Gram-positive bacteria is comparable to that of cephaloglycin, whereas the activity toward Gram-negative bacteria is moderately lower. However, the lower activity of 8 vs. cefaclor discouraged further in vitro and in vivo studies.

Experimental Section

Melting points were determined with a Mettler FP 52 apparatus equipped with a Reichert Neovar microscope and are uncorrected. IR spectra were taken on paraffin oil mulls on Perkin-Elmer 157 and 197 spectrometers. ^{1}H NMR spectra were detected with a Perkin-Elmer R 12B 60-MHz spectrometer with Me_4Si or sodium 3-(trimethylsilyl)-1-propanesulfonate (DSS) as internal standards. Evaporations were made in vacuo (rotating evaporator). Magnesium sulfate was always used as the drying agent.

Benzhydryl 3-Chloro-7β-(α-phenylacetamido)-3-cephem-4-carboxylate (16). A solution of benzhydryl 3-hydroxy-7β-(α-phenylacetamido)-3-cephem-4-carboxylate (15; 2.0 g, 4.0 mmol) [prepared as previously described[6a] by ozonolysis of benzhydryl 3-methylene-7β-(α-phenylacetamido)cepham-4α-carboxylate (14)] in anhydrous DMF (10 mL) was treated with thionyl chloride (0.86 mL, 12 mmol) and stirred at room temperature for 5 h. The mixture was diluted with ethyl acetate and washed with aqueous $NaHCO_3$. The organic phase was dried and treated with charcoal. The solvent was evaporated, and the residue was triturated with Et_2O to give 16 (1.56 g, 75%): mp 162–164 °C dec; IR ν_{max} 1775 (β-lactam), 1725 (ester), 1655 (amide) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.47 (s, 2, PhCH_2), 3.75 and 3.99 (AB q, 2, J = 18.6 Hz, SCH_2), 5.26 (d, 1, J = 4.6 Hz, CHS), 5.81 (dd, 1, J = 8.2 and 4.6 Hz, NHCH), 7.03 (s, 1, CHPh$_2$). Anal. ($C_{28}H_{23}ClN_2O_4S$) C, H, N, Cl.

Benzhydryl 7β-Amino-3-chloro-3-cephem-4-carboxylate (12). A stirred solution of 16 (1.45 g, 2.8 mmol) in CH_2Cl_2 (5 mL) was cooled to -20 °C and treated with anhydrous pyridine (5 mL and PCl_5 (0.87 g, 4.2 mmol). The mixture was stireed at -15 °C for 2 h and then treated with isobutyl alcohol (10 mL); after 2 h, it was treated with H_2O and adjusted to pH 7.5 with aqueous NH_3. The organic phase was dried, treated with charcoal, and evaporated to dryness. The residue was purified by column chromatography on silica gel, eluting with a 1:1 mixture of ethyl acetate–hexane, to yield 12 (0.3 g, 27%): mp 158–162 °C dec; IR ν_{max} 1770 (β-lactam), 1735 (ester) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.43 and 3.75 (AB q, 2, J = 18.6 Hz, CH_2S), 4.68 (d, 1, J = 4.6 Hz, CHS), 4.93 (d, 1, J = 4.6 Hz, NH_2CH), 7.04 (s, 1, CHPh$_2$). Anal. ($C_{20}H_{17}N_2O_3S$) Cl, N, S.

