tions of the ring C. The additional peaks in the azines could indicate the presence of various additional conformations arising from the partially restricted rotations around the azine bond. This aspect of the spectra is now under investigation.

Data shown in Table III indicate that the chemical shift of H-5 can be used as an indication of the presence of the azine as well as hydrazone isomers. Also, the splitting in the aromatic region, i.e., for H-1 and H-2, occurs when isomers are present. The presence of various conformers, which is indicated in the ^{13}C NMR, is shown also in the proton spectra.

The mixed estrone–naloxone azine (X) which was formed by treating 100% *anti*-estrone hydrazone with naloxone is configurationally pure anti–anti azine, based on both ^{13}C and ^{1}H NMR spectra. Thus, only one C-5 signal was observed (at 87.80 ppm), one C-6 azine carbon of the opiate (at 162.30 ppm), and one azine carbon at C-17 of the steroid (at 175.79 ppm). Only one H-5 of the opiate moiety was observed (at 5.044 ppm), and only one signal for the angular CH_3 group at 0.788 ppm.

The data from Table I show that in the hydrazones I–III the less crowded anti isomer is the major product, which suggests that the formation of these hydrazone isomers is sterically controlled. The latter suggestion is supported by our finding that in the more sterically encumbered hydrazones IV–VI, the anti isomers were obtained almost exclusively. We found a similar steric control of hydrazone formation in the case of a steroidal hydrazone, Δ4-androstene-3,17-dione dihydrazone.[10] In this steroid case only the anti isomer was obtained at the C-17 position, since at this position the syn isomer would be sterically very crowded, while a mixture of the anti and syn isomers was obtained at the less crowded position 3. Estrone hydrazone gave 100% anti hydrazone at C-17 and pregnenolone acetate hydrazone afforded 100% anti hydrazone at C-20. These steroidal hydrazones were used in syntheses of mixed azines between opiates and steroids;[12] one representative compound, X, is described here.

Acknowledgment. Thanks are expressed to Dr. Alan A. Rubin for his generous gift of naloxone and oxymorphone and to Dr. Harold M. Ginzburg for donating naltrexone. Discussions with Drs. Gavril W. Pasternak and Elliot Hahn are appreciated, as well as the samples of naloxone hydrazone and naloxone azine which Dr. Pasternak provided for a comparison of the isomer composition between his and our samples. Special thanks are expressed to Dr. James P. Snyder for communicating to us his unpublished MM-2 calculations on the energies of the chair and boat conformers of the C ring of naloxone. Thanks are also expressed to Dr. Jay A. Glasel for sending us his manuscript on a high-resolution (600 MHz) ^{1}H NMR study of conformations of morphines prior to its publication.

The biological tests of the compounds in this study were done by Dr. Lars Terenius and Ahmet Koman to whom thanks are expressed. The biological data will be published separately.[17]

Registry No. I anti, 91797-50-1; I syn, 91797-51-2; II anti, 91796-59-7; II syn, 91796-60-0; III anti, 91796-61-1; III syn, 91797-52-3; IV anti, 91796-62-2; V anti, 91796-63-3; VI anti, 91712-58-2; VII isomer 1, 91796-64-4; VII isomer 2, 91796-65-5; VII isomer 3, 91796-66-6; VIII isomer 1, 91797-53-4; VIII isomer 2, 91796-67-7; VIII isomer 3, 91796-68-8; IX isomer 1, 91796-69-9; IX isomer 2, 91796-70-2; IX isomer 3, 91796-71-3; X, 91712-59-3; *anti*-estrone hydrazone, 91796-72-4; *anti*-pregnenolone 3-acetate 20-hydrazone, 91796-73-5; pregnenolone acetate, 1778-02-5; pregnenolone, 145-13-1; naloxone hydrochloride, 357-08-4; naltrexone, 16590-41-3; oxymorphone, 76-41-5; dimethyl hydrazine, 30260-66-3; naloxone, 465-65-6.

