response induced by *p*-chloromethamphetamine (PCMA). PCMA, 6.0 mg/kg, was administered ip 1 h after ip administration of the test compound, and the rats were observed for head movements 30 min later. Of 232 control animals treated with drug vehicle (1% methylcellulose) prior to PCMA, 215 (93%) exhibited head twitches. ED_{50} values are defined as the dose of test compound necessary to antagonize the head twitch response induced by PCMA in 50% of the animals.

Acknowledgment. The authors are indebted to G. A. Doldouras for the photofluorination reaction, to W. McGaughran for some of the NMR spectral data, and to K. B. Streeter, Y. Lee, and their associates for analytical determinations.

Fluorinated Retinoic Acids and Their Analogues. 2. Synthesis and Biological Activity of Aromatic 4-Fluoro Analogues[1]

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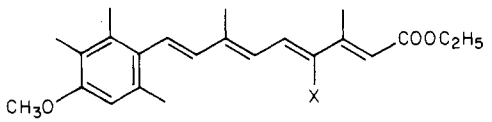
Ethyl (*E,Z,E,E*)-3,7-dimethyl-4-fluoro-9-(4-methoxy-2,3,6-trimethylphenyl)nonatetraenoate (**10a**) has been found to cause a marked regression of chemically induced skin papillomas in mice. A new synthesis of this compound was achieved by condensation of 4-fluoro aldehyde **7** or **8** with the aromatic phosphonium salt **9a**. Several analogues (**10a–e**) having different substituted aromatic moieties were also prepared and tested for their antipapilloma effect. The monochloro analogue **10b** was shown to have comparable activity to the parent compound **10a**.

The prophylactic and therapeutic effect of an aromatic retinoic acid analogue, **1**, on chemically induced benign and

