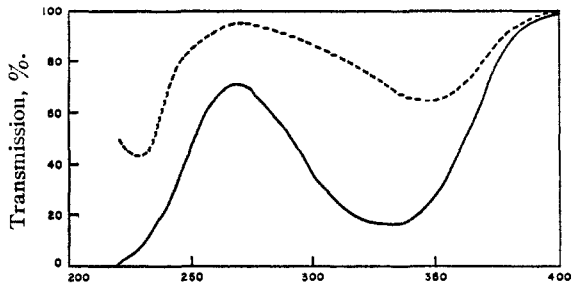


Fig. 1.—Ultraviolet absorption spectra of: —, 1-[2-(heptafluorocyclobutyl)-2,3,3,4,4-pentafluorocyclobutyl]-4-carbethoxypyridinium carbeniate, c, 4.61 × 10^{-4} mole/liter; · · · · (3,3-difluoro-2,4-dioxocyclobutyl)-3-bromopyridinium betaine, c, 1.17 × 10^{-5} mole/liter.

the method of Rickard, Ball and Harris.[9] Fluorine, in the absence of nitrogen, was determined by the method of Clark.[10]

Conclusions

It may be seen that the nature of the products obtained from the reactions of tertiary amines with polyfluoroölefins varies greatly with the type of amine. There is little similarity between the products obtained from aliphatic tertiary amines and polyfluoroölefins and those obtained from aromatic heterocyclic tertiary amines with polyfluoroölefins.

From the results of this investigation, it may be concluded that a highly fluorinated group exerts a very strong attraction for electrons. It is known that in tris-(nonafluorobutyl)-amine the presence of the unshared electrons of the nitrogen atom cannot be detected by ordinary means, such as reaction with acids, methiodide formation, picrate formation, etc. Also the powerful electrophilic character of boron trifluoride is due to the electron pull of the fluorine atoms. In this investigation the stability of 1-[2-(heptafluorocyclobutyl)-2,3,3,4,4-pentafluorocyclobutyl]-4-ethoxypyridinium carbeniate and its analogs is due greatly to the ability of the fluorinated cyclobutyl rings to absorb the unshared electrons of the trivalent carbon atom. Since this type of compound did not form with aliphatic tertiary amines and is formed in greatest quantity when the attached amine also contains an electron-attracting group, it appears that both the fluorinated alkyl groups and the aromatic groups are necessary for complete stabilization.

OAK RIDGE, TENN. RECEIVED AUGUST 10, 1951

(9) R. R. Rickard, F. L. Ball and W. W. Harris, *Anal. Chem.*, **23**, 919 (1951).

(10) H. S. Clark, *ibid.*, **23**, 659 (1951).

[JOINT CONTRIBUTION FROM THE UNIVERSITY OF TENNESSEE AND THE RESEARCH LABORATORIES, K-25 PLANT, CARBIDE AND CARBON CHEMICALS COMPANY]

Reaction of Polyfluoro Olefins. VIII.[1] Reactions of Hexafluorocyclobutene with Isoquinoline and 3-Methylisoquinoline[2]

BY ROY L. PRUETT, CARL T. BAHNER AND HILTON A. SMITH

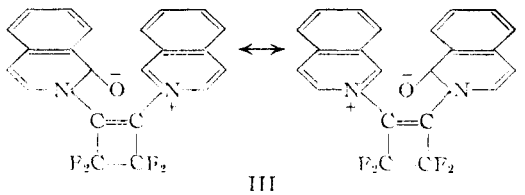
Isoquinoline reacted with hexafluorocyclobutene to give a compound sensitive to hydrolysis. The hydrolysis product was stable but could be degraded with acid to (3,3-difluoro-2,4-dioxocyclobutyl)-isoquinolinium betaine. 2-[2-Heptafluorocyclobutyl)-2,3,3,4,4-pentafluorocyclobutyl]-isoquinolinium carbeniate was produced as a secondary product. 3-Methylisoquinoline with this butene gave, after hydrolysis, (3,3-difluoro-2,4-dioxocyclobutyl)-3-methylisoquinolinium betaine, together with an unidentified product. Quinoline did not react with hexafluorocyclobutene.