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Notes

Phenylfluorocarbene from Phenylfluorodiazirine. The Crown Ether Test for Free Carbenes Revisited

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A decade ago, we found that phenylbromocarbene and phenylchlorocarbene, generated by the action of potassium tert-butoxide on the corresponding benzal halides, were not free carbenes. Their selectivities toward a standard set of alkenes differed from those of the formally identical carbenes photolytically produced from the 3-halo-3-phenyldiazirines. In the presence of the macrocyclic polyether 18-crown-6, however, the selectivities of the KO-*t*-Bu-generated species became identical with those of the photogenerated carbenes.[1] It was concluded that the diazirine photolysis gave free phenylhalocarbenes, that the same intermediates could be generated from benzal halides by using a base–crown complex, and that α-elimination in the absence of crown ether gave phenylhalocarbenoids.[1,2]

We extended this work by examining the olefinic selectivity of PhCF, generated by the action of KO-*t*-Bu on PhCHBrF in the presence and absence of 18-crown-6;[3] cf. below. Over the years, others have carried out analogous studies to either test or ensure the "freeness" of (e.g.) alkylidenecarbenes,[4] alkenylidenecarbenes,[5] cyclo-

(1) Moss, R. A.; Pilkiewicz, F. G. *J. Am. Chem. Soc.* **1974**, *96*, 5632 and references therein.
(2) The structure of the carbenoid was undefined, but most likely involved complexation of PhCX with either KX or KO-*t*-Bu.
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0022-3263/84/1949-3828$01.50/0

Table I. Relative Reactivities of Alkenes toward PhCF at 25 °C

alkene	PhCF source: diazirine photolysis, eq 1[a] (1)	α-elim, eq 2 no crown[b] (2)	α-elim, eq 2 18-crown-6[c] (3)
$Me_2C{=}CMe_2$	5.52 (0.15),[d] 4.98 (0.22)[e]	2.7	5.84,[d] 4.43 (0.05)[e,f]
$Me_2C{=}CHMe$[g]	1.80 (0.01)	1.2, 1.27 (0.01)[f]	3.0, 1.6 (0.1)[f]
$Me_2C{=}CH_2$	1.00	1.00	1.00
cis-MeCH-CHMe[g]	0.21 (<0.01)	0.12	0.28
trans-MeCH=CHMe	0.15 (<0.01)	0.10	0.20

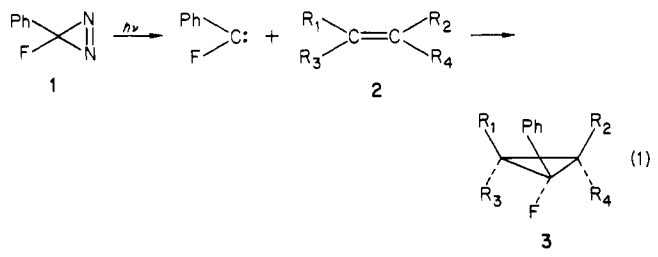
[a] This work. Numbers in parentheses are average deviations from the mean value of two or three runs. [b] Data from ref 12, reproducibilities, ±4%. [c] Data from ref 3, benzene solution, reproducibilities ±4%. [d] Alkenes and solvent were distilled off after reaction. [e] Reaction mixture not distilled. [f] New determination, this work. [g] Relative reactivities are based on the sum of syn-F and anti-F isomers.

pentadienylcarbenes,[6] cyclobutylidene,[7] and adamantylidenecarbene.[8]

When we originally applied the crown ether procedure to the generation of PhCF, a photochemical precursor was unavailable, and although we took the observed olefinic selectivity as characteristic of the free carbene,[3] we could not be certain. Now, 3-fluoro-3-phenyldiazirine can be readily prepared.[9] In view of the continuing use of the "crown ether test" for carbene "freeness",[4-8] we decided to compare the olefinic selectivities of photolytically generated PhCF with those of PhCF generated from PhCHBrF and KO-*t*-Bu in the presence and absence of 18-crown-6. In doing so, we complete a "deferred" test of the utility of crown ethers in the generation of free phenylhalocarbenes.

