 (1963).

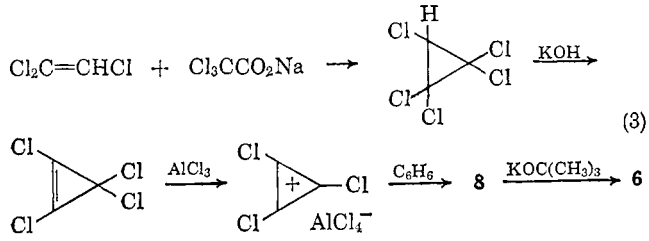
Two routes were envisioned to the key intermediate **6**. One was the potential Closs-type ring closure[8] and concomitant or subsequent solvolysis of 2-phenyltetrachloropropene (**7**) in the presence of potassium *t*-butoxide as abstracted in sequence 2. The second was a direct potassium *t*-butoxide reaction with phen-



(2)

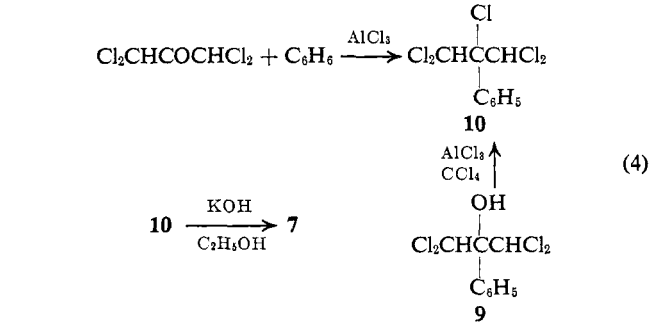
X = Cl or $OC(CH_3)_3$

yltrichlorocyclopropene (**8**), accessible as suggested in sequence 3, a preparation which appeared during the course of our work.[9]



(3)

The synthesis of the required 2-phenyltetrachloropropene had been reported by Granacher[10] as indicated in sequence 4. In our hands, reaction of *sym*-tetrachloroacetone and benzene with aluminum chloride gave the alcohol **9**, characterized as a colorless oil:



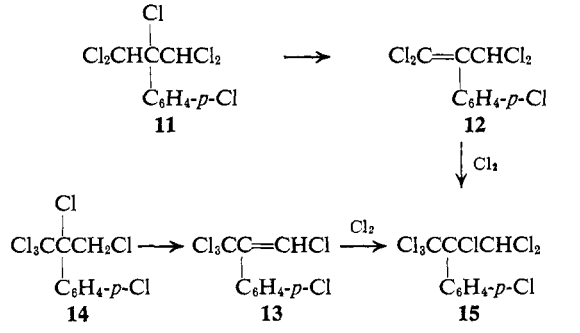
(4)

bp 172–173° (15 mm); λ_{max} (neat) 2.8 μ; τ (CCl_4) 2.4 (multiplet), 3.4 (singlet), 6.9 (singlet); area ratios 5.1:2.1:1, rather than the reported chloride **10**. Conversion of **9** to **10** was accomplished by further reaction with aluminum chloride in carbon tetrachloride. The structure of **10** was confirmed by its nmr spectrum which exhibited a multiplet for the five phenyl hydrogens at τ 2.3 and a sharp singlet for the two equivalent methine hydrogens at 3.3. Dehydrochlorination of **10** could be accomplished smoothly at room temperature with potassium hydroxide in ethanol as reported by Granacher[10] to give the olefin **7** as a white crystalline solid, mp 45–46°, easily purified by recrystallization and characterized by its nmr spectrum (CCl_4, τ 2.58, 2.92; area ratio 5:1).

(8) G. L. Closs, L. E. Closs, and W. A. Böll, *J. Am. Chem. Soc.*, **85**, 3796 (1963).
(9) S. W. Tobey and R. West, *ibid.*, **86**, 4215 (1964).
(10) C. Granacher, E. Usteri, and M. Gieger, *Helv. Chim. Acta*, **32**, 703 (1949).

It is important at this point to establish the structure of olefin **7** beyond any doubt. The evidence adduced by Granacher comes from a parallel series of reactions with the *p*-chloro derivatives. Thus, reaction of chloride **11** with ethanolic potassium hydroxide afforded the olefin **12**. The presence of an allylic hydrogen in olefin **12** rather than a vinylic hydrogen as in olefin **13** was established by independent synthesis of **13**. Reaction of chlorobenzene, *unsymmetrical* tetrachloroacetone, and aluminum chloride gave chloride **14** which was dehydrohalogenated with ethanolic potassium hydroxide to give olefin **13**. Both **12** and **13** gave the heptachlorocumene **15** upon chlorination. These transformations are summarized in Chart I.

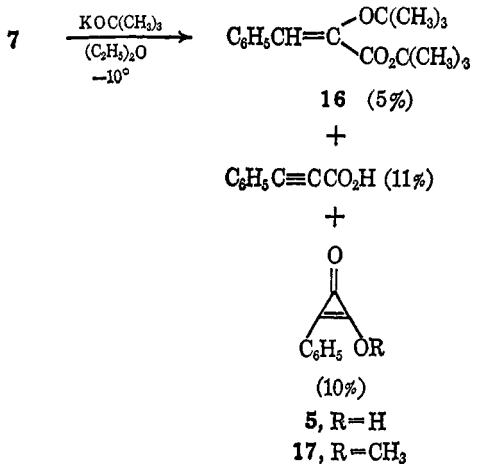
Chart I



The presence of an isopropyl rather than *n*-propyl side chain was established for the chloride **10** by catalytic hydrogenation to cumene.[10] However, we considered it necessary to execute the same demonstration for olefin **7** in order to rule out the possibility of rearrangement during dehydrohalogenation of the chlorides **10**, **11**, and **14**. Catalytic reduction of **7** afforded cumene identified by its nmr spectrum and gas chromatographic retention time.

