

Bicyclobutyl Derivatives. II. Vinylic Displacement Reactions¹⁻³

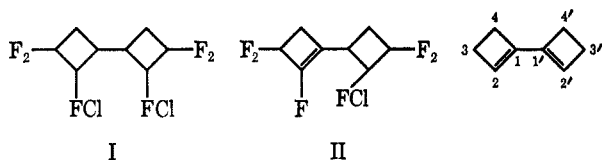
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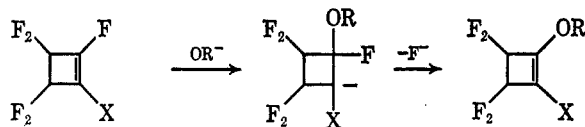
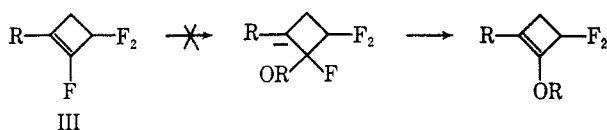
Received November 1, 1966

The vinylic fluorine atoms of 2,2',3,3,3',3'-hexafluoro(bi-1,1'-cyclobut-1-enyl)^{4,5} are very reactive to nucleophilic attack. Attack by alkoxide ion leads to a monoether at 0–100° or a diether at room temperature. Attack by secondary amines, however, leads only to a monoamino product. Sodium borohydride reduces both vinylic fluorine atoms. The corresponding 3-keto and 3,3'-diketo derivatives show even greater vinylic fluorine reactivity.

Recently a convenient and high-yield entry into the bicyclobutyl system was reported.³ This involved cycloadditions of chlorotrifluoroethylene and 1,3-butadiene. From these adducts (I and II) it has been possible to prepare a series of novel 2,2',3,3,3',3'-hexafluoro(bi-1,1'-cyclobut-1-enyl)^{4,5} derivatives. It is quite desirable to determine whether the bicyclobutenyl structure represents a new system, reacting as a diene unit, or whether it simply behaves as two cyclobutene systems, reacting independently.



Vinylic displacement reactions are well known in the cyclobutene series. Vinylic fluorine atoms of perhalocyclobutenes are especially labile to attack by nucleophiles. This reactivity is very much diminished, however, in partially halogenated cyclobutenes. Thus, alkoxide attack of 2,3,3-trifluorocyclobutene⁶ is quite difficult and attack of the corresponding 1-vinyl derivative is not even observed.³ This lack of reactivity can be explained in terms of the stability⁷ of the carbanion intermediates. While perhalocyclobutenes are capable of forming highly stabilized carbanions, 2,3,3-trifluorocyclobutenes are not nearly so capable.

R = H; CH₂=CH-

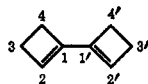
(1) Presented before the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965.

(2) This paper represents part of a Ph.D. thesis submitted to the Graduate School, University of Colorado, 1965.

(3) Previous paper in this series, J. D. Park and W. C. Frank, *J. Org. Chem.*, **29**, 1445 (1964).

(4) Naming consistent with the *Chemical Abstracts* nomenclature guide.

(5) In the text this will be shortened slightly to permit smoother reading. Thus, bicyclobutenyl will be used to designate the following structure.



(6) L. Fontanelli, Postdoctoral Fellow, University of Colorado, unpublished data.

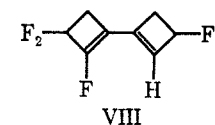
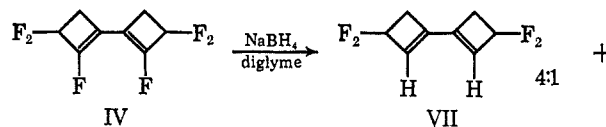
(7) J. D. Park, J. R. Dick, and J. H. Adams, *J. Org. Chem.*, **30**, 400 (1965).

Results and Discussion

2,2',3,3,3',3'-Hexafluorobicyclobutenyl (IV, Scheme I) can be regarded as two 2,3,3-trifluorocyclobutene molecules joined at their 1 positions. Unlike the latter, however, the vinylic fluorine atoms of IV were found to be very reactive to nucleophilic attack. The reactivity was, in fact, similar to that of perfluorocyclobutene. As with perfluorocyclobutene, alkoxide attack of IV tends to give a diether at room temperature.⁸ If the reaction is performed at low temperature with 1 equiv of potassium methoxide per equivalent of diene IV, a monoether, 2-methoxy-2',3,3,3',3'-pentafluorobicyclobutenyl (V) could easily be obtained. The hexafluorobicyclobutenyl (IV) could be conveniently prepared *in situ* from 1-(2-chloro-2',3',3'-trifluorocyclobutyl)-2,3,3-trifluorocyclobut-1-ene (II).

