

distal to its junction with the superior cervical ganglion. Nerve potentials were recorded monophasically under oil with a bipolar platinum electrode after capacity-coupled preamplification (low and high half-amplitude responses at 1 and 500 Hz). Nerve activity was displayed on the polygraph and quantitated using a Grass 7P10B cumulative integrator. Compound 13e was dissolved in 0.1 M citric acid at a concentration of 1 mg/mL.

Statistical Analysis. Statistical analysis for most experiments was performed using the Student's *t* test for unpaired comparisons. The values obtained at each time period in the drug-treated groups were compared to the corresponding values in the vehicle group.

The 0.05 level of probability was used to indicate statistical significance.

Acknowledgment. The authors are indebted to Michael G. Wendling and John E. Rogers who collected the hypotensive data in the conscious rat on the phenyl-piperazine isochromans, to Lubomir Baczynskyj and James R. Boal who ran and interpreted mass spectra, and to Upjohn's Physical and Analytical Chemistry Department for elemental analyses and IR spectroscopy.

Notes

Syntheses and Activities of Antioxidant Derivatives of Retinoic Acid

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The syntheses of six antioxidant derivatives (butylated hydroquinone, ethoxyquin, and *d*- α -tocopherol) of retinoic acid are reported. These derivatives were examined for activity in terms of "chemoprevention" of cancer by measuring the reverse keratinization of epithelial cells in hamster tracheal organ cultures. Ester 2A was observed to be active in 100% of the cultures examined at 10^{-9} M, relative to 88.4% activity for (*all-E*)-retinoic acid at 10^{-9} M.

Vitamin A (retinol) is an essential nutritional substance which is supplied in the diet basically from natural and/or synthetic retinyl esters and/or β -carotene. The active form of vitamin A appears to differ depending on target tissues.¹ Retinol, which is required for healthy reproductive functions,² is reversibly oxidized to retinal, which is utilized in visual proteins as photoreceptor molecules.³ Retinal is then further oxidized, irreversibly, to retinoic acid which exhibits hormonal-like properties in controlling the normal growth, development, and differentiation of epithelial tissues.⁴⁻⁶ These epithelia make up the membranes that cover, enclose, and protect the major organs of the body. Well over half of cancer begins in the epithelial tissues of the bladder, breast, colon, lung, prostate, skin, stomach, and uterus.⁷ Natural as well as synthetic retinoid analogues have been shown to prevent or delay the onset of certain forms of epithelial cancer, such as bladder, breast, lung, and skin, in animals which previously were given doses of chemical carcinogens, radiation, or viral transforming factors.⁸⁻¹¹ Natural retinoids have limited use-

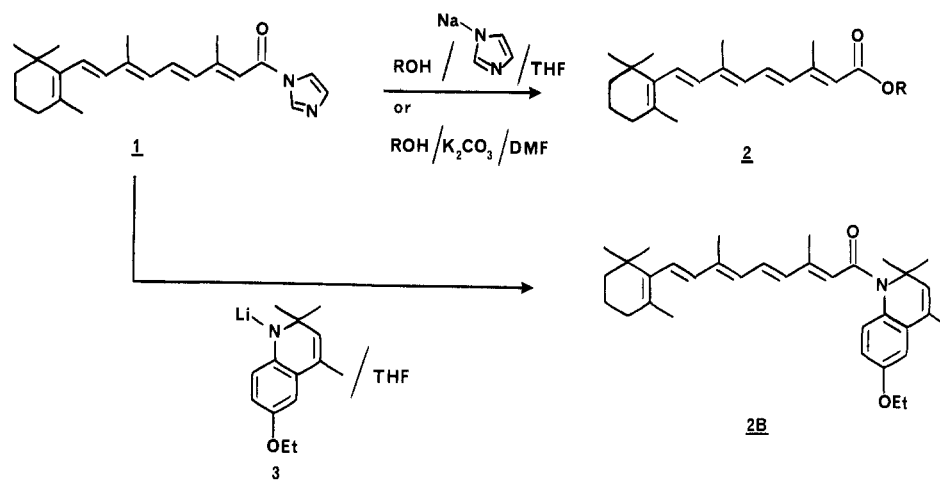
fulness for "chemoprevention"¹² of cancer, because of excessive toxicity and inadequate tissue distribution. Therefore, it would be advantageous to explore the possibility of utilizing new synthetic retinoid derivatives with proper therapeutic indexes and pharmacokinetics in order to prevent or delay the onset of epithelial malignancies.