The ring closure of **7** was attempted with potassium *t*-butoxide in ether at −10°. The product was separated into a salt fraction and an ether fraction by centrifugation. Distillation of the ether fraction afforded recovered starting material (11%) and an impure light brown oil. The major component of the oil was shown to be most probably *t*-butyl α-*t*-butoxycinnamate (**16**) (about 5% yield) by spectroscopic analysis and conversion to phenylpyruvic acid, albeit in only 22% yield, with dry HCl in ether at −20°. The infrared spectrum of the oil was consistent with the aryl unsaturated ester function with absorption at 5.90, 6.20, 6.24, and 6.32 μ. The nmr spectrum showed a very low-field vinyl proton singlet at τ 2.38 (area = 1.0) consistent with the β-vinyl proton of **16**, a five-proton multiplet at τ 2.84 consistent with the phenyl hydrogens, and two more nine-proton singlets at τ 8.60 and 8.70 for the *t*-butoxy groups. There was additional weaker resonances in the τ 8.5 to 8.8 region, presumably from impurities.

Careful acidification of the salt fraction with dilute hydrochloric acid and extraction with ether afforded a mixture of phenylpropiolic acid, isolated in 11% yield by sublimation, and a 10% yield of phenylhydroxycyclopropenone (**5**) isolated as a pale yellow, high-melting solid, insoluble in dry ether. Thus the cleavage of the *t*-butyl groups had unexpectedly taken place in the presence of the strong base, potassium *t*-butoxide.



Although the formation of the rearranged products **16** and phenylpropiolic acid could be explained by rearrangement of a carbenoid precursor (see reaction scheme 2), the isolation of phenylhydroxycyclopropenone makes ring opening of an intermediate cyclopropene an economical mechanistic route to these products as well. Thus the total extent of initial ring closure to give cyclopropene may be quite high in the reaction of olefin **7** with potassium *t*-butoxide.[11]

In practice the second proposed synthesis of phenylhydroxycyclopropenone (**5**), reaction of phenyltrichlorocyclopropene (**8**) with potassium *t*-butoxide, was a bit more effective. Tetrachlorocyclopropene was converted to crude **8** approximately according to Tobey and West's procedure[9] without purification of the intermediate. The crude **8** was treated with potassium *t*-butoxide in ether at −25° and the salt fraction was treated as before. Phenylhydroxycyclopropenone was again isolated as a pale yellow, high-melting solid in 18% yield from tetrachlorocyclopropene.

Phenylhydroxycyclopropenone as isolated in these procedures gave a poorly defined melting point near 240°. Analytical data, however, were in good agreement with a $C_9H_6O_2$ formulation, as was the neutralization equivalent of 147 (calcd 146), and the osmometric molecular weight of 80 found for the sodium salt in water (calcd for a dissociated salt, 84). The pK_a in water could be determined only approximately by the spectroscopic method[12] because of the similarity of the ultraviolet spectra of the anion and the parent acid. However, the value obtained, 2.0 ± 0.5, was in good agreement with that obtained from the half-neutralization point of the titration curve in 85% aqueous ethanol (2.2), as well as with the predicted value of 2.0 for hydroxycyclopropenone.[7] The nmr spectrum in dimethyl sulfoxide was quite in accord with the proposed structure with a five-proton broad singlet at τ 2.48 for the aromatic protons and a sharper one-proton singlet at τ 0.24 for the strongly acidic hydroxyl hydrogen. The unusual infrared spectrum of **5**, reproduced in Figure 1, provided no structural information other than confirmation of the presence of a strong acid with extensive hydrogen bonding. The infrared spectrum of the sodium salt, however, exhibited a strong, sharp peak at 5.35 μ found in many cyclopropenes and cyclopropenones,[5] as well as a strong band at 6.45 μ remarkably like that of a carboxylate anion.

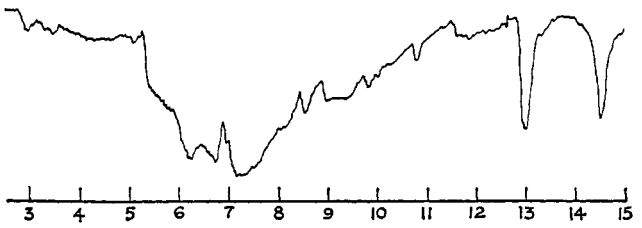
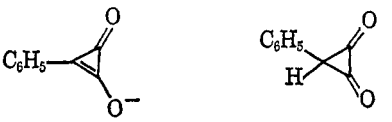


Figure 1. Infrared spectrum of phenylhydroxycyclopropenone in KBr pellet.

Recrystallization of the pale yellow, high-melting solid from acetonitrile at low temperatures afforded white needles, mp 100–101° dec. The infrared spectrum of this material was identical with that of the higher melting form although the analysis and neutralization equivalent were slightly different, and more consistent with 1/8 to 1/5 mole of water per mole of phenylhydroxycyclopropenone. The nmr spectrum was consistent with this interpretation since the ratio of the hydroxyl resonance at τ −2.6 to the phenyl resonance at τ 2.4 was 1.25 ± 0.15, in accord with the presence of about 25% water.

The similarity of the ultraviolet spectra of the anion **5a**, the parent acid **5** and its methyl ether (**17**) (*vide infra*) leaves no doubt that, in aqueous solution, phenylhydroxycyclopropenone exists essentially entirely as the enol. The solid state infrared spectrum similarly indicates a strongly acidic enol. Thus there is no evidence for the presence of the diketo form **5b**.



