21 (26 mg, 39%) were separated by preparative TLC (C) and identified by comparison with authentic materials, prepared according to Le Men et al.[25]

X-ray Structure Determination. (A) Zwitterion 7a Hydrate (XR-1). Single crystals of XR-1 suitable for X-ray diffraction study were grown from a saturated MeOH solution. The structure was solved by direct methods (program MULTAN 80): the "best" *E*-map allowed to localize 27 heavy atoms over a total of 32. The remaining heavy atoms were located on a difference Fourier map. After isotropic refinement of heavy atoms, all hydrogen atoms, with the exclusion of those of solvation water, were located on a difference Fourier map. Hydrogen atoms at C(18) and C(25) gave problems in the least-squares process and then were fixed in calculated positions. Hydrogen atoms of solvated water were not clearly localized, because of the high thermal internal motion or the disorder of the same.

(B) Isoxazolidine 8b Hydrobromide (XR-2). Single crystals of XR-2 were obtained by diffusion of diisopropyl ether into a saturated MeOH solution of **8b**·HBr. The structure was solved by locating on a Patterson map the bromine and one oxygen atom. Subsequent cycles of structure-factor calculation and difference Fourier map gave all heavy atoms. After isotropic refinement of heavy atoms, most of the hydrogen atoms became visible on a difference Fourier map, but some of these did not converge and were fixed in calculated positions.

(C) Azepine 9a Dihydrobromide as Methanol Solvate (XR-3). Suitable crystals of XR-3 were obtained by diffusing diisopropyl ether into saturated MeOH solution of **9a**·2HBr. These crystals rapidly lose MeOH with consequent destruction of crystal structure, and the sample used for data collection was sealed in a thin-walled glass capillary. Due to the relatively large linear absorption coefficient and the irregularity of crystal shape, an empirical absorption correction was applied according to Walker and Stuart.[30] The structure was solved by locating bromine atoms on a Patterson map. The atoms were obtained from structure-factor calculations and difference Fourier syntheses. Four broad peaks were successively interpreted and refined as disordered MeOH: the identification of the atoms of the solvate was based on packing contacts. Hydrogen atoms at C(23) were put in calculated position and not refined. Hydrogen atoms of disordered MeOH and one of the two formally deriving from HBr were not clearly identified while the second hydrogen atom of HBr was clearly bonded to N(4).

Tables of observed and calculated structure amplitudes and anisotropic thermal parameters are available on request (T.P.).

Acknowledgment. We thank Dr. D. Monti (Centro CNR di Studio per le Sostanze Organiche Naturali, Milan) for obtaining the 300-MHz ^{1}H NMR spectra. Gratitude is also expressed to referees for their helpful suggestions.

Supplementary Material Available: Tables of fractional coordinates, U_{eq}, bond distances, selected bond and torsion angles, ring-puckering coordinates, asymmetry parameters, and conformation of the non-benzene rings for XR-1, XR-2, and XR-3 (10 pages). Ordering information is given on any current masthead page.

(29) Main, P.; Fiske, S.; Hull, S. E.; Lessinger, L.; Germain, G.; Declerq, J. P.; Woolfson, M. M. *MULTAN 80, A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*; Universities of York, England, and Louvain, Belgium, 1980.

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The Capsaicinoids: Their Separation, Synthesis, and Mutagenicity

Peter M. Gannett,* Donald L. Nagel, Pam J. Reilly, Terence Lawson, Jody Sharpe, and Bela Toth

Eppley Institute for Research in Cancer and Allied Diseases, University of Nebraska Medical Center, 42nd and Dewey Ave., Omaha, Nebraska 68105

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Capsaicin (**1b**), the pungent ingredient in many varieties of *Capsicums* has recently been implicated as a possible carcinogen. When obtained from natural sources **1b** is always accompanied by a number of related homologues. We have isolated seven of these homologues, characterized them, and synthesized them by a general and unique route developed in our laboratories. Also reported are mutagenicity data for **1b** and an extract of red pepper as measured by the Ames assay and the V-79 mammalian cell assay.

Capsaicin **1b**, the principal pungent component in many *Capsicums* (e.g., hot peppers and hot pepper derived substances) has been the target of numerous investigations since it was first isolated 1876.[1] The structure of capsaicin was first determined by Nelson[2] in 1919. The capsaicinoids **1** and dihydrocapsaicinoids **2** have been studied to determine the source of their pungency,[3] their ability to induce sneezing and skin irritation,[4] and with regard to being inhibitors and promoters of substance P.[5] Preliminary data from our laboratories indicate that the capsaicinoids are mutagens,[6] a finding that has been recently confirmed by Nagabhushan and Bhide.[7]

The aforementioned mutagenesis studies were conducted with mixtures of **1** and **2** since natural extracts of hot peppers were used. We were interested in determining if the mutagenic species in these extracts was capsaicin (**1b**) itself, a homologue of capsaicin or dihydrocapsaicin, or some combination of **1** and **2**, hence we needed to be able to prepare each of them. In addition, we required samples of each of the homologues of **1** and **2** for studies dealing with the identification and quantification of capsaicin and its homologues in hot pepper extracts. While a procedure for the preparation of **1b** had been published[8] this method

(1) Thresh, M. *Pharm. J. Trans.* **1876**, *7*, 21, 259, 473.
(2) Nelson, E. K. *J. Am. Chem. Soc.* **1919**, *41*, 1115, 1472.
(3) (a) Issekutz, B.; Lichtneckert, I.; Winter, M. *Arch. Int. Pharmacodyn.* **1950**, *83*, 319. (b) Jancsco, N. P.; Jancsco-Gabor, A. *Naunyn-Schmeidebergs Arch. Exp. Pathol. Pharmakol.* **1959**, *236*, 142.
(4) (a) Newmann, A. A. *Chem. Prod.* **1953**, *16*, 413. (b) Newmann, A. A. *Chem. Prod.* **1954**, *17*, 14. (c) Joda, N.; Usui, H. *J. Pharmacol. Exp. Ther.* **1972**, *181*, 512.
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(6) Toth, B.; Rogan, E.; Walker, B. *Anticancer Res.* **1984**, *4*, 117.
(7) Nagabhushan, M.; Bhide, S. V. *Environ. Mut.* **1985**, *7*, 881.
(8) Crombie, L.; Dandeaonker, S. H.; Simpson, K. B. *J. Chem. Soc.* **1955**, 1025.

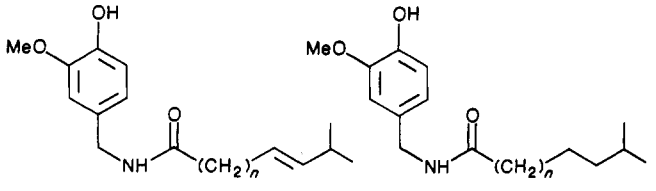
0022-3263/88/1953-1064$01.50/0

Table I. HPLC Data for the Capsaicinoids and Dihydrocapsaicinoids[a]

compd	t_R[b]	percent[c]	compd	t_R[b]	percent[c]
1d	6.38	0.19	**2b**	26.97	32.55
1a	10.20	0.37	**1c**	28.87	1.07
2a	14.80	0.81	**2c**	46.87	0.60
1b	16.31	64.42			

[a] Conditions: 9.4 mm × 25 cm C-18 column with MeOH/H_2O (60:40) as eluent, flow rate of 4 mL/min, UV detection at 279 nm. [b] In minutes. [c] Calculated assuming that 1 + 2 = 100% and that all seven compounds have the same extinction coefficient.

unfortunately lacks the generality which we required. Therefore, we set out to create a general procedure for the preparation of the homologues of **1** and **2**.



1 **2**

a, $n = 3$; **b**, $n = 4$; **c**, $n = 5$; **d**, $n = 2$

Prior to developing a synthesis of the capsaicinoids it was necessary to identify the components in hot pepper extracts.[9] Previous workers[10] had identified the following five components of "typical" extracts: nordihydrocapsaicin (**2a**), capsaicin (**1b**), dihydrocapsaicin (**2b**), homocapsaicin (**1c**), and homodihydrocapsaicin (**2c**). By the application of high pressure liquid chromatography (HPLC)[11] and gas chromatography–mass spectrometry (GC-MS) we separated and tentatively identified two additional components in our hot pepper extracts, namely, norcapsaicin (**2a**) and nornorcapsaicin (**1d**). The HPLC data, relative percentages, and retention times of each component in the extraction mixture are compiled in Table I. The HPLC data also indicated that other capsaicinoids may be present in these extracts but we have not, as of yet, been able to identify these components.

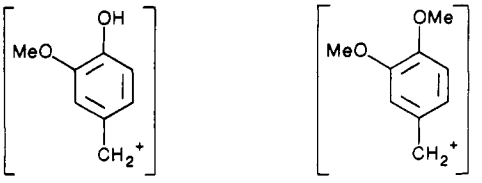
We next directed our efforts as isolating each of the above compounds by HPLC so that each could be characterized but this proved to be impossible except for the principal components of the mixture **1b** and **2b**. Our inability to separate each component of the hot pepper extract free of other components was probably due to the tendency of compounds containing long saturated aliphatic side chains to co-elute with their homologues containing one double bond and one carbon atom more.[12] As a consequence we turned our attention to the GC-MS of the mixture, tentatively identifying each component on the basis of molecular weight, and subsequently confirming each component by comparison with synthetically prepared material.