General Procedure for the Preparation of (α-Hydrazinobenzyl)cephalosporins 6a,b and 7b. Method A. This method is illustrated by the synthesis of 7β-[(*R*)-α-hydrazino-α-phenylacetamido]-3-methyl-3-cephem-4-carboxylic acid (6a). A mixture of 9 (1.07 g, 5 mmol) and hexamethyldisilazane (1.25 mL, 6 mmol) in anhydrous MeCN 10 mL) and CH_2Cl_2 (10 mL) was refluxed for 1 h, and the solvent was evaporated at reduced pressure. To a residue, dissolved in anhydrous MeCN (15 mL), was added propylene oxide (10 mL). The resulting solution was cooled to −20 °C and treated under stirring with 13a[2] (1.3 g, 5.87 mmol). The solution was stirred at room temperature for 2 h, and the precipitate was collected by filtration and dissolved in MeOH (30 mL). The solution was stirred at 0 °C with silica gel (1 g) and filtered. The solvent was evaporated, and the residues was triturated with ethyl acetate to yield 6a (0.63 g, 51%): mp 158–160 °C dec; IR ν_{max} 1775 (β-lactam), 1680 (amide), 1550 (carboxylate) cm^{-1}; ^{1}H NMR (D_2O–CF_3CO_2H) δ 2.07 (s, 3, CH_3), 3.14 and 3.38 (AB q, 2, J = 18.6 Hz, CH_2S), 4.84 (d, 1, J = 4.6 Hz, CHS), 4.97 (s, 1, PhCH), 5.56 (d, 1, J = 4.6 Hz, NHCHCH).

Procedure for the Preparation of (α-Hydrazinobenzyl)-cephalosporins 7a and 8. Method B. This method is illustrated by the synthesis of 3-chloro-7β-[(*R*)-α-hydrazino-α-phenylacetamido]-3-cephem-4-carboxylic acid (8). A stirred solution of 12 (2.75 g, 6.9 mmol) in CH_2Cl_2 (30 mL) and propylene oxide (7 mL) was cooled to −30 °C and treated with 13a[2] (1.68 g, 7.5 mmol). Stirring was continued at −20 °C for 1 h and at room temperature for 30 min, and the solvent was evaporated. The residue was crystallized from 2-propanol and dissolved at 0 °C in a 1:1 mixture of anisole and trifluoroacetic acid (7 mL). The solution was stirred for 40 min at 0 °C and treated with Et_2O (45 mL). The resulting precipitate was collected and taken up with a 2-propanol–H_2O mixture. The pH was adjusted to 4.8 with aqueous $NaHCO_3$, and the suspension was filtered. The aqueous phase was concentrated to a small volume at reduced pressure, and 2-propanol was added. The precipitate was collected to obtain 8 (0.9 g, 34%): mp 202 °C dec; IR ν_{max} 1760 (β-lactam), 1665 (amide), 1600 (carboxylate) cm^{-1}; ^{1}H NMR (CD_3COCD_3–CF_3CO_2H) δ 3.52 and 3.87 (AB q, 2, J = 17.3 Hz, CH_2S), 5.20 (d, 1, J = 4.6 Hz, CHS), 5.46 (s, 1, PhCH), 5.84 (d, 1, J = 4.6 Hz, NHCHCH).

Acknowledgment. The authors thank Dr. M. Visconti for spectroscopic assistance.

Registry No. 6a, 57820-56-1; 6b (isomer 1), 86688-18-8; 6b (isomer 2), 86688-19-9; 7a, 57820-58-3; 7b, 86632-57-7; 8, 86632-58-8; 9 trimethylsilyl ester, 41360-37-6; 10 trimethylsilyl ester, 55633-18-6; 11, 6187-87-7; 12, 53994-70-0; (*R*)-13a, 54193-10-1; (*R*)-13b, 63903-96-8; (*RS*)-13b, 54186-58-2; 14, 51762-03-9; 15, 54639-48-4; 16, 63821-56-7.

A Deuterium Isotope Effect on the Inhibition of Gastric Secretion by *N,N*-Dimethyl-*N'*-[2-(diisopropylamino)ethyl]-*N'*-(4,6-dimethyl-2-pyridyl)urea. Synthesis of Metabolites

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The use of isotopic substitution to retard the oxidative metabolism of the gastric antisecretory agent *N,N*-dimethyl-*N'*-[2-(diisopropylamino)ethyl]-*N'*-(4,6-dimethyl-2-pyridyl)urea (1) and improve its antisecretory potency was examined. The pyridine ring methyl hydrogens of 1 were replaced with either deuterium or fluorine. The hexadeuterated analogue (12) was found to be ~2.1 times more potent than the protio form (1) as an inhibitor of gastric acid secretion stimulated by gastrin tetrapeptide. The hexafluoro analogue (11) was 0.4 times as potent as 1. A useful pyridine ring synthesis was developed to prepare the metabolites of 1, 10a (4-hydroxymethyl) and 10b (6-hydroxymethyl), and the hexafluoro analogue 11. These syntheses involved the condensation of 1,3-diketones with an appropriately N-substituted amidinoacetate.

