the internal salt: IR 3400–3280 ($\nu(NH_2$, PhOH)), 1650 (ν(C=O), amide I), 1615 ($\nu(COO^-)$), 1590 ($\delta(NH_3^+)$), 1520 (δ(NH), amide II), 1230, 1200, 1160, 1060, 1020, and 1005 cm^{-1} (δ(OH), ν(C—O)).

(b) 4 was also obtained from 3 or 5 under the same experimental conditions and with the same yields as above.

34,35-Didehydro-34-deoxy-(36,37-"trans",51,52-"trans")-teicoplanin Aglycon (5). (a) From TC. A solution of 6 g (0.11 mol) of freshly prepared NaOMe in 300 mL of MeOH was added at room temperature to a stirred solution of 2.8 g (2 mmol) of TC in 300 mL of DMF/DMSO (4/1).[16] After 72 h, 7 mL of glacial AcOH was added at 0–10 °C and MeOH was evaporated. The resulting suspension was filtered and the clear filtrate was poured into 1.5 L of H_2O. The resulting cloudy solution was adjusted at pH 6 with glacial AcOH and extracted with 2 L of 1-BuOH/EtOAc (3/1). The organic layer was concentrated to a small volume (~60 mL) and Et_2O (340 mL) was added. The precipitated solid was collected, washed with Et_2O, and dried in vacuo at 40 °C overnight to give 0.95 g of product, as the internal salt: IR 3250 (ν(NH, PhOH)), 1650 (ν(C=O), amide I), 1610 ($\nu(COO^-)$), 1590 ($\delta(NH_3^+)$), 1510 (δ(NH), amide II), 1230, 1200, 1135, 1060, and 1005 cm^{-1} (δ(OH), ν(C—O)).

(b) From 3. A solution of 3 (5 mg) and 10 mg of $NaHCO_3$ in 10 mL of CH_3CN/H_2O (1/1) was stirred at room temperature for 1 h to give a 9/1 mixture (HPLC) of 5 and 3. The identity of 5 was confirmed by comparison with an authentic sample.

Microbiological Activity Determination. Antibacterial activity expressed as MIC (minimal inhibitory concentration in μg/mL) was determined by the 2-fold dilution method in microtiter using Difco Todd-Hewitt broth (*Strepto. pyogenes* and *Strepto. pneumoniae*) or Oxoid Iso-Sensitest broth (staphylococci, *Strepto. faecalis*, and Gram-negative organisms). Final inoculum was ~10^4 cfu/mL. MIC was read as the lowest concentration that showed no visible growth after overnight incubation at 37 °C. Coagulase-negative staphylococci were identified by API STAPH (Profile Index, I Ed.) according to the classification of Kloos and Schleifer.[17]

(16) Or 450 mL of DMF.

Experimental infection was carried out by using groups of five mice infected intraperitoneally with *Strepto. pyogenes* C 203. Inocula were adjusted so that untreated animals died of septicemia within 48 h. Animals were treated subcutaneously once immediately after infection. On the seventh day, ED_{50} (50% effective dose) was calculated[18] on the basis of the percentage of surviving animals at each dose.

Binding Assay. The interaction of Ac_2-L-Lys-D-Ala-D-Ala with teicoplanins and the unsaturated derivatives was determined by UV differential spectroscopy.[12] Experiments were run on a Perkin-Elmer 320 double-beam UV spectrophotometer with 4-cm-pathlength nonthermostated cells. The temperature was 24 ± 2 °C. The initial volume of antibiotic solution was 10 mL at a 30 μM concentration in 10% MeOH in sodium phosphate buffer (pH 5 or 9). The difference in absorbance (ΔA) developed on addition of test peptide was monitored at the wavelength (294 nm) that showed the maximum change. Association constants (K_a) for complex formation were obtained from the slope of the straight line resulting from a Schatchard's plot, $\Delta A/(\Delta A_{max} \times C)$ vs $\Delta A/\Delta A_{max}$, of the data. Binding constants of 10^5–10^6 or greater were obtained with a standard deviation of about 10%.[19] The values of K_a determined in alkaline buffer were always about 10 times lower than those obtained at pH 5.[13]

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Synthesis of Congeners and Prodrugs. 3.[1] Water-Soluble Prodrugs of Taxol with Potent Antitumor Activity