5a **5b**

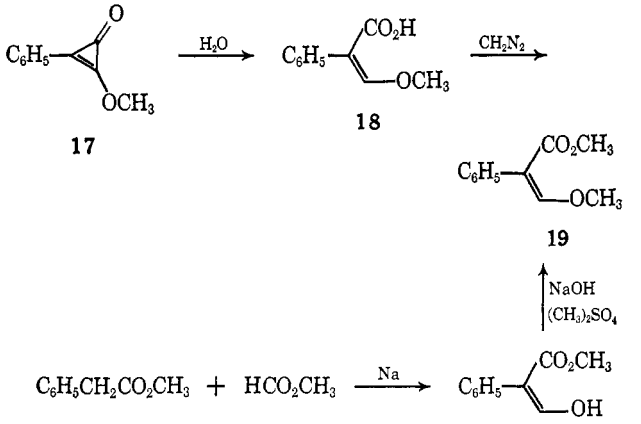
With these data in hand, it was clear that phenylhydroxycyclopropenone was the only monomeric structure consistent with the presence of a monosubstituted phenyl ring as suggested both by the origin and the nmr spectrum. Further information on both the monomeric nature and the monosubstituted phenyl was forthcoming from the methyl ether **17**, obtained from **5** and diazomethane at −25°. The moisture-sensitive, white, crystalline solid thus obtained, mp 54–57°, analyzed correctly for $C_{10}H_8O_2$ and gave a satisfactory osmometric molecular weight analysis for the monomer (calcd 160; found 160, 157). Mass spectroscopic analysis confirmed both the molecular weight and molecular formula with the appearance of a parent peak at *m/e* 160 (calcd 160) and peaks at 161 and 162 with intensities 13.4 and 1.0% of the 160 peak (calcd for $C_{10}H_8O_2$, 11.0 and 0.95%). Bands at 5.22, 5.35, and 6.05 μ in its infrared spectrum were similar to those reported for diphenylcyclopropenone.[5a] The nmr spectrum confirmed the presence of the methoxy group, which appeared as a three-proton singlet at τ 5.79, while the aromatic protons gave a five-proton multiplet centered at 2.6.

(11) In reaction scheme 2 no choice is implied or intended as to whether ring closure takes place before or after substitution of one or more chlorines by *t*-butoxide. It is probably true, however, that such substitution would increase the rate of the ring closure reaction for both steric and electronic reasons.[8]

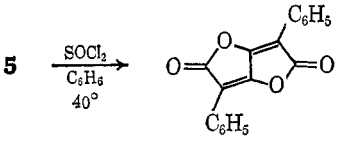
(12) L. A. Flexser, L. P. Hammett, and A. Dingwall, *J. Am. Chem. Soc.*, 57, 2103 (1935).

The presence of an unsubstituted phenyl group in **17** was further established by its facile ring opening in aqueous acetone at room temperature to give β-methoxy-α-phenylacrylic acid (**18**) (stereochemistry unknown), mp 173–174°, in high yield. The structure of this product was established by analysis, neutralization equivalent, spectroscopic data (λ_{max} 3.3–3.9 and 6.03 μ; nmr, τ 2.20, 2.35, 2.68, and 6.2; area ratios 0.9:1.1:5.0:3.1), and conversion with diazomethane to the ester **19** (stereochemistry unknown), independently synthesized as indicated in Chart II.[13]

Chart II



The sensitivity of phenylhydroxycyclopropenone to ring opening was evidenced in an attempt to reconvert it to phenyltrichlorocyclopropene with thionyl chloride at 40°. The only product isolated from this reaction was a 20% yield of the known dimeric pulvinic acid lactone (**20**) identified by comparison with a synthesized sample.[14] The unusual formation of this dimeric



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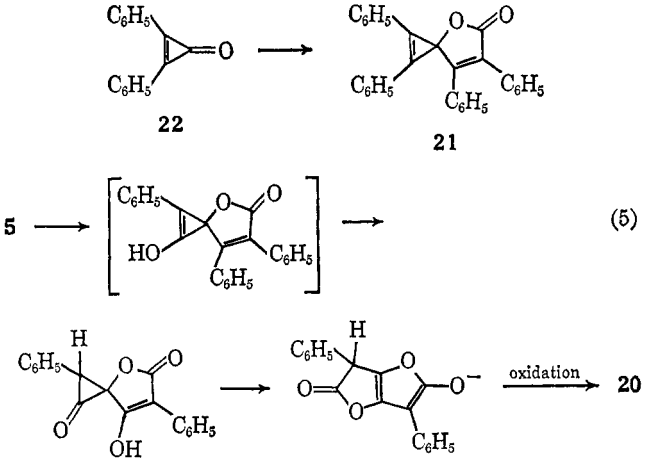
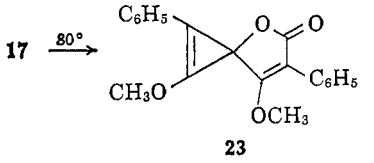
oxidation product is interpreted in reaction scheme 5 as analogous to the formation of dimer **21** from diphenylcyclopropenone **22** proposed by Breslow.[5a]



(13) W. Wislicenus and R. v. Schrötter, *Ann.*, **424**, 215 (1921); W. Wislicenus, *ibid.*, **413**, 206 (1916).

(14) F. Runge and U. Koch, *Chem. Ber.*, **91**, 1217 (1958).

Also in accord with the formulation in reaction scheme 5 is the observation that pyrolysis of the methyl ether **17** at 80° gave a 25% yield of dimeric product **23**, mp 161–161.5°. The structure proposed for this product is consistent with its analysis, nmr spectrum (τ 2.63 (broad singlet, ten phenyl hydrogens), 5.88 (singlet, three methoxy hydrogens), 6.27 (singlet, three methoxy hydrogens)) and infrared spectrum (λ_{max} 5.35 (cyclopropene), 5.78 (α,β-unsaturated γ-lactone), and 6.02 μ (double bond)).