Attack of hexafluorobicyclobutenyl (IV) with morpholine or with piperidine, however, led only to the easy formation of a monoamine, 2-morpholino- (or 2-piperidino-) 2',3,3,3',3'-pentafluorobicyclobutenyl (VIa and b). Replacement of the second vinylic fluorine atom was not possible even at higher temperatures. The 2-N-morpholino group thus strongly deactivated the 2'-fluoro group. This same type of behavior was observed with perfluorocyclobutene.^{9,10} With both, a second displacement would necessitate the formation of an α -dialkylamino carbanion intermediate. The strongly electron-donating dialkylamino group would be expected to strongly destabilize the carbanions. This explains the difficulty in obtaining a second displacement with each.

Both vinylic fluorine atoms of hexafluorobicyclobutenyl IV were found to be replaceable by hydrogen. Treatment of diene IV with sodium borohydride in diglyme at 0° gave a 4:1 mixture of 3,3,3',3'-tetrafluorobicyclobutenyl (VII) and 2,3,3,3',3'-pentafluoro-

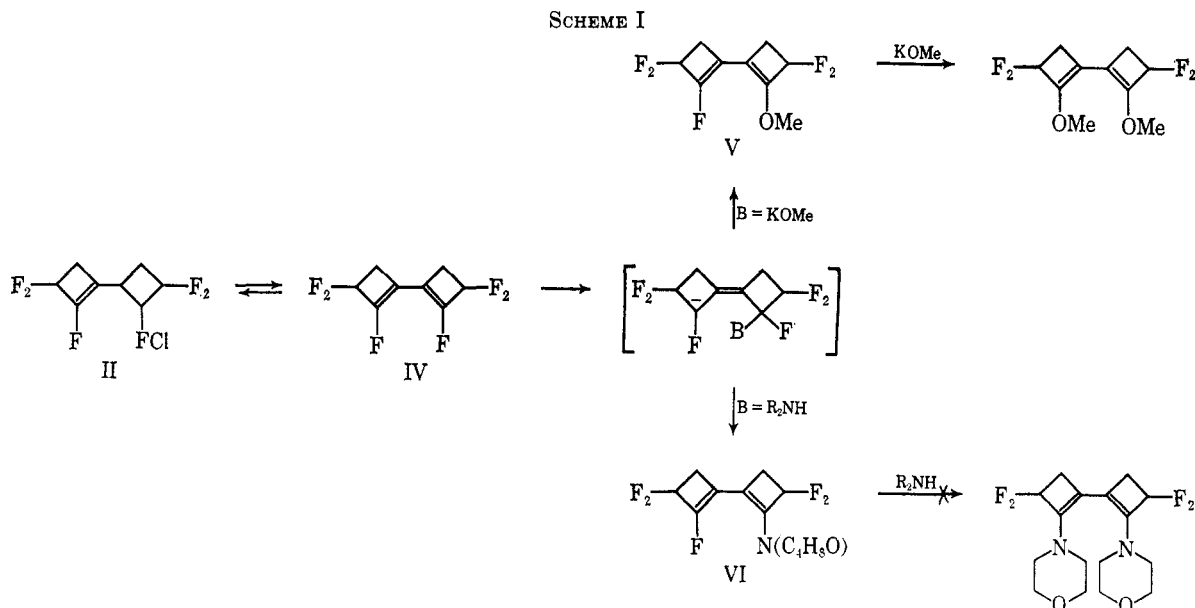


bicyclobutenyl (VIII). The latter was not isolated but observed in the infrared spectrum of the crude product and in the vapor phase chromatogram. The

(8) J. D. Park, M. L. Sharrah, and J. R. Lacher, *J. Am. Chem. Soc.*, **72**, 4480 (1950).