Results and Discussion

3-Bromo-3-phenyldiazirine[10] was converted in 71% yield to 3-fluoro-3-phenyldiazirine, **1**, by halide exchange[9] with molten, "anhydrous" *n*-$Bu_4N^+F^-$[9,11] at 25 °C. Samples of **1** were photolyzed ($\lambda > 300$ nm) in 10-fold excesses of tetramethylethylene, trimethylethylene, isobutene, *cis*-2-butene, and *trans*-2-butene. Evaporation of excess alkene, followed by short-column chromatography on silica gel with *n*-hexane, afforded 1-fluoro-1-phenylcyclopropanes **3a–e** in purities >97% (capillary GC) and in yields ranging from 42–76%; eq 1.



1 2

3 (1)

a, $R_1=R_2=R_3=R_4=Me$
b-syn-F, $R_1=R_3=R_4=Me$, $R_2=H$
b-anti-F, $R_1=R_2=R_3=Me$, $R_4=H$
c, $R_1=R_3=Me$, $R_2=R_4=H$
d-syn-F, $R_3=R_4=Me$, $R_1=R_2=H$
d-anti-F, $R_1=R_2=Me$, $R_3=R_4=H$
e, $R_1=R_4=Me$, $R_2=R_3=H$

The cyclopropanes were identified by comparisons of their ^1H NMR spectra with those of the authentic materials, previously synthesized from α-bromo-α-fluorotoluene (**4**)/KO-*t*-*bu*, and fully characterized;[12] cf. eq 2. NMR

$$PhCHBrF + K^+{}^-O\text{-}t\text{-}Bu + R_1R_3C{=}CR_2R_4 \rightarrow \mathbf{3a\text{–}e} \quad (2)$$

integration and capillary GC permitted determination of syn-F/anti-F stereoselectivities for the **3b** and **3d** product mixtures. These were (NMR, GC): 0.81, 0.92 for **3b** and 1.70, 1.48 for **3d**, in reasonable agreement with values derived by Joyce[3] from ^{19}F NMR integrations of product mixtures derived from reaction 2 *with* crown ether: 0.76 (**3b**) and 1.62 (**3d**).[3]

The olefinic selectivity of PhCF was determined at 25 °C by using the competition method;[13] the binary cyclopropane product mixtures resulting from photolytic decomposition of **1** in pairs of competing olefins (**2**) were analyzed by capillary GC. Retention times and calibration constants for the flame ionization detector were established by using mixtures of authentic samples. Relative reactivities were calculated in the standard manner,[13] average deviations from the means of duplicate experiments were <3%, and satisfactory cross-checks[13] were obtained. The resulting relative reactivities, measured *directly* against the "standard" olefin (isobutene), are displayed in Table I. There, we also record the values previously obtained for PhCF generated by the method of eq 2 in the presence and absence of 18-crown-6.[3,12]

Comparison of the data in columns 1 and 2 of Table I clearly shows that photolytically generated PhCF is not kinetically identical with the species generated from PhCHBrF and KO-*t*-Bu in the absence of crown ether. On the other hand, the selectivities of photolytically generated PhCF and the KO-*t*-Bu/18-crown-6/PhCHBrF species (column 3) are quite similar. The major discrepancy involves the $Me_2C{=}CHMe/Me_2C{=}CH_2$ competition. We repeated the older, α-elimination competitions[3,12] and found that the crown ether relative reactivity changed significantly, now coming into good agreement with the photolytic PhCF value. We are uncertain why the original crown ether value appears to have been in error, but we note that it had not been measured directly. Rather, it was calculated from the measured reactivities: $Me_2C{=}CHMe/Me_2C{=}CMe_2$ and $Me_2C{=}CMe_2/Me_2C{=}CH_2$. The present, directly measured, PhCF relative reactivities were obtained with a new GC and electronic integration and are likely to be more accurate.[14]

The conclusions drawn from our original studies[1,3] are supported by the present work. The action of KO-*t*-Bu on $PhCHX_2$ or PhCHXY generates phenylhalocarbenoids

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(14) Residual small discrepancies in photolytic and crown ether data may be due to the influence of benzene solvent in the crown ether experiments (or perhaps to the influence of crown ether directly on the free carbene). For example, *photolysis* of **1** in $Me_2C{=}CMe_2/Me_2C{=}CH_2$, containing appropriate control quantities of 18-crown-6 and benzene, gave $k_{rel}(Me_2C{=}CMe_2) = 4.53$, lower than the value (4.98) observed in the absence of benzene and crown and very similar to the value (4.43) obtained in the α-elimination method, where these additives are present (see Table I, first row of entries). In any event, the effects of benzene or crown ether on the free carbene seem only marginal.