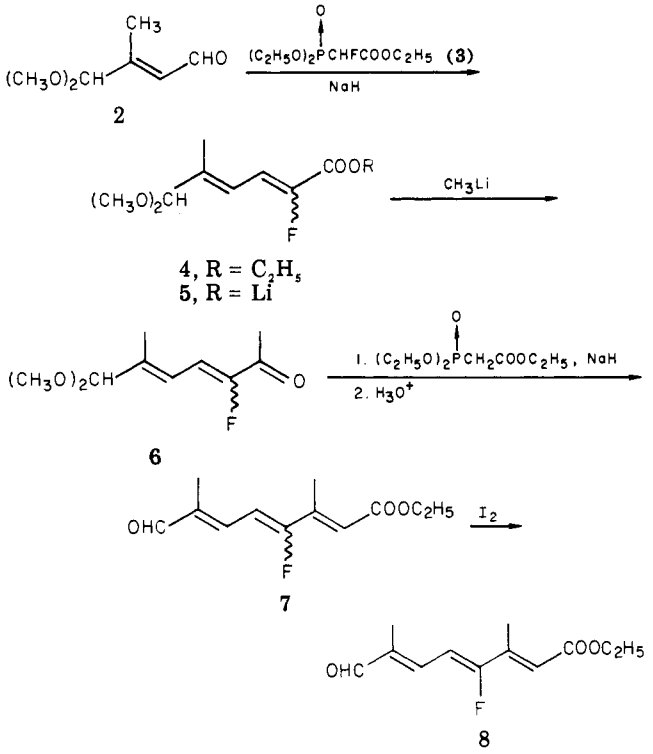


1, X = H
10a, X = F

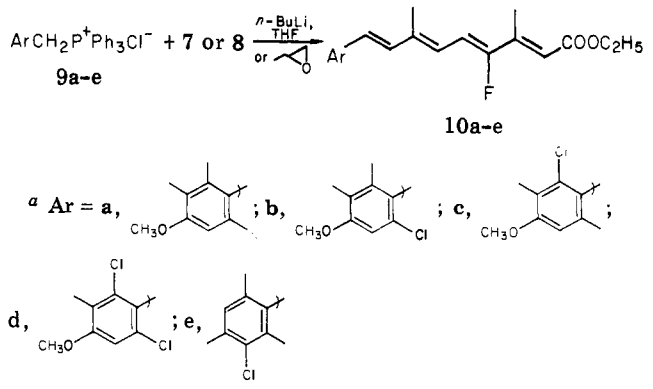
malignant epithelial tumors in mice has been well demonstrated.[2-4] In an effort to search for more effective compounds, we synthesized and studied the biological properties of various fluorinated analogues of **1** having one or two fluorine atoms or a trifluoromethyl group at different positions of the side chain.[1b] Among these analogues, the 4-fluoro derivative **10a** appeared to possess higher biological activity than compound **1** in the mouse skin antipapilloma test.[1b] Preparation of other substituted aromatic analogues of **10a** therefore was of interest. In this paper we describe the synthesis and biological activity of the aromatic 4-fluororetinoic acid analogues **10a–e** (Scheme II).

Chemistry. Preparation of analogues of **10a** having different substituted aromatic groups first required a practical synthesis of the fluoro side-chain aldehyde **7** or **8** (Scheme I). Treatment of the readily available 4,4-dimethoxy-3-methyl-2-butenal[6] (**2**) with the anion of triethyl fluorophosphonoacetate[7] afforded the 2-fluoro ester

Scheme I



Scheme II[a]



[a] Ar = a, ; b, ; c, ; d, ; e,

4 (58% yield) as a mixture of 2*Z* and 2*E* isomers. The lithium salt **5**, prepared from **4** with LiOH, was converted

(1) (a) This paper has been presented, see K.-K. Chan, "Abstracts of Papers", 178th National Meeting of the American Chemical Society, Washington, D.C., Sept 9–14, 1979; American Chemical Society: Washington, D.C., 1979; Abstr MEDI 62. (b) For paper 1 in this series, see Pawson, B. A.; Chan, K.-K.; DeNoble, J.; Han, R. J.; Piermattie, V.; Specian, A. C.; Srisethnil, S.; Trown, P. W.; Bohoslawec, O.; Machlin, L. J.; Gabriel, E. *J. Med. Chem.* **1979**, *22*, 1059.
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(6) Isler, O.; Ed. "Carotenoids"; Birkhäuser Verlag: Basel, 1971; pp 389–397. We thank Dr. Surmatis of Hoffman-La Roche Inc., Nutley, N.J., for supplying us a large amount of compound **2**.

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Table I. Biological Results

no.	hypervitaminosis A: dose, (mg/kg)/day[a]	antipapilloma act. dose, (mg/kg)/day[b]	antipapilloma act. effect, ±%
1[c]	100	80	−47
		40	−33
		20	−29
		10	+9
10a[c]	50	80	−82
		40	−69
		20	−62
		10	−76
		5	−43
10b	50	20	−59
		10	−60
		5	−41
10c	50	20	−73
10d	25	5	−58
10e	>200	80	−64
		40	−34
		20	−29

[a] Retinoids were suspended in water containing 0.1% carboxymethylcellulose and 0.01% Triton X-100 and administered ip daily Monday through Friday the first week and Monday through Thursday the second week. Evaluation for hypervitaminosis was made one day after the last injection. [b] Compounds were suspended in a 0.1% aqueous solution of carboxymethylcellulose and administered ip daily 5 times per week for 2 weeks. [c] Reference 1b.

to the methyl ketone **6** with methyllithium.[8] Condensation of **6** with triethyl phosphonoacetate gave the major fluoro aldehyde **7** as a mixture of 4(*Z*,*E*) isomers after an acidic workup [in one experiment, ca. 16% of the (2*Z*,4*Z*) isomer of **7** was isolated, see Experimental Section]. Isomerization of **7** with iodine, followed by fractional crystallization, gave the pure 4(*Z*)-fluoroaldehyde **8**. Treatment of aldehyde **7** or **8** with the phosphonium chloride **9a**[9] (Scheme II) and *n*-butyllithium in THF afforded the aromatic 4-fluororetinoic acid analogue **10a**[1b,5] (46.5%) after isomerization with iodine. Analogues **10b–e** (see NMR data under Experimental Section for assignment of stereochemistry) were similarly prepared from phosphonium salts **9b–e**[10,11] and the 4*Z* aldehyde **8**.