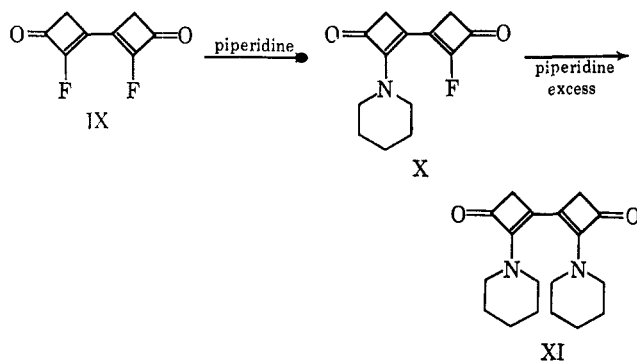
(9) R. L. Pruett, *et al.*, *ibid.*, **72**, 3646 (1950).

(10) W. C. Frank, unpublished work.



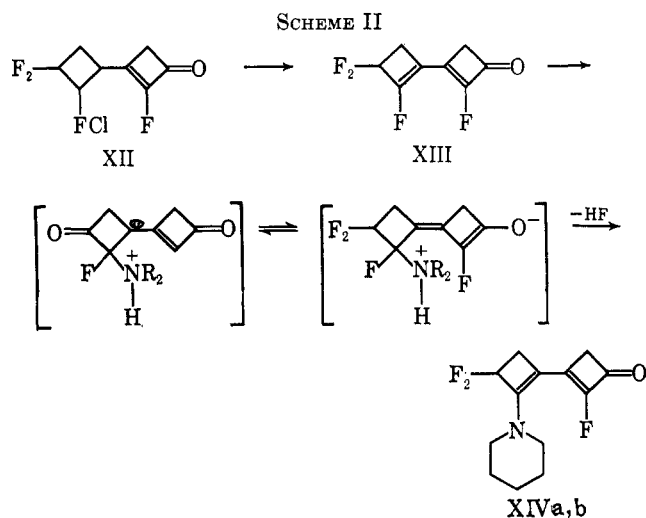
reduction of vinylic fluorine atoms with sodium borohydride in diglyme was first reported by Burton.¹¹

The vinylic fluorine atoms of 2,2'-difluoro-3,3'-diketobicyclobutenyl¹² (IX) exhibited much greater reactivity. One or both of the vinylic fluorine atoms could be displaced by piperidine depending on the base concentration to give red needles of 2-N-piperidino-2'-fluoro-3,3'-diketobicyclobutenyl (X) or orange needles of 2,2'-bis(N-piperidino)-3,3'-diketobicyclobutenyl. The difluoro diketone (IX) is thus best regarded as a vinylogous diacyl fluoride¹³ and the products are best regarded as vinylogous amides.

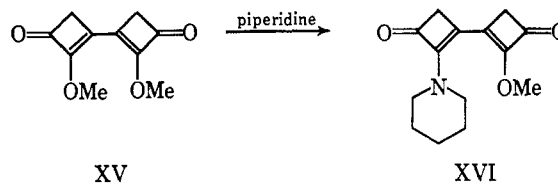


This acyl fluoride type behavior is even more striking in the reaction of morpholine or piperidine with 2,2',3,3'-tetrafluoro-3'-ketobicyclobutenyl (XIII). The latter was generated *in situ* from 1-(2-chloro-2,3,3-trifluorocyclobutyl)-2-fluoro-3-ketocyclobut-1-ene¹² (XII). In this case, it is the 2-fluoro group, not the 2'-fluoro group which is replaced to give the vinylogous monoamide, 2-N-morpholino- (or N-piperidino-) 2',3,3-trifluoro-3'-ketobicyclobutenyl. This case of extended vinylogy is also readily understood on the basis of carbanion (enol anion) intermediates (see Scheme II).

When 2,2'-dimethoxy-3,3'-diketobicyclobutenyl (XV) was dissolved in piperidine, an intense red color

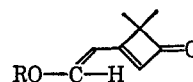


developed. On work-up, a brownish, waxy solid was obtained which could not be purified further and which is considered to be 2-piperidino-2'-methoxy-3,3'-diketobicyclobutenyl on the basis of its infrared spectrum which is quite similar to the corresponding 2'-fluoro derivative. This behavior is quite expected here and is vinylogous to the ammonolysis of esters.¹⁴ Further reaction with hot piperidine led to the formation of water-soluble, yellow-brown dyes.



Displacement of both methoxy groups of 2,2'-dimethoxy-3,3'-diketobicyclobutenyl (XV) by bases or by sulfuric acid was unsuccessful. However, on treat-

(14) An analogous facile displacement of an alkoxy group by a secondary amine has been reported with the following compound [see R. H. Hasek, D. G. Gott, and J. C. Martin, *J. Org. Chem.*, **29**, 2510 (1964)].

