(Acyloxy)carbenes from Thermolysis of Oxadiazolines in Solution. 1-Acetoxyethylidene and 1-Acetoxypropylidene

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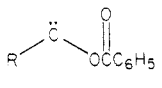
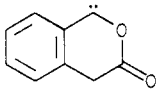
Thermolysis of 2-acetoxy-5,5-dicyclopropyl-2-methyl-Δ^3-1,3,4-oxadiazoline in CCl_4 at 79.5 °C afforded biacetyl, acetyl chloride, and dicyclopropyl ketone, among other products. It is proposed that the oxadiazoline loses nitrogen, in the first step, to form a carbonyl ylide. The latter then fragments, primarily to dicyclopropyl ketone and 1-acetoxyethylidene [(acetoxymethyl)carbene]. That carbene is partitioned between 1,2 acyl transfer to form biacetyl and abstraction of Cl from CCl_4 to form 1-acetoxy-1-chloroethyl radical. The latter undergoes β scission to form acetyl chloride and acetyl radical, which in turn abstracts from CCl_4 to form more acetyl chloride. Similarly, 2-acetoxy-5,5-dicyclopropyl-2-ethyl-Δ^3-1,3,4-oxadiazoline decomposed in CCl_4 to form 2,3-pentanedione, acetyl chloride, propionyl chloride, dicyclopropyl ketone, and other products. Again, the α-diketone is accounted for in terms of an (acyloxy)carbene precursor (1-acetoxy-1-propylidene) and the formation of two acyl chlorides supports the hypothesis that such a carbene can abstract Cl from CCl_4, with subsequent β scission of the resulting radical. 1-Acetoxyethylidene was trapped with neat 2-acetoxypropane and with neat 2-methoxypropane to form cyclopropanes.

Introduction

(Acyloxy)carbenes ($R\ddot{C}OC{=}OR''$) are little known intermediates, with only three members of the family having been reported to date. They are (benzoyloxy)methylcarbene (**1a**), (benzoyloxy)phenylcarbene (**1b**),[1,2] and the cyclic carbene **2**.[3,4] Their preparation involved thermolysis of a precursor at 460 °C (for **1a, 1b**) and 560 °C (for **2**).[2] Carbene **2** has also been generated in solution by photolysis of benzocyclobutenedione.[3,4]



1a, R = CH_3
b, R = C_6H_5



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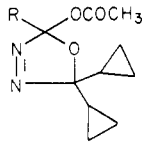
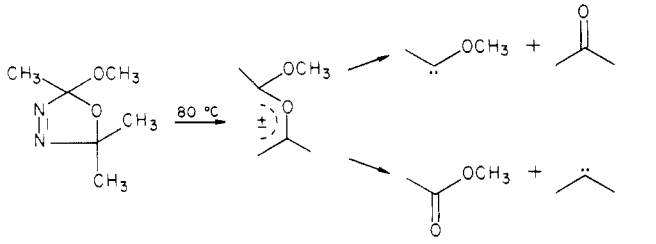


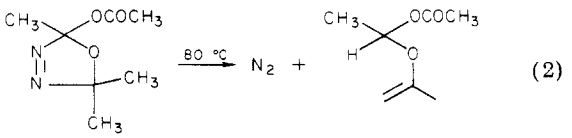
3a, R = CH_3
b, R = CH_2CH_3

Having discovered the fragmentation of methoxy-substituted carbonyl ylides to carbenes (eq 1),[5] we recognized



(1)

that the same approach with an acetoxyoxadiazoline might afford acetoxymethylcarbene were it not for the efficiency with which the former leads to an acetoxy enol ether (eq 2).[6,7,12]

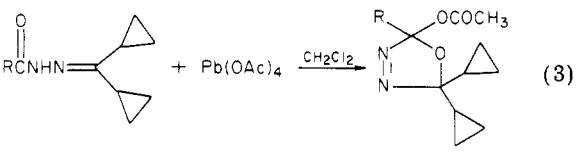


(2)

We report that the H-transfer process of eq 2 can be suppressed with cyclopropyl substituents at C-5 and that oxadiazolines **3** are the first precursors that afford (acyloxy)carbene intermediates under mild conditions of thermolysis (80 °C) in solution.