Antioxidants such as butylated hydroxyanisole (BHA) and ethoxyquin (Santoquin)¹³ have been observed to inhibit the formation of neoplasia in animals treated with several chemical carcinogens.¹⁴ Antioxidants such as BHA, ethoxyquin, and *d*- α -tocopherol (vitamin E)^{15,16} are known to function as efficient inhibitors of lipid peroxidation, and as such they may serve to protect cellular membranes from the effects of various carcinogenic sub-

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Scheme I



stances.¹³⁻¹⁶ With this background information in mind, the syntheses of antioxidant derivatives of retinoic acid listed in Table I were initiated and completed. Thus, it was hoped that with structures **2A-F** some additive or synergistic effect between the retinoid and antioxidant moieties would be observed which would be useful in terms of the "chemoprevention" of cancer. These synthetic retinoid analogues should also exhibit good lipophilicity and, therefore, they might tend to accumulate in body organs which contain high concentrations of adipose tissue, such as the breast, liver, and skin.

Chemistry. Ethoxyquin (**3**, Li = H)¹³ was cleaved to the corresponding phenol **3** (Li = Et = H) in 35% yield with sodium *n*-propyl mercaptide in hexamethylphosphoric triamide (HMPA) at 140 °C for 48 h. Esterification of retinoylimidazole amide **1**¹⁷ with phenol **3** (Li = Et = H) under the conditions of Staab and Mannschreck¹⁸ using a catalytic amount of sodium imidazolate in anhydrous tetrahydrofuran afforded retinoid **2A** in 75% yield. Retinoid **2B** was prepared in 7% yield by treatment of retinoylimidazole amide **1** with the lithium derivative of ethoxyquin in THF (Scheme I). Retinoid analogues **2C** and **2D** were synthesized by treatment of freshly prepared *d*- α -tocopherol (from *d*- α -tocopherol acetate¹⁹ and 2.2 equiv of MeLi in Et₂O/THF) by the method of Staab and Mannschreck.¹⁸ Chromatography of this reaction product gave esters **2C** and **2D** in 79 and 17% yield, respectively. Esterification of retinoylimidazole amide **1** with 4-hydroxy-2-*tert*-butylphenyl tetrahydropyranyl ether²⁰ and 4-hydroxy-3-*tert*-butylphenyl tetrahydropyranyl ether²⁰ in the presence of anhydrous potassium carbonate in dry *N,N*-dimethylformamide (DMF) affords retinoid esters **2E** and **2F** in 52 and 45% yield, respectively, after removal of the tetrahydropyranyl protecting group (*p*-TsOH, CH₃OH room temperature).

Biological Results

These antioxidant derivatives of retinoic acid were examined for activity in an in vitro hamster tracheal organ culture assay.^{8a,21} This tracheal organ culture assay mea-

Table I

Retinoid 2	Activity @ 10 ⁻⁵ M	active cultures / total cultures (%)	a, b
A		6/6 (100%)	
B		2/7 (28.6%)	
C	13- <i>trans</i>	1/6 (16.7%)	
D	13- <i>cis</i>	1/6 (16.7%)	
E		1/6 (16.7%)	
F		1/7 (14.3%)	
R'OH (<i>trans</i> -retinoic acid)		419/474 (88.4%)	
R' =			

^a See ref 8a. ^b See ref 21.

sures the intrinsic ability of retinoids to control epithelial cell differentiation by determining reverse keratinization. Tracheas are removed from hamsters that are in very early stages of vitamin A deficiency and placed in organ cultures.²¹ For 3 days the tracheas are grown in a medium containing no retinoid. After that time, the tracheas are treated with each synthetic retinoid analogue in dimethyl sulfoxide²² with appropriate control cultures. The tracheal

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(20) Isomerically pure tetrahydropyranyl ethers of *tert*-butylhydroquinone were obtained from Dr. Luke K. T. Lam, Department of Laboratory Medicine and Pathology, University of Minnesota Medical School, Minneapolis, MN. We thank Dr. Lam for his generous contribution.