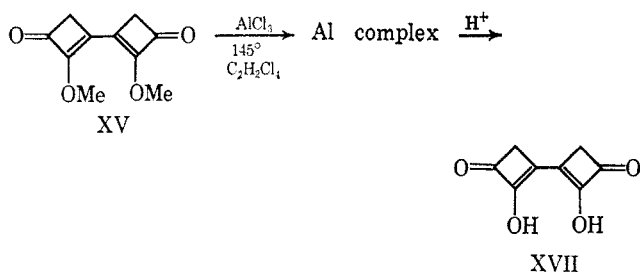


(11) D. J. Burton and R. L. Johnson, *J. Am. Chem. Soc.*, **86**, 5361 (1964).

(12) See paper III of this series [J. D. Park and W. C. Frank, *J. Org. Chem.*, **32**, 1336 (1967)] for preparation and also for infrared spectral correlation table for bicyclobutenyl derivatives prepared to date.

(13) J. D. Park, S. Cohen, and J. R. Lacher, *J. Am. Chem. Soc.*, **84**, 2919 (1962).

ment of the diketone with anhydrous aluminum chloride in refluxing tetrachloroethylene, an aluminum complex formed which on hydrolysis yielded 2,2'-dihydroxy-3,3'-diketobicyclobutenyl, (XVII), a weakly acidic, yellow powder. Dihydroxy compound XVII was found to form with silver nitrate a soluble complex which failed to precipitate when chloride ion was added.



Experimental Section

2-Methoxy-2',3,3,3',3'-pentafluorobicyclobutenyl (V).—A solution of 1-(2',3',3'-trifluoro-2-chlorocyclobutyl)-2,3,3-trifluorocyclobut-1-ene (II, 25.0 g, 0.10 mole) in 100 ml of absolute methanol was cooled to 0° and a solution of 12.0 g (0.214 mole) of potassium hydroxide in 100 ml of absolute methanol was slowly added dropwise, with stirring and cooling (0–10°). After the addition, the ice bath was allowed to warm to room temperature; the following day the reaction was poured into 700 ml of ice water and the organic layer was allowed to separate. The lower layer was dried over calcium sulfate. The crude monoether (V) amounted to 19.63 g (87%), n_D^{20} 1.4270. The infrared spectrum contained significant peaks at 2980, 1710, 1640, and 1348 cm^{-1} .

Anal. Calcd for $\text{C}_8\text{H}_7\text{F}_5\text{O}$: C, 47.7; H, 3.10; F, 42.0. Found: C, 47.47; H, 3.10; F, 41.79.

2-N-Morpholino-2',3,3,3',3'-pentafluorobicyclobutenyl (VIa).—In a 250-ml flask equipped with a stirrer, reflux condenser, and addition funnel was placed 38.0 g (0.43 mole) of morpholine and 100 ml of dioxane. To this was added dropwise with cooling 25.0 g (0.10 mole) of 1-(2-chloro-2,3,3-trifluorocyclobutyl)-2,3,3-trifluorocyclobutene (II). The temperature was kept below 40°. After the addition, heat was applied and the mixture was allowed to warm to 60–65° for 5 min. After cooling, ice water was added to the mixture with stirring. A yellowish solid separated which was filtered off and recrystallized from anhydrous methanol. The first crop amounted to 22.4 g and melted at 88.5°. The infrared spectrum contained characteristic peaks at 1690, 1630, 1350, 913, 870, 753, and 708 cm^{-1} .

Anal. Calcd for $\text{C}_{12}\text{H}_{12}\text{F}_5\text{NO}$: C, 51.2; H, 4.26; F, 33.8. Found: C, 50.80; H, 4.16; F, 32.14.

2-N-Piperidino-2',3,3,3',3'-pentafluorobicyclobutenyl (VIb).—In 50 ml of dioxane was dissolved 10 g (0.04 mole) of 1-(2,3,3-trifluoro-2-chlorocyclobutyl)-2,3,3-trifluorocyclobutene (II). To this was added dropwise with cooling and stirring 8.5 g (0.10 mole) of piperidine. After the addition the mixture was stirred at room temperature for 1 hr. The reaction was worked up by washing in ice water with shaking and filtering off and washing the creamy white solid. On drying the product 10 g of yellowish solid was obtained. The infrared spectrum contained significant peaks at 1690, 1630, 1445, and 915 cm^{-1} . The product was recrystallized from Skellysolve F. It melted at 62.0–62.5°.

