

# Difluorodiazirine. III. Synthesis of Difluorocyclopropanes<sup>1</sup>

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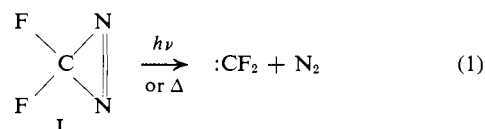
Difluorocarbene, generated by photolysis or pyrolysis of difluorodiazirine, reacts with olefins to form difluorocyclopropanes. The addition is stereospecific in nature and thus suggests a singlet state for difluorocarbene. The yield of difluorocyclopropane shows a dependence on the degree of substitution of the olefin, temperature of reaction, and amount of excess olefin.

## Introduction

The reactive intermediate bivalent carbon species called carbenes or methylenes have received considerable interest on both theoretical grounds and possible synthesis applications over the past decade. The techniques available for the facile generation of halo- and dihalocarbenes, in particular dichlorocarbene, have resulted in intensive investigations into the chemistry of these intermediates. Thus, the nondiscriminate nature of methylene vs. the halo- and dihalocarbenes has been recognized<sup>2</sup> for some time, and this difference in reactivity has been attributed to the resonance stabilization imparted by halogen substitution.<sup>2a,d,g,h,3a</sup> The technique of investigating the stereospecificity of the carbene-olefin addition and thereby gaining insight into the electronic state of the nonbonded electrons was first described by Skell<sup>2a</sup> and has since been utilized in numerous investigations in the field.<sup>2b,g,3b</sup> However, there appears to be very little in the literature concerning the chemistry of difluorocarbene.

The generation of difluorocarbene by  $\alpha$ -elimination from chlorodifluoromethane<sup>4,5</sup> and its subsequent addition to the alkoxyl anion has been reported by Hine.<sup>4a,b</sup> The halogen-metal exchange reaction of alkyllithium compounds with dibromodifluoromethane,<sup>6</sup> used to determine the half-life of difluorocarbene as  $5-10 \times 10^{-4}$  sec.,<sup>7</sup> and the decarboxylation of sodium chlorodifluoroacetate<sup>8</sup> have also been employed for its synthesis. In the latter, difluorocarbene was observed to undergo the characteristic olefin

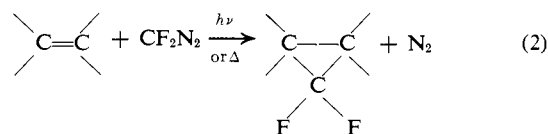
addition reaction. Recently, the pyrolysis of trifluoromethyl derivatives of iron,<sup>9</sup> phosphorus,<sup>10</sup> tin,<sup>11</sup> and germanium<sup>12</sup> has been observed to generate this reactive intermediate. Of the above organometallics,  $(CF_3)_3PF_2$ , described by Mahler,<sup>10</sup> has received the most attention as a synthesis technique.<sup>13</sup> The author has previously described the photolysis and pyrolysis of difluorodiazirine (I) as a source of difluorocarbene.<sup>14</sup> It was of interest to explore the



synthesis applications and reactivity of this resonance-stabilized carbene under conditions which are comparable with those normally used in the photolytic generation of methylene. The present paper is concerned with the addition of difluorocarbene to olefins as a general, one-step route to difluorocyclopropane derivatives.

## Results and Discussion

The physical and spectral characteristics of difluorodiazirine (I) have been reported.<sup>14</sup> In the present work, difluorocarbene, generated either by photolysis or pyrolysis of this fluorocarbon heterocycle, has been observed to add smoothly to olefins to form substituted difluorocyclopropanes (see Table I) according to eq. 2.



In general, a 5-10-mole excess of olefin was employed, and under these conditions the only side product is tetrafluoroethylene. A temperature range of 25 to 185° has been investigated in this work; however, other experiments demonstrate that photolytic generation of difluorocarbene from difluorodiazirine (I) is feasible at temperatures as low as 4°K.