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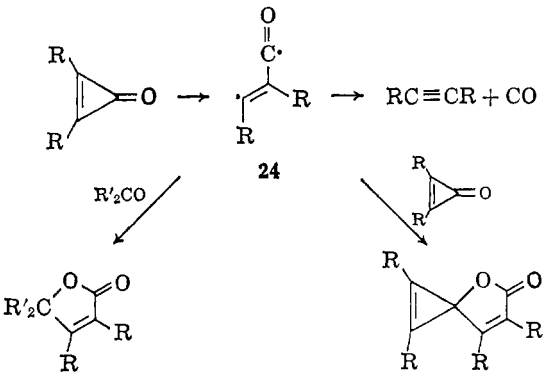
Our observations, as well as those of Breslow,[5a] of the formation of dimeric products in the pyrolysis of cyclopropenones suggest that the earlier observed decarbonylation of cyclopropenones[15] takes place in two steps. Thus it seems to be possible to trap the ring-opened intermediate (such as **24**[16]) at moderate temperatures with either additional cyclopropenone



or even with added trapping agent.[5a] It is interesting that the two-step decarbonylation of cyclopropanones and cyclopropenones is predicted to be energetically more favorable than the one-step reaction by the orbital symmetry considerations of Woodward and Hoffmann.[17]

Experimental Section[18]

2,2,4,4,6,6-Hexachlorotriketocyclohexane. According to the procedure of Zincke and Kegel[19] anhydrous phloroglucinol was prepared by heating the dihydrate (100 g) at 120° (5 mm) for 24 hr. The anhydrous phloroglucinol (75 g) and dry chloroform (250 ml) were placed in a 1-l. flask equipped with a fritted-gas inlet tube and a calcium chloride outlet tube.

The mixture was chilled to 0° and saturated with dry chlorine gas. The solution was checked for saturation at the end of 24, 48, and 72 hr. The total stirring time was 4 days. After expelling most of the

(15) R. Breslow, J. Posner, and A. Krebs, *J. Am. Chem. Soc.*, **85**, 234 (1963), and references therein.

(16) The representation **24** is one of convenience. The electronic structure might be any one or more of several possibilities.

(17) R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.*, **87**, 2046 (1965), and to be published.

(18) Melting points and boiling points are uncorrected. Analyses were performed by Scandinavian Microanalytical Laboratories, Herlev, Denmark, and Schwarzkopf Microanalytical Laboratories, Woodside, N. Y., and Galbraith Laboratories, Knoxville, Tenn. Nmr spectra were determined with a Varian A-60 spectrometer. Infrared analyses were run on a Parkin-Elmer Infracord. Mass spectra were determined on a Consolidated Engineering Type 21-103A mass spectrometer equipped with a heated inlet system.

(19) Th. Zincke and O. Kegel, *Chem. Ber.*, **22**, 1467 (1889).

excess chlorine and hydrogen chloride with dry nitrogen, the solvent was removed *in vacuo*. The crude yield (195 g) was essentially equal to the theoretical. The infrared of the pale yellow liquid had strong absorption at 5.61 μ.

***sym*-Tetrachloroacetone.** The crude product obtained above (195 g) was added dropwise to a vigorously stirred 2% solution of glacial acetic acid (500 ml). The evolution of carbon dioxide was smooth. After all the material was added, calcium carbonate (60 g) was added in *small* portions and the stirring was continued for 1 hr. The solid was removed by filtration and the filtrate was extracted four times with 50-ml portions of ether. The extracts were dried over the least amount of calcium chloride.

After distilling the solvent the product was distilled *in vacuo* at 81–82° (22 mm) (lit.[20] bp 82° (22 mm)), n^{25}D 1.4925 (lit.[20] 1.4921). The infrared (CCl_4) showed a weak singlet at 3.35 and strong peaks at 5.65 and 12.0 μ. The nmr (CCl_4) exhibited a singlet at τ 2.97.

1,1,2,3,3-Pentachloro-2-phenylpropane (10). Aluminum chloride (13.4 g) was introduced into a solution of *sym*-tetrachloroacetone (20.0 g) and dry benzene (94 g) over a period of 3 hr at 0°. The mixture was stirred for 22 hr during which time it became quite dark.

The mixture was poured into ice water (500 ml) and on stirring the purple color disappeared giving a pale yellow, organic layer. After acidification with dilute hydrochloric acid, the mixture was extracted with four 50-ml portions of ether. The extracts were dried over anhydrous magnesium sulfate. The solvent was removed by distillation at atmospheric pressure and the product was isolated by distillation *in vacuo* at 172–173° (15 mm).[21] The yield was 16.5 g.

The infrared of this oil had a sharp band at 2.8 μ indicating that it was not the desired **10** but rather the intermediate 1,1,3,3-tetrachloro-2-hydroxy-2-phenylpropane (**9**). The nmr spectrum of **9** had peaks at τ 2.4 (multiplet), 3.4 (singlet), and 6.9 (singlet) in a ratio of 5:2:1 (5.15:2.1:2).

The alcohol **9** (16.5 g) was dissolved in carbon tetrachloride (50 ml) and anhydrous aluminum chloride (1.1 equiv) was added. After stirring at room temperature for 2 hr, the dark green mixture was poured into ice water and the organic material was extracted with four 25-ml portions of ether. The ethereal extracts were dried over calcium chloride. The product (14.0 g) was isolated by distillation at 155–156° (10 mm) (lit.[10] bp 173° (15 mm)). The infrared (CCl_4) showed sharp peaks at 3.3, 6.68, and 6.90 μ. The nmr (CCl_4) had peaks at τ 2.3 (multiplet) and 3.3 in a ratio of 5:2 (5.2:2).

1,1,3,3-Tetrachloro-2-phenylpropene-1 (7). According to the general procedure of Granacher, *et al.*,[10] 56.0 g of **10** was dissolved in 95% ethanol (50 ml). This solution was added in one portion to a stirred solution of 85% potassium hydroxide (14 g) in 95% ethanol (429 ml). Although a white precipitate formed immediately, the stirring was continued for 1 hr. The solid was removed by filtration and the filtrate was reduced to a volume of 100 ml *in vacuo*. After pouring into water, the olefin was extracted with four 50-ml portions of methylene chloride. This organic layer was washed with water and then dried over calcium chloride. Removal of the solvent *in vacuo* gave a white crystalline solid (45.5 g) which melted at 45–46° (lit.[10] 45–46°).