Anal. Calcd for $\text{C}_{13}\text{H}_{14}\text{F}_5\text{N}$: C, 56.0; H, 5.02; F, 34.0. Found: C, 56.42; H, 5.05; F, 34.03.

3,3,3',3'-Tetrafluorobicyclobutenyl (VII).—In a 500-ml, round-bottom flask equipped with a mechanical stirrer, addition funnel, and ice-acetone bath was placed a solution of diene IV (21.4 g, 0.1 mole) in 75 ml of diglyme (freshly distilled over lithium aluminum hydride). When the solution temperature went below 0° a solution of sodium borohydride (2.4 g, 0.063 mole) was dropped in slowly, keeping the temperature at 0°. After the addition, the solution was stirred at 0–5° for 1.5 hr and then was allowed to rise slowly to room temperature. Ten milliliters of water was added very cautiously followed by 5 ml of 6 N hydrochloric acid. Considerable foaming occurred. The mixture was poured over 700 ml of ice water and shaken vigorously. A fluffy, white solid separated. Two hours later the solid was filtered under

slight vacuum (*caution*—product has high vapor pressure) and washed with cold water. About 18.0 g of moist product was obtained which was dissolved in Skellysolve F. The solution was dried over anhydrous magnesium sulfate, concentrated over a steam bath until saturated, then chilled to –20°; 16.5 g of product was obtained; this was found by vapor phase chromatography to contain one part of 2,3,3,3',3'-pentafluorobicyclobutenyl (VIII) to four parts of 3,3,3',3'-tetrafluorobicyclobutenyl (VII). An analytical sample was prepared by vapor phase chromatography and melted at 85–86°. The infrared spectrum contained characteristic peaks at 1545, 1435, 910, and 692 cm^{-1} .

Anal. Calcd for $\text{C}_8\text{H}_6\text{F}_4$: C, 53.9; H, 3.39; F, 42.5. Found: C, 53.86; H, 3.69; F, 41.39.

Reaction of 2,2'-Difluoro-3,3'-diketobicyclobutenyl (IX) with Piperidine. A.—About 0.1 g of diketone IX was dissolved in 10 ml of ether and several drops of piperidine was added with stirring. The solution was filtered and the filtrate was allowed to evaporate to dryness yielding long, red needles of 2-N-piperidino-2'-fluoro-3,3'-diketobicyclobutenyl (X), mp 125°. The infrared spectrum contained characteristic peaks at 1745, 1605, and 1580 cm^{-1} . A similar product could be obtained using diethylamine instead of piperidine.

Anal. Calcd for $\text{C}_{13}\text{H}_{14}\text{FNO}_2$: C, 66.2; H, 5.95; F, 8.20. Found: C, 66.1; H, 5.79; F, 8.14.

B.—About 0.2 g of diketone IX was added slowly with vigorous stirring to 5 ml of piperidine. The reaction was very exothermic. Five minutes later the deep red-orange solution was poured into 50 ml of ice water. A red-orange solid which slowly deposited was filtered off and recrystallized from hot Skellysolve C. Red-orange needles of 2,2'-bis(N-piperidino)-3,3'-diketobicyclobutenyl (XI) were obtained melting at 109–110°. The infrared spectrum contained characteristic peaks at 1720 and 1560 cm^{-1} .

Anal. Calcd for $\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_2$: C, 72.0; H, 8.00; N, 9.33. Found: C, 71.82; H, 7.96; N, 9.13.

2'-N-Morpholino-2,3',3'-trifluoro-3-ketobicyclobutenyl (XIVa).—To a solution of 5 ml of morpholine in 10 ml of monoglyme, 1.0 g of 1-(2-chloro-2,3,3-trifluorocyclobutyl)-2-fluoro-3-ketocyclobutene (XII) was added dropwise with stirring. The reaction was very exothermic and a white precipitate formed. The reaction mixture was poured into 25 ml of ice water. A bright yellow solid which separated was filtered off and recrystallized from hot Skellysolve C. Bright yellow needles of XIVa were thus obtained, melting at 111°. The infrared spectrum contained peaks at 1775, 1630, and 1605 cm^{-1} .