A recent report from these laboratories described a series of aminoalkyl-substituted pyridylureas as inhibitors of gastric acid secretion.[1] One member of this series, *N,N*-dimethyl-*N'*-[2-(diisopropylamino)ethyl]-*N'*-(4,6-di-

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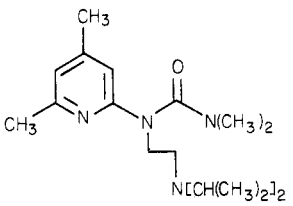
methyl-2-pyridyl)urea (1), was orally equipotent with



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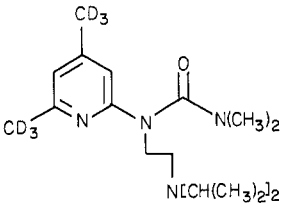


12

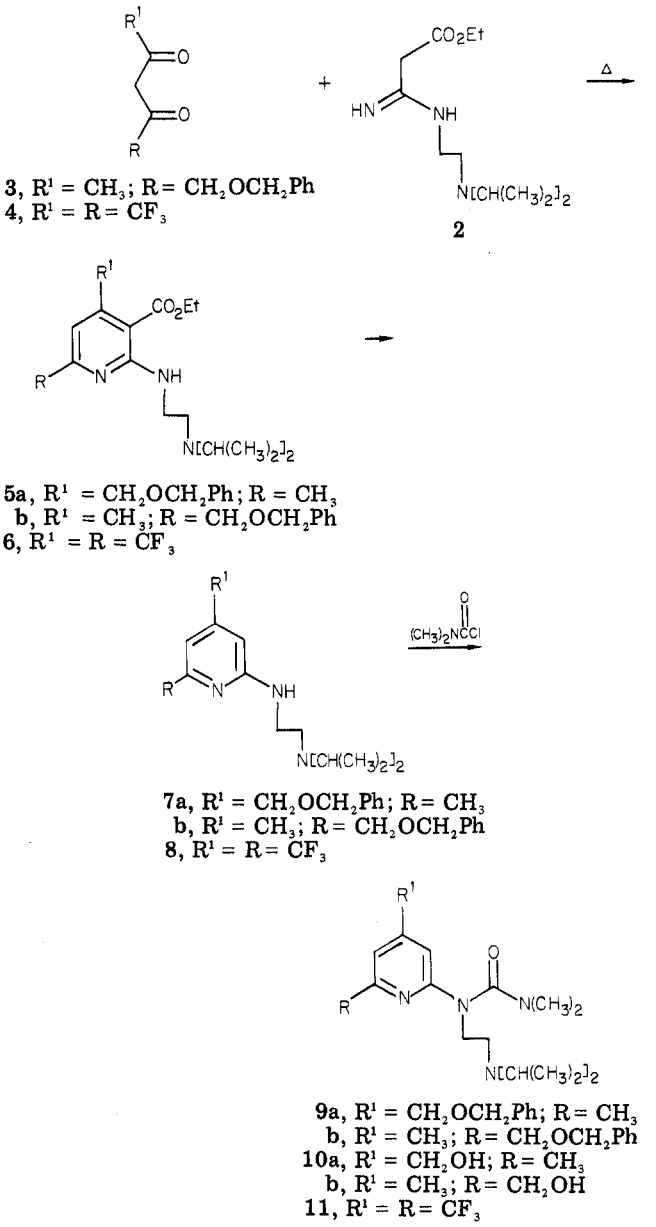
cimetidine in dogs as an inhibitor of acid secretion induced by gastrin tetrapeptide but only about one-half as potent against histamine-stimulated secretion. In addition, 1 enhanced mucus output in dogs and rats and showed a cytoprotective effect against alcohol-induced gastric necrosis in rats.[2] Metabolic studies indicated that 1 was well absorbed in dogs and excreted primarily in the urine as metabolites **10a** and **10b**, which were formed by hydroxylation of the pyridine ring methyl groups.[3]