(21) These antioxidant derivatives were submitted to Dr. Michael B. Sporn, Chief, Lung Cancer Branch, Division of Cancer Cause and Prevention, National Cancer Institute, for hamster tracheal organ culture assay. See ref 8a for further details on this method of biological assay.

(22) The final concentration of Me₂SO in the culture medium is never greater than 0.1%.

organ cultures were scored by microscopic examination for the presence of keratin and keratohyaline granules. Approximately 90% of the control cultures that receive no retinoids have keratin and keratohyaline granules present. The retinoid analogues are scored as active if neither keratin nor keratohyaline granules are seen or if keratohyaline granules alone are present.²¹ These tracheal organ culture assays are extremely sensitive. They measure the intrinsic abilities of these synthetic retinoid analogues to control epithelial cell differentiation and thereby act as cancer "chemopreventative" agents.

As can be seen from the data listed in Table I, only antioxidant derivative 2A retains activity in 100% of the cultures at 10^{-9} M relative to the standard (*all-E*)-retinoic acid,²¹ which is active in 88.4% of the cultures at 10^{-9} M. Antioxidant derivatives 2B–D, in which the para-oxygen atom is bonded to an alkyl residue, show dramatically reduced activity in the range of 16.7 to 28.6% of the cultures at 10^{-9} M. The *tert*-butylhydroquinone esters 2E–F were the least active in the series even though a para-oxygen atom is available to function as a radical scavenger or antioxidant *in vitro*. These latter esters were active in the range of 14.3–16.7% of the cultures at 10^{-9} M.

Antioxidant derivatives 2A–D are expected to be very lipophilic retinoids which should tend to localize in organs with high concentrations of adipose tissue, such as the breast, liver, or skin. Antioxidant derivatives 2C,D, even though relatively inactive by the hamster tracheal organ culture assay, might find use in the topical treatment of acne where 13-*cis*-retinoic acid has shown dramatic results.²³ Only further studies on the toxicology and pharmacokinetics of these retinoid analogues will either prove or disprove their usefulness as either cancer "chemopreventative" or antiacne agents.

Experimental Section

Materials and Techniques. Melting points were determined on a Büchi melting point apparatus and are uncorrected. Analyses were performed by Spang Micro-analytical Laboratory, Eagle Harbor, MI. Silical gel 60, F-254 (E. Merck no. 5765), and silica gel 60 (E. Merck no. 7734, 70–230 mesh) available from Brinkmann Instruments were used for thin-layer and column chromatography, respectively. Medium-pressure liquid chromatography (MPLC) consisting of Fluid Lab pump Model RPSYX [Brinkmann prepared column C having a column volume of 430 mL packed with silica gel 60 (E. Merck. no. 9385, 230–400 mesh, available from Brinkmann instruments)] was also used.²⁴ Ultraviolet (UV) spectra were recorded on a Cary 14 spectrometer in 95% ethanol. Infrared (IR) spectra were recorded on a Perkin-Elmer 237B spectrometer in spectroquality solvents as 10% solutions using 0.10-mm sodium chloride cells or as thin films between sodium chloride crystals. Nuclear magnetic resonance (NMR) spectra were measured on a Varian Associates Model XL-100 spectrometer. High-resolution mass spectra (HRMS) were recorded on a Dupont Flash CEC 21-110B spectrometer at 70 eV. For all reactions performed under an atmosphere of dry nitrogen, the equipment was dried in an oven at 120 °C for several hours and then allowed to cool in an atmosphere of dry nitrogen. All liquid transfers were made with nitrogen-filled syringes. The term "petroleum ether" refers to Baker "Analyzed Reagent", bp 30–60 °C. The term "dry tetrahydrofuran" (THF) refers to purification of commercial tetrahydrofuran by distillation from lithium aluminum hydride under nitrogen. "Dry *N,N*-dimethylformamide" (DMF) and "dry hexamethylphosphoric triamide" (HMPA) were obtained by vacuum distillation of commercial materials from

calcium hydride (–40 mesh) on to activated molecular sieves of type 4A and 13X, respectively. The nomenclature utilized is that preferred by Chemical Abstracts.²⁵