Table II. Fluorophenylcyclopropanes from Reaction 1

alkene	product	yield,[a] %	purity,[b] %	t_R,[c] min
$Me_2C{=}CMe_2$	**3a**	49	98.5	4.49
$Me_2C{=}CHMe$	**3b**[d]	52	97.2	2.92, 3.19[e]
$Me_2C{=}CH_2$	**3c**	70	99.9	1.87
cis-MeCH=CHMe	**3d**[d]	76	99.3	2.68, 2.91[e]
trans-MeCH=CHMe	**3e**	42	99.2	2.16

[a] Isolated, purified product. [b] By GC. [c] GC conditions are given above. [d] Both isomers. [e] Isomeric cyclopropanes are separated by capillary GC.

in the absence of 18-crown-6 but free phenylhalocarbenes when a base/crown ether complex is employed. The latter species displays olefinic selectivities very similar to those of the phenylhalocarbenes photolytically generated from 3-halo-3-phenyldiazirines.[15]

Experimental Section

Materials and Equipment. Tetramethylethylene and Trimethylethylene were obtained from Aldrich Chemical Co. and distilled before use unless newly received. *cis*-2-Butene, *trans*-2-butene, and isobutene were obtained from Matheson Co. and used as received. Photolyses were carried out by using a focused Osram 200-W Xe mercury lamp (Pyrex filter). Capillary GC employed a Model 3700 Varian flame ionization unit with a Varian Model 4270 electronic integrator. The instrument was fitted with a BP-1, 50 ft, 20% SE-30 capillary column, operated at 100 °C (injector, 180 °C, detector, 300 °C, nitrogen pressure, 0.7 atm).

1-Fluoro-1-phenylcyclopropanes 3. General Procedure. 3-Bromo-3-phenyldiazirine[10] was converted to 3-fluoro-3-phenyldiazirine (1) by the procedure of ref 9. Diazirine **1** (2.5 mmol) and 25 mmol of alkene **2** were contained in a screw-top Pyrex Carius tube, stirred magnetically, and irradiated for 4 h at 25 °C. The tube was cooled to −70 °C (for gaseous alkenes), opened, and carefully warmed to evaporate excess alkene. Higher boiling alkenes were removed by aspiration. Crude products were purified by short column chromatography on EM Reagents silica gel 60 using *n*-hexane or *n*-pentane as eluents. The yields, GC purities and retention times of the adducts so obtained are shown in Table II. Complete spectroscopic and analytical characterizations of these compounds have previously been published.[12]

Competition Reactions. Photolytic Method. These reactions were carried out by using 1.5-mmol samples of diazirine **1** and carefully weighed binary mixtures of alkenes **2** (each present in at least 10-fold molar excess). The procedure followed the preparative method given above, except that excess $Me_2C{=}CMe_2$ or $Me_2C{=}CHMe$ was removed by distillation (1 atm, water bath).[17] The chromatography step was omitted. GC analysis employed the column and conditions described above, and the flame ionization detector was calibrated with weighed mixtures of pure products (three mixtures for each calibration). Relative reactivities were calculated from the standard relation:[13] $k_A/k_B = (P_A/P_B)(0_B/0_A)C_{A/B}$, where (P_A/P_B) is the GC integration ratio for products A and B, $(0_B/0_A)$ is the initial molar ratio of alkenes A and B, and $C_{A/B}$ is the appropriate calibration or detector response constant. Results appear in Table I.