In this report, we describe our efforts to retard the metabolism of 1 through a strategy involving the replacement of the ring methyl hydrogens with deuterium and fluorine. A useful pyridine ring synthesis was also developed to prepare authentic samples of metabolites **10a** and **10b**.

Chemistry. The required hexadeutero analogue of 1 (12) was prepared by the base catalyzed exchange of the ring methyl hydrogens for deuterium in excess dimethyl-d_6 sulfoxide. During the monitoring of the exchange reaction by NMR, it was noted that deuterium exchange was nearly completed at the 4-methyl position before any measurable exchange occurred at the 6-methyl position. This observation coincides with the reactivity profile found in animal metabolism where the observed major metabolite resulted from preferred hydroxylation at the 4-methyl position of 1.[3]

The syntheses of the hexafluoro analogue of 1 (11) and the two hydroxylated metabolites **10a** and **10b** involved pyridine ring construction via condensation of a 1,3-diketone with an appropriately substituted amidinoacetate (Scheme I). This synthesis was based on reports describing the base-catalyzed condensations of amidinoacetamide or acetate with malonaldehyde derivatives.[4,5] It was anticipated that with the use of an amidinoacetate N-substituted with a diisopropylaminoethyl group (an internal base) the desired condensation could be effected without the addition of an external base. Indeed, the condensations of diketones 3 and 4 with amidinoacetate 2 were achieved in good yields by simply refluxing the mixture in a solvent.[6] The resultant nicotinate esters were decarboxylated under either acidic (for 6) or basic (for a mixture of **5a** and **5b**) conditions to give, respectively, the bis(trifluoromethyl) intermediate 8 and a mixture of the isomeric benzyloxy derivatives **7a** and **7b**. Carbamoylation of the anion of 8 with *N,N*-dimethylcarbamoyl chloride gave the hexafluoro-substituted pyridylurea 11. A similar

Scheme I



carbamoylation of the mixture of **7a** and **7b**, followed by catalytic debenzylation, gave a mixture of metabolites **10a** and **10b**, which were readily separated by column chromatography.

Biological Results and Discussion

All compounds were compared with pyridylurea 1 for inhibition of gastric acid secretion in dogs stimulated with gastrin tetrapeptide and were administered via a gastric fistula.[1] Results for the hexadeuterio (12) and hexafluoro (11) analogues, as well as the 4-hydroxymethyl (**10a**) and 6-hydroxymethyl (**10b**) metabolites, are listed in Table I.

Pyridylurea 1 is metabolized extensively in dogs, and two urinary metabolites (**10a** and **10b**) have been isolated in 44 and 3% relative yields.[3] Both metabolites are less potent (66 and 52%) than 1 as inhibitors of gastric secretion stimulated by gastrin tetrapeptide. Since a major mode of metabolic deactivation appeared to be hydroxylation of the pyridine ring methyl groups[7] of 1, the re-

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(7) For a related example of oxidative metabolism (hydroxylation) of nalidixic acid, see McChesney, E. W.; Froelich, E. J.; Lesher, G. Y.; Crain, A. V. R.; Rosi, D. *Toxicol. Appl. Pharmacol.* **1964**, *6*, 292.