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Taxol has shown good in vivo antitumor activity in a number of test systems. The formulation of taxol for antitumor testing has been difficult. Esterification at either C-2′ or C-7 resulted in loss of in vitro tubulin assembly activity but not cytotoxicity. These observations suggested that esters at C-2′ and/or C-7, which would tend to promote water solubility, might serve as useful prodrugs of taxol. The reaction of taxol with either succinic anhydride or glutaric anhydride in pyridine solution at room temperature gave the crystalline mono 2′-adducts **1b** and **1f**, respectively. Salts of these acids (**1b**, **1f**, **1i**) were formed by the addition of 1 equiv of the corresponding base, followed by evaporation and/or freeze-drying of the solvent(s). The salts had improved antitumor activity as compared to the free acids. The triethanolamine and *N*-methylglucamine salts showed greatly improved aqueous solubility and were more active than the sodium salts. The glutarate series was preferred because of the higher activity and the higher yields obtained. 2′-Glutaryltaxol (**1f**) was coupled with 3-(dimethylamino)-1-propylamine, using CDI, to form in excellent yield the amino amide **1o**. The hydrochloride salt (**1p**) showed good solubility and was extremely potent and active. At 10 mg/kg, in the B16 screen, **1p** gave a T/C of 352 with 5 out of 10 cures. In the MX-1 breast xenograft assay, this prodrug gave values of −100 at doses of 40 and 20 mg/kg, with all live animals being tumor free.

The natural product taxol (**1a**) was first isolated in 1971 from the Western Yew, *Taxus brevifolia* Nut. (Taxaceae) by Wani, Wall, and co-workers[2] who established its structure by chemical and X-ray crystallographic methods. A summary of pertinent taxol literature has been published.[3] Numerous studies have indicated that taxol and various taxane derivatives are highly cytotoxic and possess strong in vivo antitumor activity in a number of test systems.[2-10] The mechanism of action of taxol has been

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Table I. ^{1}H NMR Data for Various Taxol Derivatives in Deuteriochloroform[a]

protons on:	1b	1f	1i	1k
C-2	5.68 (d, 7)	5.72 (d, 7)	5.67 (d, 7)	5.68 (d, 7)
C-3	3.80 (d, 6.9)	3.81 (d, 6.9)	3.91 (d, 7)	3.81 (d, 7)
C-5	4.97 (d, 7.4)	4.99 (d, 7.4)	4.97 (d, 9.5)	4.97 (d, 7.7)
C-7	4.44 (dd, 7, 12)	4.40 (dd, 7, 11)	5.64 (m)	4.43 (m)
C-10	6.29 (s)	6.32 (s)	6.21 (s)	6.29 (s)
C-13	6.24 (t, 9)	6.22 (t, 9.6)	6.18 (t, 9)	6.24 (t, 10)
C-16,17	1.22, 1.13 (s)	1.22, 1.15 (s)	1.19, 1.15 (s)	1.22, 1.14 (s)
C-18	1.91 (s)	1.95 (s)	1.95 (s)	1.92 (s)
C-19	1.67 (s)	1.69 (s)	1.79 (s)	1.68 (s)
C-20	4.33 (d, 8.4)	4.32 (d, 8.4)	4.32 (d, 8.3)	4.20 (d, 8.3)
C-20	4.20 (d, 8.4)	4.25 (d, 8.4)	4.18 (d, 8.3)	4.32 (d, 8.3)
C-2′	5.53 (d, 3.4)	5.47 (d, 3.1)	5.58 (d, 3.7)	5.52 (3.8)
C-3′	5.98 (dd, 3.4, 9)	5.98 (m)	5.95 (dd, 3.6, 9)	5.92 (m)
N-H	7.05 (d, 9)	7.12 (d, 9)	7.08 (d, 9.2)	6.93 (d, 8.9)
OAc	2.44	2.44	2.38	2.44
	2.21	2.22	2.13	2.23
R_1 or R_2	2.61 (t, 7)	2.3–2.6 (m)	2.5–2.8 (m)	1.42 (s, t-Bu)
	2.69 (t, 7)			4.04 (d, 5.3)