The infrared (CCl_4) had peaks at 3.2, 6.25 (doublet), 6.7, and 6.9 μ. The nmr (CCl_4) exhibited two singlets at τ 2.58 and 2.92 in a ratio of 5:1.

Reduction of 2-Phenyl-1,1,3,3-tetrachloropropene. Phenyltetrachloropropene (0.158 g, 0.618 mmole) was added to a stirred suspension of palladium on charcoal (0.014 g) in methanolic potassium hydroxide (0.165 g, 2.5 mmoles). Hydrogen was passed over at atmospheric pressure (25°) until there was no further uptake. The solution was filtered to remove the catalyst and potassium chloride and then concentrated by distillation. Addition of ether and extraction with water, followed by drying the organic phase and removal of the solvent by distillation afforded a light-colored oil (0.074 g). Nmr showed τ (CCl_4) (crude) 8.89 (s), 8.79 (s), 7.46 (septet), and 2.85 (s). Gas chromatography of the oil resolved a major component with a retention time equal to that of cumene under conditions where cumene and *n*-propylbenzene were clearly resolved.

Reaction of 7 with Potassium *t*-Butoxide in Ether. In a 1-l., three-neck, round-bottom flask equipped with a constant-rate addition funnel, mechanical stirrer, and dry nitrogen inlet tube were placed the potassium *t*-butoxide (0.2 mole, 22.4 g) and anhydrous ether (400 ml). After flushing the system with dry nitrogen, the slurry was chilled to −10° and a solution of **7** (0.05 mole, 12.8 g) dissolved in dry ether (100 ml) was added dropwise with rapid stirring. When addition was complete the stirring was continued at −10° for 1 hr. The ice bath was removed and the temperature was allowed to rise to 25°. The stirring at 25° was continued for 21 hr.

The mixture was centrifuged to remove solids; 500 ml of dark red, supernatant liquid was obtained. The residue was washed with two 50-ml portions of pentane. These washes were combined with the supernatant. Removal of the solvent from this fraction *in vacuo* gave 11.0 g of a dark red, viscous oil.

A charge of this oil (6.5 g) was placed in a molecular still and heated to 40° (0.08 mm). This process caused the sublimation of a material whose melting point (45°) and infrared spectrum were identical with those of starting material. The yield (1.42 g) represents an 11% recovery. Raising the temperature to 65° caused the distillation of a light brown oil which exhibited infrared absorption at 5.90, 6.20, 7.20, and 7.32 μ. Assuming a molecular weight of 276, this represents a 5% yield of $C_{17}H_{24}O_3$.

The nmr spectrum of this oil showed a singlet at τ 2.38, a broad singlet at 2.84, and two closely spaced singlets at 8.60 and 8.7. There were additional weaker peaks in the region τ 8.5–8.8. The ratio of the areas of the peaks was 1:5:9:9, for the major component.

This oil (0.75 g) when treated with dry hydrogen chloride gas in ether at −20° followed by rapid removal of the solvent gave a tacky mass. Trituration with chloroform–carbon tetrachloride gave a small amount (100 mg) of a crystalline material which melted at 147–150°. The infrared had peaks at 2.9, 3.3 (broad), and 6.0 μ. These data are similar to those reported for phenylpyruvic acid (lit.[22] mp 151–154°). Attempted recrystallization of the compound resulted in its decomposition. The compound also slowly decomposes on standing.

The solids from centrifugation were allowed to air dry and then were dissolved in dilute hydrochloric acid. The mixture was immediately extracted with four 25-ml portions of ether. The *wet* ether extracts were reduced in volume to produce a red, viscous mass containing some solid. A small volume of ether was added and the mixture was filtered. The pale yellow solid was carefully washed with dry ether and then pentane. The crude weight of this compound (**5**) was 0.75 g (10% yield).

The filtrate from the isolation of **5** was warmed to 40° *in vacuo* until all solvent and volatile materials were evaporated. The infrared spectrum of the crude residue (2.5 g) showed strong absorption in the acetylenic region (4.5–4.8 μ). Upon heating to 80° (0.07 mm), a white, crystalline compound sublimed; the yield was 0.85 g (11% based on the weight of **7** used). The melting point (133–135°) and infrared spectrum (3.4, 4.5, 5.9, 13.25, and 14.6 μ) were identical with those of phenylpropiolic acid.[23] The nmr spectrum in carbon tetrachloride showed a singlet at τ 2.2 and a multiplet at 2.6 in a ratio of 1:5 (1:5.2).

Preparation of Tetrachlorocyclopropene.[24] A slightly modified procedure of Tobey and West was followed. In a typical experiment pentachlorocyclopropane (71 g, 0.332 mole) was added rapidly from atop a long reflux condenser into a stirred solution of 18 *M* aqueous KOH (80 g, 1.21 moles) previously heated to 80–85°. A vigorous exothermic reaction occurred followed by precipitation of KCl. After 15 min the reaction flask was cooled and petroleum ether (bp 30–60°) was added. Following extraction, the organic phase was washed with distilled water and dried over calcium chloride. Evaporation of the solvent under reduced pressure and vacuum distillation of the remaining liquid (39–40° (16 mm)) gave a 70% yield of tetrachlorocyclopropene.

Preparation of Trichlorocyclopropenium Tetrachloroaluminate.[25] A mixture of tetrachlorocyclopropene (7.0 g, 0.0394 mole) and anhydrous aluminum chloride (4.0 g, 0.03 mole) was warmed to 50°. An exothermic reaction was observed to take place. Upon cooling and removal of the excess tetrachlorocyclopropene under reduced pressure (room temperature (0.2 mm)) there remained solid trichlorocyclopropenium tetrachloroaluminate, characterized by its infrared absorption (KBr) at 7.42, 7.61, and 13.65 μ.