Anal. Calcd for $\text{C}_{12}\text{H}_{12}\text{F}_3\text{NO}_2$: C, 55.6; H, 4.64; F, 22.0; N, 5.40. Found: C, 55.66; H, 4.76; F, 22.19; N, 5.51.

Similarly, 2'-N-piperidino-2,3',3'-trifluoro-3-ketobicyclobutenyl (XIVb) was obtained by using piperidine instead of morpholine in the above procedure. Yellow-orange needles from Skellysolve C, mp 133°, were thus obtained. The infrared spectrum was similar to that of the above morpholino derivative.

Reaction of XV with Piperidine at Room Temperature.—Diketone XV (2.0 g) was allowed to dissolve slowly in 25 ml of piperidine with frequent shaking. Quickly a bright red-orange color formed. When dissolution was complete (5 hr) the solution was poured into 150 ml of cold salt water and then extracted twice with methylene chloride. The extracts were dried over anhydrous magnesium sulfate and then stripped *in vacuo*. A brownish yellow, waxy solid was thus obtained. Attempts to crystallize this were unsuccessful. The infrared spectrum contained characteristic peaks at 1740, 1635, and 1600 cm^{-1} , and supported the assignment of 2-N-piperidino-2'-methoxy-3,3'-diketobicyclobutenyl (XVI) for the product.

2,2'-Dihydroxy-3,3'-diketobicyclobutenyl (XVII).—The best procedure found consisted of separately pulverizing 2,2'-dimethoxy-3,3'-diketobicyclobutenyl (XV, 10.0 g, 0.05 mole) and 20 g of aluminum chloride (anhydrous). The two powders were then ground together. In a 250-ml, round-bottom flask equipped with a reflux condenser and a mechanical stirrer, 150 ml of tetrachloroethane was heated almost to reflux. The powder mixture was then added slowly in portions and after the addition the mixture was heated to reflux for 1 hr. The mixture was then allowed to cool and 250 ml of Skellysolve B was added. The red-orange precipitate was filtered off and pumped dry. On standing in air the aluminum complex became bright yellow in color. The aluminum complex after setting in air for a few days was dissolved in a minimum amount of water and the unreacted diether-diketone was removed by filtration. The bright yellow

filtrate was acidified with concentrated hydrochloric acid. On standing a yellow precipitate formed which on filtering amounted to 5–7 g, mp 220° dec. The infrared spectrum contained characteristic peaks at 3150, 1710, 1610, 1320, 1230, and 945 cm^{-1} . The infrared spectrum of the aluminum complex contained broad peaks at 2900–3400, 1100–1200, 840–850, and sharper peaks at 2420, 1950, and 1640 cm^{-1} . Solutions of the complex dissolved silver nitrate without formation of silver chloride. Addition of a sodium chloride solution also failed to cause precipitation indicating that a stable soluble silver complex had formed.

Anal. Calcd for $\text{C}_8\text{H}_6\text{O}_4$: C, 57.8; H, 3.62. Found: C, 56.31; H, 3.83.

Registry No.—V, 10103-12-5; VIa, 10074-64-3; VIb, 10074-65-4; VII, 10074-66-5; VIII, 10074-67-6; X, 10074-68-7; XI, 10074-69-8; XIVa, 10074-70-1; XIVb, 10074-71-2; XVI, 10074-72-3; XVII, 10074-73-4.

Acknowledgment.—The authors wish to express their appreciation to the U. S. Army Natick Laboratories, Natick, Mass., under Scientific Project Officer Dr. Malcolm C. Henry, and to the Minnesota Mining and Manufacturing Co., St. Paul, Minn., for their partial support of this work.

Bicyclobutyl Derivatives. III. Hydrolysis of Fluorinated Cyclobutenes^{1,2}

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A series of cyclobutene and bicyclobutyl derivatives was studied with respect to ease of sulfuric acid catalyzed hydrolysis. Evidence is presented in support of a proposed reaction pathway. A number of new ketones are described.

The facility with which 2,2'-dialkoxy-3,3,3',3'-tetrafluorobicyclobutenyl (I)⁴ is hydrolyzed with cold sulfuric acid to diketone II (2,2'-dialkoxy-3,3'-diketobicyclobutenyl)^{2a} has led to further investigation of the hydrolysis reactions of fluorinated cyclobutenes.