The GC-MS data is shown in Table II. Capsaicin-related materials in the mixture were determined by two methods. First, the capsaicinoids display a very characteristic fragment with an m/z of 137 (I). For each of the seven components identified in the mixture this was the base peak. Second, the capsaicinoid mixture was methylated with dimethyl sulfate[10] and GC-MS repeated on the methylated mixture. Each of the components of the mixture which had previously shown a base peak of m/z 137 now displayed one at 151 (II), indicating that the aromatic ring had been methylated. This procedure also identified other components in the mixture which are probably capsaicin related but we have, as of yet, not been able to identify them.

Table II. GC-MS Data for the Capsaicinoids, Dihydrocapsaicinoids, and Their Methylated Derivatives[a]

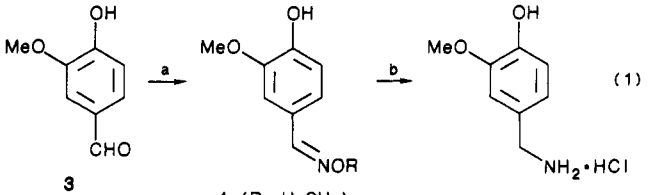
compd[b]	t_R[c]	m/z	percent[d]
1d	9.5 (10.3)	277	0.30 (0.42)
1a	10.5 (12.5)	291	0.51 (0.58)
2a	11.4 (14.3)	293	0.91 (0.93)
1b	11.9 (17.2)	305	65.01 (65.28)
2b	12.8 (18.4)	307	31.66 (31.30)
1c	14.4 (20.1)	319	1.01 (0.95)
2c	14.9 (22.8)	321	0.60 (0.58)

[a] Conditions: DB-1 wide bore capillary column, injector and detector temperature 280 °C, column temperature 210 °C. [b] Values in parentheses are for the corresponding methylated derivatives of **1** and **2**. [c] In minutes. [d] Percentages assume that the sum of **1** and **2** is 100%.



I II

The HPLC and GC-MS studies described above identified the compounds for which we would need syntheses. The benzylamine moiety common to both **1** and **2** was prepared in two steps. First the oxime **4a** or *O*-methyloxime **4b** was prepared from vanillin (**3**). Then, reduction of **4** with PtO_2 or 10% Pd/C yielded the amine hydrochloride **5**·HCl in 98% yield (eq 1). In our hands we found

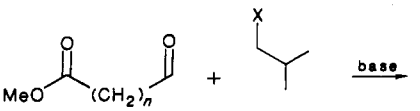


3 **4** (R = H, CH_3) **5**·HCl (1)

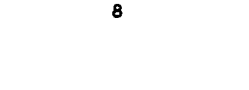
(a) NH_2OH·HCl (R = H) or NH_2OMe·HCl (R = Me), EtOH, pyridine; (b) PtO_2 or 10% Pd/C, H_2, EtOH, HCl

that palladium was a better choice as reduction with platinum occasionally lead to partial overreduction.

For the unsaturated acid portion of the molecule we were in need of a synthetic route which could accommodate all of the homologues of **1** and **2** identified above. Our scheme assembled this portion of the molecule by condensing the ω-oxo esters **6** with **7** (eq 2) to yield **8**. The ω-oxo esters were prepared by acid or base methanolysis of the lactones



7a, X = $\overset{+}{P}(C_6H_5)_3$
b, X = $SO_2C_6H_5$



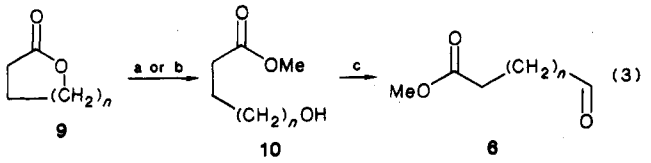
(2)

8

(9) Analysis of different lots of "natural" capsaicin reveals variations in the relative percentages of the capsaicinoids. For the purposes of this work and associated feeding studies we have used the same lot of material.

(10) Bennett, D. J.; Kirby, G. W. *J. Chem. Soc. C* **1968**, 442.
(11) (a) Saria, A.; Lembeck, F.; Skofitsch, G. *J. Chromatogr.* **1981**, *208*, 41. (b) Law, M. W. *J. Assoc. Off. Anal. Chem.* **1983**, *66*, 1304.
(12) (a) Krajewska, A. M.; Powers, J. J. *J. Chromatogr.* **1986**, *367*, 267. (b) Buchanan, M. A. *Anal. Chem.* **1959**, *31*, 1616.

9 to yield the alcohols 10 which were immediately oxidized to 6 (eq 3). An alternative approach to the preparation of 6a–c has been described by Schreiber[13] and ozonolysis of the appropriate cycloalkene 11a–c followed by treatment with triethylamine and acetic anhydride yielded the ω-oxo esters 6a–c (eq 4). Generally, however, this method offered little advantage.



(3)

a, $n = 1$; b, $n = 2$; c, $n = 3$; d, $n = 0$

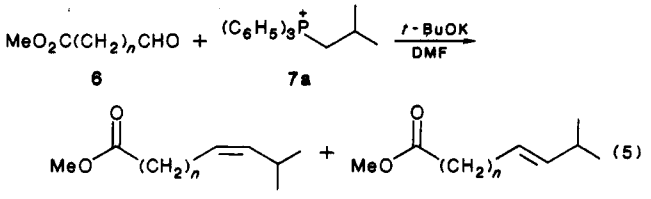
(a) MeOH, TEA ($n = 0,1$); (b) MeOH, H^+ ($n = 2,3$); (c) PCC, NaOAc, CH_2Cl_2

(4)

a, $n = 1$; b, $n = 2$; c, $n = 3$

(a) MeOH, O_3, −78 °C, CH_2Cl_2; (b) TEA, Ac_2O, MeOH

We envisioned a need for both the *E* and *Z* isomers of 1 and explored methods for making each. The condensation of aldehydes with unstabilized Wittig reagents usually leads to *Z* olefins.[14] This indeed was the case between 6 and 7a with the *E*/*Z* ratio ranging from 1:4 to 1:10 depending upon the reaction conditions (eq 5). The most favorable *E*/*Z* ratio we were able to achieve was 9:91 using potassium *tert*-butoxide, in DMF, and 6b as the aldehyde.

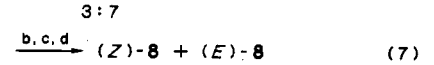


(5)

a, $n = 3$; b, $n = 4$; c, $n = 5$; d, $n = 2$

Our initial approach to the *E* isomer was isomerization of the *Z* isomer. Attempts to accomplish this photochemically[15] were partially successful and photolysis of (*Z*)-8b (hexane/I_2) lead to an *E*/*Z* ratio of 7:3 (eq 6).

(6)

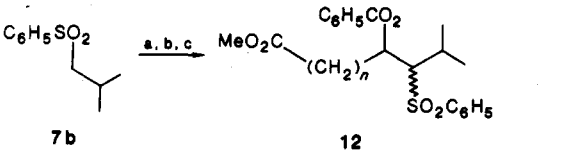


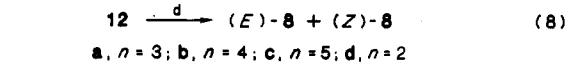
(7)

(a) $h\nu$, I_2 (cat.), hexane; (b) *m*-CPBA, CH_2Cl_2, $NaHCO_3$; (c) $(C_6H_5)_2PLi$ (3 equiv); (d) excess MeLi

Hoping to achieve a better *E*/*Z* ratio, we pursued an alternative approach by the olefin inversion method devised by Vedejs.[16] This required epoxidation of the *Z* olefin, treatment of the intermediate epoxide with excess lithium diphenylphosphide, and then excess MeI (eq 7). However, while this procedure did lead to (*E*)-8b (95:5 *E*/*Z*) the yield was low (*E*)-8b in 30% after chromatography). Thus, even though a better *E*/*Z* ratio was obtained via the olefin inversion method, the overall isolated yield of (*E*)-8b was less than that obtained via photochemical isomerization (49%).

At this point it seemed that an alternative olefination reaction was appropriate. We employed the Kocienski–Lythgo–Julia procedure[17] and condensation of isobutyl phenyl sulfone 7b with 6 followed by trapping with benzoyl chloride to lead to 12 as an approximately 3:1 mixture of diastereomers. Subsequent treatment of the crude mixture with sodium amalgam led to (*E*)-8 as a 9:1 mixture (*E*/*Z*) in yields of 70–80% (eq 8).



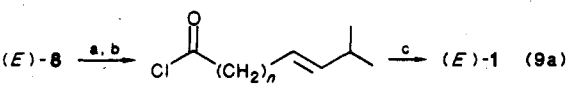


(8)

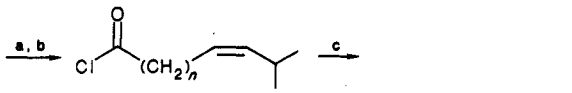
a, $n = 3$; b, $n = 4$; c, $n = 5$; d, $n = 2$

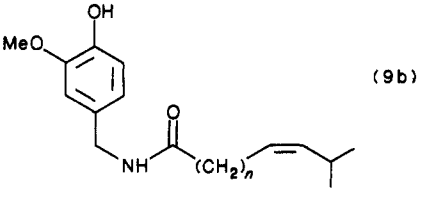
(a) *n*-BuLi, THF, −78 °C, then −40 °C; (b) −78 °C, 6, then 0 °C; (c) −78 °C, C_6H_5COCl, room temperature; (d) Na(Hg), MeOH, −20 °C

The final steps of the synthesis were straightforward. The esters (*E*)-8 or (*Z*)-8 were hydrolyzed and converted into the acid chlorides (*E*)-13 and (*Z*)-13, respectively. The acid chlorides were then reacted with the benzylamine 5 to yield either (*E*)-1 or the unnatural isomers of the capsaicinoids (*Z*)-1 (eq 9). Finally, the dihydrocapsaicinoids were prepared from 1 (either isomer) by catalytic hydrogenation (eq 10).