(20) E. H. Huntress, "Organic Chlorine Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948.

(21) Granacher[10] claims that this procedure gives **10**.

(22) M. L. Josien, M. Jousset-Dubien, and J. Vizel, *Bull. Soc. Chim. France*, 1148 (1957).

(23) "The Sadtler Standard Spectra," Midget ed, Sadtler Research Laboratories, Philadelphia, Pa., 1959, Spectrum No. 21017.

(24) S. W. Tobey and R. West, *Tetrahedron Letters*, 1179 (1963).

(25) S. W. Tobey and R. West, *J. Am. Chem. Soc.*, **86**, 1459 (1964).

Preparation of Phenyltrichlorocyclopropene (8).[9] The trichlorocyclopropenium tetrachloroaluminate salt obtained above was cooled to 0° and dry benzene (10 ml, 0.11 mole) was added. An immediate, brief evolution of hydrogen chloride gas was observed. The dark red reaction mixture was poured into ice water and stirred until a yellow oil was obtained. Immediate extraction with anhydrous ether followed by two successive dryings over calcium chloride yielded a clear yellow ethereal solution of phenyltrichlorocyclopropene.

Preparation of Phenylhydroxycyclopropenone (5) from Phenyltrichlorocyclopropene (8). The freshly prepared clear yellow solution of phenyltrichlorocyclopropene was added dropwise over a 0.5 hr to a vigorously stirred suspension of commercial (MSA[26]) potassium *t*-butoxide (9.0 g, 0.08 mole) under nitrogen in 500 ml of anhydrous ether at Dry Ice–carbon tetrachloride temperatures (−25°). A green color was generally observed which slowly faded as the reaction mixture was allowed to warm up. Stirring was continued for 24 hr.

The brown suspension was then centrifuged until all the solids had settled to the bottom and the dark, ethereal solution was clear. The solution was decanted and the solids were washed with petroleum ether (bp 30–60°) and then allowed to dry (several hours). The solids were dissolved in 5% hydrochloric acid and immediately extracted (pH of the aqueous solution = 1) with *wet* commercial ether. The ethereal solution was then evaporated under vacuum without application of any heat, until all the residual water had been removed. Dry, analytical ether (15–20 ml) was then added to the remaining, tacky material and the precipitate was filtered. A cream colored solid was obtained (0.81 g, 18.5% based on tetrachlorocyclopropene), which when washed with *dry* analytical acetonitrile gave faintly yellow plates with a poorly reproducible melting point near 240°. This material was identical in the infrared and nmr with compound **5** obtained above.

Nmr (dimethyl sulfoxide), τ −0.24 (1.1 H, broad s), 2.48 (5 H, broad s); λ_{max} (KBr) 3.4 (w), a broad band extending from 5.4 to 8.0 with fine structure at 6.2 (s), 6.7 (s), 6.9 (m), and 7.1 (s), and sharp peaks at 8.5 (m), 13.0 (m), 14.45 μ (m); ($CHCl_3$) 4.0, 4.3 (weak broad bands), a broad band from 5.38 to 8 with fine structure at 5.38 and broad peaks at 6.18 (s) and 7.38 μ (s); λ_{max} (water or 0.01 *N* aqueous NaOH) 275 mμ shoulder (ϵ 9240), 265 (18,000), 256 (18,000), and 204 (13,800); (1.25 *M* H_2SO_4) 266 mμ shoulder (ϵ 10,300), 256 (17,500), 248 (18,000), and 202 (18,800); (13.5 *M* H_2SO_4) 256 mμ (ϵ 19,000). The pK_a determined by the method of Flexser, Hammett, and Dingwall[12] was found to be 2.0 ± 0.5. The infrared spectrum (KBr) of the sodium salt exhibited intense, sharp bands at 5.35 and 6.45 μ.

Anal. Calcd for $C_9H_6O_2$: C, 73.96; H, 4.14; neut equiv, 146; mol wt of sodium salt (dissociated), 84. Found: C, 73.97; H, 3.96; neut equiv (aqueous ethanol, brom thymol blue end point), 147; mol wt of sodium salt (osmometric in water), 80.

Upon recrystallization of the solid from a large volume of distilled acetonitrile by cooling to −50° white needles were obtained, mp 100–101° with decomposition shortly thereafter. The infrared spectrum of this material was identical with that of the higher melting form obtained above. It could be reconverted to the higher melting form by concentration of a commercial ether solution and washing of the crystals with dry acetonitrile.

Anal. Calcd for $(C_9H_6O_2)_5 \cdot H_2O$: C, 72.2; H, 4.32; neut equiv, 149.7. Calcd for $(C_9H_6O_2)_8 \cdot H_2O$: C, 72.7; H, 4.24; neut equiv, 148.3. Found: C, 72.64; H, 4.15; neut equiv (conductometric in 85% aqueous ethanol), 153 ± 4.

Reaction of Phenylhydroxycyclopropenone with Thionyl Chloride Pulvinic Acid Lactone (20). A suspension of phenylhydroxycyclopropenone (133 mg, 0.9 mmole) in benzene (5 ml) and thionyl chloride (1.07 g, 9 mmoles) was warmed to 40° for 10 min until all the solid dissolved. Upon cooling, evaporation of the solution under vacuum, and trituration with anhydrous ether, a yellow solid was obtained (25.4 mg, 19.4%) which was washed and sublimed (150° (0.5 mm)) to give mp 230° depressed upon admixture with authentic pulvinic acid lactone[14] (*vide infra*); λ_{max} (KBr) 3.25 (w), 5.52 (s), 6.04 (s), and 7.32 μ (s), identical with the infrared spectrum of authentic pulvinic acid lactone.