protons on:	1l	1m	1n	1o	2a
C-2	5.88 (d, 7)	5.68 (d, 7)	5.68 (d, 7)	5.68 (d, 7.1)	5.66 (d, 7)
C-3	3.82 (d, 7.6)	3.80 (d, 7)	3.82 (d, 7.6)	3.80 (d, 6.8)	3.79 (d, 7)
C-5	4.97 (d, 8.6)	4.97 (d, 7.5)	4.97 (d, 9)	4.98 (dd, 2, 9.6)	4.90 (d, 7.5)
C-7	4.44 (m)	4.43 (dd, 6, 10)	4.41 (m)	4.44 (m)	4.41 (dd, 6.6, 10.8)
C-10	6.28 (s)	6.29 (s)	6.28 (s)	6.30 (s)	6.28 (s)
C-13	6.26 (br t)	6.24 (t, 8)	6.28 (br t)	6.22 (t, 7.2)	6.35 (br t)
C-16,17	1.23, 1.12 (s)	1.23, 1.14 (s)	1.23, 1.13 (s)	1.26, 1.14 (s)	1.29, 1.15 (s)
C-18	1.82 (s)	1.91 (s)	1.91 (s)	1.94 (s)	1.93 (d, 1)
C-19	1.68 (s)	1.68 (s)	1.67 (s)	1.68 (s)	1.66 (s)
C-20	4.32 (d, 8.3)	4.32 (d, 8.4)	4.32 (8.3)	4.31 (d, 8.6)	4.27 (d, 8.3)
C-20	4.21 (d, 8.3)	4.20 (d, 8.4)	4.21 (8.3)	4.20 (d, 8.6)	4.13 (d, 8.3)
C-2′	5.44 (br d)	5.53 (d, 3.1)	5.46 (d, 3)	5.45 (d, 3.9)	4.96 (d, 5.9)
C-3′	6.02 (d, 9)	6.02 (d, 9)	6.03 (dd, 3,9)	5.96 (dd, 4, 8.8)	5.75 (d, 5.9)
N-H	6.95 (d, 9)	6.93 (d, 9)	7.06 (d, 9)	7.03 (br d)	
OAc	2.50	2.44	2.48	2.45	2.25
	2.22	2.23	2.21	2.23	1.98
R_1 or R_2	1.37 (s, t-Bu)	5.07 (s)	4.80 (m)	2.17 (s, N-Me)	
	4.85 (m)	4.09 (t, 5.5)	3.03 (m)		
	3.02 (m)	5.23 (br t)	2.90 (m)		
	2.83 (m)				

[a] Multiplicities are indicated in parentheses with coupling constants in hertz.

extensively studied and is well summarized in an excellent review by Horwitz and Manfred.[11] In brief summary, taxol is a unique antimitotic agent that acts by promoting tubulin assembly into stable aggregated structures, which resist depolymerization by dilution, calcium ion, cold, and a number of microtubule-disrupting drugs. The formulation of taxol for antitumor testing has been difficult due to its extremely low aqueous solubility and lack of functional groups that would allow salt formation. Phase II clinical trials, that are currently under way, utilize a formulation of polyethoxylated castor oil and absolute ethanol as solvents, which is diluted with 5% dextrose in water or saline before use.[12]

Due to synthetic difficulty, structure–activity studies have been limited but, as shown in the recent work of Kingston et al.,[13] this area is showing renewed interest. An ester group at C-13 appears to be critical for strong cytotoxicity[2,6,9] and in vitro tubulin assembly activity in mammalian but not amoebal tubulin.[9] Esterification at either C-2′ or C-7 resulted in loss of in vitro tubulin assembly activity but not cytotoxicity.[6,9] Deacylation at C-10 does not result in any loss of biological activity;[5] however, oxidation of the C-10 hydroxyl group to a ketone drastically lowers cytotoxicity.[10] The configuration of the C-7 hydroxyl group does not seem to be a factor in determining cytotoxicity.[10,14] These observations suggested that esters at C-2′ and/or C-7, which would tend to promote water solubility, might serve as useful prodrugs of taxol. Our studies to test this hypothesis are summarized in this report.