Utilizing the above general procedure, a gaseous mixture of isobutylene and I in the mole ratio of 5:1 was irradiated for 20 hr. at room temperature and the resulting product mixture was separated by fractional distillation-condensation. A 71% yield of 1,1-difluoro-2,2-dimethylcyclopropane<sup>15</sup> was realized after final purification by vapor phase chromatography.

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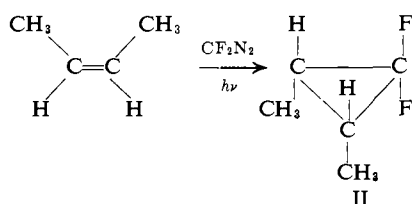
Table I. Difluorocyclopropane Derivatives

| Olefin                           | 1,1-Difluoro-<br>cyclopropane<br>derivatives | Molar<br>ratio <sup>a</sup> | Yield, <sup>d</sup><br>% | %      |       |       |      |
|----------------------------------|--|-----------------------------|--------------------------|--------|-------|-------|------|
|                                  |  |                             |                          | Calcd. |       | Found |      |
|                                  |  |                             |                          | C      | F     | C     | F    |
| Isobutylene                      | 2,2-Dimethyl                                 | 5                           | 71                       | 56.6   | 35.9  | 56.0  | 36.0 |
| 1,3-Butadiene                    | 2-Vinyl                                      | 10                          | 35 (71 <sup>b</sup> )    | 57.7   | 36.5  | 57.1  | 36.1 |
| <i>trans</i> -Butene-2           | <i>trans</i> -2,3-Dimethyl                   | 15                          | 33                       | 56.6   | 35.9  | 55.6  | 35.6 |
| <i>cis</i> -Butene-2             | <i>cis</i> -2,3-Dimethyl                     | 8                           | 26 (83 <sup>c</sup> )    | 56.6   | 35.9  | 56.1  | 35.6 |
| 1,1-Difluoro-2-vinylcyclopropane | 2,2,2',2'-Tetrafluorobicyclopropyl           | 1                           | 15 <sup>b</sup>          |        | 49.35 |       | 48.4 |

<sup>a</sup> Molar ratio = moles of olefin/moles of CF<sub>2</sub>N<sub>2</sub>. <sup>b</sup> Reactants heated to 135–145° for 60 hr. <sup>c</sup> Reactants heated at 175–185° for 2 hr. <sup>d</sup> In the photolysis experiments, tetrafluoroethylene accounted for the difluorocarbene which was not found as the difluorocyclopropane product. Under the pyrolysis conditions, the CF<sub>2</sub> which did not react with the olefin was found as C<sub>2</sub>F<sub>4</sub>, C—C<sub>3</sub>F<sub>6</sub>, and CF<sub>2</sub>=N—N=CF<sub>2</sub>, in order of decreasing yield.

The identity of the difluorocyclopropane was established on the basis of spectral considerations and its elemental analyses. In the F<sup>19</sup> nuclear magnetic resonance spectrum, the CF<sub>2</sub> group appears as a triplet of seven-fold peaks at 140.2  $\phi^*$ <sup>16</sup> due to spin-spin coupling with the protons of the CH<sub>2</sub> and two CH<sub>3</sub> groups. The proton spectrum is characterized by a triplet ( $J = 8.5$  c.p.s.) at a shielding value of  $\tau$  9.06<sup>17</sup> assigned to the CH<sub>2</sub> moiety and a second triplet ( $J = 2.0$  c.p.s.) at  $\tau$  8.81 due to the CH<sub>3</sub> groups. Difluorocarbene is more stable and less reactive than methylene. Thus, no carbon-hydrogen insertion products were detected in the above reaction or any of those discussed subsequently. It is also interesting to note that even large excesses of olefin did not eliminate the formation of tetrafluoroethylene.

