residue was crystallized from hexane to give 70 mg of **21** as white crystals (72% from **19**): mp 124–125 °C; ^{1}H NMR δ 10.88 (br 1 H), 4.01 ppm (m, 4 H); IR ν 3330–2358 (br), 2997, 2980, 1681 (s), 1423, 1317, 1173 cm^{-1}. The deuterium content at the labeled positions was estimated by NMR integration at >95%.

2,6,8-Trideuteriocubyl Iodide (22). Acid **21** (20 mg, 0.13 mmol) was dissolved in excess oxalyl chloride (0.5 mL) at room temperature and the solution gently refluxed for 1 h and then cooled to room temperature. Excess reagent was removed in vacuo at room temperature. The residue, crude acid chloride, was dissolved in dry CH_2Cl_2 (2 mL) and the solution added to a suspension of the sodium salt of *N*-hydroxypyridine-2-thione (40 mg, 0.26 mmol) in excess CF_3CH_2I (1 mL) containing a catalytic amount AIBN (cf. ref 14). This suspension was brought to reflux, irradiated with a 300-W tungsten lamp for 40 min, and then cooled to room temperature. The solvent and excess CF_3CH_2I were removed in vacuo (do not prolong pumping). The residue was extracted with pentane (3 × 1 mL). The extract was chromatographed on silica gel (70–230 mesh) with pentane to afford pure **22** (R_f = 0.60, 21 mg, 68%) as a white crystalline material: mp 32.0–33.0 °C; ^{1}H NMR δ 4.21 (m, 1 H), 4.18 ppm (m, 3 H); MS (EI) *m/e* 233 (weak), 127 (23), 106 (54), 79 (100), 52 (23). In the observed ^{1}H NMR spectrum the 3-hydrogen mutiplet at δ 4.33 ppm present in the spectrum of nondeuteriated material is missing entirely.

Acknowledgment. The National Science Foundation, the Office of Naval Research, and Geo-Centers, Inc. (ARDEC) provided support for this work. We thank Professor Peter Beak for helpful discussions.

Registry No. **1**, 94161-36-1; **7**, 29412-62-2; **7** monoester, 24539-28-4; **8a**, 130602-27-6; **8b**, 141807-74-1; **9a**, 141807-75-2; **9b**, 141807-73-0; **10a**, 130640-41-4; **10b**, 141807-72-9; **13**, 141807-76-3; **14**, 141807-77-4; **17**, 141807-78-5; **18**, 141807-79-6; **19**, 141807-80-9; **21**, 141807-81-0; **22**, 141807-82-1.

Notes

Electrophilic Fluorination of Pharmacologically Active 1,3-Dicarbonyl Compounds

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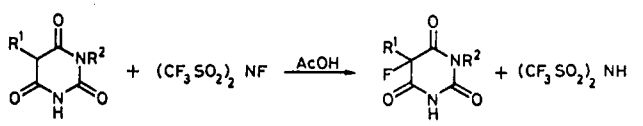
Received January 30, 1992

Compounds containing the N–F functionality are attracting increasing interest as stable, nonhygroscopic, and safe reagents for electrophilic fluorinations.

Sulfonimides[2-4] and related compounds[5] are particularly attractive with respect to other structural classes of products containing the N–F moiety[6-13] as they are endowed with a high reactivity, but at the same time they are easy to handle and can be stored for a long time without any deterioration.

The first perfluorinated compounds of this type were the *N*-fluoroperfluoroalkylsulfonimides[14,15] that we have synthesized and shown to work as efficient reagents for the fluorination of several kinds of substrates.[16-18]

Scheme I



2a-i 1 3a-i 4

Starting material	R^1	R^2	Isolated yield (%)
2a	H	H	88 (R^1=F in 3a)
2b	CH_3	H	92
2c	C_2H_5	H	89
2d	n-C_4H_9	H	90
2e	C_6H_5	H	91
2f	OCH_3	H	90
2g	CH_3	CH_3	92
2h	C_2H_5	CH_3	83
2i	C_6H_5	CH_3	91

In order to further study the synthetic potentials of *N*-fluorobis[(trifluoromethyl)sulfonyl]imide (**1**), we have examined the fluorination of several compounds endowed with useful pharmacological and therapeutic properties.

The substrates employed became a severe test of the selectivity and mildness of an electrophilic fluorinating agent, inasmuch as they bear several functional groups susceptible to electrophilic attack, acid- or base-catalyzed hydrolyses, oxidation, and rearrangement. The selectively fluorinated products that were isolated may be of interest in themselves.