6-Hydroxy-1,2-dihydro-2,2,4-trimethylquinoline (3, Li = Et = H). To a stirred HMPA suspension (10 mL) of NaH (845 mg, 21.5 mmol) was added 1-propanethiol (1.96 mL, 21.5 mmol). After the evolution of H₂ had ceased, a HMPA solution (5 mL) of ethoxyquin (3, Li = H; 550 mg, 2.54 mmol)¹³ was added, and the resultant solution was heated at 140 °C for 48 h. The reaction mixture was then cooled to room temperature and partitioned between saturated NaHCO₃ (100 mL) and Et₂O (200 mL). The ethereal solution was washed with saturated NaHCO₃ (2 × 25 mL), dried (MgSO₄), filtered (MgSO₄), and concentrated *in vacuo*. Column chromatography using 50 to 100% Et₂O/petroleum ether as an eluant gave 210 mg of ethoxyquin and 168 mg (35%) of phenol 3 (Li = Et = H): mp 180–181 °C; IR (Nujol) 3300 (NH), 3200 (OH), 1586 (C=C) cm⁻¹; NMR (acetone-*d*₆) δ 1.20 (s, 6, 2 CH₃), 1.92 (s, 3, C=CCH₃), 5.53 (br s, 1, C=CH), 6.0–6.7 (m, 3, ArH), 7.1 (br s, 1, OH). Anal. (C₁₂H₁₅NO) C, H, N.

1,2-Dihydro-2,2,4-trimethyl-6-quinolinyl Retinoate (2A). To a solution of 1 (350 mg, 1.00 mmol) and phenol 3 (Li = Et = H; 189 mg, 1.00 mmol) in dry THF (25 mL) was added a catalytic amount of sodium imidazolate (0.1 equiv) dissolved in THF (10 mL) [prepared from 0.1 equiv each of imidazole and NaH in THF]. After stirring under N₂ at room temperature for 15 h, the reaction mixture was diluted with Et₂O (150 mL), extracted with 5% NaOH (2 × 25 mL), dried (MgSO₄), filtered (MgSO₄), and concentrated *in vacuo*. Column chromatography using 15% Et₂O/85% petroleum ether as an eluant afforded 351 mg (75%) of *all-E*-ester (2A): mp 112–114 °C (Et₂O/petroleum ether); UV max (95% EtOH) 365 nm; IR (CCl₄) 1725 (CO₂R), 1605 and 1580 (C=C) cm⁻¹; NMR (CDCl₃) δ 1.03 (s, 6), 1.28 [s, 6, NC(CH₃)₂], 1.4–1.8 (m, 4), 1.73 (s, 3), 1.9–2.1 (m, 2), 2.00 (s, 3, C=CCH₃), 2.03 (s, 3), 2.42 (s, 3), 5.33 (br s, 1, ArCCH₃=CH), 5.9–7.3 (m, 9, C=CH and ArH). Anal. (C₃₂H₄₁NO₂) C, H, N.