In order to demonstrate further the versatility of the technique described herein and to examine the stereospecificity of difluorocarbene addition to olefins, *cis*-butene-2 was treated with difluorodiazirine (I) under two different sets of conditions. In the first case, which utilized ultraviolet irradiation at 25°, a 26% yield of 1,1-difluoro-2,3-*cis*-dimethylcyclopropane (II) was obtained. No *trans* isomer was detected. The latter material was obtained in a 33% yield in an independent experiment. The F<sup>19</sup> nuclear magnetic



resonance spectrum of II is characterized by an AB-type pattern at shielding values of 127.8 and 157.1  $\phi^*$  ( $J_{AB} = 157.6$  c.p.s.) due to nonequivalence of the two fluorine atoms. Absorptions at about  $\tau$  8.54 and 8.91 in the proton spectrum are assigned to the CH and CH<sub>3</sub> groups, respectively. The equivalent nature of the two fluorine atoms in 1,1-difluoro-2,3-*trans*-dimethylcyclopropane results in a single absorption at 142.3  $\phi^*$ . The proton spectrum of the *trans* isomer is quite complex, showing the CH<sub>3</sub> at a shielding value of  $\tau$  8.84 and a weaker absorption on the high field side, probably due to the CH group.

A thermal technique for the generation of difluorocarbene in the absence of ultraviolet irradiation, in

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(17) G. V. D. Tiers, *ibid.*, **62**, 1151 (1958).

which the identical mole ratios of *cis*-butene-2 and I were heated at 175–185° for 2 hr., was employed in the second experiment. As anticipated,<sup>18</sup> a considerable increase in yield (83%) of the *cis*-difluorocyclopropane (II) resulting from stereospecific addition to the olefin was realized.

As a result of the above experiments with *cis*- and *trans*-butene-2, it is also possible at this time to draw some conclusions concerning the electronic structure of the two nonbonded electrons in difluorocarbene. The fact that even a large excess of olefin and higher temperatures did not prevent the formation of tetrafluoroethylene is interpreted as indicating a large number of ineffective collisions and suggests that we are observing the reactions of the ground-state<sup>19</sup> difluorocarbene. It therefore follows that difluorocarbene, generated by photolysis or pyrolysis of difluorodiazirine, exists in a singlet state with the nonbonded electrons paired.

It is also evident from previous publications<sup>2a,d,g,h,3a</sup> that fluorine atoms would have a greater ability toward stabilization of an electron-deficient carbon that have the other halogens and that the resonance-stabilized structures of the transition state of carbene-olefin adducts are polarized toward a positive olefin-carbon and a negative dihalocarbon. The relative rates of addition of difluorocarbene would therefore be expected to be more markedly influenced by structural variations on the double bond than are the corresponding reactions of other halo- and dihalocarbenes.

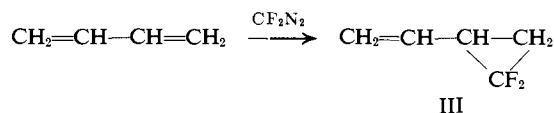
This discriminate nature of :CF<sub>2</sub> was conclusively demonstrated by a comparison of the relative rates of its addition to isobutylene and *cis*-butene-2 vs. similar competitive reactions with chloro- and dichlorocarbene. The reaction of difluorocarbene with isobutylene is 12.8 times faster than the reaction with *cis*-butene-2. The corresponding ratios for dichlorocarbene<sup>2d</sup> and the essentially nondiscriminate chlorocarbene<sup>2h</sup> are 5.2 and 1.1, respectively.

In a manner analogous to the studies with *cis*-butene-2, 1,3-butadiene was treated with difluorocarbene both photolytically at 25° and thermally at

(18) W. von E. Doering and W. A. Henderson, Jr., *J. Am. Chem. Soc.*, **80**, 5274 (1958), have demonstrated that the free energy of activation in the addition of dichlorocarbene to an olefin is greater than zero. In the present work, increasing the temperature of the reaction increased the yields of difluorocyclopropane, suggesting that the activation energy of the olefin-CF<sub>2</sub> addition reaction is greater than that of the reactions leading to C<sub>2</sub>F<sub>4</sub>.