Results and Discussion

When a suspension of 2,4,6-trihydroxypyrimidine **2a** was treated at room temperature with 2 equiv of the *N*-fluoroimide **1** a slightly exothermic reaction occurred and the corresponding 5,5-difluoro derivative **3a** was exclusively

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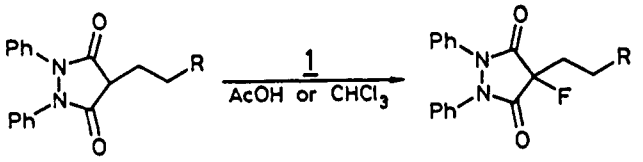
Scheme II



5 a,b 6 a,b

	R	Isolated yield (%)
a	C_2H_5	95
b	S-Ph (=O)	90

formed in high yield (Scheme I). The hypnotic and sedative activity of the 2,4,6-pyrimidintrione moiety is strictly dependent on the nature of the substituents present on C-5 and on the acidity of the lactam–lactim protons.[19] For this reason, we have also carried out the fluorination of the barbituric derivatives **2b–i** which carried an alkyl, or aryl, or methoxy residue on C-5 and hydrogen or a methyl on N-1. When these substrates were treated with 1 equiv of the *N*-fluoroimide **1**, the 5-monofluoro derivatives **3b–i** were formed and could be easily isolated in pure form through crystallization or chromatography.

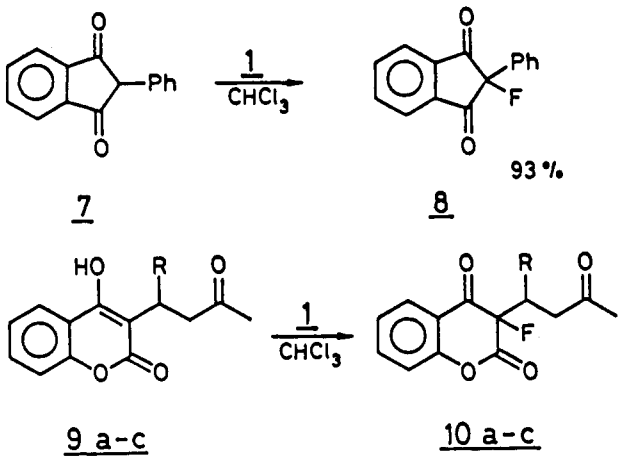
In all cases anhydrous acetic acid was used as a solvent as a consequence of the low solubility of some starting compounds **2** in other solvents. Yields were invariably higher than those obtained when the same products were prepared through total synthesis[20] or through other methods of electrophilic fluorination.[21-24]

A detailed mass spectrometric study on the effect of fluorine in the fragmentation pathways of substituted barbituric acids has been carried out.[25] In contrast to the parent acids **2**, which undergo initial ring cleavage at the ketoimidic bond, fluorinated analogues **3** undergo cleavage of the carbon–carbon bond. Single-crystal X-ray analysis has been carried out on **3a** and **3e** to provide further details on the structural effects of fluorine substitution at C-5.[26]

Phenylbutazone **5a** and sulfinpyrazone **5b** are analgesic and antipiretic drugs frequently used in rheumatoid and gouty arthritis. When these compounds were treated with 1 equiv of the *N*-fluoroimide **1**, in acetic acid and chloroform solution, respectively, fluorination occurred cleanly in position four, and corresponding products **6a** and **6b** were obtained in 95% and 90% isolated yields (Scheme II).

Similarly, phenindione **7**, an orally active anticoagulant drug commonly employed in human therapy, afforded the product of fluorination in position two when treated with

Scheme III



7 8 (93%)

9 a-c 10 a-c

	R	Isolated yield (%)
a	H	91
b	C_6H_5	92
c	p-Cl-C_6H_4	90

1 in chloroform solution (Scheme III).

Warfarin (**9b**) is another well-known anticoagulant drug routinely employed for human therapy. When a suspension of this drug in chloroform was treated with the *N*-fluoroimide **1** a rapid reaction occured at 35 °C and the 3-fluoro derivative **10b** was formed as a diastereoisomer mixture in nearly quantitative yields.[27] The byproduct formed during the fluorination reaction was bis(trifluoromethylsulfonyl)imide (**4**). Compound **10b** could thus be obtained in pure form by simply removing the imide through water extraction and by crystallizing the residue. Under the same reaction conditions, a similar behavior was shown by the *p*-chlorophenyl analogue **9c** and by 3-(3-oxobutyl)-4-hydroxycumarin (**9a**). The 3-fluoro derivatives **10c** and **10a** were formed cleanly, but the latter product was highly sensitive to the acidity[28] of the formed bis(trifluoromethylsulfonyl)imide and a rapid hydrolysis of its ester function occurred to give 2-(2-carboxy-2-fluoro-1,5-dioxohexyl)phenol (**12**). By simply performing the fluorination reaction in the presence of sodium hydrogen carbonate, this hydrolysis was prevented (the imide giving its sodium salt through an acid–base reaction) and the pure 3-fluoro-3-(3-oxobutyl)-2*H*-benzopyran-2,4-dione (**10a**) could be isolated in 85% yield. Some general comments can be made on the above described reactions. Fluorination on the enolizable position of the β-dicarbonyl systems occurred in all cases as it was always preferred independently from the specific nature of the substrate (β-diamide for **2** and **5**, β-diketone for **7**, β-keto ester for **9**).