(9a)

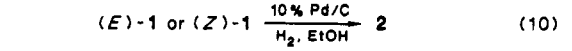




(9b)

a, $n = 3$; b, $n = 4$; c, $n = 5$; d, $n = 2$

(a) KOH, EtOH; (b) $SOCl_2$; (c) 5, pyridine, Et_2O, room temperature, 3 days



(10)

The mutagenicity of 1b, 2b, and an ethanolic extract of red pepper has been carried out.[18] These studies have used the Ames assay and a mammalian cell mutagenicity assay referred to here as the V79 assay.[19] The fundamental difference between these two assays is cellular with the Ames' assay being based on bacteria while the V79 assay is based on mammalian cells. Though the V79 assay

(13) (a) Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867. (b) Claus, R. E.; Schreiber, S. L. *Org. Synth.* **1985**, *64*, 150.

(14) (a) Maryanoff, B. E.; Reitz, A. B.; Duhl-Emswiler, B. D. *J. Am. Chem. Soc.* **1985**, *107*, 217. (b) Schow, S. R.; McMorris, T. C. *J. Org. Chem.* **1979**, *44*, 3760.

(15) Iida, H.; Watanabe, Y.; Kibayashi, C. *J. Am. Chem. Soc.* **1985**, *107*, 5534.

(16) Vedejs, E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1973**, *95*, 822.

(17) Kocienski, P. J.; Lythgoe, B.; Waterhouse, I. *J. Chem. Soc.* **1980**, 1045.

(18) HPLC analysis of these red pepper extracts showed the presence of 2a, 1b, 2b, 1c, and 2c (relative ratio: 7:60:30:2:1, respectively).

(19) Hubeman, E.; Sachs, L. *Proc. Natl. Acad. Sci. U.S.A.* **1976**, *73*, 188.

Table III. Ames Assay Mutagenicity Data for Capsaicin, Dihydrocapsaicin, and the Ethanol Extract of Red Pepper

compd	μg/plate	TA 98[a] −S9[c]	TA 98[a] +S9[d]	TA 1535[b] −S9[e]	TA 1535[b] +S9[f]
1b	1000	47 ± 13 (2.6)	44 ± 12 (1.4)	10 ± 3 (0.3)	15 ± 3 (0.8)
	300	26 ± 3 (1.4)	69 ± 10 (2.2)	26 ± 7 (0.8)	20 ± 6 (1.1)
	100	36 ± 5 (2.0)	78 ± 13 (2.5)	21 ± 12 (0.7)	23 ± 5 (1.3)
2b	1000	166 ± 82 (9.2)	46 ± 5 (1.5)	92 ± 12 (2.9)	10 ± 2 (0.6)
	300	27 ± 4 (1.5)	50 ± 2 (1.6)	15 ± 1 (0.5)	8 ± 2 (0.4)
	100	33 ± 11 (1.8)	50 ± 9 (1.6)	16 ± 2 (0.5)	20 ± 6 (1.1)
red pepper extract	1000	21 ± 5 (0.7)	46 ± 14 (2.6)	15 ± 3 (0.5)	13 ± 4 (0.9)
	300	17 ± 3 (0.5)	16 ± 6 (0.9)	12 ± 3 (0.4)	7 ± 2 (0.5)
	100	27 ± 6 (0.8)	15 ± 4 (0.8)	18 ± 4 (0.6)	14 ± 4 (1.0)

[a] Strain TA 98, −S9 without activation, +S9 with rat aroclor 1254 induced S9. [b] Values reported are revertants/plate (relative to control). [c] Strain TA 1535, otherwise as in (a). [c] Control value 18 ± 1 2-aminoanthracene (2-AA) gave 2498 ± 147. [d] Control value 43 ± 4, 2-AA 2656 ± 69. [e] Control value 35 ± 5, 2-AA 2764 ± 39. [f] Control value 14 ± 2, 2-AA 2520 ± 390.

Table IV. Mutagenicity of 1b, 2b, and the Red Pepper Extract[a]

compd	concentration (μg/mL) 100	50	25	10	5
1b	*b*	143	95	70	30
2b	*b*	*b*	*b*	35	10
red pepper extract	75	25	15	5	0[c]

[a] Mutagenicity is normalized to that of dimethylnitrosamine which is arbitrarily set to 100. Reported values in the table are in units of mutants/(10^6 surviving cells). [b] The compound is toxic when administered at the indicated dose. [c] No mutants and the dose was not toxic.

is more expensive and time consuming to conduct than is the Ames assay, we have found it to better correlate a compound's mutagenicity and tumorigenicity.[20]

In Table III is presented the Ames assay data, and in Table IV, the V79 mammalian cell assay data obtained for **1b**, **2b**, and the red pepper extract. Data for the V79 assay are normalized to *N*,*N*-dimethylnitrosamine. Inspection of these data reveals that by the Ames assay, in TA 98 and TA 1535 strains, without and with activation, **1b**, **2b**, and the red pepper extract are nonmutagenic. In contrast, the V79 assay data show **1b**, **2b**, and the red pepper extract to be mutagenic.

Analysis of the red pepper extract revealed that it contained about 4% **1** and **2** by weight and that approximately 90% of the capsaicinoids present were **1b** and **2b**. If the mutagenicity data presented in Table IV for the red pepper extracts is adjusted for the amounts of **1b** and **2b** present at the 10 μg/mL level, a value of 100 mutants/(10^6 surviving cells) is obtained. This is about twice the value one would calculate on the basis of the mutagenicity data given for **1b** and **2b** ((0.06 × 7.0) + (0.3 × 35) = 52).[21] At higher levels, since **2b** was toxic, a similar type of calculation is not possible. Nevertheless, the data presented in Table IV suggest that the mutagenicity of the red pepper extracts is only partially caused by the capsaicinoids present. Clearly, then, future studies of aimed at determining the mutagenicity of the capsaicinoids should use the pure compounds in testing rather than extracts.

In conclusion, seven components of pepper extracts have been separated and characterized by a combination of HPLC and GC-MS. Their structures have been confirmed by their independent synthesis. To prepare these compounds, a general synthesis of the capsaicinoids and dihydrocapsaicinoids has been developed. This scheme leads to the preparation of the four natural (*E* isomer) capsaicinoids, the corresponding dihydrocapsaicinoids, and the three unnatural (*Z* isomer) capsaicinoids. The method developed is quite general and should be useful in isolation and characterization of additional capsaicinoids and dihydrocapsaicinoids. Mutagenicity data obtained on capsaicin and dihydrocapsaicin show them to be mutagenic by the V79 mammalian cell assay. Finally, since red pepper extracts contain other mutagenic compounds in addition to **1** and **2**, further studies on capsaicin and its homologues should use synthetically prepared materials.

Experimental Section

General Procedures. NMR chemical shifts are reported downfield from either tetramethylsilane (for $CDCl_3$ or acetone-d_6 solutions) or sodium 3-(trimethylsilyl)propionate-d_4 (for D_2O solutions). GC analyses of the capsaicin mixtures were conducted on a DB-1 wide bore capillary column (column temperature 210 °C; injector and detector temperature 260 °C; carrier gas He). This column and these conditions were used for both the GC isomer quantification and GC-MS work. Melting points are uncorrected.

All reactions were performed under an inert atmosphere unless otherwise specified. The following solvents were distilled before use: tetrahydrofuran (THF, from lithium aluminum hydride, LAH), methylene chloride (CH_2Cl_2, from P_2O_5), acetic anhydride (Ac_2O, from P_2O_5), methanol (MeOH, from Mg turnings), pyridine (Pyr, from calcium hydride (CaH_2)), triethylamine (TEA, from CaH_2), diethyl ether (Et_2O, from LAH), dimethylformamide (DMF, from $BaSO_4$). Alkyllithium reagents were obtained from Aldrich Chemical Co. and were titrated prior to use. Bulb-to-bulb distillations of the Kugelrohr type were conducted at the air oven temperatures and pressures cited.

Analytical thin-layer chromatography (TLC) was performed with Merck silica gel 60 F-254 plates. Column chromatography used Aldrich 60–200-mesh silica gel powder. Low pressure liquid chromatography (LPLC) was conducted with EM LoBar (Li-Chroprep) columns with a FMI (Model RS-PY) pump and pulse damper. High pressure liquid chromatography (HPLC) was carried out on either a Whatman Partisil ODS-3 column (9.4 mm × 25 cm, 10 μm) for preparative work or on a Whatman Partisil ODS-3 column (4.6 mm × 25 cm, 5 μm) for analytical work. The capsaicinoids were detected by UV–vis absorption at 279 nm with 60:40 MeOH/H_2O as eluent.

Analysis and Separation of the Capsaicinoids. Under the HPLC conditions indicated above (preparative column) and with a flow rate of 4 mL/min, the capsaicin mixture displays a minimum of 10 components. Seven of these have been isolated and characterized. These are **1d** (t_R 6.38 min), **2a** (t_R 10.2 min), **1a** (t_R 14.8 min), **1b** (t_R 16.31 min), **2b** (t_R 26.97 min), **1c** (t_R 28.87 min), and **2c** (t_R 46.9 min) and were present in the following percentages (sum of **1a–d** and **2a–c** taken as 100%) 0.19:0.37:0.81:64.42:32.55:1.07:0.6, respectively.