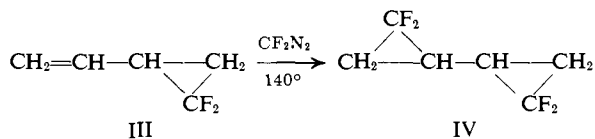
(19) See F. A. S. Anet, R. F. W. Bader, and A. Van der Auwera, *ibid.*, **82**, 3218 (1960), and H. M. Frey, *ibid.*, **82**, 5947 (1960), for a discussion of methylene excited state-ground state degradation through collisions with inert gas molecules.

135–145°. The 35% yield of 1,1-difluoro-2-vinylcyclopropane (III) which was obtained in the ultraviolet experiment was increased to 71% by means of



the pyrolysis technique. Identification of III was accomplished by elemental and spectral analyses. The nonequivalent fluorine atoms of the cyclopropane appear as an AB-type pattern at shielding values of 128.8 and 142.1  $\phi^*$  ( $J_{AB} = 158.9$  c.p.s.) in the  $F^{19}$  nuclear magnetic resonance spectrum. Further splitting into a triplet ( $J = 12.4$  c.p.s.) of doublets ( $J = 5.0$  c.p.s.) and a doublet ( $J = 12.0$  c.p.s.) of doublets ( $J = 5.0$  c.p.s.) is observed for the 128.8 and 142.1  $\phi^*$  peaks, respectively. The splitting due to the third hydrogen is apparently very small in the latter case. No detailed analysis of the proton spectrum was attempted because of its complex nature; however, the major absorptions were about  $\tau$  8.47 (ring protons) and 4.67 (vinyl protons). The observed 1,2-addition of difluorocarbene to 1,3-butadiene is in agreement with similar experiments reported for dibromo-<sup>20</sup> and dichlorocarbene.<sup>20, 21</sup>

The further addition of difluorocarbene to III affords a relatively low yield of the novel bicyclopropyl derivative, 2,2,2',2'-tetrafluorobicyclopropyl (IV). It



should be noted, however, that excess olefin was not employed in this reaction. The structure of the bicyclopropyl (IV) was established on the basis of its elemental and spectral analyses. The nonequivalence of the fluorine atoms in each of the cyclopropyl groups is demonstrated by a typical AB-type absorption with shielding values of 130.6 and 143.6  $\phi^*$  ( $J_{AB} = 161.2$  c.p.s.) in the  $F^{19}$  nuclear magnetic resonance spectrum. As in the case of III, the complex proton spectrum of IV exhibits a broad absorption with a maximum about  $\tau$  8.67 and a shoulder on the low field side at about  $\tau$  8.45 assigned to the cyclopropyl protons, but no evidence for vinyl protons.

Further support for the bicyclopropyl structure can be derived from its infrared spectrum. The most characteristic feature of the infrared spectra of the various difluorocyclopropanes prepared in this work is a band of *medium* intensity in the 6.70–6.80- $\mu$  region. On the other hand, the *major* absorption in the spectrum of IV is at 6.80  $\mu$ .

## Experimental

**General.** The isobutylene, 1,3-butadiene, *cis*-butene-2, and *trans*-butene-2 were all C.P. grade obtained from the Matheson Co. Chromatographic analyses were performed with a Model 154-D Perkin-Elmer vapor fractometer, utilizing a fluorocarbon type stationary phase. The elemental analyses and preparative-scale separations were obtained using a 0.5-in.