The *N*-fluoroimide **1** can fluorinate aromatic substrates,[14] and the reaction is quite easy on phenolic derivatives.[18] However, this kind of side reactions has not been observed even for substrates in which the phenyl ring

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was activated by a nitrogen or oxygen residue (compounds **5** or **9**, respectively).

Finally, oxidation to sulfonyl residue and Pummerer rearrangement are typical reactions of the sulfinyl group. Neither reaction has been observed on sulfinpyrazone **5b** despite the fact the *N*-fluoroimide has been observed to behave as an oxidizing species on some other sulfur compounds and the imide **4**, formed through the fluorination reaction, is a very strong acid.[29]

Experimental Section

All reactions were performed in glass apparatus. Commercially available, reagent-grade solvents were employed without purification. Flash column chromatography on silica gel was performed as described in the original paper.[30] Unless otherwise stated $CDCl_3$ was used as a lock solvent and $CFCl_3$ and tetramethylsilane as internal references in ^{19}F (188 MHz), ^1H (300 MHz), and ^{13}C (75 MHz) NMR. Expected IR spectra were obtained for all compounds.

Fluorination of Barbituric Acid Derivatives 3a–i. General Procedure. A solution of the *N*-fluoroimide **1** (0.54 mmol for **2a**; 0.27 mmol for **2b–i**) in anhydrous acetic acid (1.5 mL) was added dropwise at 20 °C into a suspension of barbituric acid derivatives **2a–i** (0.25 mmol) in the same solvent (1.5 mL). Stirring was continued at room temperature for 10 min after a complete dissolution occurred (20–100 min). Acetic acid was removed on a rotary evaporator, and the residue was left overnight in the vacuum (5 mmHg). 5-Fluorobarbituric acid derivatives **3a–h** were isolated in pure form through crystallization from CH_3CN/iPr_2O. The *N*-methyl 5-fluoro-5-phenylbarbituric acid **2i** was purified through flash chromatography (*n*-pentane/Et_2O (3:7)). In all cases products **3a–i** were isolated in 86–92% yield of pure product. **5,5-Difluoro-2,4,6-pyrimidinetrione (3a)** was prepared starting from barbituric acid (**2a**): mp 211–213 °C dec (lit.[21] mp 210–213 °C); ^{19}F NMR (CD_3CN) δ −112.0; ^{13}C NMR (CD_3CN) δ 160.6 (t, $^2J_{C,F}$ = 28.1 Hz, C-4 and C-6), 148.0 (C-2), 99.6 (t, $^1J_{C,F}$ = 247.7 Hz, C-5). **5-Fluoro-5-methyl-2,4,6-pyrimidinetrione (3b)** was prepared starting from 5-methyl-2,4,6-pyrimidinetrione (**2b**): mp 252–255 °C dec; ^1H NMR (CD_3CN) δ 1.79 (d, $J_{H,F}$ = 22.0 Hz, CH_3), 2.42 (br s, 2 H, 2 × NH); ^{19}F NMR (CD_3CN) δ −167.9 (m, $^3J_{F,H}$ = 22 Hz); ^{13}C NMR δ (CD_3CN) 168.0 (d, $^2J_{C,F}$ = 23.3 Hz, C-4 and C-6), 149.0 (C-2), 88.5 (d, $^1J_{C,F}$ = 190.0 Hz, C-5), 24.4 (d, $^2J_{C,F}$ = 25.3 Hz). Anal. Calcd for $C_5H_5CN_2O_3$: C, 37.51; H, 3.15; N, 17.50. Found: C, 37.74; H, 3.34; N, 17.38. **5-Fluoro-5-ethyl-2,4,6-pyrimidinetrione (3c)** was prepared from 5-ethyl-2,4,6-pyrimidinetrione (**2c**): mp 201–203 °C (lit.[22] mp 202 °C); ^1H NMR (CD_3CN) δ 0.98 (t, 3 H, $J_{H,H}$ = 7.5 Hz, CH_3), 2.09 and 2.19 (dq each, 1 H each, $J_{H,F}$ = 22.4 Hz, CH_2), 2.39 (br s, 2 H, 2 × NH); ^{19}F NMR (CD_3CN) δ −177.9 (m, $^3J_{F,H}$ = 21 Hz); ^{13}C NMR (CD_3CN) δ 167.7 (d, $^2J_{C,F}$ = 23.4 Hz, C-4 and C-6), 149.4 (C-2), 91.9 (d, $^1J_{C,F}$ = 193.6 Hz, C-5), 32.4 (d, $^2J_{C,F}$ = 24.5 Hz, CH_2), 7.2 (d, $^3J_{C,F}$ = 4.5 Hz, CH_3). **5-Fluoro-5-*n*-butyl-2,4,6-pyrimidinetrione (3d)** was prepared from 5-*n*-butyl-2,4,6-pyrimidinetrione (**2d**): mp 194–196 °C (lit.