Chemistry. The ^{1}H NMR data for the compounds prepared in this study are summarized in Table I. The reaction of taxol with either succinic anhydride or glutaric anhydride in pyridine solution at room temperature gave the crystalline mono 2′-adducts **1b** and **1f**, respectively. The contaminating diesters (about 5% or less) were easily removed by crystallization. This site selectivity is in agreement with published results, which indicated much higher reactivity of the 2′-hydroxyl as compared to the

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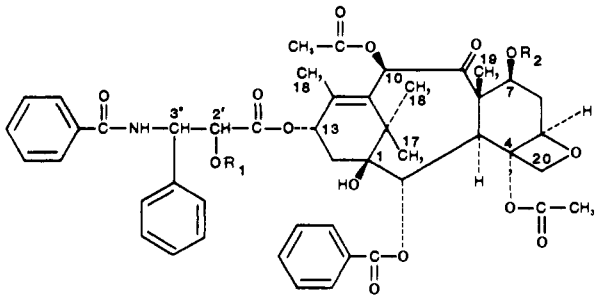
7-hydroxyl group for acylation reactions. Formation of 2′,7-bis(succinate) **1i**, in high yield, required the use of DMAP as a catalyst and higher temperature. Salts of all of these acids (**1b**, **1f**, **1i**) were formed by the addition of 1 equiv of the corresponding base, followed by evaporation and/or freeze-drying of the solvent(s) (compounds **1c–e,g,h,j**).

In order to prepare esters containing basic groups, the coupling of protected amino acids with taxol was investigated. When mixtures of taxol and either t-BOC-glycine or t-BOC-L-phenylalanine were treated with tosyl chloride in pyridine[15] solution, coupled products were obtained in good yield. With the use of preparative centrifugal TLC, the corresponding t-BOC esters, **1k** and **1l**, were isolated. These esters were deprotected under several conditions, such as 3 M HCl in ethyl acetate or 25% TFA in methylene chloride. In all cases, the t-BOC group was removed, but very complex mixtures resulted and no pure product could be isolated.



1a: $R_1 = R_2 = H$

$R_1 = CO(CH_2)_2CO_2X$; $R_2 = H$
1b: X = H **1c**: X = Na **1d**: X = $(HOCH_2CH_2)_3NH$
1e: X = *N*-methylglucammonium

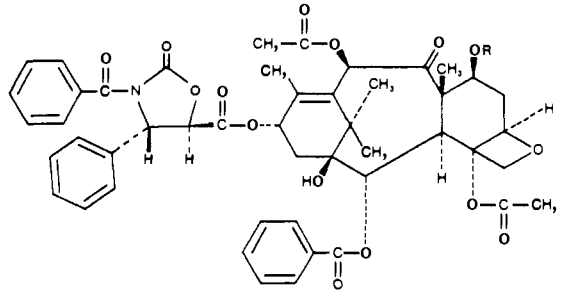
$R_1 = CO(CH_2)_3CO_2X$; $R_2 = H$
1f: X = H **1g**: X = Na **1h**: X = $(HOCH_2CH_2)_3NH$