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Table II. Vapor Phase Chromatography Data

| Olefin                           | $T_r^a$            | 1,1-Difluoro-cyclopropane derivatives | $T_r$              |
|----------------------------------|--------------------|---------------------------------------|--------------------|
| Isobutylene                      | 28.4               | 2,2-Dimethyl                          | 137.0              |
| 1,3-Butadiene                    | 27.6               | 2-Vinyl                               | 186.1              |
| <i>trans</i> -Butene-2           | 32.1               | <i>trans</i> -2,3-Dimethyl            | 171.0              |
| <i>cis</i> -Butene-2             | 37.1               | <i>cis</i> -2,3-Dimethyl              | 242.0              |
| 2-Vinyl-1,1-difluorocyclopropane | 200.2 <sup>b</sup> | 2,2,2',2'-Tetrafluorobicyclopropyl    | 854.0 <sup>b</sup> |

<sup>a</sup>  $T_a = \text{relative retention time} = (T_{\text{compd}} - T_{\text{air}})/(T_{\text{CFCl}_3} - T_{\text{air}}) \times 100$ . <sup>b</sup> 33% Kel-F grease on Celite, 0.25-in. tube 10 ft. long, operating at 75°.

o.d. tube 2 m. long and packed with 33% KF-8126<sup>22</sup> oil on Celite.

Infrared spectra were obtained using a Perkin-Elmer Model 21 double-beam instrument, utilizing a 2.5-cm. gas cell with NaCl windows. Fluorine and proton nuclear magnetic resonance spectra were measured with a Varian V-4300-2 instrument operating at 40.0 Mc.; internal standards of  $\text{CFCl}_3$  and  $(\text{CH}_3)_4\text{Si}$  were used for the determination of shielding values. The shielding values are reported in  $\phi^*$ -<sup>16</sup> and  $\tau$ -units<sup>17</sup> for fluorine and proton, respectively, at dilutions of about 20–30%.

**Preparation of 1,1-Difluorocyclopropanes.** In general, the two techniques (a and b) available for the generation of difluorocarbene from difluorodiazirine, namely photolysis and pyrolysis, determine the two experimental procedures utilized in this work.

Procedure a employing gas-phase photolysis of a mixture of difluorodiazirine and excess olefin is common to most starting olefins. The reactants are condensed into a 300–500-cc. glass storage bulb at liquid nitrogen temperatures by suitable gas-transfer techniques. After degassing and warming to ambient room temperature, the mixture is irradiated for 20–24 hr. with a Hanovia 125-w. ultraviolet light source. Preliminary separation of the 1,1-difluorocyclopropane from the excess olefin can sometimes be accomplished by simple fractional distillation–condensation techniques. Preparative vapor phase chromatography is employed for the final purification. The reported yields represent the quantity of pure difluorocyclopropane which is separated from the reaction mixture by vapor phase chromatographic trapping techniques.

Procedure b utilizes the facile generation of difluorocarbene by thermal decomposition of difluorodiazirine. The reactants are condensed into a 20-cc., heavy-walled glass ampoule cooled to  $-196^\circ$ . After degassing, the ampoule is sealed and the mixture is heated to and maintained at the desired temperature by means of a muffle furnace. As in the photolysis technique, preliminary fractional distillation–condensation and vapor phase chromatography are utilized to separate the reaction mixture into its pure components.

**Competition Experiment.** Pure samples of isobutylene ( $5.0 \times 10^{-3}$  moles) and *cis*-butene-2 ( $5.0 \times 10^{-3}$  moles) were condensed into a 500-cc. glass bulb which contained difluorodiazirine ( $1 \times 10^{-3}$  mole) at

(22) Minnesota Mining and Manufacturing Co., Kel-F 8126 oil; a chlorotrifluoroethylene tetramer.

liquid nitrogen temperature. After allowing the bulb and its contents to warm to and remain at room temperature for at least 3 hr., the mixture was exposed to ultraviolet irradiation from a 125-w. Hanovia lamp. The irradiation was discontinued at the end of 16 hr. and the mixture was analyzed by vapor phase chromatography. The ratio of the isobutylene-difluorocarbene adduct to the *cis*-butene-2 product was found to be 12.8:1 by area measurements. It had previously been determined that the vapor phase chromatography

sensitivities of the pure components were essentially equal.