[22] mp 185–187 °C); ^1H NMR (CD_3CN) δ 0.88 (br t, 3 H, CH_3), 1.35 (m, 4 H, 2 × CH_2), 2.10 (m, 2 H, CH_2), 2.77 (br s, 2 H, 2 × NH); ^{19}F NMR (CD_3CN) δ −176.15 (m, $^3J_{F,H}$ = 19.4 Hz); ^{13}C NMR (CD_3CN) δ 167.7 (d, $^2J_{C,F}$ = 23.6 Hz, C-4 and C-6), 149.3 (C-2), 91.6 (d, $^1J_{C,F}$ = 193.5 Hz, C-5), 13.9, 22.8, and 25.1 ($CH_2CH_2CH_3$), 38.3 (d, $^2J_{C,F}$ = 23.8 Hz, CH_2). **5-Fluoro-5-phenyl-2,4,6-pyrimidinetrione (3e)** was prepared starting from 5-phenyl-2,4,6-pyrimidinetrione (**2e**): mp 257–259 °C (lit.[29] mp 251–253 °C); ^1H NMR (CD_3CN) δ 7.5 (m, 5 H, C_6H_5), 2.46 (br s, 2 H, 2 × NH); ^{19}F NMR (CD_3CN) δ −164.5 (t, $J_{F,H}$ = 10.3 Hz); ^{13}C NMR (CD_3CN) δ 166.5 (d, $^2J_{C,F}$ = 24.9 Hz, C-4 and C-6), 149.0 (C-2), 134.3 (d, $^2J_{C,F}$ = 24.2 Hz, C-1 of Ph), 131.9 (C-4 of Ph), 130.5 (C-3 of Ph), 126.1 (d, $^3J_{C,F}$ = 5.6 Hz, C-2 of Ph), 90.8 (d, $^1J_{C,F}$ = 194.2, C-5). **5-Fluoro-5-methoxy-2,4,6-pyrimidinetrione (3f)** was prepared starting from 5-methoxy-2,4,6-pyrimidinetrione (**2f**): mp 117–119 °C; ^1H NMR (CD_3CN) δ 2.48 (br s, 2 H, 2 × NH), 3.56 (d, 3 H, $J_{H,F}$ = 1.6 Hz, OCH_3); ^{19}F NMR (CD_3CN) δ −139.9; ^{13}C NMR (CD_3CN) δ 163.2 (d, $^2J_{C,F}$ = 33.6 Hz, C-4 and C-6); 148.7 (C-2), 98.4 (d, $^1J_{C,F}$ = 230.9 Hz, C-5), 54.7 (OCH_3). Anal. Calcd for $C_5H_5FN_2O_4$: C, 34.10; H, 2.86; N, 15.91. Found: C, 34.28; H, 3.04; N, 15.80. ***N*-Methyl-5-fluoro-5-methyl-2,4,6-pyrimidinetrione (3g)** was prepared starting from *N*-methyl 5-methyl-2,4,6-pyrimidinetrione (**2g**): mp 162–164 °C; ^1H NMR (CD_3CN) δ 1.78 (d, 3 H, $J_{H,F}$ = 22.5 Hz, CH_3CF), 2.38 (br s, 1 H, NH), 3.16 (s, 3 H, CH_3N); ^{19}F NMR (CD_3CN) δ −165.2 (m, $^3J_{F,H}$ = 21.8 Hz); ^{13}C NMR (CD_3CN) δ 168.8 and 167.7 (d, each, $^2J_{C,F}$ = 22.9 and 23.2, C-4 and C-6), 150.3 (C-2), 88.3 (d, $^1J_{C,F}$ = 189.6 Hz, C-5), 28.6 (CH_3N), 24.9 (d, $^2J_{C,F}$ = 25.4 Hz, CH_3CF). ***N*-Methyl-5-fluoro-5-ethyl-2,4,6-pyrimidinetrione (3h)** was prepared starting from *N*-methyl 5-ethyl-2,4,6-pyrimidinetrione (**2h**): mp 121–123 °C; ^1H NMR (CD_3CN) δ 0.96 (t, 3 H, CH_3), 2.07 and 2.18 (q each, 1 H each, CH_2), 2.20 (br s, 1 H, NH), 3.16 (s, 3 H, CH_3N); ^{19}F NMR (CD_3CN) δ −175.2 (m, $^3J_{F,H}$ = 20.9 Hz); ^{13}C NMR (CD_3CN) δ 168.3 and 167.1 (d each, $^2J_{C,F}$ = 23.2 and 23.8, respectively, C-4 and C-6), 150.4 (C-2), 92.1 (d, $^1J_{C,F}$ = 192.8 Hz, C-5), 32.6 (d, $^2J_{C,F}$ = 24.5 Hz, CH_2), 28.6 (CH_3N), 7.2 (d, $^3J_{C,F}$ = 4.3 Hz, CH_3CH_2). Anal. Calcd for $C_7H_9FN_2O_3$: C, 44.70; H, 4.82; N, 14.89. Found: C, 44.88; H, 5.06; N, 14.69. ***N*-Methyl-5-fluoro-5-phenyl-2,4,6-pyrimidinetrione (3i)** was prepared starting from *N*-methyl 5-phenylpyrimidinetrione (**2i**): mp 139–141 °C; ^1H NMR (CD_3CN) δ 3.21 (s, 3 H, CH_3), 7.5 (m, 5 H, C_6H_5); ^{19}F NMR (CD_3CN) δ −161.1; ^{13}C NMR (CD_3CN) δ 167.1 and 165.9 (d each, $^2J_{C,F}$ = 24.5 and 25.0 Hz, C-4 and C-6), 150.1 (C-2), 134.5 (d, $^2J_{C,F}$ = 24.2 Hz, C-1 of Ph), 131.8 (C-4 of Ph), 130.4 (C-3 of Ph), 126.1 (d, $^3J_{C,F}$ = 5.4 Hz, C-2 of Ph), 91.0 (d, $^1J_{C,F}$ = 193.3 Hz, C-5), 28.8 (CH_3). Anal. Calcd for $C_{11}H_9FN_2O_3$: C, 55.94; H, 3.84; N, 11.86. Found: C, 56.18; H, 4.01; N, 11.80.