Results and Discussion

Oxadiazolines **3** were prepared by oxidation of the appropriate acylhydrazones of dicyclopropyl ketone with lead tetraacetate (eq 3).[13] The crude products were purified

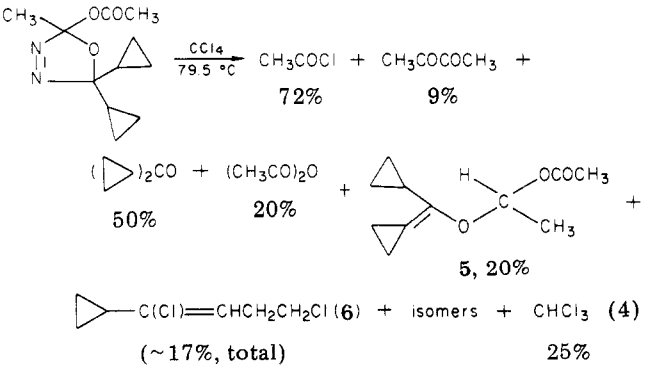


(3)

3a, R = CH_3
b, R = CH_2CH_3

by bulb-to-bulb distillation at 10^{-2} torr with the pot temperature at 30–35 °C. Both are colorless liquids.

Oxadiazoline **3a** decomposes with first-order kinetics in CCl_4, with $k^{79.5} = 8.0 \times 10^{-5}$ s^{-1}. The main products and their yields are given in eq 4.[14] These products can be



(4)

accounted for in terms of the following reactions (Scheme I).

(1) Brown, R. F. C.; Eastwood, F. W. *J. Chem. Soc., Chem. Commun.* **1975**, 328.
(2) Brown, R. F. C.; Eastwood, F. W.; McMullen, G. L. *Aust. J. Chem.* **1976**, *29*, 1705.
(3) Brown, R. F. C.; Solly, R. K. *Tetrahedron Lett.* **1966**, *2*, 169.
(4) Staab, H. A.; Ipaktschi, *J. Chem. Ber.* **1968**, *101*, 1457.
(5) Bĕkhazi, M.; Warkentin, J. *J. Am. Chem. Soc.* **1981**, *103*, 2473.
(6) Yeung, D. W. K.; MacAlpine, G. A.; Warkentin, J. *J. Am. Chem. Soc.* **1978**, *100*, 1962.

(7) Although we had considered a carbonyl ylide mechanism for eq 2 (see ref 6), we favored a mechanism wherein a 1,5-diradical formed in a slow step lost azo nitrogen in concert with H transfer. That interpretation, which was based in part on ring size effects,[6] has been criticized[8] and we recognize from the results of related work[5,9–12] that the ylide mechanism is more likely.

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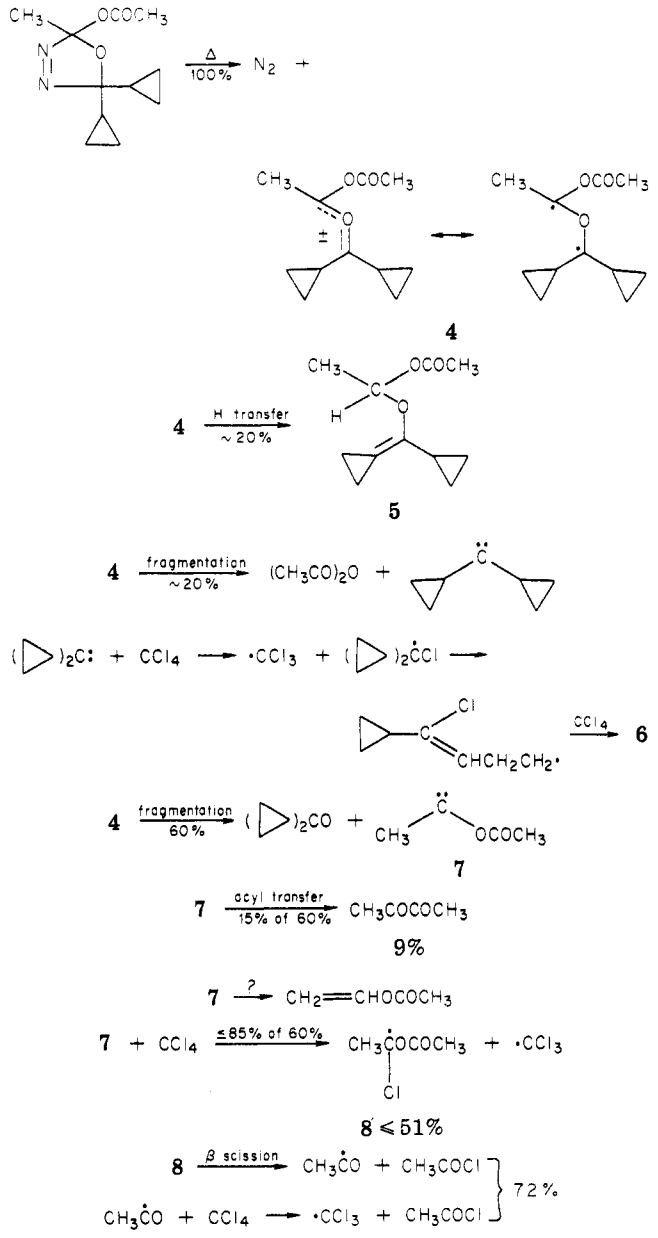
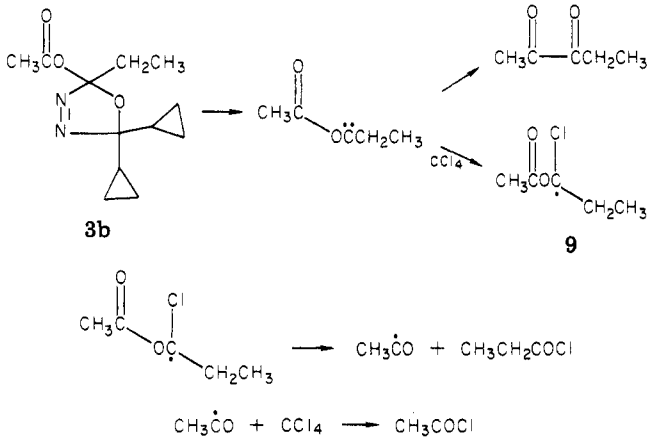
Scheme I