(*all-E*)-1-[3,7-Dimethyl-1-oxo-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenyl]-6-ethoxy-1,2-dihydro-2,2,4-trimethylquinoline (2B). To a solution of ethoxyquin (3, Li = H; 217 mg, 1.0 mmol, freshly purified by column chromatography using 20% Et₂O/80% petroleum ether as an eluant) in THF (10 mL) at –78 °C (dry ice/acetone) under N₂ was added *n*-butyllithium (0.625 mL, 1.0 mmol, 1.6 M in hexane, Aldrich catalog no. 18, 617-1). After stirring for 15 min, this solution was then added via syringe to a solution of 1 (350 mg, 1.0 mmol) in THF (10 mL) at –78 °C. The reaction mixture was allowed to warm to room temperature (2 h) and then partitioned between saturated NaHCO₃ (50 mL) and Et₂O (200 mL). The ethereal solution was washed with 5% NaOH (25 mL), dried (MgSO₄), filtered (MgSO₄), and concentrated *in vacuo*. Column chromatography using 30% Et₂O/70% petroleum ether as an eluant gave 34 mg (7%) of *all-E*-amide 2B as a yellow oil: UV max (95% EtOH) 379 nm; IR (CCl₄) 1750 (CONR₂), 1605 and 1575 (C=C) cm⁻¹; NMR (CDCl₃) δ 1.03 (s, 6), 1.38 (t, 3, *J* = 7 Hz, OCH₂CH₃), 1.4–1.8 (m, 4), 1.58 [s, 6, NC(CH₃)₂], 1.72 (s, 3), 1.9–2.2 (m, 8, C-4 CH₂, C-13 CH₃, and ArCCH₃=C), 2.33 (s, 3), 4.02 (q, 2, *J* = 7 Hz, OCH₂CH₃), 5.53 (br s, 1, ArC=CH), 5.7–7.1 (m, 6). Anal. (C₃₅H₄₅NO₂) C, H, N, O.

(13E)- and (13Z)-*d*- α -Tocopherol Retinoate (2C and 2D). To a solution of 1 (350 mg, 1.0 mmol) and *d*- α -tocopherol (430 mg, 1.0 mmol, freshly prepared from *d*- α -tocopherol acetate, Sigma Chemical Co., 2.2 equiv of methyllithium) in THF (25 mL) was added to a solution of sodium imidazolate in THF (10 mL, ~0.1 equiv, prepared from 0.1 equiv each of NaH and imidazole in THF). After stirring under N₂ at room temperature for 15 h, the reaction mixture was diluted with Et₂O (150 mL). The resulting ethereal solution was washed with 5% NaOH (2 × 25 mL), dried (MgSO₄), filtered (MgSO₄), and concentrated *in vacuo*. Column chromatography using 5% Et₂O/95% petroleum ether as an eluant afforded 790 mg (96%) of C-13 *E/Z* esters. MPLC using 3% Et₂O/97% petroleum ether as an eluant gave 565 mg (79%) of *all-E*-ester (2C) as a yellow oil: UV max (95% EtOH) 365 nm; IR (CHCl₃) 1725 (CO₂R), 1605 and 1583 (C=C) cm⁻¹; NMR

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(CDCl₃) δ 0.87 (d, 12, J = 6 Hz, 4 CHCH₃), 1.04 (s, 6, 2 C-1 CH₃), 1.0-1.8 (m, 30, CH and OCCH₃), 1.73 (s, 3, C-5 CH₃), 1.99, 2.03, and 2.10 (apparent 3 s, 14, C-4 CH₂, C-9 CH₃, and 3 ArCH₃), 2.40 (s, 3, C-13 CH₃), 2.57 (br t, 2, J = 7 Hz, ArCH₂), 6.0-6.5 (m, 5, C-7, -8, -10, -12, and -14 C=CH), 7.04 (d of d, 1, J = 11 and 15 Hz, C-11 C=CH). Anal. Calcd for C₄₉H₇₆O₃: 712.5794. Found: 712.5775 (2.6 ppm error by HRMS). There was also obtained 123 mg (17%) of the less polar (13Z)-ester **2D** as a yellow oil: UV max (95% EtOH) 369 nm; IR (CCl₄) 1725 (CO₂R), 1606 and 1585 (C=C) cm⁻¹; NMR (CDCl₃) δ 0.88 (d, 12, J = 6 Hz, 4 CHCH₃), 1.03 (s, 6, 2 C-1 CH₃), 1.0-1.8 (m, 30, CH and OCCH₃), 1.72 (s, 3, C-5 CH₃), 2.02, 2.03, 2.12, and 2.17 (apparent 4 s, 17, C-4 CH₂, C-9 and C-13 CH₃, and 3 ArCH₃), 2.60 (br t, 2, J = 7 Hz, ArCH₂), 5.9-6.4 (m, 4, C-7, -8, -10, and -14 C=CH), 7.00 (d of d, 1, J = 11 and 15 Hz, C-11 C=CH), 7.87 (d, 1, J = 15 Hz, C-12 C=CH). Anal. (C₄₉H₇₆O₃) C, H, O.