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## The Diterpene Alkaloids. Correlation of the Atisine and Garrya Series of Alkaloids<sup>1</sup>

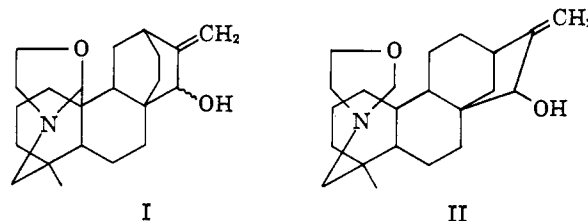
S. William Pelletier<sup>2</sup> and David M. Locke

Contribution from the Department of Chemistry, The University of Georgia, Athens, Georgia, and the Laboratories of the Rockefeller Institute, New York, New York. Received October 15, 1964

This paper reports the details of the correlation of atisine and veatchine via the bisnor ester V. Two reaction pathways from atisine to V and one from veatchine to V are described. Thus one pathway from atisine involves the sequence I → VIII → IX → VI → VII → X → XI → XII → XIII → V and the other route, the sequence XVI → XVII → XVIII → XIX → XX → XXI → XXII → XXIII → XXIV → XIV → XXIX → V. The route from veatchine (II) involves intermediates XXX → XXXI → XXXII → XXXIII → XXXIV → XXXV → XXXVI → XXXVII → XXXVIII → XXXIX → XL → V. The structures of certain byproducts encountered in the course of these degradations are discussed. This correlation provides the first unequivocal evidence for the common stereochemistry of the atisine- and garrya-type alkaloids.

Several years ago structures I and II were assigned to the diterpene alkaloids<sup>3,4</sup> atisine<sup>5,6</sup> [*Aconitum heterophyllum* Wall (*Ranunculaceae*)] and veatchine<sup>5,7</sup> [*Garrya veatchii* Kellogg (*Garryaceae*)], respectively. At the time, little was known about the precise stereochemistry of the compounds, and the question of whether they possessed the same stereochemistry was an interesting

one since the alkaloids occur in unrelated plant families. Subsequent information indicated that in veatchine the five-membered ring bearing the allylic alcohol moiety was *trans* to the heterocycle ring.<sup>8,9</sup> The failure to interrelate atisine and veatchine by vigorous acid isomerization of dihydroveatchine<sup>10</sup> underscored the need for further experimental studies to determine whether the allyl alcohol grouping in atisine occupies the *trans* (as in veatchine) or the *cis* bridge (with respect to nitrogen) of the bicyclo[2.2.2]octane system. Since evidence from this<sup>11</sup> and another laboratory<sup>12</sup> indicated



that atisine, like veatchine, has the allyl alcohol group in a *trans* relationship to the nitrogen ring, we were prompted to undertake an unambiguous correlation of atisine and veatchine. This paper reports the successful correlation of atisine (III)<sup>13</sup> and veatchine (IV)<sup>13</sup> via the bisnor ester V. A preliminary account of this

(1) This investigation was supported in part by Grants RG 5807, RG 5807(C1), GM 10921-01, and GM 10921-02 from the National Institutes of Health, U. S. Public Health Service.

(2) The Department of Chemistry, The University of Georgia, Athens, Ga.

(3) Recent review articles on the diterpene alkaloids are: (a) S. W. Pelletier, *Experientia*, 20, 1 (1964); (b) S. W. Pelletier, *Tetrahedron*, 14, 76 (1961).

(4) See also (a) H. G. Boit, "Ergebnisse der Alkaloid-Chemie bis 1960," Akademie-Verlag, Berlin, 1961, pp. 851-905, 1009-1011; (b) E. S. Stern in "The Alkaloids," Vol. VII, R. H. F. Manske, Ed., Academic Press, Inc., New York, N. Y., 1960, pp. 473-503; (c) K. Wiesner and Z. Valenta, "Progress in the Chemistry of Organic Natural Products," Vol. XVI, Springer-Verlag, Vienna, 1958, pp. 26-63.

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(12) D. Dvornik and O. E. Edwards, *ibid.*, 623 (1958).

(13) Since the detailed stereochemistry of atisine<sup>3b,14-18</sup> and veatchine<sup>17</sup> is now well known, the correct absolute stereochemistry is indicated from formula III on.

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