1,2-Diphenyl-4-*n*-butyl-4-fluoropyrazolidine-3,5-dione (6a). A solution of the *N*-fluoroimide **1** (415 mg, 1.65 mmol) in anhydrous acetic acid (1.5 mL) was added at 20 °C to a solution of phenylbutazone **5a** (425 mg, 1.38 mmol) in the same solvent (1.5 mL). After being stirred for 30 min at room temperature the reaction mixture was added to a stirred solution of ethyl acetate (50 mL) and saturated aqueous solution of sodium carbonate (25 mL). The aqueous phase was extracted with ethyl acetate (3 × 50 mL). Collected organic phases were dried with anhydrous sodium sulfate and evaporated under reduced pressure. The residue was flash-chromatographed (*n*-pentane/ethyl ether (9:1)) to give the pure fluorination product **6a** in 95% yield: ^1H NMR δ 0.85 (t, 3 H, CH_3), 1.2–1.5 (m, 4 H, 2 × CH_2), 2.2 (m, 2 H, CH_2CF), 7.2–7.4 (m, 10 H, 2 × Ph); ^{19}F NMR δ −168.2 (t, $J_{F,H}$ = 15.2 Hz); ^{13}C NMR δ 165.7 (d, $^2J_{C,F}$ = 21.3 Hz, C-3 and C-5), 134.7 (C-1 of Ph), 129.2 and 122.8 (C-2 and C-3 of Ph), 127.6 (C-4 of Ph), 88.4 (d, $^1J_{C,F}$ = 197.6, C-4), 33.8 (d, $^2J_{C,F}$ = 24.5 Hz, CH_2CF), 23.6 (d, $^3J_{C,F}$ = 7.1 Hz, CH_2CH_2CF), 22.5 (CH_2), 13.6 (CH_3); mass spectrum (CI) *m/e* 327 (M+1), 307, 208, 183. Anal. Calcd for $C_{19}H_{19}N_2O_2$: C, 69.92; H, 5.87; N, 8.58. Found: C, 70.17; H, 5.99; N, 8.36. **1,2-Diphenyl-4-fluoro-4-[(2-phenylsulfinyl)ethyl]-pyrazolidine-3,5-dione (6b).** A procedure similar to that described above for phenylbutazone **5a** was used, with the difference that chloroform was employed as a solvent: flash chromatography *n*-hexane/ethyl acetate (1:1); yield 90%; ^1H NMR δ 2.32 (m, 1 H), 2.69 (m, 1 H), 3.08 (m, 1 H), 3.50 (m, 1 H), 7.2–7.6 (m, 10 H); ^{19}F NMR δ −172.7 (t, $J_{F,H}$ = 21.8 Hz); ^{13}C NMR δ 164.4 (d, $^2J_{C,F}$ = 21.4 Hz, C-3 and C-5), 142.3, 134.3, 131.3, 129.4, 129.3, 127.9, 124.0, 123.1 (C and CH of Ph), 86.4 (d, $^1J_{C,F}$ = 199.5 Hz, C-4); 47.4 (CH_2S), 26.0 (d, $^2J_{C,F}$ = 26 Hz, CH_2CF); mass spectrum (EI) *m/e* 422 (M), 297, 296, 240, 239, 148. Anal. Calcd for $C_{23}H_{19}FN_2O_3S$: C, 65.39; H, 4.53; N, 6.62. Found: C, 65.58; H, 4.31; N, 6.49.