Upon methylation[10] the above seven components, when chromatographed under the above conditions, displayed increased retention times as expected although the relative ordering re-

(20) (a) Langenbach, R.; Gingell, R.; Kuszynski, C.; Walker, B.; Nagel, D.; Pour, P. *Cancer Res.* **1980**, *40*, 3403. (b) Langenbach, R.; Kuszynski, C.; Gingell, R.; Lawson, T.; Nagel, D.; Pour, P.; Nesnow, S. In *Structure–Activity Correlation as a Predictive Tool in Toxicology*; Golberg, L., Ed.; Hemisphere Publishing Co.: Washington, DC, 1983; p 241.

(21) The red pepper extract contained 60% **1b** and 30% **2b**. These values were used to adjust the observed mutagenicity data for **1b** and **2b**.

mained the same. Similar results were obtained when the capsaicinoids and methylcapsaicinoid mixture was separated by GC (DB-1 wide bore capillary, column temperature 210 °C, injector and detector temperature 260 °C, carrier gas N_2, flow rate of 18 mL/min). Further confirmation of this came from GC-MS analysis of the mixture (GC conditions as described above) as each peak of the methylcapsaicinoid mixture had a mass 14 units greater than that for the capsaicinoid mixture. Final confirmation of the isolated capsaicinoids' structures came from their independent syntheses.

4-Hydroxy-3-methoxybenzaldehyde Oxime (4a). A mixture of **3** (1.52 g, 10 mmole) and pyridine (10 mL) was stirred at ambient temperature for 24 h. The reaction mixture was diluted with water (200 mL), the ethanol removed at reduced pressure, and the aqueous layer extracted with Et_2O (5 × 100 mL). The combined organic extracts were washed with 100-mL portions each of 10% aqueous $NaHCO_3$, 10% aqueous $NaHSO_3$, and brine, dried ($MgSO_4$), filtered, concentrated at reduced pressure, and Kugelrohr distilled (120 °C at 0.1 mmHg) to yield **4a** (1.63 g, 83%) as a white crystalline solid: mp 118–119 °C (lit.[8] mp 119–120 °C); IR (KBr) 3580, 3537 (NOH), 3400 (OH), 2700 (CH=N), 1630 (C=N), 1580 (C=C) cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 3.06 (2 H, br s, OH), 3.85 (3 H, s, CH_3O), 6.84 (1 H, d, J = 8.1 Hz, 5-ArH), 7.03 (1 H, dd, J = 8.1, 2.1 Hz, 6-ArH), 7.25 (1 H, d, J = 2.1 Hz, 2-ArH), 8.03 (1 H, s, CH=N); ^{13}C NMR (75 MHz, acetone-d_6) δ 62.12, 115.6, 121.74, 127.8, 132.0, 154.6, 155.2, 155.3; MS, m/z (relative intensity) 167 (100), 124 (63), 109 (16); UV (MeOH) λ_{max} (log ϵ) 299 (3.91), 266 (4.15), 217 (4.2); exact mass calcd for $C_8H_9NO_3$ 167.0582, found 167.0576.

4-Hydroxy-3-methoxybenzaldehyde *O*-Methyloxime (4b). A mixture of **3** (4.14 g, 27.2 mmol) and methoxyamine hydrochloride (2.5 g, 30 mmol) in pyridine (150 mL) was stirred at room temperature overnight. The pyridine was then removed at reduced pressure, and the residue was taken up in water (30 mL) and extracted with chloroform (4 × 30 mL). The combined organic extracts were washed with water (30 mL), dried ($MgSO_4$), filtered, and concentrated at reduced pressure. The residue was chromatographed (EtOAc eluent) and Kugelrohr distilled (100 °C at 0.1 mmHg) to yield **4b** (4.9 g, 98%) as a colorless oil: IR ($CHCl_3$) 3537 (OH), 3008 (ArH), 2940 (CH), 1630 (C=N), 1590, 1513 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.86 (3 H, s, CH_3O), 3.95 (3 H, s, CH_3O), 6.2 (1 H, br s, OH), 6.89 (1 H, d, J = 8.4 Hz, 5-ArH), 6.95 (1 H, dd, J = 8.4, 2.0 Hz, 6-ArH), 7.23 (1 H, d, J = 2.0 Hz, 2-ArH), 7.98 (1 H, s, CH=N); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.53, 61.52, 107.6, 114.3, 122.3, 123.9, 147.0, 147.6, 148.7; MS, m/z (relative intensity) 181 (100), 150 (21), 139 (18), 123 (34); UV λ_{max} (log ϵ) 299 (4.47), 274 (4.62), 214 (4.78); exact mass calcd for $C_9H_{11}NO_3$ 181.0738, found 181.0788.

4-Hydroxy-3-methoxybenzylamine Hydrochloride (5·HCl). A solution of **4a** (or **4b**) (0.25 g, 1.38 mmol) in ethanol (25 mL) and concentrated hydrochloric acid (1 mL) was hydrogenated at atmospheric pressure in the presence of 10% Pd/C (50 mg) for 4 h. The hydrogenation mixture is then filtered through Celite in a sintered glass funnel and the filtrate concentrated to dryness, taken up in ethanol (25 mL), and again concentrated to dryness to yield **5**·HCl as a light yellow solid (0.28 g, 98%): mp 219–222 °C dec °C (lit.[8] mp 221–223 °C dec); IR (KBr) 3168, 3107 (NH_3^+), 3024 (ArH), 1612, 1525 (C=C), cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.72 (3 H, s, CH_3O), 3.83 (2 H, q, $ArCH_2$), 6.73 (2 H, d, J = 8.1 Hz, 5-ArH), 6.80 (1 H, dd, J = 8.1, 1.8 Hz, 6-ArH), 7.10 (1 H, d, J = 1.8 Hz, 2-ArH), 8.24 (3 H, br s, NH_3^+), 9.17 (1 H, br s, OH); ^{13}C NMR (75 MHz, D_2O) δ 45.78, 58.76, 115.9, 118.5, 125.0, 127.9, 148.3, 150.3; UV (D_2O) λ_{max} (log ϵ) 279 (3.92), 230 (4.34), 210 (4.31). Anal. Calcd for $C_9H_{12}NClO_2$: C, 63.34; H, 6.38; N, 7.39; Cl, 18.69. Found: C, 63.25; H, 6.25; N, 7.45; Cl, 18.75.

Methyl ω-Oxo Esters. Procedure A was used to prepare **6a** and **6d** and procedure B was used to prepare **6b** and **6c**.

(A) Base-Catalyzed Methanolysis/PCC Oxidation. The lactone (10 mmol) was treated with MeOH and TEA as described by Corey.[22] The resulting crude methyl ω-hydroxy ester was taken up in CH_2Cl_2 (30 mL), and sodium acetate (0.26 g, 3.2 mmol) and pyridinium chlorochromate (PCC) (3.27 g, 15 mmol) were added. After being stirred at room temperature for 1.5 h, Et_2O (300 mL) was added, the reaction mixture was filtered through Florisil, and the filtrate was concentrated at reduced pressure and Kugelrohr-distilled (80 °C at 0.2 mmHg) to give **6d** or **6a** in 72% and 85% yield, respectively.

Methyl 5-oxopentanoate (6a): IR (CCl_4) 2949, 2863 (CH), 2715 (CHO), 1740 (C=O), 1201 (C—O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.95 (2 H, p, J = 7.5 Hz, CH_2), 2.37 (2 H, t, J = 7.5 Hz, CH_2CO_2), 2.53 (2 H, dt, J = 7.5, 1.2 Hz, CH_2C=O), 3.61 (3 H, s, CH_3), 9.71 (1 H, t, J = 1.2 Hz, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.09, 34.67, 44.63, 53.33, 174.7, 203.0; MS, m/z (relative intensity) 130 (3), 115 (42), 100 (65), 60 (100); exact mass calcd for $C_6H_{10}O_3$ 130.0629, found 130.0625. **Methyl 4-oxobutanoate (6d):** IR (CCl_4) 2950, 2871 (CH), 2713 (CHO), 1738 (C=O), 1200 (C—O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.59 (2 H, t, J = 6.9 Hz, CH_2CO_2), 2.76 (2 H, td, J = 6.9, 2.1 Hz, CH_2C=O), 3.70 (3 H, s, CH_3O), 9.88 (1 H, t, J = 2.1 Hz, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.71, 50.01, 54.00, 177.1, 205.1; MS, m/z (relative intensity) 116 (4), 101 (45), 84 (100); exact mass calcd for $C_5H_8O_3$ 116.0473, found 116.0471.

(B) Acid-Catalyzed Methanolysis/PCC Oxidation. The lactone (10 mmol) was dissolved in MeOH (30 mL) and concentrated H_2SO_4 added (0.5 mL). The resulting mixture was gently refluxed overnight, cooled to room temperature, and concentrated to a volume of approximately 2 mL, water was added (10 mL), and the pH was adjusted to 7. The aqueous layer was then extracted with Et_2O (3 × 10 mL), the combined organic layers were dried (Na_2SO_4), filtered, concentrated, and the residue was oxidized as described under A above. By this method **6b** and **6c** were prepared in 79% and 85% yield, respectively.