Scheme II



There is much precedent for formation of carbonyl ylides from Δ^3-1,3,4-oxadiazolines.[5,9-11] Formation of an enol ether (in this case **5**) is a known reaction of carbonyl ylides[5,9] and supports the hypothesis that **4** is formed in the present case. Thermal fragmentation of a carbonyl ylide with a donor substituent has been shown to be a reasonable process, from the point view of the thermodynamics,[15] and one piece of experimental evidence for the occurrence of fragmentations has been published.[5] In the present case, fragmentation in the two possible senses leads to acetic anhydride and dicyclopropylcarbene on the one hand and to dicyclopropyl ketone and acetoxymethylcarbene on the other. The latter carbene is expected to rearrange to biacetyl, by analogy to known rearrangements of (acyloxy)carbenes.[1] In fact, formation of biacetyl is strong evidence for an (acyloxy)carbene intermediate.

A reasonable pathway to acetyl chloride is based on the known abstraction from CCl_4 by singlet carbenes[16-20] to form **8** in this case. Fragmentation of **8** by β scission is a reasonable process for which there is much precedent and abstraction of Cl from CCl_4 by acetyl radical is expected. We have not been able to find an estimate of the rate constant for that abstraction in the literature, but the absence of chloromethane among the reaction products indicates that decarbonylation can not compete with Cl abstraction in CCl_4.

Further work will be necessary to delineate additional reactions of the new (acyloxy)carbenes. The known properties of other carbenes suggest that 1,2 H transfer, to form vinyl acetate (Scheme I), might occur. Although vinyl acetate itself was not present, it is unlikely to survive in CCl_4 solution with radicals present. Until the fates of **7** are mapped out fully, the inferred yield of **7** must be regarded as a maximum value and the measured yield of CH_3COCl (72%) can not be dissected into contributions from the two sources (Scheme I). However, the results from decomposition of **3b** lend support to the proposed pathways for formation of acyl chloride. From **3b** one would get, by analogy to Scheme I, radical **9** (Scheme II). It is difficult to imagine a reasonable route to 2,3-pentanedione and to *both* propionyl and acetyl chlorides from **3b** other than Scheme II in which the carbene is in the singlet state. If that scheme is accepted, the present results can be taken as support for atom abstraction by singlet carbenes,[16] a reaction that had been reported for only a few carbenes at the time of writing.[17-20]

