[CONTRIBUTION NO. 2258 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

Small-Ring Compounds. XVII. 2-Hydroxy-3-phenyl-2-cyclobutenone and Related Substances[1]

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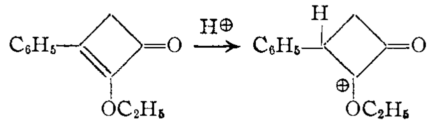
RECEIVED JANUARY 9, 1958

1,1,2-Trifluoro-2-chloro-3-phenylcyclobutane (I) undergoes dehydrohalogenation with one mole of ethanolic potassium hydroxide and is converted to 1,1,2-trifluoro-3-phenyl-2-cyclobutene (II). With excess ethanolic potassium hydroxide, I, II or 1,1,2,2-tetrafluoro-3-phenylcyclobutane (IV) yield 1,1-difluoro-2-ethoxy-3-phenyl-2-cyclobutene (III). Hydrolysis of III in 92% sulfuric acid affords 2-ethoxy-3-phenyl-2-cyclobutenone (V) which is rather more stable toward acid hydrolysis than ordinary vinyl ethers. Treatment of I with excess potassium *t*-butoxide in *t*-butyl alcohol yields 1,1-difluoro-2-*t*-butoxy-3-phenyl-2-cyclobutene (VI) which, on acid hydrolysis, gives 2-hydroxy-3-phenyl-2-cyclobutenone (VII). The pK_A of VII was found to be 3–4 units lower than the pK_A's of 2-hydroxy-2-cyclopentenone and 2-hydroxy-2-cyclohexenone.

Four-membered carbocyclic rings can be simply prepared in favorable cases by cycloaddition reactions involving two unsaturated compounds.[3] The present research is concerned with the utilization of such cycloaddition products from fluorochloroethylenes for the preparation of non-halogen containing cyclobutane derivatives.

Styrene adds very well to trifluorochloroethylene to yield 1,1,2-trifluoro-2-chloro-3-phenylcyclobutane (I).[4] The dehydrochlorination of I (the stereochemistry of which has not been investigated) to 1,1,2-trifluoro-3-phenyl-2-cyclobutene (II) has been described previously.[4] It has now been found that either I or II, when heated at reflux with an excess of potassium hydroxide in ethanol, is converted to 1,1-difluoro-2-ethoxy-3-phenyl-2-cyclobutene (III); III also can be obtained from 1,1,2,2-tetrafluoro-3-phenylcyclobutane (IV) by treatment with a twofold excess of potassium hydroxide in ethanol. Replacement of vinylic fluorine by alkoxide under similar conditions has been observed previously.[5] Compound III was converted to 2-ethoxy-3-phenyl-2-cyclobutenone (V), by hydrolysis of the *gem*-fluorines with 92% sulfuric acid, a procedure of considerable generality for preparation of 3-phenyl-2-cyclobutenones from 1,1-difluoro-3-phenyl-2-cyclobutenes.[3,4]

Interestingly, the vinyl ether function of III and V does not hydrolyze under the conditions for the synthesis of V. In fact, V was resistant to hydrolysis in refluxing 48% hydriodic acid (2 hr.) or 1.4 *M* sulfuric acid in aqueous ethanol (18 hr.). This rather remarkable hydrolytic stability can be rationalized as follows. The hydrolysis of vinyl ethers probably involves the hydration of the carbon–carbon double bond.[6] With III and V, the addition of a proton from the catalyzing acid to the double bond[7] necessitates breaking up the conjugated system and placing a positive charge adjacent to a carbon bearing two fluorine substituents (in the case of III) or a carbonyl carbon (in the case of V).



V

The hydrolysis of saturated primary ethers proceeds by way of protonation of the ether–oxygen atom followed by an SN2-type attack of water acting as a nucleophilic agent.[8] Apparently, under the conditions used, III and V are resistant to hydrolysis *via* this mechanism also.