Methyl 4-oxohexanoate (6b): IR (CCl_4) 2952 (CH), 2712 (CHO), 1739 (C=O), 1205 (C—O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.66 (4 H, p, J = 6.9 Hz, CH_2), 2.34 (2 H, t, J = 6.9 Hz, CH_2CO_2), 2.46 (2 H, dt, J = 6.9, 1.5 Hz, CH_2C=O), 3.64 (3 H, s, CH_3O), 9.88 (1 H, t, J = 1.5 Hz, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.52, 24.26, 33.65, 43.47, 51.53, 173.7, 202.0; MS, m/z (relative intensity) 143 (3), 129 (40), 114 (66), 74 (100); exact mass calcd for $C_7H_{12}O_3$ 144.0749, found 144.0767. **Methyl 5-oxoheptanoate (6c):** IR (CCl_4) 2948 (CH), 2715 (CHO), 1740 (C=O), 1201 (CO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (2 H, p, J = 7.5 Hz, CH_2), 1.58 (4 H, p, J = 7.5 Hz, CH_2), 2.25 (2 H, t, J = 7.5 Hz, CH_2C=O), 2.38 (2 H, dt, J = 7.5, 1.8 Hz, CH_2C=O), 3.61 (3 H, s, CH_3O), 9.71 (1 H, t, J = 1.2, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.16, 24.27, 28.07, 33.43, 43.12, 51.00, 173.4, 202.0; MS, m/z (relative intensity) 158 (3), 143 (26), 115 (43), 83 (42), 74 (100); exact mass calcd for $C_8H_{14}O_3$ 158.0905, found 158.0924.

Method 2. The procedure of Schreiber[13] was followed. Samples of **6a**, **6b**, and **6c** prepared by either method were identical by GC, IR, ^1H NMR, ^{13}C NMR, and MS.

Isopropyltriphenylphosphonium Bromide (7a). A solution of 1-bromo-2-methylpropane (10 g, 73 mmol) and triphenylphosphine (19.12 g, 73 mmol) in toluene (20 mL) was refluxed for 24 h, cooled to room temperature, diluted with Et_2O (20 mL), and filtered, and the filter cake was washed with Et_2O (60 mL). The filter cake was then recrystallized from acetonitrile and dried at reduced pressure over P_2O_5 to yield **7a** (14.5 g, 49.8%): mp 199–201 °C (lit. mp 198–200 °C); IR (KBr) 3020 (ArH), 2951 (CH), 1585, 1485 (C=C), cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (6 H, d, J = 6.9 Hz, CH_3), 2.05 (1 H, m, CH), 3.70 (2 H, dd, J = 12.6, 6.9 Hz, CH_2), 7.6–7.9 (15 H, m, ArH); ^{13}C NMR (75 Hz, $CDCl_3$) δ 24.51, 24.78, 30.6, 118.93, 130.4, 133.7, 134.9. Anal. Calcd for $C_{22}H_{24}PBr$: C, 66.18; H, 6.06; Br, 20.01; P, 7.76. Found: C, 66.01; H, 6.10; Br, 20.2; P, 7.75.

Preparation of the *Z* Olefins by Wittig Condensation. The same general procedure was used with **8a–d** for the preparation of the *Z* isomers of the methyl esters of **8**.

To a suspension of potassium *tert*-butoxide (0.823 g, 7.35 mmol) in DMF (40 mL) was added **7a** (2.93 g, 7.35 mmol). After stirring 5 min at room temperature, a solution of **6** (7 mmol) in DMF (1 mL) was added dropwise. The resulting mixture was stirred for 20 h at room temperature and 1 h at 90 °C and, after cooling to room temperature, poured onto ice (100 g). The water/DMF solution was then extracted (hexane, 4 × 100 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, concentrated, and chromatographed (LPLC, 3:1 hexane/toluene).

(*Z*)-Methyl 7-methyloct-5-enoate ((*Z*)-8a): IR (CCl_4) 3021 (C=C), 2961 (CH), 1734 (C=O), 1215 (C—O), 730 (C=C) cm^{-1};

(22) Corey, E. J.; Albright, J. C.; Barton, A. E.; Hashimoto, S. I. *J. Am. Chem. Soc.* **1980**, *102*, 1435.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76 (6 H, d, J = 6.3 Hz, CH_3), 1.50 (2 H, p, J = 7.5 Hz, CH_2), 1.925 (2 H, q, J = 6.6 Hz, CH_2C=C), 2.12 (2 H, t, J = 7.5 Hz, CH_2C=O), 2.39 (1 H, m, CH), 3.47 (3 H, s, CH_3) 5.03 (2 H, m, HC=CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.87, 24.87, 26.46, 29.57, 33.03, 50.87, 125.7, 138.1, 173.5; MS, m/z (relative intensity) 170 (15), 87 (45), 74 (100); exact mass calcd for $C_{10}H_{18}O_2$ 170.1306, found 170.1312. **(*Z*)-Methyl 8-methylnon-6-enoate ((*Z*)-8b)**: IR (CCl_4) 3020 (C=CH), 2955 (CH), 1736 (C=O), 1220, 1100 (C—O), 725 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (6 H, d, J = 6.6 Hz, CH_3), 1.32 (2 H, p, J = 6.3 Hz, CH_2), 1.58 (2 H, p, J = 6.3 Hz, CH_2), 1.99 (2 H, q, J = 6.6 Hz, CH_2C=C), 2.24 (2 H, t, J = 7.5 Hz, CH_2C=O), 2.52 (1 H, m, CH), 3.59 (3 H, s, CH_3O), 5.13 (2 H, m, HC=CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.07, 24.49, 26.38, 26.81, 29.28, 33.83, 51.92, 126.6, 137.9, 173.9; MS, m/z (relative intensity) 184 (23), 169 (27), 87 (33), 74 (100); exact mass calcd for $C_{11}H_{20}O_2$ 184.1462, found 184.1467. **(*Z*)-Methyl 9-methyldec-7-enoate ((*Z*)-8c)**: IR (CCl_4) 3021 (C=CH), 2957 (CH), 1734 (C=O), 1230, 1110 (C—O), 721 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (6 H, d, J = 6.6 Hz, CH_3), 1.25 (2 H, p, J = 6.3 Hz, CH_3), 1.55 (4 H, m, CH_2), 1.95 (2 H, q, J = 6.6 Hz, CH_2C=C), 2.25 (2 H, t, J = 7.2 Hz, CH_2C=O), 2.49 (1 H, m, H), 3.60 (3 H, s, CH_3O), 5.10 (2 H, m, HC=CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.00, 23.91, 24.71, 26.20, 26.91, 30.02, 33.80, 52.05, 127.0, 137.3, 174.2; MS, m/z (relative intensity) 198 (19), 168 (25), 87 (44), 74 (100); exact mass calcd for $C_{12}H_{22}O_2$ 198.1619, found 198.1625. **(*Z*)-Methyl 6-methylhep-4-enoate ((*Z*)-8d)**: IR (CCl_4) 3012 (C=C), 2950 (CH), 1735 (C=O), 1220, 1105 (C=C), 720 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (6 H, d, J = 6.6 Hz, CH_3), 2.11 (2 H, q, J = 6.6 Hz, CH_2C=C), 2.41 (2 H, t, J = 6.6 Hz, CH_2C=O), 2.59 (1 H, m, CH), 3.65 (3 H, s, CH_3), 5.11 (2 H, m, HC=CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.05, 28.28, 29.67, 33.32, 50.80, 125.8, 138.1, 176.6; MS, m/z (relative intensity) 156 (21), 87 (30), 74 (100); exact mass calcd for $C_9H_{16}O_2$ 156.1150, found 156.1150.

Isobutyl Phenyl Sulfone (7b). This material was prepared in two steps from isobutyl alcohol and diphenyl disulfide:[23] IR (CCl_4) 3068 (ArH), 2964 (CH), 1446 (C—C), 1316 (SO) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (6 H, d, J = 6.9 Hz, CH_3), 2.2 (1 H, m, CH), 2.98 (2 H, d, J = 6.3 Hz, CH_2), 7.55 (2 H, m, ArH), 7.65 (2 H, m, ArH), 7.90 (1 H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.68, 24.07, 63.92, 127.76, 129.26, 133.54, 140.17; MS, m/z (relative intensity) 198 (13), 143 (58), 77 (47), 57 (100); UV (MeCN) λ_{max} (log ε) 265 (2.79), 215 (3.89); exact mass calcd for $C_{10}H_{14}SO_2$ 198.0713, found 198.0713.

Preparation of the *E* Olefins by the Kocienski–Lythgo–Julia Condensation.[17] The following procedure given here was used to prepare the E isomers of 8.

To a solution of **7b** (1.0 g, 5.05 mmol) in THF (15 mL) at −78 °C was added a solution of n-BuLi in hexane (1.49 M, 3.73 mL, 1.1 equiv). The resulting solution was stirred at −30 °C for 40 min and cooled to −78 °C, **6** (5.05 mmol, 1 equiv) in THF (5 mL) was added, and the resulting mixture was stirred for 1.5 h at 0 °C. After re-cooling to −78 °C, benzoyl chloride (0.78 mL, 5.6 mmol) was added, and the mixture was stirred overnight at room temperature. The reaction was quenched by pouring it into 10% aqueous $NaHCO_3$ (55 mL) and worked up by separating the layers, extracting the aqueous layer with EtOAc (3 × 50 mL), drying the combined organic layers ($MgSO_4$), filtering, and concentrating in vacuo. The residue was chromatographed (LPLC) (14:1 hexane/EtOAc, silica gel) to yield the sulfone benzoyl ester **12** as a mixture of diastereomers.