2-Fluoro-2-phenylindan-1,3-dione (8). The procedure described above for sulfinpyrazone **5b** was used: flash chromatography *n*-pentane/ethyl ether (1:1); mp 89–91 °C; ^1H NMR δ 7.4 (m, 5 H, Ph), 7.9–8.1 (m, 4 H, C_6H_4); ^{19}F NMR δ −164.0; ^{13}C NMR δ 192.9 (d, $^2J_{C,F}$ = 19.2 Hz, C-1 and C-3), 140.7, 137.2, 132.0 (d, $^2J_{C,F}$ = 24.4 Hz), 129.8, 128.8, 126.1, 126.0, 124.3 (C and CH ar.), 91.8 (d, $^1J_{C,F}$ = 202.5 Hz, C-2); mass spectrum (EI) *m/e* 240 (M), 212, 163.

3-Fluoro-3-(3-oxobutyl)-2*H*-benzopyran-2,4-dione (10a). When 3-(3-oxobutyl)-4-hydroxycoumarin (**9a**) was treated with the *N*-fluoroimide **1** in chloroform/water solution at 35 °C for 5 min, the desired 3-fluoro derivative **10a** was formed in nearly quantitative yield (^1H NMR of the reaction mixture), but a rapid hydrolysis to give a mixture of **10a** and 2-(2-carboxy-2-fluoro-