α-Elimination Method. The competition reaction between $Me_2C{=}CHMe$ and $Me_2C{=}CH_2$ for PhCF was also carried out with PhCHBrF and KO-*t*-Bu (MSA Corp.) following the procedure described in ref 12 (Moss and Przybyla). GC analysis (present conditions) gave $k_{Me_2C=CHMe}/k_{Me_2C=CH_2} = 1.27 \pm 0.01$ for two reactions. The previous value was 1.2.[12] The same reaction was repeated using the (Thesis) procedure of ref 3. The base was a solution of 0.5 g (4.5 mmol) of KO-*t*-Bu and 1.7 g (6.4 mmol) of 18-crown-6 (Aldrich) in 20 mL of dry benzene. This was mixed at −70 °C with 38–70 mmol of each alkene and 0.34 g (1.8 mmol) of PhCHBrF,[12] originally diluted with 0.5 mL of benzene and contained in a small, breakable glass ampule. All reagents were sealed in a screw-top Carius tube and warmed to 25 °C. The ampule was broken by shaking, and the tube was rotated end-over-end for 24 h. The tube was then cooled and opened, and alkenes were evaporated. The residue was washed twice with 20-mL portions of water and once with saturated aqueous $NaHCO_3$. The organic phase was dried, benzene was removed by distillation, and the residue was analyzed by GC. Two runs gave $k_{Me_2C=CHMe}/k_{Me_2C=CH_2} = 1.6 \pm 0.1$. The previous value[3] was 3.0.

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Registry No. 1, 87282-19-7; **2a**, 563-79-1; **2b**, 513-35-9; **2c**, 115-11-7; **2d**, 590-18-1; **2e**, 624-64-6; **3a**, 17815-89-3; **3b** (syn-F), 19294-50-9; **3b** (anti-F), 19294-51-0; **3c**, 17815-90-6; **3d** (syn-F), 19294-48-5; **3d** (anti-F), 19294-49-6; **3e**, 91423-75-5; fluorophenylcarbene, 17825-75-1.

(15) The crown ether PhCF selectivities[3] were previously used to calculate a carbene selectivity index,[16] $m_{PhCF} = 0.89$ for "free" PhCF. Using the photolytic data of Table I [column 1], including $k_{rel} = 4.98$ for $Me_2C{=}CMe_2$, we now calculate $m_{PhCF} = 0.89$ ($r = 0.993$), identical with the previous value.

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(17) In several experiments, $Me_2C{=}CMe_2$ was not removed after reactions. Distillation of $Me_2C{=}CMe_2$ removes small quantities of products and inflates both the **3a**/**3c** product ratio and $k_{rel}(Me_2C{=}CMe_2)$. The lower values of $k_{rel}(Me_2C{=}CMe_2)$ in columns 1 and 3 of Table I are believed to be the more accurate ones.

Revised Structure of Zizanol[1]

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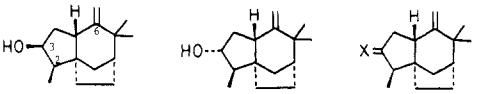
In the course of the total synthesis of the tricyclic sesquiterpene zizanol,[2] an analysis of the ^{13}C NMR chemical shifts for the C_2 methyl group in several zizaene derivatives suggested that the original assignment[3] of the relative stereochemistry of the C_3 hydroxyl group in zizanol as shown in structure **1** is in error. On the basis of both



1 **2** **3**, X = O **4**, H_2

chemical and spectroscopic evidence we report that the relative stereochemistry of the C_2 methyl and C_3 hydroxyl groups in zizanol is trans. Since the assignment of the stereochemistry of the C_2 methyl group is secure (X-ray analysis[4]), the correct structure for zizanol is that depicted in formula **2**.

An examination of the ^{13}C NMR chemical shift data shown in Table I reveals, as expected, a marked upfield shift, ca. 6.2 ppm, for the C_2 methyl group of ketone **3** compared with that of the hydrocarbon zizaene (**4**) due to the steric interaction between the sp^2 oxygen atom and the C_2 methyl group in ketone **3**.[5] For the two corresponding C_3 alcohols **1** and **2**, if the hydroxyl and methyl groups are cis as originally proposed for zizanol (e.g., **1**), the C_2 methyl group would be expected to be upfield relative to that in

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