The product from above was dissolved in THF (24 mL) and MeOH (8 mL) and cooled to −20 °C, and Na(Hg) (3.0 g) was added. The resulting mixture was stirred at −20 °C for 4 h after which a second portion of Na(Hg) (3.0 g) was added and stirring was at −20 °C continued for 4 h. The reaction mixture was taken up in Et_2O (40 mL) and washed with brine (100 mL), and the brine was back-extracted with Et_2O (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated, and the residue was chromatographed (silica gel, 14:1 hexane/EtOAc eluent) to yield **(*E*)-8**.

(*E*)-Methyl 7-methyloct-5-enoate (E-8a): IR (CCl_4) 3019 (C=CH), 2961 (CH), 1734 (C=O), 1261, 1215 (C—O), 964 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (6 H, d, J = 6.6 Hz, CH_3), 1.61 (2 H, p, J = 6.3 Hz, CH_2), 1.99 (2 H, q, J = 6.6 Hz, CH_2C=C), 2.25 (2 H, t, J = 7.2 Hz, CH_2C=O), 2.48 (1 H, m, CH_2C=O), 3.59 (3 H, s, CH_3), 5.29 (2 H, m, HC=CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.28, 24.71, 26.43, 29.71, 33.57, 51.17, 125.9, 138.5, 173.1; MS, m/z (relative intensity) 170 (15), 155 (24), 87 (34), 74 (100); exact mass calcd for $C_{10}H_{18}O_2$ 170.1306, found 170.1303. **(*E*)-Methyl 8-methylnon-6-enoate ((*E*)-8b)**: IR (CCl_4) 3018 (C=CH), 2955 (CH), 1732 (C=O), 1220, 1101 (C—O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (6 H, d, J = 6.6 Hz, CH_3), 1.37 (2 H, p, J = 7.8 Hz, CH_2), 1.62 (2 H, p, J = 7.2 Hz, CH_2), 2.03, (1 H, q, J = 6.5 Hz, CH_2C=C), 2.30 (2 H, t, J = 7.5 Hz, CH_2C=O), 3.66 (3 H, s, CH_3O), 5.35 (2 H, m, HC=CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.64, 24.40, 29.09, 30.60, 32.08, 33.95, 51.38, 126.5, 138.1, 174.2; MS, m/z (relative intensity) 184 (23), 144 (35), 87 (21), 74 (100); exact mass calcd for $C_{11}H_{20}O_2$ 184.1462, found 184.1461. **(*E*)-Methyl 9-methyldec-8-enoate ((*E*)-8c)**: IR (CCl_4) 2966 (CH), 1734 (C=O), 1249, 1205, 1101 (C—O), 965 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (6 H, d, J = 6.6 Hz, CH_3), 1.39 (2 H, p, J = 6.3 Hz, CH_2), 1.62 (4 H, p, J = 6.9 Hz, CH_2), 2.01 (2 H, q, J = 6.6 Hz, CH_2C=C), 2.27 (2 H, t, J = 7.2 Hz, CH_2C=O), 2.51 (1 H, m, CH), 3.61 (3 H, s, CH_3), 5.33 (2 H, m, HC=CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.10, 23.11, 25.40, 28.90, 31.05, 33.51, 34.95, 50.95, 125.5, 137.9, 174.1; MS, m/z (relative intensity) 198 (20), 183 (21), 168 (21), 87 (33), 74 (100); exact mass calcd for $C_{12}H_{22}O_2$ 198.1619, found 198.1630. **(*E*)-Methyl 6-methylhep-4-enoate ((*E*)-8d)**: IR (CCl_4) 2959 (CH), 1732 (C=O), 1251, 1200, 1105 (C—O), 975 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (6 H, d, J = 6.6 Hz, CH_3), 2.20 (2 H, q, J = 6.9 Hz, CH_2C=C), 2.31 (2 H, t, J = 6.6 Hz, CH_2C=O), 2.59 (1 H, m, CH), 3.64 (3 H, s, CH_3), 5.39 (2 H, m, HC=CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.64, 29.09, 33.95, 35.08, 52.09, 125.5, 138.0, 174.0; MS, m/z (relative intensity) 156 (20), 87 (35), 74 (100); exact mass calcd for $C_9H_{16}O_2$ 156.1150, found 156.1156.

General Procedure for Synthesis of the Capsaicinoids. The same general synthetic procedure was used to prepare **(*E*)-1a–d** and **(*Z*)-1a–d**.

A solution of the methyl ester **(*E*)-8** (1.9 mmol) in 50% aqueous EtOH (8 mL) and KOH (0.126 g, 85%, 6 equiv) was heated to a gentle reflux for 1 h and cooled to room temperature. The reaction mixture was then concentrated to approximately 3 mL and extracted with Et_2O (2 × 5 mL). The aqueous layer was then acidified (10% aqueous HCl) and extracted with Et_2O (3 × 10 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo to give the acid of **(*E*)-8**.

To the above material (1.85 mmol) was added thionyl chloride (0.28 g, 2.41 mmol, 1.3 equiv) and this mixture was allowed to stand for 18 h at room temperature followed by heating to 100 °C for 30 min after which the excess thionyl chloride was removed at reduced pressure. The resulting acid chloride was dissolved in Et_2O (10 mL) and a solution of **5** (0.544 g, 2 equiv), as the free base, in Et_2O (15 mL) was added. This mixture was stirred for 3 days at room temperature and poured into water. The layers were separated, the aqueous layer was extracted with Et_2O (3 × 20 mL), the combined organic layers were dried (Na_2SO_4), filtered, and concentrated, and the residue was crystallized from pentane to yield **(*E*)-1**.

(*E*)-*N*-(4-Hydroxy-3-methoxybenzyl)-7-methyloct-5-enamide ((*E*)-1a): IR ($CHCl_3$) 3600, 3529 (NH), 3439 (OH), 3010 (C=CH), 2965 (RH), 1660 (C=O), 1275, 1149 (C—O), 970 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (6 H, d, J = 7.2 Hz, CH_3), 1.61 (2 H, p, J = 6.9 Hz, CH_2), 2.00 (2 H, q, J = 6.6 Hz, CH_2C=C), 2.29 (2 H, t, J = 7.2 Hz, CH_2C=O), 2.28 (1 H, m, CH), 3.43 (3 H, s, CH_3O), 4.32 (2 H, d, J = 5.7 Hz, $ArCH_2$), 5.31 (2 H, m, HC=CH), 5.88 (2 H, br s, OH, NH), 6.74 (1 H, d, J = 9.3 Hz, 6-ArH), 6.80 (1 H, s, 2-ArH), 6.84 (1 H, d, J = 9.3 Hz, 5-ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.01, 29.30, 30.20, 32.94, 36.91, 43.66, 55.50, 111.1, 112.4, 120.5, 125.8, 130.1, 136.1, 144.9, 147.0, 171.7; MS, m/z (relative intensity) 293 (22), 137 (100), 57 (15); UV (MeOH) λ_{max} (log ε) 228 (3.93), 279 (3.45); exact mass calcd for $C_{17}H_{25}NO_3$ 291.1833, found 291.1847. **(*E*)-*N*-(4-Hydroxy-3-methoxybenzyl)-8-methylnon-6-enamide ((*E*)-1b)**: mp 64–65 °C (lit[8] mp 65 °C); IR ($CHCl_3$) 3692, 3541 (NH), 3445 (OH), 3016 (C=CH), 2958 (CH), 1660 (C=O), 1271, 1217 (C—O), 972 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (6 H, d, J = 7.8 Hz, CH_3), 1.37 (2 H, p, J = 6.8 Hz, CH_2), 1.62 (2 H, p, J = 8.1 Hz, CH_2),

(23) Nakagawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, 1409.