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1,5-dioxohexyl)phenol (12) occurred. 12: ^{1}H NMR δ 2.17 (s, 3 H, CH_3), 2.45–2.75 (m, 4 H, 2 × CH_2), 6.87 and 7.50 (dd each, 1 H each, J = 7.3 Hz, H-4 and H-5), 7.00 and 7.95 (d each, 1 H each, J = 8.2 Hz, H-3 and H-6); ^{19}F NMR δ −158.5 (t, $J_{F,H}$ = 21.8 Hz); ^{13}C NMR δ 207.9 (C-5′), 195.4 (d, $^2J_{C,F}$ = 24.4 Hz, C-1′), 169.0 (d, $^2J_{C,F}$ = 25.9 Hz, CO_2H), 163.5 (COH), 137.5, 131.0, 130.8, 119.4, 118.6 (C and CH ar), 97.5 (d, $^1J_{C,F}$ = 198.4, C-2′), 36.7 (C-4′), 29.8 (C-6′), 27.7 (d, $^2J_{C,F}$ = 21.6 Hz, C-3′). Another procedure was therefore employed. The *N*-fluoroimide 1 (480 mg, 1.6 mmol) in chloroform solution (4.0 mL) was added at 0 °C to a vigorously stirred suspension of **9a** (348 mg, 1.5 mmol) and sodium hydrogen carbonate (143 mg, 1.7 mmol) in the same solvent (4.9 mL). After 5 min at room temperature the reaction mixture was washed with water (3 × 3.0 mL), and the residue was dried with anhydrous sodium sulfate, evaporated, and crystallized from diisopropyl ether to give 341 mg (91% yield) of pure 3-fluoro-3-(3-oxobutyl)-2*H*-benzopyran-2,4-dione (**10a**): mp 70–72 °C; ^{1}H NMR δ 2.18 (s, 3 H, C-4′), 2.39 (m, 1 H, Ha-1′), 2.50 (m, 1 H, Hb-1′), 2.78 (t, 2 H, J = 7.2 Hz, H_2-2′), 7.28 (br d, 1 H, J = 8.0 Hz), 7.37 (dm, 1 H, J = 7.5 Hz), 7.75 (ddd, 1 H), 7.93 (dd, 1 H, J = 7.9 Hz); ^{19}F NMR δ −179.4 (t, $J_{F,H}$ = 22.4 Hz); ^{13}C NMR δ 206.0 (C-3′), 187.2 (d, $^2J_{C,F}$ = 18.0 Hz, C-4), 164.7 (d, $^2J_{C,F}$ = 24.0 Hz, C-2), 153.8 (C-O), 137.9, 127.8, 125.8, 118.1, 117.7 (C and CH ar), 95.0 (d, $^1J_{C,F}$ = 204.6, C-3), 35.5 (C-2′), 30.6 (d, $^2J_{C,F}$ = 23.0 Hz, C-1′), 29.83 (C-4′). **3-Fluoro-3-(1-phenyl-3-oxobutyl)-2*H*-benzopyran-2,4-dione (10b).** A solution of the *N*-fluoroimide 1 (965 mg, 3.25 mmol) in chloroform (2.0 mL) was added at room temperature to a suspension of 3-(1-phenyl-3-oxobutyl)-4-hydroxycoumarin (925 mg, 2.70 mmol) in chloroform/water (1:1; 5.0 mL). The resulting heterogeneous system was vigorously stirred for 15 min at 35 °C, water was removed, and the organic phase was washed with water (2 × 5.0 mL). The organic layer was dried with anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the residue was crystallized from diisopropyl ether to give 898 mg (92% yield) of pure 3-fluoro derivative **10b** as a 3:1 mixture of two diastereoisomers: mp 125–127 °C; mass spectrum (CI) *m/e* 327 (M + 1), 147. Major diastereoisomer: ^{1}H NMR δ 2.08 (s, 3 H, CH_3), 3.01 (dd, 1 H, J = 18.4 and 7.7 Hz, H_a-2′), 3.33 (dd, 1 H, $J_{H,H}$ = 18.4 and 5.3 Hz, H_b-2′), 4.03 (ddd, 1 H, $J_{H,F}$ = 25.5 Hz, H-1′), 6.7–7.7 (m, 9 H, CH ar.); ^{19}F NMR δ −182.2 (d, $J_{F,H}$ = 25.4 Hz); ^{13}C NMR δ 204.5 (C-3′), 186.1 (d, $^2J_{C,F}$ = 18.3 Hz, C-4), 164.5 (d, $^2J_{C,F}$ = 23.7 Hz, C-2), 153.3, 137.3, 134.6 (C ar.), 128.5, 128.7, 127.1, 117.6 (CH ar.), 98.03 (d, $^1J_{C,F}$ = 209.1 Hz, C-3), 47.0 (d, $^2J_{C,F}$ = 21.4 Hz, C-1′), 42.4 (d, $^3J_{C,F}$ = 3.1 Hz, C-2′), 30.21 (C-4′). Minor diastereoisomer (chemical shifts are given when they are different from those reported above): ^{1}H NMR δ 2.06 (s, 3 H, CH_3), 2.96 (dd, 1 H, $J_{H,H}$ = 18.4 and 7.5 Hz, H_a-2′), 3.31 (dd, 1 H, $J_{H,H}$ = 18.3 and ≃ 6.5 Hz, H-2′), 4.03 (ddd, 1 H, H-1′); ^{19}F NMR δ −181.6 (d, $J_{F,H}$ = 24.5 Hz); ^{13}C NMR δ 204.47 (C-3′), 187.51 (d, $^2J_{C,F}$ = 18.2 Hz, C-4), 163.28 (d, $^2J_{C,F}$ = 24.5 Hz, C-2), 153.76, 137.77, 135.27 (C ar.), 128.66, 128.56, 127.67, 125.50, 118.78, 117.29 (CH ar.), 98.09 (d, $^1J_{C,F}$ = 209.0 Hz, C-3), 46.94 (d, $^2J_{C,F}$ = 21.4 Hz, C-1′), 41.95 (d, $^3J_{C,F}$ = 3.0 Hz, C-2′), 30.15 (C-4′). **3-Fluoro-3-[1-(4-chlorophenyl)-3-oxobutyl]-2*H*-benzopyran-2,4-dione (10c).** The same procedure described above for warfarin (**10b**) was employed. A 2:1 mixture of the two diastereomers was obtained in 90% yield: mp 145–149 °C; mass spectrum (CI) *m/e* 361, 363 (M + 1), 181, 183. Major diastereoisomer: ^{1}H NMR δ 2.10 (s, 3 H, CH_3), 2.97 (dd, 1 H, $J_{H,H}$ = 18.4 and 7.7 Hz, H_a-2′), 3.31 (dd, 1 H, $J_{H,H}$ = 18.5 and 5.1 Hz, H_b-2′), 4.00 (ddd, 1 H, $J_{H,F}$ = 26.2 Hz, H-1′), 6.9–7.7 (m, 8 H, CH ar.); ^{19}F NMR δ −183.2 (d, $J_{F,H}$ = 26.7 Hz); ^{13}C NMR δ 204.15 (C-3′), 185.77 (d, $^2J_{C,F}$ = 18.4 Hz, C-4), 164.08 (d, $^2J_{C,F}$ = 24.0 Hz, C-2), 153.19, 137.59, 134.35, 133.26 (C ar.), 129.95, 128.65, 127.08, 125.78, 119.26, 117.54 (CH ar.), 97.90 (d, $^1J_{C,F}$ = 210.6 Hz, C-3), 46.04 (d, $^2J_{C,F}$ = 21.3 Hz, C-1′), 42.48 (C-2′), 30.02 (C-4′). Minor diastereoisomer (chemical shifts are given when they are different from those reported above): ^{1}H NMR δ 2.07 (s, 3 H, CH_3), 2.91 (dd, 1 H, H_a-2′), 3.29 (dd, 1 H, H_b-2′); ^{19}F NMR δ −182.6 (d, $J_{F,H}$ = 25.4 Hz); ^{13}C NMR δ 187.10 (d, $^2J_{C,F}$ = 18.0 Hz, C-4), 163.00 (d, $^2J_{C,F}$ = 24.7 Hz, C-2), 153.64, 137.82, 134.44, 133.88 (C ar.), 128.86, 127.69, 125.57, 118.49, 117.26 (CH ar.), 97.95 (d, $^1J_{C,F}$ = 208.9 Hz, C-3), 45.92 (d, $^2J_{C,F}$ = 21.3 Hz, C-1′), 41.88 (d, $^3J_{C,F}$ = 2.9 Hz, C-2). Anal. Calcd for $C_{19}H_{14}ClFO_4$: C, 63.26; H, 3.91. Found: C, 63.31; H, 4.03.