Acyclic α -difluoro ethers⁵ and amines⁶ are easily hydrolyzed to the corresponding esters and amides, respectively, in acid. The pathway for the hydrolyses has been quite uncertain.⁷

Also, a series of 2-substituted 1-phenyl-3,3-difluorocyclobutenes has been hydrolyzed to the corresponding 3-ketones by Roberts and his group.⁸ Their work reveals no clear-cut influence of 2 substituents on the ease of acid-catalyzed hydrolysis.

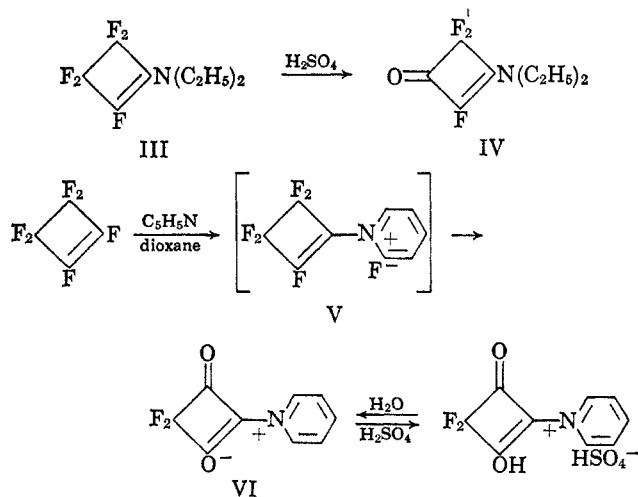
The acid-catalyzed hydrolysis of benzotrifluorides has been reviewed recently⁹ and the reaction has been shown to be dependent on the ring substituents. Thus, electron-donating groups *ortho* or *para* to the CF_3 greatly enhance the reaction, while electron-withdrawing groups in these positions have the opposite effect. *meta* substituents show little or no effect on the hydrolysis.

Results

When 1-diethylaminopentafluorocyclobutene (III) was dissolved in cold sulfuric acid, hydrolysis occurred rapidly and a monoketone was obtained in high yield as the sole product. This was shown to be 1-diethylamino-3-keto-2,4,4-trifluorocyclobutene (IV) by its F^{19} nmr spectrum.

On the other hand, perfluorocyclobutene forms an unstable complex (V) with pyridine which reacts with moisture to form 3,3-difluoro-2,4-diketocyclobutylpyridiniumbetaine (VI, see Scheme I). This type of behavior was first observed by Pruett¹⁰ in the reaction of trialkylamines with perfluorocyclobutene. The pyridinium betaine which dissolved in sulfuric acid without further hydrolysis, was recovered unchanged on quenching in water.

SCHEME I
HYDROLYSIS OF PERFLUOROCYCLOBUTENYLAMINES

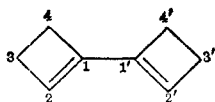


(1) Presented at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965.

(2) Previous papers in this series: (a) J. D. Park and W. C. Frank, *J. Org. Chem.*, **29**, 1445 (1964); (b) *ibid.*, **32**, 1333 (1967).

(3) This paper represents part of a Ph.D. thesis submitted by W. C. Frank to the Graduate School, University of Colorado, 1965.

(4) This structure is more properly written (bi-1,1'-cyclobut-1-enyl) consistent with *Chemical Abstracts* Nomenclature Guide. To permit smoother reading the shortened form will be used throughout the text. The numbering for the bicyclobutenyl structure is as follows.



(5) J. A. Young and P. Tarrant, *J. Am. Chem. Soc.*, **71**, 2432 (1949); **72**, 1860 (1950).

(6) R. L. Pruett, *et al.*, *ibid.*, **72**, 3646 (1950).

(7) E. R. Larson, *J. Org. Chem.*, **28**, 1133 (1963).

(8) (a) J. D. Roberts, *et al.*, *J. Am. Chem. Soc.*, **80**, 4083 (1958); (b) *ibid.*, **80**, 5840 (1958); (c) *ibid.*, **82**, 3106 (1960); (d) *ibid.*, **86**, 2645 (1964).

(9) R. Fillar and H. Novar, *Chem. Ind. (London)*, 1273 (1960).

The effect of 1 substituents on the hydrolysis of 2,3,3-trifluorocyclobutenes was studied and the results

(10) R. L. Pruett, C. T. Bahner, and H. A. Smith, *J. Am. Chem. Soc.*, **74**, 1633 (1952).