When I is heated with potassium *t*-butoxide in *t*-butyl alcohol, 1,1-difluoro-2-*t*-butoxy-3-phenyl-2-cyclobutene (VI) is formed. When this compound is heated with 88% sulfuric acid, both the *gem*-difluoro and vinyl ether groups are hydrolyzed, yielding the 2-hydroxy-3-phenyl-2-cyclobutenone (VII). Compound VI and 2-*t*-butoxy-3-phenyl-2-cyclobutenone (a possible intermediate in the conversion of VI to VII) are not expected to be more prone to hydrolysis than III and V if the normal hydration mechanism[6,7] is involved. However, saturated tertiary ethers are hydrolyzed much more readily than primary ethers,[9] and it is likely that the conjugate acid of VI or of 2-*t*-butoxy-3-phenyl-2-cyclobutenone is cleaved with *t*-butyl–oxygen fission by an SN1-type mechanism.

Theoretically, VII can exist in tautomeric equilibrium with 1,2-diketo-3-phenylcyclobutane (VIII) and 2-hydroxy-4-phenyl-2-cyclobutenone (IX)[10]; VII and IX are expected to be favored over VIII because 1,2-cyclohexanedione and 1,2-cyclopentanedione exist wholly as the monoenols.[11] Compound VII should be more stable than IX since it has the unsaturated system of the four-ring conjugated with the phenyl group. The assigned struc-

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[2] National Science Foundation Postdoctoral Fellow, 1955–1956.

[3] See J. D. Roberts, G. B. Kline and H. E. Simmons, Jr., THIS JOURNAL, **75**, 4765 (1953), for refs. and discussion.

[4] E. F. Silversmith, Y. Kitahara and J. D. Roberts, *ibid.*, **80**, 4088 (1958).

[5] J. D. Park, M. L. Sharrah and J. R. Lacher, *ibid.*, **71**, 2337 (1949).

[6] (a) M. F. Shostakovskiĭ, *Doklady Akad. Nauk, S.S.S.R.*, **41**, 124 (1943); *C. A.*, **38**, 3607 (1944); (b) M. F. Shostakovskiĭ, *J. Gen. Chem.* (*U.S.S.R.*), **16**, 1143 (1946), *C. A.*, **41**, 2691 (1947); (c) M. F. Shostakovskiĭ and N. A. Gershteln, *J. Gen. Chem.* (*U.S.S.R.*), **16**, 937 (1946), *C. A.*, **41**, 1999 (1947); (d) R. Skrabal, *Z. physik. Chem.*, **A185**, 81 (1939).

[7] (a) R. W. Taft, Jr., THIS JOURNAL, **74**, 5372 (1952); (b) R. W. Taft, Jr., E. L. Purlee, P. Riesz and C. A. DeFazio, *ibid.*, **77**, 1584 (1955).

[8] R. L. Burwell, Jr., *Chem. Revs.*, **54**, 615 (1954).

[9] (a) J. L. E. Erickson and W. H. Ashton, THIS JOURNAL, **63**, 1769 (1941); (b) J. F. Norris and G. W. Rigby, *ibid.*, **54**, 2088 (1932); (c) T. W. Evans and K. R. Edlund, *Ind. Eng. Chem.*, **28**, 1186 (1936).

[10] The possibility of VII being in equilibrium with 1,2-dihydroxy-3-phenylcyclobutadiene is here discounted because of the failure to observe enolization of 2,4-dichloro-3-phenylcyclobutenone; E. F. Jenny and J. D. Roberts, THIS JOURNAL, **78**, 2005 (1956).

[11] G. Schwarzenbach and C. Wittwer, *Helv. Chim. Acta*, **30**, 663 (1947).

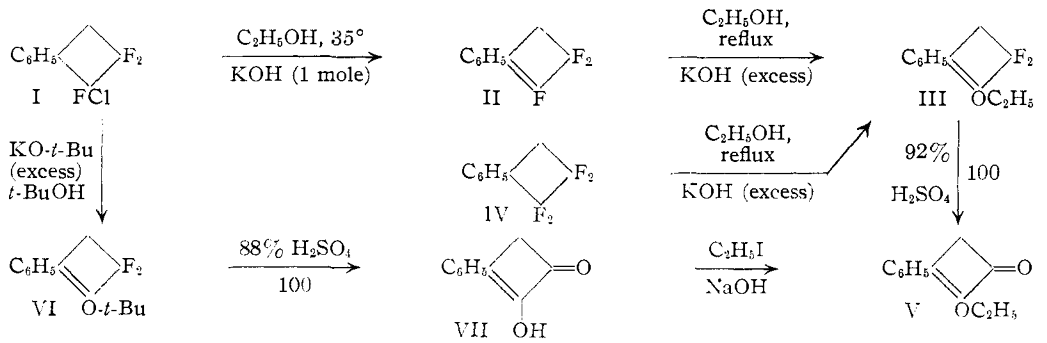
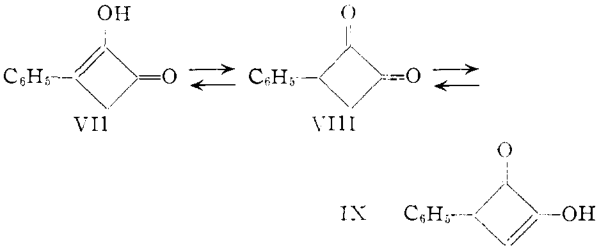


