Fluorination with Xenon Difluoride. 16. Fluorination of Some Benzocyclenes[1]

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The fluorination of indan with xenon difluoride in the presence of hydrogen fluoride occurred only at the β position, while further fluorination resulted in 5,6-difluoroindan. The fluorination of tetralin and o-xylene occurred both at α and β positions, with β attack predominating over α attack.

The influence of the attached alicyclic ring on the chemistry of benzocyclenes has received considerable attention from three main points of view. The first is the almost outdated hypothesis of bond fixation of the Kekule benzene structures, suggested by Mills and Nixon[2,3] in order to explain the influence of an alicyclic ring condensed with the benzene nucleus on the direction of electrophilic substitution, as in 5-hydroxyindane and 6-hydroxy-1,2,3,4-tetrahydronaphthalene. The second is the influence of strained energy in the ground state, arising from fusion of the alicyclic ring as evidenced by heat of combustion and hydrogenation.[4] The question of the Baker–Nathan effect (hyperconjugation)[5] of the alicyclic ring, in which the conformation of the ring may be quite significant, is the third main point of view.

In our continuing interest in acid-catalyzed liquid-phase fluorination with xenon difluoride,[6] we found it interesting to study the reaction with some benzocyclenes. We now report the reaction of xenon difluoride with indane, tetralin, and o-xylene.

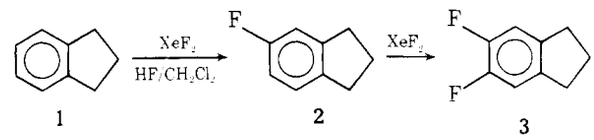
Results and Discussion

Most of the work on tetralin and indan has been directed toward supporting or disproving the possibility first postulated in 1930 by Mills and Nixon[2] of bond fixation of these compounds. Further examination of molecular models of the hydrocarbons orthoxylene, indane, and tetralin shows that the methylene groups adjacent to the aromatic ring in indane offer less steric hindrance in the α position than do the methyl or methylene groups in o-xylene and tetralin. Experimental evidence supports this conclusion.[7] However, bromination of the above mentioned systems hardly supported such an explanation and for this reason it has been suggested[8] that the transition state for α and β substitution must be taken into account.

We now report the reaction of xenon difluoride with some benzocyclenes. In a typical experiment we dissolved 1 mmol of compound in methylene chloride; anhydrous hydrogen fluoride (1 mmol) was introduced into the reaction mixture and under stirring at room temperature pure xenon difluoride (1 mmol) was added. The colorless solution turned dark blue and xenon gas was quickly evolved. After 10–30 min, when gas evolution had ceased, the crude reaction mixture was isolated by the usual work-up procedure, analyzed by NMR, and separated by preparative GLC or TLC. The crude reaction mixture formed by fluorination of indane (1) shows in its ^{19}F NMR a multiplet signal at δ −115.5 ppm, while the reaction mixture formed by further fluorination shows in its ^{19}F NMR a triplet signal at δ −139.5 ppm. Comparison of the NMR data of the products formed by fluorination to those of similar compounds[9] enabled us to establish that primary attack of the fluorine atom proceeds only at the β position and that further fluorination occurs again at the β position, thus forming 5,6-difluoroindane (3) (Scheme I).

Fluorination of o-xylene (4) resulted in a crude reaction mixture which shows in its ^{19}F NMR two signals at δ −122.25 ppm and at δ −123 ppm, in relative yields of 20 and 80%, respectively. Comparison with the literature data showed that β attack occurred predominantly (Scheme II).

Scheme I



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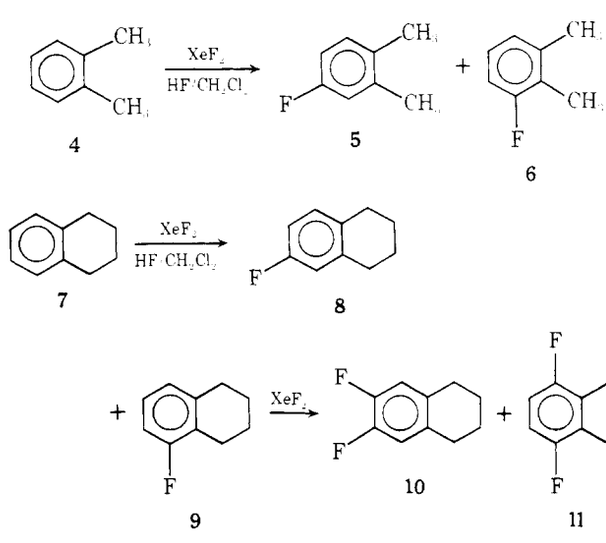
Fluorination of tetralin (7) also resulted in the formation of two products with relative yields of 30% (9) and 70% (8). We were unable to separate the isomers. However, further fluorination of the above-mentioned mixture yielded two products, which were separated by preparative GLC. The major product formed (10) shows in its ^{19}F NMR spectrum a triplet signal very similar to that displayed by 5,6-difluoroindane at δ −127 ppm and the minor product (11) shows in ^{19}F NMR a broad singlet signal at δ −101.25 ppm. On the basis of the above-mentioned data and their comparison to the NMR data of similar compounds, the major product could be established as 6,7-difluorotetralin (10) and the minor product as 5,8-difluorotetralin (11). In this case β attack was also favored.