4-Hydroxy-3-tert-butylphenyl Retinoate (2E). A solution of **1** (392 mg, 1.12 mmol), 4-hydroxy-2-tert-butylphenyl tetrahydropyranyl ether (230 mg, 1.12 mmol),²⁰ and anhydrous K₂CO₃ (0.55 g, 4.0 mmol) in dry DMF (5 mL) was stirred at room temperature under N₂ for 4 h. The reaction mixture was diluted with H₂O (100 mL) and extracted with Et₂O (5 \times 20 mL). The combined ethereal extracts were washed with 5% NaOH (25 mL), dried (MgSO₄), filtered (MgSO₄), and concentrated in vacuo. Column chromatography using 10% Et₂O/90% petroleum ether as an eluant gave 363 mg (61%) of *all-E*-ester tetrahydropyranyl ether. This material was dissolved in MeOH (5 mL) containing a catalytic amount of *p*-toluenesulfonic acid. After the solution was stirred at room temperature for 24 h, most of the MeOH was removed in vacuo, and the residue was dissolved in Et₂O (150 mL). This ethereal solution was washed with H₂O (2 \times 25 mL), dried (MgSO₄), filtered (MgSO₄), and concentrated in vacuo. Column chromatography using 25% Et₂O/75% petroleum ether as an eluant, followed by crystallization from petroleum ether, afforded 253 mg (85%) of *all-E*-ester **2E**: mp 147-149 °C; UV max (95% EtOH) 365 nm; IR (CHCl₃) 1719 (CO₂R), 1606 and 1578 (C=C) cm⁻¹; NMR (CDCl₃) δ 1.03 (s, 6), 1.37 [s, 9, C(CH₃)₃], 1.4-1.8 (m, 4), 1.72 (s, 3), 2.02 (s, 3 overlapping with m, 2), 2.40 (s, 3), 5.33

(br s, 1, OH), 5.9-7.3 (m, 9, C=CH and ArH). Anal. (C₃₀H₄₀O₃) C, H.

4-Hydroxy-2-tert-butylphenyl Retinoate (2F). A solution of **1** (420 mg, 1.20 mmol), 4-hydroxy-3-tert-butylphenyl tetrahydropyranyl ether (300 mg, 1.20 mmol),²⁰ and anhydrous K₂CO₃ (0.55 g, 4.0 mmol) in dry DMF (10 mL) was stirred under N₂ at room temperature for 4 h. The reaction mixture was diluted with H₂O (100 mL) and extracted with Et₂O (5 \times 20 mL). The combined ethereal extracts were washed with 5% NaOH (25 mL), dried (MgSO₄), filtered (MgSO₄), and concentrated in vacuo. Column chromatography using 10% Et₂O/90% petroleum ether as an eluant gave 248 mg (46%) of *all-E*-ester tetrahydropyranyl ether. This material was dissolved in MeOH (5 mL) containing a catalytic amount of *p*-toluenesulfonic acid. After the solution was stirred at room temperature for 24 h, most of the MeOH was removed in vacuo, and the residue was dissolved in Et₂O (150 mL). This ethereal solution was washed with H₂O (2 \times 25 mL), dried (MgSO₄), filtered (MgSO₄), and concentrated in vacuo. Column chromatography using 25% Et₂O/75% petroleum ether as an eluant, followed by crystallization from petroleum ether, afforded 196 mg (97%) of *all-E*-ester **2F**: mp 168-170 °C dec; UV max (95% EtOH) 368 nm; IR (CHCl₃) 1717 (CO₂R), 1606 and 1575 (C=C) cm⁻¹; NMR (CDCl₃) δ 1.03 (s, 6), 1.30 [s, 9, C(CH₃)₃], 1.4-1.8 (m, 4), 1.72 (s, 3), 2.02 (s, 3 and m, 2), 2.38 (s, 3), 5.63 (br s, 1, OH), 5.9-7.3 (m, 9, C=CH and ArH). Anal. (C₃₀H₄₀O₃) C, H.