Biological Results

In Vivo Studies. The compounds described in this paper were tested for their therapeutic effect on chemically induced skin papillomas in mice as reported previously.[12,13] The hypervitaminosis dose, a measure of toxicity, was determined as described by Bollag.[3]

The effect of substitution of chlorine for a methyl group on the aromatic moiety is shown in Table I. Compound **10b**, having a chlorine substituent at C(6) of the aromatic ring, showed almost the same activity as the parent compound **10a**, whereas compound **10c**, with a C(2) chlorine substituent, appeared to be slightly more active based on limited data. The 2,6-dichloro analogue **10d** also appeared to be slightly more toxic, but more active than **10a**, again based on limited data. The chrlorotrimethyl analogue **10e**, having the C(3) aromatic methyl group replaced by chlorine and the methoxy group replaced by a methyl moiety, was much less toxic but also less active than **10a**. Based on this and previous studies,[1b,5] the 4-fluoro aromatic retinoid **10a** and its monochloro analogue **10b** appear to possess comparable activity.

Experimental Section

Spectra and analyses were made by the Physical Chemistry Department of Hoffmann-La Roche Inc., Nutley, N.J. Melting points were taken on a Kofler hot stage and are uncorrected.

Reagents. All solvents were ACS grade and were not further purified unless otherwise noted. Dry tetrahydrofuran (THF) and dimethoxyethane (DME) were prepared by distillation from sodium bis(2-methoxyethoxy)aluminum hydride.[14] The mineral oil in sodium hydride was removed by washing three times with petroleum ether (35–60 °C) or pentane. Ethyl bromofluoroacetate was purchased from PCR Inc., Gainesville, Fla. Unless otherwise indicated, reaction mixtures were partitioned between water and the organic solvent, and the aqueous layer was extracted twice with the organic solvent. The organic extracts were combined, washed with water, dried with anhydrous $MgSO_4$, filtered, and concentrated at reduced pressure (20–40 mmHg) at 35–40 °C on a rotary evaporator. For reactions carried out in an argon atmosphere, the apparatus was evacuated and filled with argon at least three times. Column chromatography was performed using E. Merck (Darmstadt) silica gel 60, 70–230 mesh. Reactions were monitored for completion by thin-layer chromatography (TLC) on silica gel in an ethyl acetate–hexane (3:7) solvent system unless otherwise indicated. Since several compounds were prepared by similar procedures, only one representative sample is described under Experimental Section. Satisfactory elemental analyses (±0.4% of calculated values) were obtained for each compound listed in Scheme II.

Ethyl (*E*/*Z*,*E*)-2-Fluoro-5-methyl-6,6-dimethoxy-2,4-hexadienoate (4). A suspension of 100.3 g (2.10 mol) of sodium hydride (50% in oil suspension) in 200 mL of dry DME was stirred at ~4 °C under argon, while a solution of 508.6 g (2.1 mol) of triethyl phosphonofluoroacetate[7] (**3**) in 500 mL of dry DME was added dropwise over a period of 45 min. The mixture was stirred at 23 °C for 1.5 h. To the resulting orange-brown mixture was added a solution of 300 g (2.08 mol) of 4,4-dimethoxy-3-methyl-2-butenal (**2**) in 500 mL of dry DME dropwise over a period of 1 h. The mixture was stirred at 23 °C for 17 h and further heated at 60 °C for 3 h under argon. It was cooled to ~20 °C and 500 mL of cold water was slowly added. The resulting solution was further diluted with 1.5 L of water and worked up with ether in the usual manner to give 486.2 g of crude product. Vacuum distillation of this material afforded 281 g (58% yield) of **4** as a colorless liquid: bp 99–117 °C (0.6–0.75 mm); IR (neat) 1730 ($COOC_2H_5$), 1650 (C=C) cm^{-1}; UV max (C_2H_5OH) 270 nm (ϵ 20 070); NMR (CCl_4) δ 7.1–6.4 (m, 2), 4.56 [s, $CH(OCH_3)_2$, ~55%], 4.51 [s, $CH(OCH_3)_2$, ~45%], 4.25 (2 sets of q, 2, OCH_2CH_3), 3.25 (s, 6), 1.8 (d, $J \cong 2$, $CH_3C{=}C$), 1.73 (d, $J \cong 2$, $CH_3C{=}C$), 1.35 (2 sets of t, 3); MS (*m*/*e*) 201 ($M^+ - OCH_3$), 75 (base peak). Anal. ($C_{11}H_{17}FO_4$) C, H; F: calcd, 5.18; found, 5.97.