Discussion

In previous papers of this series, the reactions of hexafluorocyclobutene with aliphatic tertiary amines[3] and with pyridine and its derivatives[1] have been described. The reaction products of these two types of compounds with hexafluorocyclobutene were found to be only slightly similar in nature. Isoquinoline and 3-methylisoquinoline have been found to react in a manner analogous to each of these types, and also to produce a third type of reaction.

3-Methylisoquinoline reacted slowly with hexafluorocyclobutene in ether solution to give, in short periods of time, a compound which hydrolyzed to give a product having the betaine structure, (3,3-difluoro-2,4-dioxocyclobutyl)-3-methylisoquinolinium betaine (I). With longer periods of time this compound was also produced, but the major product was a solid which could not be purified.

Isoquinoline reacted easily with hexafluorocyclobutene in ether solution. Two products were isolated from the reaction mixture. One of these proved to be 2-[2-(heptafluorocyclobutyl)-2,3,3,-4,4-pentafluorocyclobutyl]-isoquinolinium carbeniate (II), an analog of the type of product which was isolated in the cases of ethyl nicotinate and ethyl isonicotinate with hexafluorocyclobutene.[1] The other, which was the major product, was isolated after hydrolysis, and analysis and molecular weight determinations indicated the formula $C_{22}H_{14}N_2OF_4$. Three of the possible structural formulas are

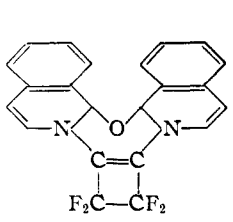


III

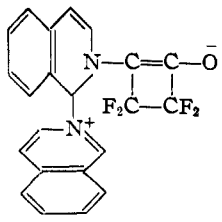
(1) The previous paper in this series is: R. L. Pruett, C. T. Bahner and H. A. Smith, THIS JOURNAL, **74**, 1638 (1952).

(2) This document is based on work performed for the Atomic Energy Commission by Carbide and Carbon Chemicals Company at Oak Ridge, Tennessee.

(3) R. L. Pruett, C. T. Bahner and H. A. Smith, THIS JOURNAL, **74**, 1633 (1952).



IV



V

Another possibility would be that the structure is actually a resonance hybrid of III and IV.

There are several objections which may be raised concerning each of the above structures, both as to means of preparation and as to properties of the final product. For this reason, no definite assignment has been made.

The final product (III, IV or V) reacted easily with acidic substances. With concentrated hydrobromic acid, it formed (2-bromo-3,3,4,4-tetrafluorocyclobutenyl)-isoquinolinium bromide. This bromide hydrolyzed easily in boiling water to produce (3,3 - difluoro - 2,4 - dioxocyclobutyl) - isoquinolinium betaine. With concentrated hydrochloric acid, the intermediate chloride could not be isolated, probably due to its greater reactivity with water.

The ultraviolet absorption spectra of the two betaines, the carbeniate, and the unknown isoquinolinium derivative were obtained in the region 220–440 mμ. The absorption in the region of 230 mμ cannot be taken as an indication of the betaine structure in those cases where an isoquinoline ring was present, since this ring itself would be expected to absorb at this wave length.[4] This was confirmed by measuring the absorption of isoquinoline ethiodide, which was found to absorb at this wave length.

Experimental

Materials.—The amines were obtained from Eastman Kodak Company and used without further purification. The hexafluorocyclobutene was prepared as previously described.[5]

Compound $C_{22}H_{14}N_2OF_4$ (III, IV or V).—Forty-one grams of isoquinoline was dissolved in 300 ml. of absolute ether and the solution was placed in a stainless-steel reaction vessel. The vessel and contents were cooled in liquid nitrogen and 37 g. of hexafluorocyclobutene was added by distillation. After all the butene had been added, the vessel was closed and allowed to warm to room temperature.

After standing at room temperature for forty hours, the reactor was opened. The ether solution was mixed with about 200 ml. of water and, after the reaction had subsided, the water layer was separated. The ether layer was evaporated nearly to dryness and the residue was mixed with methanol and the mixture filtered. This produced 37 g. of solid, m.p. 158–161° dec. The yield was 59% calculated from isoquinoline or 41% calculated from the butene. Purification by recrystallization from chloroform gave a final melting point of 168–169° dec.

Anal. Calcd. for $C_{22}H_{14}N_2OF_4$: C, 66.16; H, 3.53; N, 7.02; F, 19.0; mol. wt., 398. Found: C, 65.82, 65.88, 65.93; H, 3.70, 3.59, 3.58; N, 7.05, 6.59, 6.32; F, 17.4, 17.6, 18.8; mol. wt., 397, 433.