Acknowledgment. We thank the National Cancer Institute, Division of Cancer Cause and Prevention, for the funds (CP 75935) to support this research program. We also thank Dr. Michael B. Sporn for the tracheal organ culture assay of these synthetic retinoids. We express our sincere gratitude to Hoffmann-La Roche, Nutley, NJ, and BASF, Germany, for generous gifts of retinoid starting materials. We also thank Professor E. Wenkert and Terry Marriott, Rice University, for the high-resolution mass spectra.

Synthesis and Antileukemic Activity of Fluorinated Analogues of 2,3-Dihydro-5-phenyl-6,7-bis(hydroxymethyl)-1H-pyrrolizine Biscarbamate¹

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A series of five difluorophenyl-substituted pyrrolizine biscarbamates was synthesized and evaluated against P388 lymphocytic leukemia. All of the compounds prepared were active, and no significant trends were observed in potency, activity, or toxicity as a function of fluorine substitution.

Bis(acyloxymethyl) derivatives of pyrrolizines and pyrroles have been shown to possess significant reproducible activity against a wide range of experimental murine neoplasias,² but the absence of oral activity coupled with low water solubility combine to pose a potential problem in the formulation of selected agents in this class. An increase in the potency of compounds in this class would

be tantamount to an increase in water solubility, and a combination of both factors would greatly reduce the magnitude of the formulation problem.

In an earlier report we noted that 5-(4-fluorophenyl)-2,3-dihydro-6,7-bis(hydroxymethyl)-1H-pyrrolizine bis(*N*-methylcarbamate) (**1**) exhibited significant reproducible activity against P388 lymphocytic leukemia at doses as low as 0.78 mg/kg.^{2b} In subsequent experiments, the fluoro compound **1** appeared to be more potent than **2** but failed to elicit the broad spectrum of antineoplastic activity that was seen for **2**.^{2b} This report describes the synthesis and preliminary antileukemic evaluation of a series of difluoro analogues of **2**.

Chemistry. The target compounds **7** and **8** were prepared from the requisite α -amido acid **4**. Treatment of **4** with acetic anhydride-dimethyl acetylenedicarboxylate gave the 1,3-dipolar cycloaddition product **5**; the reaction proceeded through the intermediacy of a mesoionic oxazolone that was generated in situ from **4**. Subsequent

- (1) Vinylogous Carbinolamine Tumor Inhibitors. 10. For part 9 in this series, see: Anderson, W. K. *Cancer Res.*, in press.
- (2) (a) Anderson, W. K.; Corey, P. F. *J. Org. Chem.* 1977, 42, 559. (b) *J. Med. Chem.* 1977, 20, 812. (c) *Ibid.* 1977, 20, 1691. (d) Anderson, W. K.; Halat, M. J. *Ibid.* 1979, 22, 977. (e) Anderson, W. K.; Halat, M. J.; Rick, A. C. *Ibid.* 1980, 23, 87. (f) Anderson, W. K.; New, J. S.; McPherson, H. L., Jr. *J. Heterocycl. Chem.* 1980, 17, 513. (g) Anderson, W. K.; New, J. S.; Corey, P. F. *Arzneim.-Forsch.* 1980, 30(1), 765. (h) Anderson, W. K.; Chang, C.-P.; Corey, P. F.; Halat, M. J.; Jones, A. N.; McPherson, H. L., Jr.; New, J. S.; Rick, A. C. *Cancer Treat. Rep.*, in press.