(*E*/*Z*,*E*)-3-Fluoro-6-methyl-7,7-dimethoxy-3,5-heptadien-2-one (6). A solution of 533 g (2.29 mol) of fluoro ester **4** in 3 L of absolute ethanol was treated with 54.9 g (2.29 mol) of lithium hydroxide. The resulting mixture was stirred at 23 °C, in the dark, under argon for 24 h and then filtered. Concentration of the

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(11) We thank Dr. Ruegg of Hoffman-La Roche, Basel, for providing us with some intermediates and procedures for the preparation of phosphonium chlorides **9b–e**.

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(14) Eastman Organic Chemical Bulletin, **1970**, *42*, 3.

filtrate at 65 °C on a rotary evaporator gave 510 g of a brown residue, which was pulverized and further dried over P_2O_5 at 25 °C (0.5 mm) to yield 497.6 g of the lithium salt **5** as a yellowish brown powder. It was used directly for the reaction described below.

A solution of 245 g (1.16 mol) of **5** in 1.5 L of dry THF was cooled to −72 °C in a dry ice–acetone bath. To this solution, 818 mL (1.39 mol) of methyllithium (1.7 M in ether) was added dropwise with stirring under argon. The reaction mixture was stirred at −72 °C for 1.5 h. The excess of methyllithium was carefully destroyed at ~0 °C by adding 1.0 L of water dropwise. After THF was removed on a rotary evaporator, the aqueous phase was worked up with ether in the usual manner to give 185 g (78%) of crude fluoro ketone **6** as a yellow-orange oil, which was used directly for the preparation of the aldehyde **7** as described below: NMR ($CDCl_3$ 60 MHz) δ 7.10 (d, CH_3 C=C**H** of 3*E* isomer), 6.40 (dd, J_{HH} = 12 Hz, J_{HF} = 20 Hz, C**H**=CF of major 3*E* isomer), 7.05, 6.87, 6.54, 6.44, 6.2 (olefinic protons of minor 3*Z* isomer, pattern not clear), 4.80 [s, C**H**$(OCH_3)_2$ of 3*Z* isomer, ~35%], 4.60 [s, C**H**$(OCH_3)_2$ of 3*E* isomer, ~65%], 3.30 (s, 6, OCH_3), 2.30 (d, $J \cong 3$ Hz, CH_3CO of 3*Z* isomer), 2.28 (d, $J \cong 5$ Hz, CH_3CO of 3*E* isomer), 1.80 (d, $J \cong 1.5$ Hz, CH_3C=CH), 1.75 (d, $J \cong 1.5$ Hz, CH_3C=CH); MS (*m/e*) 202 (M^+), 186, 171, 159, 127, 75, 43 (base peak); IR (KBr) 1720 cm^{-1} (CH_3C=O); UV max (C_2H_5OH) 210 nm (ε 6900), 299 (23 850).