(8) Engel, P. *Chem. Rev.* **1980**, *80*, 99.
(9) Shimizu, M.; Bartlett, P. D. *J. Am. Chem. Soc.* **1978**, *100*, 4260.
(10) Rajagopalan, P.; Advani, B. G. *Tetrahedron Lett.* **1967**, 2689.
(11) Hoffmann, R. W.; Luthardt, H. L. *Chem. Ber.* **1968**, *101*, 3861.
(12) Hitchcock, A. P.; Zweep, S.; Steel, T.; Békhazi, M.; Warkentin, J., submitted to *Can. J. Chem.*
(13) For reviews of oxidative cyclization of derivatives of carbonyl compounds, see, for example: (a) Butler, R. N.; Scott, F. L.; O'Mahoney, T. A. F. *Chem. Rev.* **1973**, *73*, 93. (b) Warkentin, J. *Synthesis* **1970**, 279.
(14) Yields are expressed as moles/mole of substrate, in the usual way. Since the products come from several competing reactions, with different stoichiometries, the material balance is best seen by summation of yields of products originating from various parts of the substrate molecule. For example, the balance on methyl groups is [0.72 + 2(0.09) + 2(0.20) + 2(0.20)]/2, or 85%.
(15) Houk, K. N.; Rondan, N. G.; Santiago, C.; Gallo, C. J.; Gandour, R. W.; Griffin, G. W. *J. Am. Chem. Soc.* **1980**, 102, 1504.
(16) Many theoretical calculations concerning the ground states of variously substituted carbenes have been published but (acyloxy)carbenes have not been included. The consensus appears to be that hydroxy- and alkoxycarbenes (and, by inference, (acyloxy)carbenes) have singlet ground states. Leading references include the following: (a) Lucchese, R. L.; Schaefer, H. F., III *J. Am. Chem. Soc.* **1978**, *100*, 298. (b) Baird, N. C.; Taylor, K. F. *Ibid.* **1978**, *100*, 1333. (c) Mueller, P. H.; Rondan, N. G.; Houk, K. N.; Harrison, J. F.; Hooper, D.; Willen, B. H.; Liebman, J. F. *J. Am. Chem. Soc.* **1981**, *103*, 5049.
(17) Roth, H. D.; Manion, M. L. *J. Am. Chem. Soc.* **1976**, *98*, 3392.
(18) Roth, H. D. *Acc. Chem. Res.* **1977**, *10*, 85.
(19) Wong, P. C.; Griller, D.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 5934.
(20) Zupancic, J. J.; Schuster, G. B. *J. Am. Chem. Soc.* **1980**, *102*, 5958.

Acetic anhydride is accounted for readily from fragmentation of 4 to form dicyclopropylcarbene and evidence for the intermediacy of the latter comes from the isolation of 6. Again, the proposed route to 6 (Scheme I) involves Cl abstraction from CCl_4 by a singlet carbene, although intersystem crossing to the triplet and subsequent Cl abstraction can not be ruled out at this time.[21] Subsequent steps involve the well-known cyclopropylcarbinyl-to-homoallyl radical rearrangement and abstraction of Cl from CCl_4.

Experimental Section

Dicyclopropyl Ketone Acetylhydrazone. Acetylhydrazine (7.4 g, 0.10 mol) was refluxed for 30 min with dicyclopropyl ketone (11.0 g, 0.10 mol) in 100 mL of ethanol (95%) containing 2 mL of acetic acid. The ethanol was then distilled off and the residue was heated at 120 °C for 3 h before it was cooled and recrystallized from acetone (15.0 g, 90%): mp 114–115 °C; ^{1}H NMR ($CDCl_3$) δ 0.50–1.00 (8 H, m), 1.13–1.60 (2 H, m), 2.20 (3 H, s). Anal. Calcd for $C_9H_{14}N_2O$: C, 65.03; H, 8.50; N, 16.85. Found: C, 65.00; H, 8.39; N, 16.98.

Dicyclopropyl Ketone Propionylhydrazone. A procedure analogous to the one described above gave the title compound, mp 109–110 °C, in 74% yield: ^{1}H NMR ($CDCl_3$) δ 0.36–0.97 (8 H, m), 0.93 (3 H, t, J = 7.5 Hz), 1.15–1.63 (2 H, m), 2.48 (2 H, q, J = 7.5 Hz).