Table I. Chemical and Biological Data on Pyridylureas

compd	mp or bp (mm),[b] °C	formula[c]	inhibn of acid output in dogs:[a] peroral ED_{50}, μmol/kg (95% CL)
1	192-195[d]	$C_{18}H_{32}N_4O \cdot HCl$	15.3 (9.68, 20.61)
10a	210-212[d]	$C_{18}H_{32}N_4O_2 \cdot HCl$	23.3 (14.0, 38.8)
10b	168-170[d]	$C_{18}H_{32}N_4O_2 \cdot HCl$	29.4 (24.7, 35.4)
11	122-124 (0.2)	$C_{18}H_{26}F_6N_4O$	43.9 (25.2, 75.9)
12	190-193[d]	$C_{18}H_{26}D_6N_4O \cdot HCl$	7.26 (5.85, 8.97)
cimetidine[e]			14.3 (10.3, 19.4)

[a] Gastric secretion evoked by a maximal stimulating dose of gastrin tetrapeptide (64 μg/kg sc), three–six dose levels, 12 to 30 dogs. [b] Uncorrected. [c] Analysis for C, H, and N were within 0.4% of theoretical values. [d] Hydrochloride salt. [e] Synthesized in these laboratories.

tardation of this metabolic pathway would be expected to increase drug half-life and improve its antisecretory properties.

The utility of isotopic substitution in the elucidation of metabolic pathways and the study of kinetic isotope effects in drugs is well documented.[8,9] Indeed, such substitution has been used to increase the plasma half-life of a number of drugs.[9] Thus, the ring methyl protons of **1** were substituted with deuterium; this bis(trideuteriomethyl) analogue (**12**) was administered via gastric fistula, and the percent decrease in the concentration of gastric acid was determined. Based on the ratio of the ED_{50}'s ($p < 0.05$), the deuterated analogue **12** is ca. 2.1 times more potent than the protio form **1**. On an equimolar dose basis, the monitored drug levels in the plasma were comparable, but the half-life of the protio form **1** was slightly shorter than that of the deuterio analogue **12** (0.8 vs. 1.0 h).[10] Since metabolites **10a** and **10b** are only slightly less potent than **1** and the plasma half-lives of **1** and the deuterated analogue **12** are nearly comparable, the enhanced antisecretory potency of **12** cannot be explained adequately by retardation of ring methyl hydroxylation. The possibility that the observed isotope effect is the result of inhibition of a subsequent more rapid further oxidation of the initial hydroxy metabolites cannot be determined with the data available. Since it is not known whether metabolites equivalent to **10a** and **10b** were excreted when the deuterio analogue **12** was administered, it is possible that metabolism was diverted from the hydroxylation pathway to another pathway. Nevertheless, potency was enhanced by the selective deuteration of the ring methyl groups of **1**.

The administration of the bis(trifluoromethyl) analogue **11** to dogs had a negative effect (35% of **1**) on the inhibition of gastric acid secretion. While substitution of fluorine for hydrogen might be expected to inhibit metabolism,[11] such substitution may have altered other physicochemical properties of **11** unfavorably and contributed to the observed decreased antisecretory activity.

In summary, the gastric antisecretory activity of pyridylurea **1** was improved by selective perdeuteration of the pyridyl ring methyl groups, the sites of metabolic oxidation in dogs.

Experimental Section

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Analyses indicated by symbols of the elements were within ±0.4% of the theoretical values. Routine NMR spectra, obtained on Varian Associates spectrometers, Models T-60 and EM-390, were consistent with the structures indicated. Yields were not optimized.

Ethyl 3-Imino-3-[[2-(diisopropylamino)ethyl]amino]propionate (2). To a solution of *N,N*-diisopropyl-1,2-ethanediamine (14.4 g, 0.1 mol) in absolute ethanol (40 mL) under anhydrous conditions was added in one portion ethyl (ethoxycarbonyl)acetimidate hydrochloride[5] (20.0 g, 0.1 mol). The solution was stirred at room temperature for 12–24 h, and then the solvent was removed under vacuum. The residue was dissolved in water, the solution was made alkaline with aqueous sodium carbonate, the product was extracted into methylene chloride, the extract was dried (Na_2SO_4), and the solvent was evaporated. The product slowly crystallized in nearly quantitative yield, mp 64–67 °C. Anal. ($C_{13}H_{27}N_3O_2$) C, H, N.