Ethyl (*E,Z/E,E*)- and (*E,Z,E*)-3,7-Dimethyl-4-fluoro-8-oxo-2,4,6-octatrienoate (7 and 8). A solution of 524.6 g (2.34 mol) of triethyl phosphonoacetate in 1.0 L of dry DME was added dropwise over a period of 3 h at 23 °C, under argon, with mechanical stirring, to a suspension of 112.3 g (2.34 mol) of sodium hydride (50% oil dispersion) in 500 mL of DME. After the addition was complete, the mixture was stirred at 23 °C under argon for 16 h. To the resulting brown mixture was slowly added a solution of 395 g (1.95 mol) of the crude fluoro ketone **6** in 1.0 L of DME. The reaction mixture was stirred at 23 °C under argon for 2.0 h and then adjusted to pH ~2 by adding slowly 500 mL of cold 3 N HCl. It was further diluted with 1.0 L of water, and the resulting solution was extracted with ether. The combined ether extracts were washed with water, dried ($MgSO_4$), concentrated to ca. 1 L, and quickly passed through 2.0 kg of Florisil. Elution with ether–petroleum ether (7:3) gave 302 g of a red-brown oil, which was further passed through a column of Florisil (2 kg) and eluted with ether–petroleum ether (1:1) to yield 251 g of crude oily aldehyde. This was dissolved in 4.0 L of ether and treated with 2.6 g of iodine crystals. The resulting solution was stirred at 23 °C, under argon, and in the dark for 24 h. It was washed with 5% sodium thiosulfate and water, dried over $MgSO_4$, filtered, and passed through 500 g of Florisil. Concentration of ether gave 247 g of orange oil, which on crystallization from ether yielded 147 g of orange crystals. The mother liquor (99 g) was again treated with 1.0 g of iodine crystals in 1.5 L of ether as described above to give another 42 g of crystalline substance. Recrystallization of the combined crystalline products (189 g) from ether–petroleum ether (7:10) yielded 109 g (25% from crude ketone **6**) of 4(*Z/E*) aldehyde **7** as yellowish-orange crystals: mp 60–68 °C; IR (KBr) 1716, ($COOC_2H_5$), 1708 ($COOC_2H_5$), 1680 (CHO), 1670 (CHO), 1620 cm^{-1}; MS (*m/e*) 226 (M^+), 197, 181, 177, 153; UV max (EtOH) 225 nm (ε 10 500), 302 (sh, 25 500), 316 (31 300), 330 (sh, 25 500); ^1H NMR ($CDCl_3$) δ 9.52 (s, CHO, 4*E* isomer, ~43%), 9.45 (s, CHO, 4*Z* isomer, ~57%), 7.25 (br d, CH_3C=C**H** of 4*Z* isomer), 7.03 (br d, CH_3C=C**H** of 4*E* isomer), 6.42 (dd, J_{HH} = 12 Hz, J_{HF} = 19 Hz, C**H**=CF of 4*E* isomer), 6.35 (br s, CH_3C=C**H**$COOC_2H_5$), 6.34 (dd, J_{HH} = 12 Hz, J_{HF} = 31 Hz, C**H**=CF, 4*Z* isomer), 6.10 (br s, CH_3C=C**H**$COOC_2H_5$), 4.25 (q, 2 sets, OCH_2CH_3), 2.36 [s, (2*E*)-CH_3C=C$COOC_2H_5$], 1.90 [s, OHCC(CH_3)=C], 1.86 [s, OHCC(CH_3)=C], 1.31 (t, OCH_2CH_3); ^{19}F NMR ($CDCl_3$) δ 109.9 (d, J_{HF} = 31 Hz, 4*Z* isomer), 103.2 (d, J_{HF} = 19 Hz, 4*E* isomer); LC (SR-I, 50 cm R-108, 109 column, mobile phase 5% THF/heptane, at 1.1 mL/min, monitored at 310 nm) retention time 13.9 min (*k'* = 1.5), 57.7%; 14.8 min (*k'* = 1.7), 40.4%. Anal. ($C_{12}H_{15}FO_3$) C, H, F.

The mother liquor from the above recrystallization was evaporated, and the resulting crystalline substance was recrystallized from ether–petroleum ether (1:1) to afford 63.6 g (14.4% yield from **6**) of the 4*Z* aldehyde **8** as yellow crystals, shown to be 95% pure by LC. Recrystallization once from ether–petroleum ether gave the analytical sample: mp 72–78 °C; ^1H NMR (CCl_4) δ 9.47 (s, CHO), 7.19 (d, J = 12 Hz, OHCCH_3C=C**H**), 6.36 (dd, J_{HH} = 12 Hz, J_{HF} = 31 Hz, C**H**=CF), 6.30 (s, CH_3C=C**H**$COOC_2H_5$), 4.15 (q, OCH_2CH_3), 2.35 [s, (2*E*)-CH_3C=CHCOOEt], 1.88 (d, $J \cong 2$, CH_3C=CH), 1.31 (t, OCH_2CH_3); UV max (EtOH) 225 nm (ε 4600), 302 (sh, ε 33 600), 317 (46 500), 330 (sh, ε 39 500); IR (KBr) 1720, 1683, 1623 cm^{-1}. Anal. ($C_{12}H_{15}FO_3$) C, H, F.