2-Acetoxy-5,5-dicyclopropyl-2-methyl-Δ^3-1,3,4-oxadiazoline (3a). Dicyclopropyl ketone acetylhydrazone (3.3 g, 0.020 mol) was added to a stirring, ice-cold solution of lead tetraacetate (9.0 g, 0.020 mol) in dichloromethane (100 mL). Stirring and cooling were kept up until the initial yellow color was discharged. The heterogeneous mixture was filtered with suction through a bed of Celite, more CH_2Cl_2 was added, and the organic layer was washed with aqueous $NaHCO_3$ (5%). Drying over $CaCl_2$ and evaporation of the solvent with a rotary evaporator afforded crude, liquid oxadiazoline, which was purified by bulb-to-bulb distillation at room temperature and 10^{-2} torr: 3.6 g, 80% yield; ^{1}H NMR ($CDCl_3$) δ 0.30–1.60 (10 H, m), 1.93 (3 H, s), 2.03 (3 H, s); ^{13}C NMR ($CDCl_3$, −20 °C) δ 1.34, 1.56, 2.08, 16.25, 22.10, 128.21 (C-5), 129.74 (C-2), 168.33 (carbonyl).

2-Acetoxy-5,5-dicyclopropyl-2-ethyl-Δ^3-1,3,4-oxadiazoline (3b). A procedure analogous to that for preparation of **3a** afforded **3b** in 80% yield as a clear liquid: ^{1}H NMR ($CDCl_3$) δ 0.30–1.53 (10 H, m), 1.04 (3 H, t, J = 7.5 Hz), 2.01 (3 H, s), 2.40 (2 H, q, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, −20 °C) δ 1.56, 1.78, 2.00, 16.33, 22.03, 27.94, 127.91 (C-5), 131.86 (C-2), 168.25 (carbonyl).

Thermolysis of 3a in CCl_4. A solution of oxadiazoline **3a** (100 mg, 4.5×10^{-4} mol) in CCl_4 (5.0 mL) was degassed with several freeze–pump–thaw cycles at 10^{-2} torr and sealed into a thick-walled tube. After 3 days at 79.5 °C the contents of the tube were frozen, the tube was cut, and the solution was separated into three fractions by bulb-to-bulb distillation. Fraction one contained material that distilled rapidly at 10^{-2} torr from an unheated pot to a receiver at liquid nitrogen temperature. Fraction two contained material that distilled under the same conditions except for the pot temperature, which was 60 °C. Fraction three was the residue.

Fraction one contained acetyl chloride, biacetyl, acetic anhydride, dicyclopropyl ketone, chloroform, and carbon tetrachloride (solvent). These products were separated by GLC with a column (6 ft × 0.25 in.) packed with OV-17 (10%) and operating at 40 °C with 25 mL/min of carrier gas flow. Each separated product was identified by comparing its IR spectrum and its ^{1}H NMR spectrum to those of authentic samples.

Fraction two was separated by preparative thin-layer chromatography, on plates coated with silica (60F-254, 2 mm thick). Ether (20%) in CCl_4 separated dicyclopropyl ketone from 1-acetoxyethyl cyclopropylidenecyclopropylmethyl ether (**5**): ^{1}H NMR ($CDCl_3$) δ 0.83–1.35 (8 H, m), 1.43 (3 H, d, J = 6.0 Hz), 1.88–2.25 (1 H, m), 2.03 (3 H, s), 6.71 (1 H, q, J = 6.0 Hz); IR ($CDCl_3$) 1742 cm^{-1} (C=O); MS, m/z 196 (M^+).

Fraction three was placed on chromatography plates (silica gel, 60F-254, 2 mm thick), which were developed with CH_2Cl_2. The leading band was scraped off and the organic material was extracted with CH_2Cl_2, which was then evaporated. The extract was separated by GLC on a column (6 ft × 0.25 in.) packed with Carbowax (15%, flow rate 25 mL min^{-1}), which was kept at 70 °C for 5 min and then programmed at 1 °C increase min^{-1} to a maximum temperature of 200 °C. A major component collected was 1,4-dichloro-1-cyclopropyl-1-butene (**6**, E isomer assumed): ^{1}H NMR ($CDCl_3$) δ 0.60–1.20 (5 H, m), 2.65 (2 H, q, J = 7.0 Hz, CH_2), 3.55 (2 H, t, J = 7.0 Hz, CH_2Cl), 5.74 (1 H, t, J = 7.0 Hz, =CH), assignments confirmed by decoupling; MS (m/z, followed by relative intensities in brackets) 164 (19), 166 (12), 168 (2) ($C_7H_{10}Cl_2^+$), 115 (92), 117 (30) ($C_6H_8Cl^+$), 129 (10), 131 (3) ($C_7H_{10}Cl^+$), 79 (100) ($C_6H_7^+$). Other components of fraction three were not identified.