The observed results of the fluorination of benzocyclane are parallel to those observed by bromination[8] of the same systems. However, we observed a higher degree of regioselectivity (Scheme IV).

The mechanism of the fluorination with xenon difluoride must involve catalysis by hydrogen fluoride since the reaction proved to be very slow without it. It may be expected that in the presence of hydrogen fluoride xenon difluoride behaves as an electrophile. Previously this has been suggested by Filler et al.[10] for the fluorination of some aromatic compounds. In the next step a π complex is probably formed between this electrophilic species and indane (or benzocyclane) (Scheme

Scheme II



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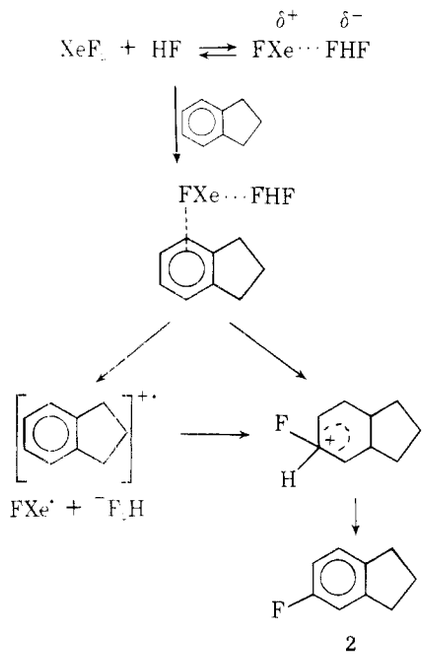
Scheme III



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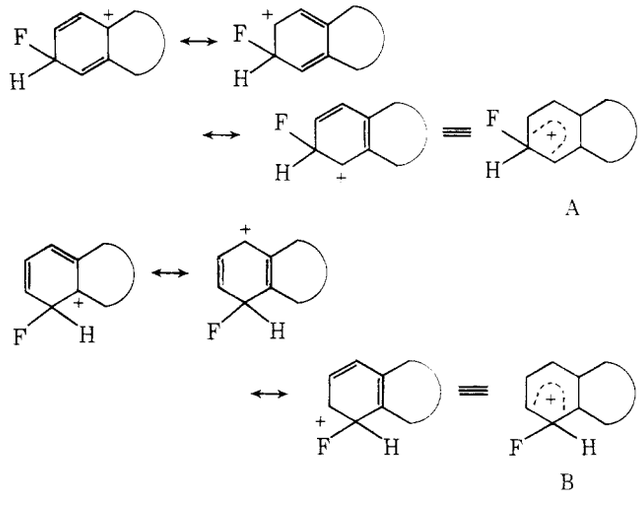
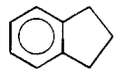
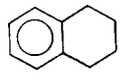
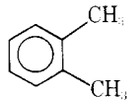
III) which could be transformed by heterolytic Xe–F bond cleavage into β-fluorocarbonium ion intermediates (in the case of *o*-xylene and tetralin also β-fluorocarbonium ion intermediates are formed), resulting, after the elimination of the proton, in β-substituted products. Furthermore, another possibility is the formation of the ion radical which has already been observed in the fluorination of some aromatic compounds[12] transforming in the next step by $XeF^{\cdot}$ or XeF_2 into a β-fluorocarbonium ion. The high regioselectivity of the fluorination of indane strongly supports an ionic intermediate. The important difference between the two sets of resonant forms (Scheme IV) is reflected in the fact that in α substitution the bond common to the two rings has effectively two-thirds of the double bond character, while in β substitution it has one-third of the double bond character. Differences in the stabilization of fluorocarbonium ions A and B formed after β or α attack are probably greater than those in the case of bromination,[8] which is then reflected in the higher regioselectivity. This means that β attack is more predominant in the case of fluorination than in the case of bromination, as is shown in Scheme IV.