Acknowledgment. The partial financial support of this research by the National Science Foundation and the award of a NATO Fellowship (G.R.) are gratefully acknowledged.

Registry No. 1, 108388-06-3; **2a**, 67-52-7; **2b**, 2417-22-3; **2c**, 2518-72-1; **2d**, 1953-33-9; **2e**, 22275-34-9; **2f**, 60703-43-7; **2g**, 7391-67-5; **2h**, 55974-64-6; **2i**, 103858-65-7; **3a**, 55052-01-2; **3b**, 83049-84-7; **3c**, 649-07-0; **3d**, 53162-56-4; **3e**, 53162-61-1; **3f**, 141293-03-0; **3g**, 141293-04-1; **3h**, 141103-65-3; **3i**, 141293-05-2; **5a**, 50-33-9; **5b**, 57-96-5; **6a**, 141293-06-3; **6b**, 141293-07-4; **7**, 83-12-5; **8**, 2625-08-3; **9a**, 104416-34-4; **9b**, 81-81-2; **9c**, 81-82-3; **10a**, 141293-08-5; (*R**,*S**)-**10b**, 141293-09-6; (*R**,*R**)-**10b**, 141293-10-9; (*R**,*S**)-**10c**, 141293-11-0; (*R**,*R**)-**10c**, 141293-12-1; **12**, 141293-13-2.

Calibration of a Fast Benzylic Radical "Clock" Reaction[1]

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Received January 21, 1992

Radicals which undergo essentially irreversible rearrangements can be used as mechanistic probes and, when the rate of the rearrangement has been determined, can be used to "clock" the rates of radical–molecule reactions.[4] The radical clock approach has proved to be particularly valuable in chemical and biochemical systems which simply are not amenable to more conventional methodologies. For example, the clock technique has been fruitfully applied in investigations of the rates and mechanism(s) of alkane hydroxylation by cytochrome P-450.[5–7] For primary, secondary, and tertiary alkyl radicals there are entire families of "calibrated" clocks, some slow, others extremely fast. There has, however, been no benzylic radical clock. That is, we recently demonstrated[8] that an earlier claim that the α-cyclopropylbenzyl radical underwent a fairly rapid and essentially irreversible ring-opening at 22 °C,[9] reaction 1, was in error. In truth, not only is this reaction reversible but, at ordinary temperatures, the ring-closed form is thermodynamically preferred.[8]

$$C_6H_5\dot{C}HCHCH_2CH_2 \rightleftarrows C_6H_5CH{=}CHCH_2CH_2^{\bullet} \quad (1)$$

Certain fungal enzymes have been shown to be efficient benzylic hydroxylating agents.[10,11] Calibrated, fast benzylic clocks are required to investigate the mechanism of these and other biotransformations which may involve benzyl radicals as intermediates.

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0022-3263/92/1957-4284$03.00/0 Published 1992 by the American Chemical Society