Anal. Calcd for $C_{18}H_{10}O_4$: C, 74.50; H, 3.45. Found: C, 74.14; H, 3.65.

Preparation of Pulvinic Acid Lactone (20). Pyridine (6.68 g, 0.085 mole) in 30 ml of anhydrous ether was added dropwise to a mixture of phenylacetyl chloride (5.79 g, 0.038 mole) and oxalyl chloride (4.9 g, 0.0386 mole) in 20 ml of anhydrous ether. The mixture was stirred overnight at room temperature.

A yellow precipitate was evident immediately. The precipitate was filtered and extracted with ether. The ether solution when concentrated gave a 5% yield of pulvinic acid lactone, mp 230° (lit.[14] mp 226°).

Preparation of Phenylmethoxycyclopropenone (17). An equimolar amount of a dry ethereal solution of diazomethane (distilled and dried over KOH) was added to a stirred slurry of phenylhydroxycyclopropenone (0.5 g, 0.0034 mole) in 30 ml of anhydrous ether at −25° (Dry Ice–CCl_4). Evolution of nitrogen was observed and all the solid dissolved. Any residue was filtered off and the ether was immediately removed under reduced pressure. A cream-colored solid was obtained (0.47 g, 86%). Sublimation (77° (0.65 mm)) afforded colorless crystals. An analytical sample was prepared by repeated sublimations to give mp 54–57° (this moisture-sensitive compound is reasonably stable under N_2 in a freezer): λ_{max} (KBr) 5.22 (s), 5.35 (s), and 6.05 μ (s); nmr (CCl_4, TMS), τ 2.6; λ_{max} shoulder (ϵ 7370), 263 mμ (ϵ 14,500), 255 (14,900), 207 (13,250); (18 *M* H_2SO_4) 248 mμ (ϵ 22,500).

Anal. Calcd for $C_{10}H_8O_2$: C, 74.99; H, 5.02; mol wt, 160. Found: C, 74.57; H, 5.39; mol wt (osmometric, acetone), 160, 157.

Pyrolysis of Phenylmethoxycyclopropenone. Formation of Dimer 23. Phenylmethoxycyclopropenone (160 mg, 1 mmole) was heated under nitrogen and at slightly reduced pressure for 36 hr at 80°. Addition of anhydrous ether (3 ml) and storing at −50° for a period of a few days produced a crystalline solid (40 mg, 25%): mp 161–161.5°; λ_{max} l (KBr) 5.35, 5.78, and 6.02 μ; nmr ($CDCl_3$, TMS), τ 2.63 (10 H, broad s), 5.88 (2.9 H), and 6.27 (3.1 H).

Anal. Calcd for $C_{20}H_{16}O_4$: C, 74.99; H, 5.02; mol wt, 320. Found: C, 74.67; H, 4.67; mol wt, 320 (mass spectrum).

Hydrolysis of Phenylmethoxycyclopropenone. β-Methoxy-α-phenylacrylic Acid (18). Phenylmethoxycyclopropenone (20 mg, 0.124 mmole) was stirred in an actone–water solution (1:5) at room temperature overnight. Extraction into ether followed by drying over calcium chloride and evaporation afforded a colorless, crystalline solid (19.7 mg): mp 173–174° (low-temperature recrystallization from ether); λ_{max} (KBr) 3.3–3.5, 3.75, 3.9, and 6.03 μ; nmr ($CDCl_3$, TMS) τ −2.20 (0.9 H), 2.35 (1.1 H), 2.68 (5.0 H, multiplet), and 6.2 (3.1 H).

Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.42; H, 5.62; neut equiv, 178. Found: C, 67.36; H, 5.58; neut equiv (conductometric, 85% aqueous ethanol), 183 ± 2.

Esterification of 18 with Diazomethane. Methyl β-Methoxy-α-phenylacrylate (19). An equimolar amount of dry diazomethane in ether was added to the hydrolysis product **18** obtained above (50 mg, 0.28 mmole) at 0°. The reaction proceeded with evolution of nitrogen gas. After warming to room temperature, the ethereal solution under reduced pressure afforded a crystalline solid in high yield: mp 51–52° (low-temperature recrystallization from ether), undepressed upon admixture with methyl β-methoxy-α-phenylacrylate (*vide infra*); λ_{max} (KBr) 5.89 and 6.11 μ, identical with that of methyl-β-methoxy-α-phenylacrylate; nmr (CCl_4, TMS), τ 2.62 (0.95 H), 2.81 (5 H, multiplet), 6.28 (3 H) (concn, 83 mg/ml).

Preparation of Methyl β-Hydroxy-α-phenylacrylate. The method of Wislicenus was followed.[13] Methylphenylacetate (100 g, 0.667 mole) and methyl formate (45 g, 0.75 mole) were added over a 30-min period to sodium wire (15-mm diameter, 15.5 g, 0.675 g-atom) in 400 ml of anhydrous ether. The temperature of the mildly exothermic reaction was controlled by means of a water bath kept near room temperature. Effective stirring promoted the reaction which precipitated a yellow solid. After about 24 hr, filtration of the brown solution gave a yellow solid (106 g, 80%). The solid was washed with ether, dissolved in dilute sulfuric acid, extracted with ether, dried, and distilled. The colorless oil which collected at 109–111° (4.4 mm), slowly crystallized. Recrystallization from ether at low temperatures gave a solid: mp 40–41° (lit.[13] mp 41°); λ_{max} (KBr) 3.3, 3.4, 6.0, and 6.2 μ; nmr ($CDCl_3$), τ 2.74, 2.81, 2.94 (total of 7 H), and 6.38 (3.2 H). Reaction with phenyl isocyanate in pyridine converted the product to a crystalline phenylurethan, mp 136–137° (lit.[13] mp 133–134°).