Yields were determined as follows. A degassed sample of **3a** in CCl_4, in a sealed NMR tube containing CH_2Cl_2 as internal standard, was heated for 6 half-lives at 79.5 °C. The ^{1}H NMR spectrum at 400 MHz was obtained with expansion of the δ scale to permit integration by the cut-and-weigh procedure. All yields could be determined in this way, using the spectra of separated components (above) for assignment of bands, except for the yield of **6**. The number (17%) in Scheme I is a composite including the yield of **6** and of other chlorinated products, as yet unidentified, assumed to be isomers of **6** for purpose of yield estimates. Dicyclopropyl ketone was also assayed by IR, using the complete product mixture and standard solutions prepared with authentic dicyclopropyl ketone.

Similar samples of **3a** in CCl_4 were used to determine the rate law and the rate constant for thermolysis at 79.5 °C. Integration of the CH_3CO signal of **3a** relative to that of internal standard led to a linear plot of ln $[\mathbf{3a}]_{rel}$ vs. t and to a first-order rate constant, $k^{79.5} = 8.0 \times 10^{-5}$ s^{-1}.

Thermolysis of 3b in CCl_4. A procedure analogous to that described above for the products of thermolysis of **3a** showed the presence of acetyl chloride and propionyl chloride, in ca. 3:2 ratio, and 2,3-pentanedione: ^{1}H NMR ($CDCl_3$) δ 2.68 (2 H, q), 2.24 (3 H, s), 1.02 (3 H, t). The assignment of structure for propionyl chloride was confirmed by injecting authentic material into a GC–FTIR system. Both the retention time and the vapor-phase IR spectrum of one component of the reaction mixture matched those of propionyl chloride: ^{1}H NMR (CCl_4) δ 1.23 (3 H, t), 2.96 (2 H, q).

Trapping of 1-Acetoxyethylidene with Olefinic Substrates. A degassed solution of **3a** (0.020 g, 8.9×10^{-5} mol) in 2-acetoxypropene (0.5 mL) was heated at 80 °C for 5 half-lives. The sealed tube was cut and the contents were subjected to bulb-to-bulb distillation at ca. 10^{-2} torr with the final pot temperature at 50 °C. Some of the distillate was subjected to preparative GLC with a column (10 ft × 14 in.) packed with OV-17 (10%). From the peak heights for dicyclopropyl ketone and for *trans*-1,2-diacetoxy-1,2-dimethylcyclopropane, the yield of the latter was estimated to be 20% by assuming that the dicyclopropyl ketone yield corresponded to the yield of 1-acetoxyethylidene. Spectra of *trans*-1,2-diacetoxy-1,2-dimethylcyclopropane: ^{1}H NMR ($CDCl_3$) δ 1.08 (2 H, s), 1.54 (6 H, s), 2.04 (6 H, s); MS (m/z, followed by relative intensity and ion composition in brackets) 143 (20, $C_7H_{11}O_3$), 123 (14, $C_7H_7O_2$), 101 (100, $C_5H_9O_2$), 69 (58, C_4H_5O).

The analogous procedure, with 2-methoxypropene instead of 2-acetoxypropene, gave 1-acetoxy-2-methoxy-1,2-dimethylcyclopropane of unknown stereochemistry in ca. 15% yield: ^{1}H NMR δ ($CDCl_3$) 0.79 (1 H, d, J = 6.0 Hz), 0.86 (1 H, d, J = 6.0 Hz), 1.37 (3 H, s), 1.60 (3 H, s), 2.02 (3 H, s), 3.37 (3 H, s); MS (m/z, followed by relative intensity and ion composition in brackets) 115 (97, $C_6H_{11}O_2$), 101 (25, $C_5H_9O_2$), 99 (25, $C_5H_7O_2$), 87 (80, $C_5H_{11}O$), 73 (100, C_4H_9O), 69 (22, C_4H_5O).

Acknowledgment. This work was financed from a grant provided by the Natural Sciences and Engineering Research Council of Canada (NSERC). The high-field NMR spectra were obtained at the Southwestern Ontario

(21) The ground state of dicyclopropylcarbene is probably the triplet state, based on analogy to cyclopropyl carbene for which a triplet ground state has been calculated. Hoffmann, R.; Zeiss, G. D.; Van Dine, G. W. *J. Am. Chem. Soc.* **1968**, *90*, 1485. Phenylcyclopropylcarbenes are most likely ground-state triplets also. Barcus, R. L.; Palik, E. C.; Platz, M. S. *Tetrahedron Lett.* **1982**, *23*, 1323.