In an earlier experiment, the crude reaction mixture (4.98 g, from 6.5 g of crude ketone **6**) was directly purified by column chromatography (silica gel; 1:9 to 1:4 diethyl ether–petroleum ether) to give 2.82 g (39% based on crude **6**) of 4(*Z/E*) aldehyde **7** as a less polar component (R_f 0.43; silica gel; ethyl acetate–hexane, 3:7): mp 55–75 °C; ^{19}F NMR (CCl_4, δ upfield from Freon) 93.2 (d, J_{HF} = 19 Hz, 4*E* isomer, 75%), 111.1 (d, J_{HF} = 32 Hz, 4*Z* isomer, 25%). A more polar substance was also eluted from the column and it was crystallized from ether–petroleum ether (1:4) to give 0.4 g (5.5% yield from **6**) of yellow crystals, shown to be the (2*Z*,4*Z*) isomer of **7**: mp 38–43 °C; ^{19}F NMR (CCl_4) δ 100.02 (d, J_{HF} = 32 Hz); ^1H NMR (CCl_4) δ 9.47 (s, CHO), 7.5 (1 H, d, J = 12 Hz), 6.4 (1 H, dd, J_{HH} = 12 Hz, J_{HF} = 32 Hz), 5.90 (1 H, s), 4.14 (2 H, d), 2.07 [3 H, s, (2*Z*)-CH_3C=CHCOOC$_2H_5$], 1.86 (3 H, s), 1.29 (3 H, t); UV max (C_2H_5OH) 227 (ε 4500), 311 (ε 29 800). In subsequent smaller scale experiments (6.0–50 g of ketone **6**), it was found that isomerization of the above mixture of isomers with iodine and purification of the reaction mixture by fractional crystallization gave directly the pure (2*E*,4*Z*)-aldehyde **8** in yields from 50 to 61%. The minor (2*Z*,4*Z*) isomer was removed in the crystallization process.

Ethyl (*E,Z,E,E*)-3,7-Dimethyl-4-fluoro-9-(4-methoxy-2,3,6-trimethylphenyl)nonatetraenoate (10a). A solution of *n*-BuLi (325 mL, 1.6 M in hexane) was added slowly over a period of 75 min, at −20 °C under argon, with mechanical stirring to a suspension of (2,3,6-trimethyl-4-methoxybenzyl)triphenylphosphonium chloride[9] (**9a**) (138 g, 0.30 mol) in 800 mL of dry THF. The resulting red-orange colored mixture was stirred at −20 °C under argon for 1 h and then treated dropwise with a solution of 60 g (0.26 mol) of 4(*Z/E*) aldehyde **7** in 300 mL of THF. After the mixture was stirred at −20 °C for 1 h and at 25 °C for 2.0 h, the THF was evaporated. The resulting residue was taken into 1.0 L of CH_2Cl_2 and washed with water. The aqueous phase was twice extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were processed in the usual manner and passed through a short column of Florisil (1.0 kg). Concentration gave 151 g of crude brown oil, which was quickly chromatographed on 2.2 kg of silica gel. Elution with ether–petroleum ether (1:9) yielded 82.1 g of yellow oil, which was dissolved in 2.0 L of dry ether and treated with 820 mg of crystalline iodine. The resulting solution was stirred at 25 °C under argon for 16 h. Workup as described for the conversion of **7** to **8** gave ca. 71.9 g of yellow crystalline substance, which was recrystallized from CH_2Cl_2–hexane (1:5) to give 45.8 g (46.5% yield from **7**) of **10a** as yellow crystals: mp 92–94 °C. Anal. ($C_{23}H_{29}FO_3$) C, H, F. A second crop (6.6 g) of **10a** was obtained from the mother liquor by crystallization from ether–petroleum ether (1:4). The above material was shown to be identical with a sample of **10a** synthesized previously[1b] by a different route.