2-[2-(Heptafluorocyclobutyl)-2,3,3,4,4-pentafluorocyclobutyl]-isoquinolinium Carbeniate.—Forty-one grams of isoquinoline, 300 ml. of ether and 40 g. of hexafluorocyclobutene were sealed together in a reaction vessel and allowed to stand at room temperature for 40 hours. One hundred milliliters of the resulting ether solution was mixed with 50 ml. of methanol. After standing overnight at room temperature, the solution was concentrated by distillation at room temperature and reduced pressure to a volume of 30 ml. Continued cooling at −78° caused crystals to appear in the concentrate. After filtering the solution and drying the retained crystals, the product weighed 4.0 g. and melted slowly above 60°. The yield of this crude material was 10% calculated from isoquinoline or 24% calculated from hexafluorocyclobutene.

The yellow crystals were purified by dissolving in methanol at room temperature and cooling this solution in a Dry Ice–trichloroethylene-bath. Three recrystallizations conducted in this manner gave a snow-white solid, m.p. 68–69°.

Anal. Calcd. for $C_{17}H_7NF_{12}$: C, 45.04; H, 1.56; N, 3.09. Found: C, 45.23; H, 1.52; N, 3.24.

(2-Bromo-3,3,4,4-tetrafluorocyclobutenyl)-isoquinolinium Bromide.—Three grams of compound $C_{22}H_{14}N_2OF_4$ was heated with 10 ml. of 48% hydrobromic acid for five minutes. During that time the solid dissolved; then a precipitate formed. The mixture was cooled and filtered. This produced 2.7 g. of an orange-yellow solid, dec. 176–178°. The yield was 87%. Purification was accomplished by recrystallization from glacial acetic acid. Two recrystallizations from this solvent gave golden-yellow crystals, dec. 176–178°.

Anal. Calcd. for $C_{13}H_7NF_4Br_2$: C, 37.80; H, 1.71; N, 3.39; F, 18.4. Found: C, 38.09; H, 1.94; N, 3.40; F, 18.5.

(3,3,4,4-Tetrafluoro-2-iodocyclobutenyl)-isoquinolinium Iodide.—Three grams of compound $C_{22}H_{14}N_2OF_4$ was heated for five minutes at 90° with 10 ml. of 57% hydriodic acid. During this time the crystal form appeared to change and the mixture became blood red. It was cooled and filtered, and the resulting crystals were dried. The red crystals thus obtained weighed 3.5 g. (92%) and melted at 145–148° with decomposition. No method was found for further purification of this solid due to its tendency to decompose in solution.

(3,3-Difluoro-2,4-dioxocyclobutyl)-isoquinolinium Betaine.—Twenty-one grams of (2-bromo-3,3,4,4-tetrafluorocyclobutenyl)-isoquinolinium bromide was dissolved in 35 ml. of boiling glacial acetic acid. This solution was added with stirring to 200 ml. of boiling water. After heating the mixture for one minute, excess ice was added. The cooled mixture was allowed to stand for one-half hour and then the water solution was decanted from the lower layer of semi-solid. The residue was macerated with methanol and the mixture was filtered. Recrystallization of this solid from methanol gave 4.5 g. (36%) of (3,3-difluoro-2,4-dioxocyclobutyl)-isoquinolinium betaine, m.p. 248–249° dec.

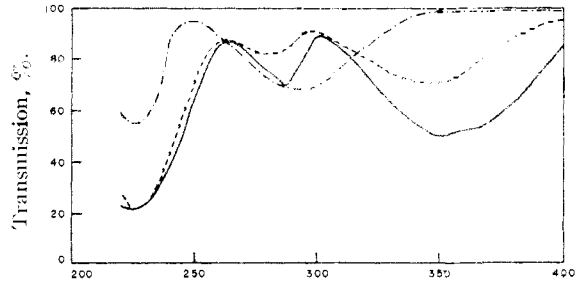
Anal. Calcd. for $C_{13}H_7NO_2F_2$: C, 63.16; H, 2.85; N, 5.67. Found: C, 63.67; H, 3.02; N, 5.77.