1.97 (2 H, q, J = 6.6 Hz, CH_2C=C), 2.18 (2 H, t, J = 7.5 Hz, CH_2C=O), 2.20 (1 H, m, CH), 3.85 (3 H, s, CH_3O), 4.33 (2 H, d, J = 6.0 Hz, $ArCH_2$), 5.33 (2 H, m, HC=CH), 5.82 (2 H, br s, OH, NH), 6.73 (1 H, d, J = 9.0 Hz, 6-ArH), 6.78 (1 H, s, 2-ArH), 6.84 (1 H, d, J = 9.0 Hz, 5-ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.66, 25.27, 29.29, 30.95, 32.20, 36.66, 43.53, 55.91, 110.7, 114.4, 120.7, 126.5, 130.3, 138.1, 145.2, 146.8, 172.9; MS, m/z (relative intensity) 305 (16), 152 (11), 137 (100); UV (MeOH) λ_{max} (log ϵ) 227 (3.91), 280 (3.43); exact mass calcd for $C_{18}H_{27}NO_3$ 305.1990, found 305.1993. **(*E*)-*N*-(4-Hydroxy-3-methoxybenzyl)-9-methyldec-7-enamide ((*E*)-1c)**: IR (CCl_4) 3595, 3525 (NH), 3440 (OH), OH), (C=CH), 2960 (RH), 1661 (C=O), 1270, 1150 (C—O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (6 H, d, J = 6.9 Hz, CH_3), 1.26 (2 H, p, J = 6.9 Hz, CH_2), 1.37 (2 H, p, J = 6.6 Hz, CH_2), 1.61 (2 H, p, J = 6.9 Hz, CH_2), 1.96 (2 H, q, J = 7.2 Hz, CH_2C=C), 2.18 (2 H, t, J = 7.2 Hz, CH_2C=O), 2.62 (1 H, m, CH), 3.80 (3 H, s, CH_3O), 4.33 (2 H, d, J = 6.0 Hz, $ArCH_2$), 5.33 (2 H, m, HC=CH), 5.91 (2 H, br s, NH, OH, 6.70 (1 H, d, J = 8.7 Hz, 6-ArH), 6.79 (1 H, s, 2-ArH), 6.85 (1 H, d, J = 8.7 Hz, 5-ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.05, 22.91, 29.11, 30.18, 32.01, 37.05, 43.35, 54.91, 110.0, 111.9, 121.8, 126.1, 131.9, 137.7, 145.6, 148.1, 172.6; MS, m/z (relative intensity) 319 (2), 137 (100), 85 (2), 57 (5); UV (MeOH) λ_{max} (log ϵ) 227 (3.90), 281 (3.40); exact mass calcd for $C_{19}H_{29}NO_3$ 319.2146, found 319.2153. **(*E*)-*N*-(4-Hydroxy-3-methoxybenzyl)-6-methylhept-4-enamide ((*E*)-1d)**: IR (CCl_4) 3687, 3536 (NH), 3449 (OH), 3013 (C=CH), 2968 (RH), 1661 (C=O), 1274 (C—O), 971 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (6 H, d, J = 7.2 Hz, CH_3), 1.98 (2 H, q, J = 7.2 Hz, CH_2C=C), 2.21 (2 H, t, J = 6.6 Hz, CH_2C=O), 2.25 (1 H, m, CH), 3.85 (3 H, s, CH_3O), 4.36 (2 H, d, J = 5.7 Hz, $ArCH_2$), 5.34 (2 H, m, HC=CH), 5.8 (2 H, br s, NH, OH), 6.78 (1 H, d, J = 9.0 Hz, 6-ArH) 6.80 (1 H, s, 2-ArH), 6.85 (1 H, d, J = 9.0 Hz, 5-ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.81, 29.31, 31.20, 36.33, 44.10, 55.11, 111.5, 113.2, 121.3, 126.7, 129.9, 138.4, 145.0, 147.2, 171.8; MS, m/z (relative intensity) 319 (8.1), 137 (100), 85 (5.0), 57 (16); UV (MeOH) λ_{max} (log ϵ) 226 (3.96), 279 (3.49); exact mass calcd for $C_{16}H_{23}NO_3$ 277.1677, found 277.1680. **(*Z*)-*N*-(4-Hydroxy-3-methoxybenzyl)-7-methyloct-5-enamide ((*Z*)-1a)**: IR (CCl_4) 3688, 3540 (NH), 3450 (OH), 3015 (C=CH), 2967 (RH), 1662 (C—O), 1270 (C—O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (6 H, d, J = 7.5 Hz, CH_3), 1.61 (2 H, p, J = 7.2 Hz, CH_2), 1.94 (2 H, q, J = 7.5 Hz, CH_2C=C), 2.15 (2 H, t, J = 7.2 Hz, CH_2C=O), 2.25 (1 H, m, CH), 3.83 (3 H, s, CH_3), 4.32 (2 H, d, J = 6.0 Hz, $ArCH_2$), 5.31 (2 H, m, HC=CH), 5.95 (2 H, br s, NH, OH), 6.76 (1 H, d, J = 8.4 Hz, 6-ArH), 6.81 (1 H, s, 2-ArH), 6.86 (1 H, d, J = 8.4 Hz, 5-ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.79, 25.70, 27.20, 29.96, 36.59, 43.76, 56.70, 110.7, 114.9, 120.8, 126.9, 130.0, 137.4, 145.0, 147.1, 172.8; MS, m/z (relative intensity) 291 (18), 137 (100), 122 (3), 57 (6); UV (MeOH) λ_{max} (log ϵ) 229 (3.92), 280 (3.42); exact mass calcd for $C_{17}H_{25}NO_3$ 291.1833, found 291.1849. **(*Z*)-*N*-(4-Hydroxy-3-methoxybenzyl)-8-methylnon-6-enamide ((*Z*)-1b)**: IR (CCl_4) 3690, 3540 (NH), 3449 (OH), 3010 (C=CH), 2961 (RH), 1660 (C=O), 1275, 1215 (C—O), 733 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (6 H, d, J = 6.9 Hz, CH_3), 1.39 (2 H, p, J = 7.5 Hz, CH_2), 1.62 (2 H, p, J = 7.7 Hz, CH_2), 1.95 (2 H, q, J = 8.1 Hz, CH_2C=C), 2.04 (2 H, t, J = 8.4 Hz, CH_2C=O), 2.19 (1 H, m, CH), 3.82 (3 H, s, CH_3O), 4.31 (2 H, d, J = 5.5 Hz, $ArCH_2$), 5.32 (2 H, m, HC=CH), 5.98 (2 H, br s, NH, OH), 6.74 (1 H, d, J = 7.8 Hz, 6-ArH), 6.78 (1 H, s, 2-ArH), 6.85 (1 H, d, J = 7.8 Hz, 5-ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.33, 25.57, 26.61, 27.17, 29.70, 36.86, 43.67, 56.04, 110.7, 114.4, 120.8, 126.7, 130.3, 138.0, 145.1, 147.0, 172.7; MS, m/z (relative intensity) 305 (15), 137 (100), 69 (6), 57 (7); UV (MeOH) λ_{max} (log ϵ) 228 (3.90), 280 (3.41); exact mass calcd for $C_{18}H_{27}NO_3$ 305.1990, found 305.1999. **(*Z*)-*N*-(4-Hydroxy-3-methoxybenzyl)-9-methyldec-7-enamide ((*Z*)-1c)**: IR (CCl_4) 3685, 3550 (NH), 3440 (OH), 3011 (C=CH), 2962 (RH), 1663 (C=O), 1271, 1225 (C—O), 730 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (6 H, d, J = 7.5 Hz, CH_3), 1.26 (2 H, p, J = 7.2 Hz, CH_2), 1.38 (2 H, p, J = 7.5 Hz, CH_2), 1.66 (2 H, p, J = 7.2 Hz, CH_2), 1.99 (2 H, q, J = 7.5 Hz, CH_2), 2.20 (2 H, t, J = 7.2 Hz, CH_2C=O), 2.27 (1 H, m, CH), 3.80 (3 H, s, CH_3), 4.29 (2 H, d, J = 5.7 Hz, $ArCH_2$), 5.33 (2 H, m, HC=CH), 6.01 (2 H, br s, NH, OH), 6.75 (1 H, d, J = 8.0 Hz, 6-ArH), 6.81 (1 H, s, 2-ArH), 6.85 (1 H, d, J = 8.0 Hz, 5-ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.81, 23.31, 25.75, 26.17, 27.16, 30.07, 36.80, 44.00, 55.59, 110.9, 114.3, 121.1, 125.9, 130.2, 138.1, 144.5, 147.3, 172.0; MS, m/z (relative intensity) 319 (8), 137 (100), 121 (4), 59 (10); UV (MeOH) λ_{max} (log ϵ) 228 (3.95), 279 (3.41); exact mass calcd for $C_{19}H_{29}NO_3$ 319.2146, found 319.2150.

General Procedure for the Synthesis of the Dihydrocapsaicinoids. The same general procedure was applied to the synthesis of **2a–c**.

A solution of **1** (1 mmol) and 10% Pd/C (250 mg) in ethanol (50 mL) was hydrogenated at atmospheric pressure for 4 h after which the catalyst was removed by filtration through Celite, and the solvent was removed at reduced pressure. The residue was crystallized from pentane to yield **2**.