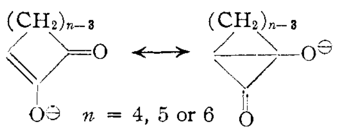
Fig. 1.—Reaction flow sheet.

ture VII is based on the following evidence. Clemmensen reduction gave phenylcyclobutane (four-membered ring), sodium carbonate solution dissolved the compound while ferric chloride solution produced a dark green color (enol) and treatment with alkali and ethyl iodide afforded the previously prepared 2-ethoxy-3-phenyl-2-cyclobutenone (V). The infrared spectrum showed absorption bands at 3.13 μ (associated hydroxyl), 6.05 μ (carbon–carbon double bond) and 6.89 μ (methylene group). The proton n.m.r. spectrum at 40 mc. in acetone solution showed resonance lines characteristic of hydroxyl, phenyl and unsplit methylene hydrogens. No vinyl proton resonance lines were noted as would be expected for IX. Interestingly, VII,



VIII and IX do not appear to be rapidly interconverted in the presence of excess alkali. Dissolution of VII in a sodium deuteroxide–deuterium oxide solution resulted in quite slow exchange of the methylene hydrogens with the solvent even on warming to 50°. On heating in strong alkaline solution, the hydroxyketone VII undergoes a ring-opening reaction.[12]

The pK_A of VII in water at 28° was determined by the half-neutralization method[13] and found to be 6.25 ± 0.05. Schwarzenbach and Wittwer[11] have reported the pK_A's of 2-hydroxy-2-cyclohexenone and 2-hydroxy-2-cyclopentenone to be 10.30 and 9.14, respectively. The phenyl group of VII could account for some of the difference in acid strength between VII and the enolic forms of the five- and six-membered α-diketones. A rough estimate of the effect of a phenyl group on acidity of a β-phenyl-substituted enol system is provided by the pK_A's of phenol (9.94[14]), o-phenylphenol (9.93[15]) and p-phenylphenol (9.51[15]). From these data, it seems unlikely that the phenyl group of VII can account for more than a small fraction of the three or four pK_A units by which the acidity of VII differs from those of the five- and six-ring hydroxycyclenones. The major difference may be due to varying degrees of stabilization of the anions by π-type interactions between electrons in the p-orbitals on the 1- and 3-positions. The importance of such interactions is expected to in-



crease as the 1,3-distance decreases. Thus, the stabilities of the anions would tend to increase with decreasing ring-size. Similar 1,3-interactions would also stabilize the undissociated acids, but would be less significant because of the concomitant charge separation.[16] Figure 1 shows a flow sheet of the various reactions studied in the present research.

Experimental

1,1,2,2-Tetrafluoro-3-phenylcyclobutane (IV).—1,1,2,2-Tetrafluoro-3-phenyl-3-cyclobutene[17] (20.7 g.) was dissolved in 100 ml. of methanol and reduced with hydrogen over 10% palladium-on-charcoal catalyst (1 g.). The theoretical quantity of hydrogen was absorbed in 30 min. The catalyst was removed by filtration and distillation gave 14.8 g. (74%) of IV, b.p. 68.0–68.2° (7.0 mm.), n^{25}D 1.4505.

1,1-Difluoro-2-ethoxy-3-phenyl-2-cyclobutene (III).—A solution of 25.8 g. of 1,1,2-trifluoro-2-chloro-3-phenylcyclobutane (I) and 20 g. of potassium hydroxide in 150 ml. of 95% ethanol was heated under reflux for 2.8 hr. The mixture was diluted with 500 ml. of water and extracted with four portions of ether. The ether extracts were combined, washed with two 100-ml. portions of water and dried over magnesium sulfate. The ether was removed and the product fractionated; III (20.9 g., 85%) was collected at 77–79° (1 mm.).