This betaine could also be produced directly from the original $C_{22}H_{14}N_2OF_4$ by the use of hydrochloric acid. Sixteen grams of this original compound was dissolved in 40 ml. of boiling concentrated hydrochloric acid. Eighty milliliters of boiling water was then added and the resulting solution was boiled for a few minutes. Eighty milliliters of boiling water was again added and the solution boiled for a short time. Cooling caused a yellow solid to separate. This was removed by filtration. The dried solid weighed 4.5 g. (45%) and melted at 240–243° with decomposition. Recrystallization from ethanol raised the melting point to 248–249° dec.

Reaction of 3-Methylisoquinoline with Hexafluorocyclobutene. 1. Short Reaction Time.—Twenty-eight and six-tenths grams of 3-methylisoquinoline was dissolved in 150 ml. of absolute ether. This solution was placed in a stainless-steel reaction vessel. The vessel and contents were cooled in liquid nitrogen and 40 g. of hexafluorocyclobutene was then added by distillation. The vessel and contents were warmed to room temperature and maintained at this temperature for three days. The ether solution was then shaken with water, separated and evaporated to dryness. The brown solid which was produced by this method was treated with dilute (1:1) hydrochloric acid. The solid dissolved and then reprecipitated. The solution was filtered and the solid was dried, after which it weighed 8.0 g. (15%). This (3,3-difluoro-2,4-dioxocyclobutyl)-3-methylisoquinolinium betaine was purified by recrystallization from abso-

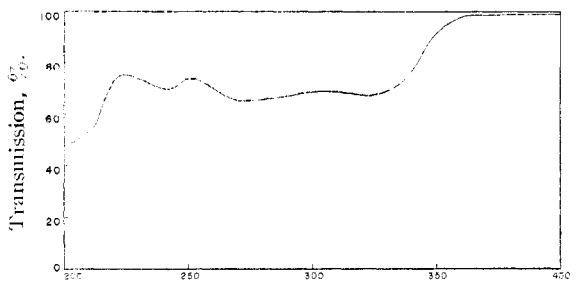
(4) E. A. Braude, *Ann. Repts. Progress Chem.*, **42**, 105 (1945).

(5) K. E. Rapp, R. L. Pruett, J. T. Barr, C. T. Bahner, J. D. Gibson and R. H. Lafferty, Jr., THIS JOURNAL, **72**, 3642 (1950).



Wave length, millimicrons.

Fig. 1.—Ultraviolet absorption spectra of: ——, (3,3-difluoro-2,4-dioxocyclobutyl)-isoquinolinium betaine, c, 1.66×10^{-5} mole/liter; - - - -, (3,3-difluoro-2,4-dioxocyclobutyl)-3-methylisoquinolinium betaine, c, 1.12×10^{-5} mole/liter; ——·——, 2-[2-heptafluorocyclobutyl)-2,3,3,4,4-pentafluorocyclobutyl]-isoquinolinium carbeniate, c, 2.10×10^{-5} mole/liter.



Wave length, millimicrons.

Fig. 2.—Ultraviolet absorption spectrum of unidentified compound obtained from the reaction of isoquinoline with hexafluorocyclobutene ($C_{22}H_{14}N_2OF_4$), c, 1.01×10^{-5} mole/liter.

lute ethanol. The final product was yellow and had a decomposition point of 240–243°.

Anal. Calcd. for $C_{14}H_9NO_2F_2$: C, 64.37; H, 3.47; N, 5.36; F, 14.6. Found: C, 64.85; H, 3.48; N, 5.46; F, 15.3.

2. **Long Reaction Time.**—When 40 g. of 3-methylisoquinoline, 85 ml. of ether and 34 g. of hexafluorocyclobutene were allowed to stand together for about one month, the predominant product was a dark solid which was not purified. As before, a small amount of the betaine was isolated.

Ultraviolet Absorption Spectra.—The ultraviolet spectra of the compounds produced were obtained by means of a Beckman model DU spectrophotometer. A quartz prism and a hydrogen discharge lamp were used. The quartz absorption cells were of 1.000 cm. length. The samples were dissolved in absolute ethanol and then diluted to the required concentration. Readings were taken every 5 mμ, except in the regions of maximum absorption, in which case they were taken every 2 mμ. The spectra are recorded in Figs. 1 and 2.