Mixture of 2-[[2-(Diisopropylamino)ethyl]amino]-4-[(benzyloxy)methyl]-3-(ethoxycarbonyl)-6-methylpyridine (5a) and 2-[[2-(Diisopropylamino)ethyl]amino]-6-[(benzyloxy)methyl]-3-(ethoxycarbonyl)-4-methylpyridine (5b). A solution of 1-(benzyloxy)-2,4-pentanedione[12] (6.18 g, 30 mmol) and ethyl 3-imino-3-[[2-(diisopropylamino)ethyl]amino]propionate (7.7 g, 30 mmol) in dry benzene (60 mL) was heated at reflux for 18 h. Upon cooling, anhydrous Na_2SO_4 was added to absorb the water generated, and the mixture was filtered and evaporated to give 12.4 g (97%) of an oil, which was a mixture of isomers **5a** and **5b** (ratio ca. 1:2). This ratio was determined by the integration of the NMR signal for the pyridine ring proton (δ 6.73 and 6.53) and ring methyl resonances (δ 2.38 and 2.43) for **5a** and **5b**, respectively. This crude mixture was used without further purification.

Compound **6** was prepared similarly from **4** in 48% distilled yield, bp 128–132 °C (0.5 mm).

Mixture of 2-[[2-(Diisopropylamino)ethyl]amino]-4-[(benzyloxy)methyl]-6-methylpyridine (7a) and 2-[[2-(Diisopropylamino)ethyl]amino]-6-[(benzyloxy)methyl]-4-methylpyridine (7b). A mixture of the isomeric esters **5a** and **5b** (103.7 g, 0.235 mol) was heated at reflux for 16 h in a solution of potassium hydroxide (31.0 g, 0.47 mol) in ethanol (500mL). After cooling, the mixture was neutralized with 6 N ethanolic HCl (78 mL, 0.47 mol) and filtered, and the filtrate was evaporated to give 94 g of a mixture of the corresponding carboxylic acids.

This mixture of isomeric carboxylic acids was dissolved in 1,3-dimethoxybenzene (200 mL), and copper powder (10 g) was added. This mixture was heated at at 210–215 °C for 3 h under N_2, cooled, diluted with diethyl ether (200 mL), and filtered. The filtrate was extracted with 3 N HCl, and the acidic extract was neutralized with sodium carbonate and extracted into diethyl ether. This ether solution was filtered through a pad of charcoal, and the filtrate was dried and evaporated to give 51.2 g (61% overall yield) of a mixture of isomers **7a** and **7b** (ratio ca. 1:2) as a viscous oil. The product ratio was determined by integration of the NMR signal for the pyridine ring methyl resonances (δ 2.37 and 2.23) of **7a** and **7b**, respectively. This mixture was used without further purification.

Mixture of *N,N*-Dimethyl-*N'*-[4-[(benzyloxy)methyl]-6-methyl-2-pyridyl]-*N'*-[2-(diisopropylamino)ethyl]urea (9a) and *N,N*-Dimethyl-*N'*-[6-[(benzyloxy)methyl]-4-methyl-2-pyridyl]-*N'*-[2-(diisopropylamino)ethyl]urea (9b). A 1.42 M solution of *n*-butyllithium in hexane (20 mL, 28 mmol) was added dropwise to a solution of the mixture of isomeric pyridines **7a** and

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7b (7.9 g, 22 mmol) in dry benzene (80 mL) under N_2 while maintaining the temperature below 25 °C. After 30 min, dimethylcarbamoyl chloride (2.9 g, 27 mmol) in benzene (5 mL) was added, and the reaction mixture was stirred at ambient temperature overnight. The mixture was cooled in ice and diluted with diethyl ether (100 mL) and water (25 mL). The organic layer was separated, washed with brine, dried (Na_2SO_4), and filtered, and the filtrate was evaporated to give 9.2 g (97%) of an oil containing a mixture of isomers **9a** and **9b** (ratio ca. 1:2). The product ratio was determined by integration of the NMR signal for the pyridine ring methyl resonances (δ 2.42 and 2.26) of **9a** and **9b**, respectively. This mixture was used without further purification.