Scheme IV



	β attack, %: Br_2/AcOH	XeF_2/HF, CH_2Cl_2
	78 ± 3	100
	56 ± 2	70
	71 ± 3	80

Experimental Section

IR spectra were recorded by using a Perkin-Elmer 257 spectrometer and ^1H and ^{19}F NMR spectra by a JEOL JNM-PS-100 from CCl_4 solution with Me_4Si or CCl_3F as internal reference. Mass spectra and high-resolution measurements were taken on a CEC-21-110 spectrometer. Gas–liquid partition chromatography was carried out on a Varian Aerograph, Model 1800, and TLC on Merck PSC-Fertigplatten silica gel F-254 (activated for 3 h at 120 °C before use).

Materials. Orthoxylene, indane, and tetralin are commercially available and were distilled before use. Hydrogen fluoride of Fluka Purum quality was used without further purification. Methylene chloride was purified[11] and stored over molecular sieves. Xenon difluoride was prepared by a photosynthetic method[12] and its purity was better than 99.5%.

5-Fluoroindane (2). To a solution of 1 mmol of 1 in methylene chloride (6 mL) was added 1 mmol of xenon difluoride at 25 °C and under stirring 1 mmol of HF was introduced into the reaction mixture. After a few seconds the colorless solution turned dark blue and xenon gas was slowly evolved. After 10 min gas evolution had ceased and the reaction appeared to be complete. The reaction mixture was diluted with methylene chloride (15 mL), washed with 10 mL of 5% $NaHCO_3$ and water, and dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo. The crude product (82%) was purified by preparative GLC (DDP, Varaport 30 70/80, 10%, T = 120 °C) and 60% of colorless liquid product (**2**) resulted: mass spectrum, Calcd for C_9H_9F *m/e* 136.0688, Found *m/e* 136.0686; *m/e* 136 (M^+, 98), 135 (100), 134 (13), 133 (46), 119 (40), 118 (16), 117 (40), 115 (31), 109 (41); F NMR δ −115.5 ppm (m); H NMR δ 2 (m, 2 H), 2.9 (m, 4 H), 7 ppm (m, 3 H).

5,6-Difluoroindane (3). To a solution of 1 mmol of **2** in methylene chloride (6 mL) was added 1 mmol of xenon difluoride at 25 °C and under stirring 1 mmol of HF was introduced into the reaction mixture. After 10 min gas evolution had ceased and the reaction appeared to be complete. The reaction mixture was diluted with methylene chloride (15 mL), washed with 10 mL of 5% $NaHCO_3$, and dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo, the crude product (80%) was purified by preparative GLC (DDP, Varaport 30 70/80, 10%, T = 120 °C), and 62% of colorless liquid product resulted: mass spectrum, Calcd for $C_9H_8F_2$ *m/e* 154.0594, Found *m/e* 154.0593; *m/e* 154 (M^+, 100%), 153 (90), 151 (34), 136 (70), 135 (96), 134 (23), 133 (49), 127 (28), 109 (19), 103 (47); F NMR δ −139.5 ppm (t, J = 10 Hz); H NMR δ 2 (m, 2 H), 2.7 (m, 4 H), 7 ppm (m, 2 H).

4-Fluoro-1,2-dimethylbenzene (5) and 3-Fluoro-1,2-dimethylbenzene (6). The fluorination, work-up procedure, and GLC purification were essentially the same as described for **2** or **3**. **5** was isolated as a colorless liquid product in 55% yield and **6** was isolated as a colorless liquid product in 12% yield. Both products have very similar mass spectra and their NMR data are in agreement with the literature ones[11]: F NMR for product **5**, δ F −123 ppm (m); H NMR for **5**, δ 6.8 (m, 3 H), 2.18 (s, 3 H), 2.185 ppm (s, 3 H); H NMR for **5**, F NMR for product **6**, δ −122.25 ppm (m); H NMR for **6**, δ 6.8 (m, 3 H), 2.18 (s, 3 H), 2.185 ppm (s, 3 H).

5-Fluorotetralin (9) and 6-Fluorotetralin (8). The fluorination and work-up procedure were essentially the same as for **2** and **3**. We were unable to separate the two isomers, although we have tried many different stationary phases. The crude reaction mixture showed in its ^{19}F NMR spectrum two signals: F NMR δ −120.75 ppm (30%) (**9**), −121.8 ppm (70%) (**8**); mass spectrum, Calcd for $C_{10}H_{11}F$ *m/e* 150.0845, Found *m/e* 150.0855; *m/e* 151 (M^+, 22.4), 150 (91), 149 (43), 146 (20), 135 (33), 133 (30), 123 (27), 122 (100), 109 (80), 96 (18).