Preparation of Methyl β-Methoxy-α-phenylacrylate (19). Following the procedure of Wislicenus for the analogous ethyl ester,[13] methyl β-hydroxy-α-phenylacrylate (15.0 g, 0.084 mole) and dimethyl sulfate (10 g, 0.079 mole) were cooled to 0° and a concentrated aqueous solution of sodium hydroxide (3.2 g, 0.08 mole) was added over a 15-min period with good stirring. After stirring for an additional 15 min, the reaction mixture was extracted with

(26) MSA Research Corp., Callery, Pa.

ether, dried, evaporated, and distilled. The major fraction was collected at 100–104° (0.3 mm). The colorless oil slowly crystallized. The solid was recrystallized from ether at low temperature (−50°) to give mp 51–52°; nmr (CCl_4, TMS) (concentrated solution), τ 2.62 (1 H), 2.81 (5 H, multiplet), 6.4 (6 H); (concn, 94.5 mg/ml), 2.6 (1 H), 2.79 (5 H), 6.30 (3 H), and 6.36 (3 H).

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.72; H, 6.29. Found: C, 68.74; H, 6.09.

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The Aminolysis and Amidinolysis of *p*-Nitrophenyl Acetate in Chlorobenzene. A Facile Bifunctional Reactivity.

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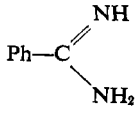
Abstract: Benzamidine has been shown to react with *p*-nitrophenyl acetate in chlorobenzene with a second-order rate constant of 3.45 M^{-1} sec^{-1}. *n*-Butylamine, a nucleophile with a basicity similar to that of benzamidine, reacts with *p*-nitrophenyl acetate in chlorobenzene by means of a third-order process, the rate of which is little affected by the presence of large amounts of a tertiary amine. Benzamidine reacts at least 15,000 times faster than *n*-butylamine monomer. This reactivity of benzamidine with the ester in the aprotic solvent is attributed to the bifunctional nature of the nucleophile. The mechanism of proteolytic enzyme action is discussed in terms of these results.

The rates of nucleophilic reactions of carboxylic acid derivatives in media containing high concentrations of organic solvents are slow compared with the rates in pure water.[1] Jencks and Gilchrist[2] have recently shown, for example, that tetrahydrofuran and ethanol inhibit the reaction of methylamine with phenyl acetate in water. It is therefore tempting to assume that the reactive sites of proteolytic enzymes are regions of high water content. On the basis of this assumption, most models of these enzymes have been studied in aqueous solutions. It is possible, however, that the catalytic sites of the enzymes are nonpolar regions and that the transition states of the enzymatic reactions are neutral in character. Indeed, none of the transition states described in the recently proposed mechanism for α-chymotrypsin-catalyzed reactions[3] involves creation of charge. In order to test the idea that a nucleophilic attack on an ester may occur readily in a nonpolar medium if the process proceeds by means of a neutral transition state and tetrahedral intermediate, we have examined the reaction of benzamidine with *p*-nitrophenyl acetate (*p*-NPA) in chlorobenzene at 25°. Benzamidine is a bifunctional nucleophile which can concertedly attack the carbonyl carbon of the ester and deliver a proton to the carbonyl oxygen, thereby forming the tetrahedral intermediate without creation of charge. For comparison purposes, the reaction of *n*-butylamine with *p*-NPA in chlorobenzene was also examined. *n*-Butylamine is similar to benzamidine in basicity but does not possess its bifunctional character.



Experimental Section

Materials. Chlorobenzene was reagent grade material which had been distilled three times from P_2O_5 through an efficient column. Two kinetic runs were performed in chlorobenzene which had been shaken with several portions of H_2SO_4, washed with aqueous K_2CO_3, and distilled five times from P_2O_5. The more careful purification of the solvent did not change the rate constants. Acetonitrile, spectro quality, was distilled repeatedly from P_2O_5.

Benzamidine was prepared from its hydrochloride salt (Aldrich), sublimed three times, and handled under nitrogen in a dry box: λ_{max} (H_2O, pH 7) 268 mμ (log ε 2.91) and 229 mμ (log ε 3.96) (lit.[4] 268 mμ (log ε 2.95) and 228 mμ (log ε 4.06)).

n-Butylamine was reagent grade material distilled twice from KOH and once from zinc dust.

Kinetics. The reaction of benzamidine with *p*-NPA was followed by measuring the increase in absorbance at 320.0 mμ, due to *p*-nitrophenol formation, using a Cary 14 spectrophotometer thermostated at 25.0 ± 0.1°. The reactions were initiated by adding 50 μl of benzamidine in acetonitrile to a cuvette containing 3.00 ml of 1.07 × 10^{-5} *M* *p*-NPA in chlorobenzene. In all the runs the benzamidine was in greater than 20-fold excess over the ester, so that pseudo-first-order conditions prevailed. The reactions with the three highest concentrations of benzamidine were followed to completion, and the first-order plots were linear to greater than 85% reaction. Stoppered cuvettes were used in all cases.

The *n*-butylamine reactions were carried out in a similar manner except that the ester was added to the amine and that 360.0 mμ was used. The absorbance readings at completion of the reactions varied somewhat with the *n*-butylamine concentration, indicative of complexation. However, Beer's law is strictly obeyed at any constant excess *n*-butylamine concentration for a large range of *p*-nitrophenol concentrations, as would be expected from the Benesi–Hildebrand equation.[5]

Release of *p*-nitrophenol was quantitative with both the aminolysis and amidinolysis of *p*-NPA. The second product of the reaction between *p*-NPA and benzamidine, N-acetylbenzamidine, could not be detected by ultraviolet spectrophotometry under the conditions used for the kinetics because of solvent absorption. It is known that amidines and esters do indeed react to give acylamidines. For example, Titherly and Hughes[6] heated phenyl benzoate with benzamidine at 50° to prepare N-benzoylbenzamidine. When

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