Anal. Calcd. for $C_{12}H_{12}OF_2$: C, 68.56; H, 5.75. Found: C, 68.38; H, 5.69.

A solution of 4.0 g. of 1,1,2,2-tetrafluoro-3-phenylcyclobutane (IV) and 7 g. of 85% potassium hydroxide in 40 ml.

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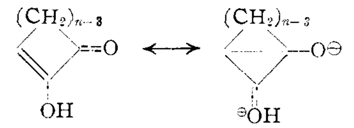
[12] L. Skattebøl and J. D. Roberts, This Journal, **80**, 4085 (1958).

[13] *Cf.* H. C. Brown, D. H. McDaniel and O. Häfliger in E. A. Braude and F. C. Nachod, "Determination of Organic Structures by Physical Methods," Academic Press, Inc., New York, N. Y., 1955, p. 571.

[14] G. R. Sprengling and C. W. Lewis, This Journal, **75**, 5709 (1953).

[15] F. Kieffer and P. Rumpf, *Compt. rend.*, **238**, 360 (1954).

[16] In unpublished research, Dr. E. J. Smutny has considered the importance of 1,3-interactions in determining the acidity of other hydroxycyclobutenones.



[17] Prepared by the addition of tetrafluoroethylene to phenylacetylene to be described elsewhere.

of ethanol was heated under reflux for 2.5 hr. and the product isolated as described above. A 68% yield of III, b.p. 77–79° (1 mm.), was obtained. The infrared spectrum was identical with that of the material prepared from I; III was also prepared from II by the same procedure.

2-Ethoxy-3-phenyl-2-cyclobutenone (V).—Compound III (20.8 g.) was added to a well-stirred mixture of 30 ml. of concentrated sulfuric acid and 5 ml. of water which had been preheated on a steam-bath. The whole was heated and stirred for 3 min., and the resulting dark-brown solution was poured into an ice–water slurry. The mixture was extracted with two 75-ml. portions of ether and the combined extracts were dried over magnesium sulfate. The ether was removed and the product was fractionated through a 10-cm. Vigreux column. A total of 13.7 g. (74%) of V was collected as an orange oil at 110.7–113.0° (1.4 mm.). The color persisted when the material was redistilled. The infrared, ultraviolet and nuclear magnetic resonance spectra were in accord with the proposed structure.

The 2,4-dinitrophenylhydrazone of V was prepared and found to have m.p. 272.0–273.6°, after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{18}H_{16}N_4O_4$: C, 58.70; H, 4.35. Found: C, 58.60; H, 4.41.

Five-gram samples of V were heated under reflux with (1) a mixture of 15 ml. of ethanol, 20 ml. of water and 3 ml. of concentrated sulfuric acid for 18 hr., and (2) 20 ml. of 48% hydriodic acid for 2 hr. After the stated reaction times, water was added and the product was extracted with ether. The extracts were washed with water, dried, and the ether distilled. The infrared spectra of the reaction products were identical with that of the starting material. The recovery from the hydriodic acid reaction was about 40%.

1,1-Difluoro-2-*t*-butoxy-3-phenyl-2-cyclobutene (VI).—1,1,2,-Trifluoro-2-chloro-3-phenylcyclobutane (I, 16 g., 0.073 mole) was added to a slurry of potassium *t*-butoxide from the reaction of 6 g. (0.154 g. atom) of potassium metal with 90 ml. of *t*-butyl alcohol and the mixture was heated under reflux for 14 hr. Water (500 ml.) was added and the whole extracted with three 100-ml. portions of ether. The combined extracts were washed with two 100-ml. portions of water, dried and the ether was removed by distillation. Fractionation of the residue yielded a small forerun of II and 13.0 g. (75%) of VI, b.p. 93–96° (1.6 mm.).

Anal. Calcd. for $C_{14}H_{16}OF_2$: C, 70.57; H, 6.77. Found: C, 70.49; H, 6.75.