NMR Centre funded by a grant from NSERC.

Registry No. 3a, 83313-92-2; **3b**, 83313-93-3; **5**, 83313-94-4; (*E*)-**6**, 83313-95-5; dicyclopropyl ketone acetylhydrazone, 83313-96-6; dicyclopropyl ketone propionylhydrazone, 83313-97-7; 1-acetoxyethylidene, 83313-98-8; *trans*-1,2-diacetoxy-1,2-dimethylcyclopropane, 67079-75-8; 1-acetoxy-2-methoxy-1,2-dimethylcyclopropane, 83313-99-9; acetylhydrazine, 1068-57-1; dicyclopropyl ketone, 1121-37-5; acetyl chloride, 75-36-5; biacetyl, 431-03-8; acetic anhydride, 108-24-7; propionyl chloride, 79-03-8; 2,3-pentanedione, 600-14-6; 2-acetoxypropene, 108-22-5; 2-methoxypropene, 116-11-0; $CH_3COOCCH_2CH_3$, 83350-10-1.

Fluoranthene: Synthesis and Mutagenicity of Four Diol Epoxides

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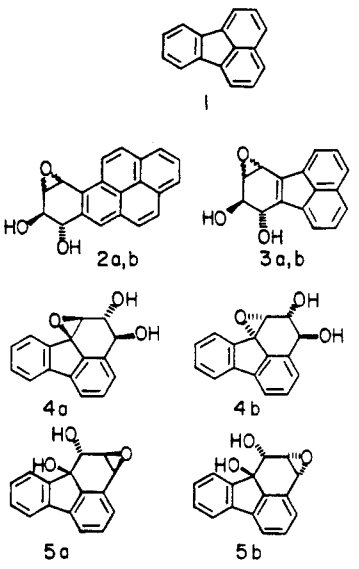
The syntheses of diol epoxides **4a,b** and **5a,b** of the mutagenic hydrocarbon fluoranthene (1) are described. Standard methodology is applied to the synthesis of targets **4a,b** but fails for the synthesis of **5a,b**. The latter two diol epoxides can be assembled by a route utilizing stereoselective, directed epoxidations. Simple molecular orbital calculations have been used to predict the reactivity of the diol epoxides in their opening to triol carbocations. Diol epoxides **4a,b** are predicted to be substantially more reactive than isomers **5a,b**. The more reactive pair, **4a,b**, may yield carbocations capable of alkylating cellular genetic material. This prediction is borne out in terms of the relative mutagenicity of the diol epoxides in a bacterial screen.

Fluoranthene (1, Chart I) occurs in various fossil fuels and combustion effluents at concentrations considerably greater than those of the most frequently studied polycyclic aromatic hydrocarbon, benzo[*a*]pyrene.[2] Further, we have found fluoranthene and benzo[*a*]pyrene to be approximately equipotent as mutagens for *Salmonella typhimurium*[3a] and as mutagens for human lymphoblasts.[3b] We have sought the syntheses of potential oxidative metabolites of fluoranthene to help identify the mode(s) of in vivo metabolism of the hydrocarbon and the structure(s) of the covalent adducts presumably formed from the activated hydrocarbon and DNA. Herein we outline our progress directed toward these ends. Specifically, we detail the syntheses and mutation assay of six possible metabolites of fluoranthene, the dihydrodiols **11** and **23** (see Schemes I and II), and the diol epoxides **4a,b** and **5a,b** (Chart I).

Chart I



syn-Isomers: epoxide oxygen syn to benzylic (allylic) OH, e.g., 4a and 5a

anti-Isomers: epoxide oxygen anti to benzylic (allylic) OH, e.g., 4b and 5b

Strategy

Extensive study of the metabolic activation of polycyclic aromatic hydrocarbons, such as benzo[*a*]pyrene,[4a] has identified the diol epoxides (see **2a,b**, Chart I) as agents responsible for the alkylation of cellular macromolecules. The genesis of the diol epoxides occurs through oxidation of the parent hydrocarbon to an arene oxide, followed by hydration of the oxide to the corresponding *trans*-dihydrodiol, and oxidation of the dihydrodiol to one or both

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