***N*-(4-Hydroxy-3-methoxybenzyl)-7-methyloctanamide (2a)**: IR ($CHCl_3$) 3540 (NH), 3441 (OH), 3008 (C=CH), 2931 (RH), 1662 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (6 H, d, J = 6.9 Hz, CH_3), 1.15 (2 H, m, CH_2), 1.27 (4 H, m, CH_2), 1.51 (1 H, m, CH), 1.66 (2 H, p, J = 6.6 Hz, CH_2), 2.19 (2 H, t, J = 6.9 Hz, CH_2C=O), 3.83 (3 H, s, CH_3), 4.33 (2 H, d, J = 5.7 Hz, $ArCH_2$), 5.74 (2 H, br s, NH, OH), 6.75 (1 H, d, J = 8.4 Hz, 6-ArH), 6.80 (1 H, s, 2-ArH), 6.86 (1 H, d, J = 8.4 Hz, 5-ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.75, 25.37, 38.61, 29.87, 29.97, 37.00, 39.08, 43.46, 56.06, 110.4, 114.4, 120.8, 130.0, 145.6, 146.6, 172.6; MS, m/z (relative intensity) 293 (9), 137 (100), 71 (7), 57 (19); UV (MeOH) λ_{max} (log ϵ) 229 (3.93), 279 (3.44); exact mass calcd for $C_{17}H_{27}NO_3$ 293.1990, found 293.1991. ***N*-(4-Hydroxy-3-methoxybenzyl)-8-methylnonanamide (2b)**: mp 63–64 °C (lit.[8] 64–65 °C); IR ($CHCl_3$) 3544 (NH), 3445 (OH), 3009 (C=CH), 2928 (CH), 1662 (C=O), 1271, 1153 (C—O), cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (6 H, d, J = 6.3 Hz, CH_3), 1.14 (2 H, m, CH_2), 1.26 (4 H, m, CH_2), 1.495 (1 H, m, CH), 1.62 (2 H, p, J = 7.2 Hz, CH_2), 2.18, (2 H, t, J = 8.4 Hz, CH_2C=O), 3.86 (3 H, s, CH_3O), 4.34, (2 H, d, J = 5.4 Hz, $ArCH_2$), 5.72 (2 H, br s, NH, OH), 6.75 (1 H, dd, J = 8.0, 2.0 Hz, 6-ArH), 6.80 (1 H, d, J = 2.0 Hz, 2-ArH), 6.85 (1 H, d, J = 8.0 Hz, 5-ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.73, 25.93, 27.35, 28.06, 29.49, 29.73, 36.97, 39.08, 43.64, 56.04, 110.7, 114.4, 120.7, 130.4, 145.1, 146.7, 172.8; MS, m/z (relative intensity) 307 (11e, 137 (100), 69 (4), 59 (5); UV (MeOH) λ_{max} nm (log ϵ) 228 (3.91), 280 (3.43); exact mass calcd for $C_{18}H_{29}NO_3$ 307.2146, found 307.2163. ***N*-(4-Hydroxy-3-methoxybenzyl)-9-methyldecanamide (2c)**: IR (CCl_4) 3544 (NH), 3449 (OH), 3011 (ArH), 2936 (RH), 1660 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (6 H, d, J = 7.5 Hz, CH_3), 1.15 (4 H, m, CH_2), 1.25 (6 H, m, CH_2), 1.49 (1 H, m, CH), 1.63 (2 H, p, J = 7.2 Hz, CH_2), 2.17 (2 H, t, J = 7.5 Hz, CH_2C=O), 3.89 (3 H, s, CH_3O), 4.33 (2 H, d, J = 5.7 Hz, $ArCH_2$), 5.81 (2 H, br s, NH, OH), 6.76 (1 H, d, J = 8.5 Hz, 6-ArH), 6.80 (1 H, s, 2-ArH), 6.86 (1 H, d, J = 8.5 Hz, 5-ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.30, 22.75, 25.94, 27.42, 28.09, 29.55, 29.73, 37.14, 39.14, 43.10, 56.09, 110.4, 114.3, 120.6, 130.4, 145.8, 146.2, 172.0; MS, m/z (relative intensity) 321 (11), 137 (100), 105 (5), 71 (9), 59 (10); UV (MeOH) λ_{max} (log ϵ) 228 (3.95), 280 (3.40); exact mass calcd for $C_{19}H_{31}NO_3$ 321.2302, found 321.2308.

Mutagenicity Data. Experimental procedures for the Ames assay and V79 mammalian cell assay followed standard procedures.[24] Ethanol extracts of red pepper (Spicecraft, St. Louis, MO) were prepared as described by Bhide.[6] Quantitation of **1** and **2** in these extracts was determined by two methods.

Method 1. Weighed amounts of the red pepper extract were dissolved in MeOH and a total concentration of **1** and **2** was calculated from the observed extinction coefficient at 279 nm. By this method a value of 3.8% total for **1** + **2** was calculated.

Method 2. Standard GC calibration curves were established for **1a–d** and **2a–c**. Weighed quantities of the red pepper extracts were then injected and the amounts of **1a–d** and **2a–c** determined. By this procedure the total concentration of **1** and **2** of 4.2% was determined; of this, 2.5% was **1b**.

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Registry No. **1a**, 61229-08-1; (*Z*)-**1a**, 112375-60-7; **1b**, 404-86-4; (*Z*)-**1b**, 25775-90-0; **1c**, 58493-48-4; (*Z*)-**1c**, 112375-61-8; **1d**, 61229-09-2; **2a**, 28789-35-7; **2b**, 19408-84-5; **2c**, 20279-06-5; **3**, 121-33-5; **4a**, 2874-33-1; **4b**, 93249-67-3; **5**, 1196-92-5; **5**·HCl, 7149-10-2; **6a**, 13865-19-5; **6b**, 6026-86-4; **6c**, 6654-36-0; **6d**, 63857-17-0; **7a**, 22884-29-3; **7b**, 34009-07-9; (*Z*)-**8a**, 112375-41-4; (*E*)-**8a**, 112375-53-8; (*E*)-**8a** (acid), 61229-06-9; (*E*)-**8a** (acid chloride), 112375-57-2; (*Z*)-**8b**, 112375-42-5; (*E*)-**8b**, 112375-54-9; (*E*)-**8b** (acid), 59320-77-3; (*E*)-**8b** (acid chloride), 95636-02-5; (*Z*)-**8c**, 112375-43-6; (*E*)-**8c**, 112375-55-0; (*E*)-**8c** (acid), 61229-05-8; (*E*)-**8c** (acid chloride), 112375-58-3; (*Z*)-**8d**, 112375-44-7; (*E*)-**8d**, 112375-56-1; (*E*)-**8d** (acid), 61229-07-0; (*E*)-**8d** (acid chloride), 112375-59-4; **9a**, 96-48-0; **9b**, 542-28-9; **9c**, 502-44-3; **9d**, 57-57-8; **10a**, 925-57-5; **10b**, 14273-92-8; **10c**, 4547-43-7; **10d**, 6149-41-3; (*R**,*R**)-**12a**, 112375-45-8; (*R**,*S**)-**12a**, 112375-46-9; (*R**,*R**)-**12b**, 112375-47-0; (*R**,*S**)-**12b**, 112375-48-1; (*R**,*R**)-**12c**, 112375-49-2; (*R**,*S**)-**12c**, 112375-50-5; (*R**,*R**)-**12d**, 112375-51-6; (*R**,*S**)-**12d**, 112375-52-7; methoxyamine hydrochloride, 593-56-6; 1-bromo-2-methylpropane, 78-77-3.

The Reaction of OH Radicals with Dimethyl Sulfoxide. A Comparative Study of Fenton's Reagent and the Radiolysis of Aqueous Dimethyl Sulfoxide Solutions

Manfred K. Eberhardt* and Ramon Colina

Department of Pathology, University of Puerto Rico, Medical Sciences Câmpus, San Juan, Puerto Rico 00936

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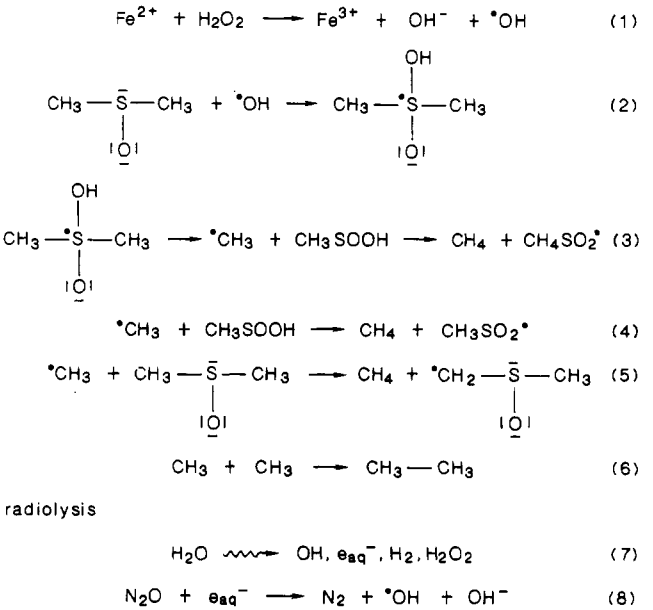
The reaction of OH radicals with dimethyl sulfoxide (DMSO) in aqueous solutions was investigated. The OH radicals were produced via radiolysis of N_2O saturated aqueous solutions and via Fenton's reagent. With Fenton's reagent we observed a quantitative conversion of OH radicals to CH_3 radicals, giving CH_4 and C_2H_6. The maximum yield in the radiolysis experiments was 86%. In both cases C_2H_6 was a major product with the C_2H_6/CH_4 ratio as high as 45. The C_2H_6/CH_4 ratio depends on the steady-state concentration of CH_3 radicals and on the DMSO concentration. Our results show that CH_3 radicals in addition to abstracting hydrogen from methanesulfinic acid also abstract hydrogen from DMSO to give CH_4. In the radiolysis of deuteriated DMSO we observed a much higher ethane/methane ratio than in the nondeuteriated DMSO. This isotope effect supports the hydrogen abstraction from DMSO by CH_3 radicals.

Dimethyl sulfoxide (DMSO) has been used as a probe for OH radicals in biological systems.[1] The mechanism of this reaction has been studied in detail both by ESR and by radiolysis techniques.[2,3] In a radiolysis study[4] the product of the reaction was found to be mainly methane with only small amounts of ethane. In this study the authors concluded that only a small fraction of OH radicals (about 25%) are converted to methyl radicals. On the other hand a pulse radiolysis study[3] reached the conclusion that OH radicals are converted quantitatively to methyl radicals. Because of the importance of this reaction for the detection of OH radicals we have studied the reaction of OH radicals with DMSO, producing OH radicals both by radiolysis of water and via the Fenton reaction.[5]

Results and Discussion

The results of the radiolysis experiments are shown in Tables I–III, and those using Fenton's reagent are shown in Tables IV–V. The reaction of OH radicals with DMSO to yield CH_3 radicals was first observed by Norman and co-workers.[6] Subsequent work by this research group using ESR techniques[2] and more recently by Asmus and co-workers[3] using pulse radiolysis have established the mechanism outlined in Scheme I. In the radiolysis of water OH radicals and e_{aq}^- are formed in about equal amounts along with some minor molecular products.[7] In presence of N_2O the solvated electrons are converted to OH radicals. The yield of these species is given by the G value (number of molecules produced per 100 eV of energy

Scheme I



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