***N,N*-Dimethyl-*N'*-[4-(hydroxymethyl)-6-methyl-2-pyridyl]-*N'*-[2-(diisopropylamino)ethyl]urea (10a) and *N,N*-dimethyl-*N'*-[6-(hydroxymethyl)-4-methyl-2-pyridyl]-*N'*-[2-(diisopropylamino)ethyl]urea (10b).** A solution of the mixture of isomeric benzyl ethers **9a** and **9b** (9.1 g, 21 mmol) in glacial acetic acid (75 mL) was hydrogenated over 10% Pd/C (3.0 g) under 50 psi of hydrogen in a Parr apparatus over a period of 3 days. The catalyst was removed by filtration, and the solvent was evaporated to give a residual oil, which was dissolved in methylene chloride. This solution was washed with dilute sodium hydroxide solution and then brine, dried (Na_2SO_4), and evaporated to give 5.3 g of a mixture of the debenzylated isomers. Chromatography of this mixture on silica gel eluting with chloroform saturated with ammonia gave 2.6 g (37%) of **10b** and 1.7 g (24%) of **10a** as oils. The NMR spectra were identical with that reported for the isolated metabolites.[3] Each isomer was dissolved in ethanol, treated with an equivalent of ethanolic HCl, and the respective solutions were diluted with diethyl ether to give the crystallin hydrochloride salts of **10b**, mp 168–170 °C, and **10a**, mp 210–212 °C. Anal. ($C_{18}H_{32}N_4O_2$·HCl) C, H, N.

2-[[2-(Diisopropylamino)ethyl]amino]-4,6-bis(trifluoromethyl)pyridine (8). A solution of **6** (16.2 g, 37.7 mmol) in 50% sulfuric acid (130 mL) was refluxed for 12 h. The cooled solution was diluted with water (200 mL) and neutralized with 10 N sodium hydroxide. The resultant oil was extracted into methylene chloride, dried (Na_2SO_4), and evaporated to give 12.5 g (93%) of **8** of high purity.

***N,N*-Dimethyl-*N'*-[4,6-bis(trifluoromethyl)-2-pyridyl]-*N'*-[2-(diisopropylamino)ethyl]urea (11).** A solution of 1.34 M *n*-butyllithium in hexane (29.6 mL, 40 mmol) was added to 2,2,6,6-tetramethylpiperdine (6.55 g, 46 mmol) in dry benzene (110 mL) under N_2. At 10-min intervals, a solution of **8** (11.8 g, 33 mmol) in benzene (30 mL) was added, followed by a solution of dimethylcarbamoyl chloride (4.5 g, 42 mmol) in benzene (30 mL). After stirring overnight at ambient temperature, the reaction mixture was quenched with methanol (6 mL) and saturated Na_2CO_3 (30 mL). The organic layer was separated, and the aqueous layer was extracted with methylene chloride. The combined organic extracts were washed with brine, dried (Na_2SO_4), and filtered and the filtrate was evaporated to give 15.0 g of crude product. This material was twice distilled to give 9.8 g (69%) of **11**, bp 122–124 °C (0.2 mm). Anal. ($C_{18}H_{26}F_6N_4O$) C, H, N.