Analyses.[6]—Carbon, hydrogen and nitrogen were determined by combustion. Halogens, with the exception of fluorine, were determined by the Carius tube method. Fluorine was determined by the method of Rickard, Ball and Harris.[7]

(6) Analyses were performed by Clark Microanalytical Laboratory, Urbana, Illinois; Galbraith Laboratories, Knoxville, Tennessee; and Frances Ball and R. R. Rickard of the Microchemical Group of the Analytical Research Section of this Laboratory.

(7) R. R. Rickard, F. L. Ball and W. W. Harris, *Anal. Chem.*, **23**, 919 (1951).

OAK RIDGE, TENN. RECEIVED AUGUST 10, 1951

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, AND THE BAKER LABORATORY OF CHEMISTRY, CORNELL UNIVERSITY]

Pteridines. VII. The Synthesis of 2-Alkylaminopteridines[1,2]

BY E. C. TAYLOR, JR.,[3] AND C. K. CAIN[4]

The synthesis of several 4-amino-2-alkylaminopteridines by reaction of 4-amino-2-mercapto- or 4-amino-2-methylmercaptopteridines with amines is described. The ultraviolet absorption spectra of these compounds are reported, and a brief discussion of the effects of alkyl substitution in the 2-amino group of a 2,4-diaminopteridine on the spectra and physical properties of the compound is given. It has been found that the replacement of the hydrogen atoms of the 2-amino group of 2,4-diamino-6,7-diphenylpteridine by alkyl groups results in a reduction in antifolic acid activity.

Several 2,4-diaminopteridine (Ia) and 4-aminopteroylglutamic acid derivatives (IIb) have been shown to possess marked biological activity, particularly as inhibitors of pteroylglutamic acid (folic acid) (IIa).[5] Most of the compounds of these types so far prepared are not particularly well suited for pharmacological testing, however, because of their toxicity and general insolubility both in water and in organic solvents. Several attempts have been made to modify the structures of the more active antifolic acid compounds so as to decrease their toxicity or increase their solubility. To this end, Cain, Taylor and Daniel[6] prepared and tested a number of derivatives of 2,4-diamino-6,7-diphenylpteridine (Ia, X = Y = —C_6H_5); Elion and Hitchings[7] examined some 2,4-diamino- (Ia) and 2-amino-4-alkylaminopteridine (Ib) derivatives; and Roth, Smith and Hultquist[8] prepared a number of 4-alkylamino-2-aminopteroylglutamic acid derivatives (IIc). All such changes, however, resulted in a marked decrease in antifolic acid activity. It therefore seemed of considerable interest to examine the chemical and biological

(1) For the previous paper in this series, see E. C. Taylor, Jr., and C. K. Cain, THIS JOURNAL, **73**, 4384 (1951).

(2) Presented in part before the Organic Division at the 116th Meeting of the American Chemical Society, Atlantic City, New Jersey, September, 1949.

(3) du Pont Postdoctoral Fellow in Chemistry, University of Illinois, 1950–1951; U. S. Rubber Company Fellow in Chemistry, Cornell University, 1948–1949.

(4) McNeil Laboratories, Inc., Philadelphia, Pa.

(5) For leading references, see (a) M. F. Mallette, E. C. Taylor, Jr., and C. K. Cain, THIS JOURNAL, **69**, 1814 (1947); (b) L. J. Daniel, L. C. Norris, M. L. Scott and G. F. Heuser, *J. Biol. Chem.*, **169**, 689 (1947); (c) L. J. Daniel and L. C. Norris, *ibid.*, **170**, 747 (1947); (d) D. R. Seeger, J. M. Smith, Jr., and M. E. Hultquist, THIS JOURNAL, **69**, 2567 (1947); (e) D. R. Seeger, D. B. Cosulich, J. M. Smith, Jr., and M. E. Hultquist, *ibid.*, **71**, 1753 (1949); (f) A. L. Franklin, M. Belt, E. L. R. Stokstad and T. H. Jukes, *J. Biol. Chem.*, **177**, 621 (1949).

(6) C. K. Cain, E. C. Taylor, Jr., and L. J. Daniel, THIS JOURNAL, **71**, 892 (1949).

(7) G. B. Elion and G. H. Hitchings, *J. Biol. Chem.*, **188**, 611 (1951).

(8) B. Roth, J. M. Smith, Jr., and M. E. Hultquist, THIS JOURNAL, **72**, 1914 (1950).