Ethyl (*E,Z,E,E*)-9-(6-Chloro-4-methoxy-2,3-dimethylphenyl)-4-fluoro-3,7-dimethyl-2,4,6,8-nonatetraenoate (10b). A mixture of 6.0 g (12.5 mmol) of (6-chloro-4-methoxy-2,3-dimethylbenzyl)triphenylphosphonium chloride (**9b**) and 2.71 g (12 mmol) of fluoro aldehyde **8** in 15 mL of 1,2-butylene oxide was heated at 110 °C in a sealed tube for 60 h. It was cooled to ~25 °C, diluted with ether, and then washed with water. The aqueous phase was extracted again with ether. The combined ether extracts were dried ($MgSO_4$) and concentrated to give 13.5 g of crude product, which was chromatographed on 300 g of silica gel. Elution with ether–petroleum ether (1:4) yielded 4.65 g of yellow crystalline substance, which on recrystallization from $CHCl_3$–ether–petroleum ether (1:1:13) afforded 2.2 g (47% yield) of **10b** as yellow crystals: mp 126–128 °C; IR (KBr) 1716, 1273, 1260, 1175 cm^{-1}; UV max (EtOH) 205 nm (ε 30 000), 363 (45 300); ^1H NMR ($CDCl_3$) δ 6.68 (1 H, S, aromatic H), 6.63 [d, 1 H, J = 17 Hz, (*E*)-C**H**=CHC], 6.51 (d, J = 12 Hz, CH_3C=C**H**), 6.38 [d, J = 17 Hz, (*E*)-CH=C**H**], 6.27 (dd, J_{HH} = 12 Hz, J_{HF} = 32 Hz, C**H**=CF), 6.14 (s, CH_3C=CHCOOEt), 4.11 (2 H, q), 3.78 (3 H, s), 2.32 [3 H, (2*E*)-CH_3C=CHCOOEt], 2.27, 2.10 (6 H, 2 s, aromatic CH_3), 2.07 (3

H, s, CH_3C=CH), 1.28 (3 H, t); ^{19}F NMR (CCl_4) 118 ppm upfield from $CFCl_3$ [d, J_{HF} = 30 Hz, (4*Z*)-fluoro]. Anal. ($C_{22}H_{26}ClFO_3$) C, H, Cl, F.

Ethyl (*E,Z,E,E*)-3,7-Dimethyl-4-fluoro-9-(2-chloro-4-methoxy-3,6-dimethylphenyl)-2,4,6,8-nonatetraenoate (10c). The compound was prepared in 47% yield using a procedure similar to that described for **10b**: yellow crystals; mp 115–117 °C (CH_2Cl_2–petroleum ether); IR (KBr) 1716 cm^{-1} ($COOC_2H_5$); UV max (EtOH) 208 nm (ε 24500), 365 (45400); ^1H NMR ($CDCl_3$) δ 6.76 [d, *J* = 16 Hz, (*E*)-ArCH=CH], 6.55 (d, *J* = 12 Hz, CH_3C=CH), 6.47 (d, *J* = 16 Hz, ArCH=CH), 6.38 (dd, J_{HH} = 12 Hz, J_{HF} = 36 Hz, CH=CF), 6.21 (s, CH=$COOC_2H_5$), 4.18 (2 H, q), 3.80 (3 H, s), 2.37, 2.25 (2 s, 2 aromatic CH_3's), 2.33 [s, (2*E*)-CH_3C=CHCOOC$_2H_5$], 2.08 (s, CH_3C=CH), 1.29 (3 H, t); ^{19}F NMR ($CDCl_3$) δ 118.5 ppm upfield from $CFCl_3$ (d, J_{FH} = 36 Hz). Anal. ($C_{22}H_{26}ClFO_3$) C, H, Cl, F.