Further fluorination of the crude reaction mixture under the conditions mentioned above resulted in the formation of two products, which could be separated by preparative GLC (DDP, Varaport 30 70/80, 10%, T = 120 °C). 6,7-Difluorotetralin (**10**) and 5,8-difluorotetralin (**11**), both colorless liquid products, were isolated in 50 and 13% yield respectively. Product **10**: F NMR δ −127 ppm (t, J = 10 Hz); H NMR δ 1.8 (m, 4 H), 2.75 (m, 4 H), 6.75 ppm (t, 2 H); mass spectrum,

Calcd for $C_{10}H_{10}F_2$ *m/e* 168.0745, Found *m/e* 168.0745; *m/e* 168 (M^+, 24), 151 (16), 150 (86), 149 (25), 140 (42), 135 (14), 133 (14), 127 (22), 122 (100), 109 (90). Product **11**: F NMR δ −101.25 ppm (broad singlet); H NMR δ 1.75 (m, 4 H), 2.25 (m, 4 H), 6.3 ppm (broad singlet, 2 H); mass spectrum, Calcd for $C_{10}H_{10}F_2$ *m/e* 168.0745, Found *m/e* 168.0750; *m/e* 168 (M^+, 53), 151 (19), 150 (87), 149 (26), 140 (72), 135 (20), 133 (21), 127 (28), 122 (100), 109 (84).

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Products and Kinetics of Decarboxylation of Activated and Unactivated Aromatic Cuprous Carboxylates in Pyridine and in Quinoline[1a]

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Aromatic cuprous carboxylates can be prepared in a state suitable for kinetic and product studies of their decarboxylations in quinoline and pyridine by reducing the cupric salt with copper in the decarboxylation solvent. The results were indistinguishable from those obtained from the same salts prepared by treatment of the acids with cuprous *tert*-butoxide, a more tedious procedure. The major neutral product, besides carbon dioxide, for the decarboxylation of $ArCO_2Cu$ is ArH except in the case of cuprous *o*-nitrobenzoate in which it is Ar_2. The hydrogen which replaces the carboxyl group appears to be derived largely from the solvent and is released during the substitution of aryl groups into solvent molecules and the coupling of solvent molecules. In quinoline, the latter type of product consists mainly of biquinolyls and some oxybiquinolyls. Since approximately the same composition of solvent-derived products is obtained from the decarboxylations of all of the aromatic salts and by heating pentafluorophenylcopper in quinoline, it is believed that arylcopper and quinolylcopper intermediates are involved; this is the first evidence for such intermediates in the case of nonactivated cuprous carboxylates. Such intermediates, the clean first-order kinetics, evidence against a radical process, and the similarity with respect to substituent, solvent, and ligand effects between this reaction and the Ullmann biaryl coupling as well as copper-induced exchange processes lead to a new mechanistic suggestion which involves an oxidative addition of the carboxyl C–C bond to the copper(I) followed by loss of carbon dioxide. An efficient method of preparation of 2-deuterioquinoline is presented, as is a nearly complete analysis of the 250-MHz spectrum of 2,2′-difluorobenzophenone.

Introduction

The decarboxylation of aromatic carboxylic acids by heating them in quinoline solution in the presence of copper metal or copper salts (the copper–quinoline decarboxylation) has been widely used[2] since its discovery in 1930 by Shepard, Winslow, and Johnson.[3] Previous work in this laboratory indicates that cuprous and cupric salts decarboxylate at approximately the same rate, but that the latter are converted to the former under the reaction conditions.[4,5] For preparative purposes, the reaction is most easily performed by heating the acid in quinoline under an inert atmosphere in the presence of cuprous oxide.[4,6]

The work of Nilsson and co-workers provided early evidence that in the decarboxylations of *o*-nitrobenzoic, 2-furoic, 2-thenoic, and 3,4,5-trichloro-2-thenoic acids or their copper(I) salts arylcopper intermediates are involved.[6,7] The intermediates are capable of condensing with aryl iodides present in the quinoline to form mixed biaryls. Furthermore, the first of these yielded some 2,2′-dinitrobiphenyl, a product expected from self-coupling of *o*-nitrophenylcopper. In the case of the chlorinated thenoic acid, the quenching with hydrochloric acid of samples withdrawn during the course of the reaction revealed a protonatable intermediate.[8]

This conclusion was confirmed by an experiment reported by Cairncross, Roland, Henderson, and Sheppard, who were able to isolate the relatively stable pentafluorophenylcopper from the low temperature decarboxylation of cuprous pentafluorobenzoate.[9] However, these workers provided evidence that *o*-nitrophenylcopper does not accumulate in the quinoline during the decarboxylation of cuprous *o*-nitrobenzoate, although its presence was demonstrated by the Nilsson method of trapping the intermediate with aryl iodide and by its self-coupling to form biaryl.

Our own work[4] and that of Cairncross et al.[9] demonstrated that the rate of reaction is greater the better the ability of the

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