2-Hydroxy-3-phenyl-2-cyclobutenone (VII).—1,1-Difluoro-2-*t*-butoxy-3-phenyl-2-cyclobutene (VI, 4.6 g.) was added at once to a stirred mixture of 3 ml. of water and 12 ml. of concentrated sulfuric acid that had been preheated on a steam-bath. The whole was heated and stirred for 2 min. and then poured into an ice–water slurry. The resulting yellow solid was separated by filtration and dried in a vacuum desiccator. The crude product was purified by dissolving it in a small amount of acetone, adding 60–70° ligroin, boiling off the acetone, and allowing the product to crystallize. In several runs the yield varied between 50 and 70%. The purest sample obtained had m.p. 155–165° dec.

Anal. Calcd. for $C_{10}H_8O_2$: C, 74.99; H, 5.03. Found: C, 75.36; H, 4.71.

The phenylurethan of VII was prepared and found to have m.p. 134.2–134.8° after recrystallization from 86–100° ligroin.

Anal. Calcd. for $C_{17}H_{13}O_3N$: C, 73.11; H, 4.69. Found: C, 73.21; H, 4.72.

The ultraviolet, infrared and nuclear magnetic resonance spectra of VII were in agreement with the proposed structure. Even pure samples underwent fairly rapid decomposition in air or under vacuum—the initially white crystals become brown within two weeks; VII was found to give a dark-green color with ferric chloride solution.

A mixture of 1.00 g. of VII, 0.25 g. of sodium hydroxide, 25 ml. of ethanol, 5 ml. of water and 10 ml. of ethyl iodide was heated under reflux for 15.5 hr. Water (200 ml.) was added and the mixture was extracted with ether. The extracts were washed with water, dried, and the ether was removed. The infrared spectrum of the residue was identical with that of the ethoxyketone V.

Compound VII (5 g.) was reduced with zinc amalgam and hydrochloric acid by the procedure used for 2,4-dichloro-3-phenylcyclobutenone,[3] except that the mixture was heated for 13.5 hr. instead of 2 hr. Fractionation of the product gave 0.33 g. of phenylcyclobutane, b.p. 46–47° (2.3 mm.), n^{25}_D 1.5243 (lit.[18] b.p. 101–102° (41 mm.), n^{20}_D 1.5277). The infrared spectrum was indistinguishable from that of authentic phenylcyclobutane.[3,19]

The dissociation constant of VII was measured as follows. A solution of 0.02 g. of VII in 180 ml. of boiled water was titrated with approximately 0.02 *N* carbonate-free[20] sodium hydroxide solution. The *p*H of the solution was measured at intervals with the aid of a Beckman model G *p*H meter with Beckman calomel and type E glass electrodes. A stream of nitrogen was bubbled through the solution during the titration. Two determinations were made, and the average pK_A (*p*H at the half-neutralization point[18]) was 6.25 ± 0.05 (28°).

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[18] F. H. Case, THIS JOURNAL, **56**, 715 (1934).

[19] E. J. Smutny and J. D. Roberts, *ibid.*, **77**, 3420 (1955).

[20] I. M. Kolthoff and E. B. Sandell, "Textbook of Quantitative Inorganic Analysis," The Macmillan Co., New York, N. Y., 1952, pp. 526–528.

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[CONTRIBUTION NO. 2296 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

Small-Ring Compounds. XVIII. Alkali-induced Ring Opening of Some Phenylcyclobutenone Derivatives[1]

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Phenylcyclobutenedione (I) has been found to decompose by the action of alkali to benzylidenepyruvic acid (X) and benzaldehyde. Similarly 2-hydroxy-3-phenyl-2-cyclobutenone (V) yields benzylpyruvic acid (VII), and 4-hydroxy-3-phenylcyclobutenedione (XI) gives phenylpyruvic acid (XII) and 1,3-diphenylpropene (XIII). Possible reaction mechanisms for the formation of these substances are proposed.

Preparations of phenylcyclobutenedione (phenylcyclobutadienoquinone, I) and several of its substitution products have been reported recently.[2] A number of reactions of these unusual substances have been investigated[3] and one of the most interesting is the conversion of I by hot alkali to benzaldehyde, 33% yield.[4] The object of the present research was to clarify the mechanism of this

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[1] Supported in part by the National Science Foundation.

[2] J. D. Roberts and E. J. Smutny, THIS JOURNAL, **77**, 3420 (1955).

[3] J. D. Roberts, *Rec. Chem. Progr.*, **17**, 95 (1956), and unpublished results in this Laboratory.

[4] First observed by Dr. E. J. Smutny.