***N,N*-Dimethyl-*N'*-[4,6-bis(trideuteriomethyl)-2-pyridyl]-*N'*-[2-(diisopropylamino)ethyl]urea (12).** A solution of **1** (10.6 g, 33 mmol) in dimethyl-d_6 sulfoxide (35 mL) containing potassium *tert*-butoxide (100 mg) was heated under nitrogen at 90 °C for 21 h. The reaction mixture was diluted with methylene chloride, thoroughly washed with water, dried (Na_2SO_4), and filtered through a charcoal pad, and the solvent was evaporated. The residue was dissolved in 2-propanol, and 1 equivalent of ethanolic HCl was added. Upon dilution with diethyl ether, **12** precipitated and, after recrystallization from 2-propanol, gave 9.5 g (79%) of **12** as the hydrochloride salt, mp 190–193 °C. Anal. ($C_{18}H_{26}D_6N_4O$·HCl) C, H, N.

The progress of this exchange reaction was monitored by the disappearance of the methyl resonances (4-CH_3, δ 2.22; 6-CH_3, δ 2.37) of **1** in the NMR. The 4-CH_3 resonance disappeared appreciably before any measurable exchange at the 6-CH_3 position occurred.

Acknowledgment. The authors are indebted to Ms. J. Stranick for microanalytical determinations, Dr. D. W. Cochran and Ms. J. S. Murphy for spectroscopic data, Ms. P. G. Cook, Ms. C. A. Wesley, Ms. B. L. Westrick, and Ms. S. R. Wiese for expert technical assistance with in vivo evaluations, and Ms. M. Banker for manuscript preparation.

Registry No. **1**, 75308-65-5; **2**, 75329-62-3; **3**, 75329-65-6; **4**, 1522-22-1; **5a**, 75329-63-4; **5a** acid, 75329-66-7; **5b**, 75329-64-5; **5b** acid, 75329-67-8; **6**, 86569-00-8; **7a**, 75329-68-9; **7b**, 75329-69-0; **8**, 86569-01-9; **9a**, 75329-71-4; **9b**, 75329-70-3; **10a**, 75329-72-5; **10a**·HCl, 75329-74-7; **10b**, 75329-53-2; **10b**·HCl, 75329-73-6; **11**, 86569-02-0; **12**, 86569-03-1; **12**·HCl, 75338-52-2; *N,N*-diisopropyl-2,2-ethanediamine, 121-05-1; ethyl (ethoxycarbonyl)-acetimidate hydrochloride, 2318-25-4; dimethylcarbamoyl chloride, 79-44-7.

Synthesis and Pharmacological Activity of 6-[(*E*)-2-(2,6,6-Trimethyl-1-cyclohexen-1-yl)ethen-1-yl]- and 6-(1,2,3,4-Tetrahydro-1,1,4,4-tetramethyl-6-naphthyl)-2-naphthalenecarboxylic Acids

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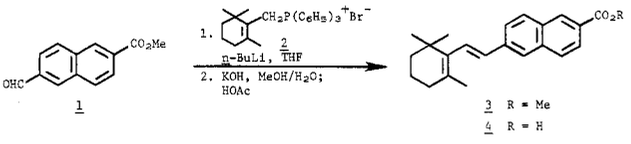
6-[(*E*)-2-(2,6,6-Trimethyl-1-cyclohexen-1-yl)ethen-1-yl]- and 6-(1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-6-naphthyl)-2-naphthalenecarboxylic acids (4 and 8) have been synthesized and show significant activity in reversing the keratinization process in hamster tracheal organ culture and in inhibiting the induction of ornithine decarboxylase in mouse skin by 12-*O*-tetradecanoylphorbol-13-acetate, two assays used to measure retinoid activity. The 2-naphthalenecarboxylic acid **8** was more active than **4**.

The potential value of retinoids as therapeutic agents for the treatment and chemoprevention of such diseases as epithelial cancer, psoriasis, and acne[1] has increased interest in retinoid chemistry and the study of retinoid structure–activity relationships and has led to the design of new retinoid analogues.[2-5] For these reasons, we report new structural modifications of the retinoid skeleton, 6-[(*E*)-2-(2,6,6-trimethyl-1-cyclohexen-1-yl)ethen-1-yl]- and

Scheme I



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0022-2623/83/1826-1653$01.50/0 © 1983 American Chemical Society