Ethyl (*E,Z,E,E*)-3,7-Dimethyl-4-fluoro-9-(2,6-dichloro-3-methyl-4-methoxyphenyl)-2,4,6,8-nonatetraenoate (10d). This compound was prepared in 55% yield using a procedure similar to that described for **10a**: yellow crystals; mp 127–132 °C (CH_2Cl_2–hexane); UV max (EtOH) 206 nm (ε 32100), 364 (48000); MS (*m/e*) 412 (M^+), ^1H NMR (CCl_4) δ 6.80 (1 H, d, *J* = 16 Hz), 6.75 (1 H, s), 6.60 (1 H, d, *J* = 16 Hz), 6.51 (d, *J* = 12 Hz, CH_3C=CH), 6.23 (dd, J_{HH} = 12 Hz, J_{HF} = 30 Hz, CH=CF), 6.14 (1 H, s), 4.11 (2 H, q), 3.22 (3 H, s), 2.31 (s, CH_3C=CHCOOC$_2H_5$), 2.22 (3 H, s), 2.06 (3 H, s, CH_3C=CH), 1.28 (3 H, t). Anal. ($C_{21}H_{23}Cl_2FO_3$) C, H, Cl, F.

Ethyl (*E,Z,E,E*)-3,7-Dimethyl-4-fluoro-9-(3-chloro-2,4,6-trimethylphenyl)-2,4,6,8-nonatetraenoate (10e). This compound was prepared in 52% yield using a procedure similar to that described for **10b**: yellow crystals; mp 100–104 °C (hexane); IR (KBr) 1719 ($COOC_2H_5$), 1620, 1190 cm^{-1}; UV max (EtOH) 355 nm (ε 49200); MS (*m/e*) 376 (M^+); ^1H NMR (CCl_4) δ 6.83 (1 H, s), 6.66–6.0 (5 olefinic protons), 4.11 (2 H, q), 2.26, 2.29 (9 H, br s), 2.20 (3 H, s), 2.04 (3 H, s), 1.28 (3 H, t). Anal. ($C_{22}H_{26}ClFO_2$) C, H, Cl, F.

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Notes

Synthesis and Angiotensin-Converting Enzyme Inhibitory Activity of 3-(Mercaptomethyl)-2-oxo-1-pyrrolidineacetic Acids and 3-(Mercaptomethyl)-2-oxo-1-piperidineacetic Acids

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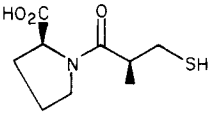
A number of γ- and δ-lactam derivatives were synthesized and their in vitro angiotensin-converting enzyme (ACE) inhibitory activities were compared. The structures of these compounds were designed to include many of the important features of captopril. The synthesis involved the preparation of a variety of novel 3-methylene-2-pyrrolidinones (**3–5** and **16**) and 3-methylene-2-piperidinones (**3a–5a**, **10–12**, and **17**). The key intermediate 3-methylenelactams **3** and **3a** were obtained from 3-(hydroxymethyl)lactams **2** and **2a** by a direct dehydration with dicyclohexylcarbodiimide using cuprous iodide as a catalyst. Introduction of the sulfhydryl group was accomplished by a Michael addition to these α,β-unsaturated lactams. The compound with the highest in vitro activity was 3-(mercaptomethyl)-2-oxo-1-piperidineacetic acid (**7a**). The activity of the **7a** both in vitro and in vivo (dog) was shown to be less than that of captopril by a factor of about 100.

In the last few years several papers have been published describing antihypertensive agents of the type that work by inhibiting the angiotensin-converting enzyme (ACE).[1-5] The most exciting compound thus far has been the clinically proven, orally effective agent captopril (SQ 14225; I). In the reports on structural variations of I, it was



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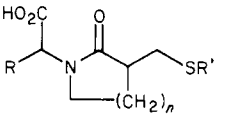

II, R = H, CH_3, *n*-Pr, Ph; R' = H, Ac; *n* = 1, 2

usually found that the ACE inhibitory activity was best when the important functional groups were retained.

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