$R_1 = R_2 = CO(CH_2)_2CO_2X$
1i: X = H **1j**: X = Na

$R_1 = COCHX(NH\text{-}tBOC)$; $R_2 = H$
1k: X = H **1l**: X = CH_2Ph

$R_1 = COCHX(NH\text{-}CBZ)$; $R_2 = H$
1m: X = H **1n**: X = CH_2Ph

1o: $R_1 = CO(CH_2)_3CONH(CH_2)_3N(CH_3)_2$; $R_2 = H$
1p: $R_1 = CO(CH_2)_3CONH(CH_2)_3N(CH_3)_2 \cdot HCl$; $R_2 = H$



2a: R = H
2b: R = $COOCH_2CCl_3$

Mixing taxol and the CBZ derivatives of either glycine or L-phenylalanine and carbonyldiimidazole (CDI), in DMF soultion, yielded corresponding derivatives **1m** and **1n** in moderate yield, as well as the same byproduct from each reaction mixture. This crystalline byproduct, given the trivial name "uretaxol" (**2a**), had MW = 879 (taxol + 26) as determined by FAB^+ mass spectral analysis and formed a monoacetate. ^1H NMR analysis of **2a** showed that the 2′-hydroxyl group had reacted in some manner other than to form a normal ester, the 7-hydroxyl was unchanged, and the amide N–H absorption was no longer present, but no other major changes had apparently occurred. Uretaxol has been assigned the cyclic acyl urethane structure **2a**, similar to a compound (**2b**) recently synthesized by Kingston et al.[13] Reactions of CDI with amino alcohols to form cyclic urethanes are known.[16] After isolation by TLC, the esters **1m** and **1n** were deprotected under standard conditions (H_2–Pd/C). The resulting deprotected esters were accompanied by taxol (10–25%). Attempts to isolate the pure esters by centrifugal TLC failed, leading to products with greater amounts of taxol. Because of these stability problems, the syntheses of other amino acid esters were attempted. Tosyl chloride mediated coupling of dimethylglycine and taxol was tried. Again, preparative TLC failed to lead to a pure material, as the product reverted to taxol. Mixtures of betaine chloride acid chloride [$(CH_3)_3N^+CH_2COCl \cdot Cl^-$] and taxol in pyridine solution showed no apparent reaction and yielded only unreacted taxol.

Another approach to the preparation of esters with basic group was explored by studying the coupling reaction of acid **1f** with 3-(dimethylamino)-1-propylamine in the presence of CDI with acetonitrile as a solvent. The amino amide **1o** was isolated in good yield by crystallization from a mixture of methylene chloride and ethyl acetate. The hydrochloride salt (**1p**) was prepared by the addition of 1 equiv of hydrochloric acid, followed by freeze-drying of the aqueous solution.

Results and Discussion

The in vivo screening results for most of the compounds synthesized in this study are shown in Table II. One of our first goals was the synthesis of compounds with improved aqueous solubility, since taxol is essentially insoluble in water. Although the mono and bis(succinates) **1b** and **1i** are not water soluble, their sodium salts **1c** and **1j** are soluble to the extent of about 0.1% and 0.3%, respectively. In each case, the sodium salt has somewhat improved antitumor activity as compared to the free acid. It is interesting to note that the 2′,7-biscompound **1i** and its salt **1j** are, in each case, considerably less active than the corresponding 2′-mono derivative **1b** and its salt **1c**. On the basis of this information, all further synthetic efforts were directed toward 2′-monoderivatives, which would be screened only as the more soluble salts.

Since salts prepared with different counterions often have substantially different properties, compounds **1d** and **1e** were made from monosuccinate **1b** with triethanolamine and *N*-methylglucamine, respectively. Both of these salts have greatly improved aqueous solubility, forming "normal" solutions up to about 1% concentration. Above this level, although still soluble, the solutions were not clear and became very viscous, resembling concentrated soap solutions. Compounds **1d** and **1e** were both more active than **1c**, with the triethanolamine salt **1d** being especially active and potent. Another conveniently prepared acid prodrug of taxol was the 2′-monoglutarate (**1f**). Both the sodium salt **1g** and the triethanolamine salt **1h** are very active and potent and in general seem to have improved properties as compared to the corresponding succinates **1c** and **1d**. The glutarate series is also preferred because of the higher yield obtained in the synthesis of **1f**.

All attempts to prepare basic prodrugs of taxol with amino acid esters failed. Apparently these compounds are quite unstable and readily revert to taxol. A byproduct

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Table II. Antitumor Activity of Taxol Derivatives[a]

compd no.	dose per inj,[b] mg/kg, ip (μmol/kg)	survivors day 4[c]	wt diff, g (T − C)[c]	% T/C[c] (cures)	compd no.	dose per inj,[b] mg/kg, ip (μmol/kg)	survivors day 4[c]	wt diff, g (T − C)[c]	% T/C[c] (cures)
				A. B16 Melanoma System					
1a	40 (46.8)	10/10	−1.2	toxic	**1g**	49 (46.9)	7/7	0.8	339
	20 (23.4)	10/10	0	96		24.5 (23.5)	7/7	1.5	225
	10 (11.)	10/10	0	139		12.25 (11.7)	8/8	0.6	192
	5 (5.9)	10/10	−0.2	175		6.13 (5.9)	8/8	0.4	159
1b	40 (41.2)	10/10	0	185 (2)	**1h**	53 (46.7)	8/8	0.4	300 (1)
	20 (20.6)	10/10	0	154		26.5 (23.3)	8/8	0.4	239 (2)
	10 (10.3)	10/10	0.4	159 (1)		13.25 (11.7)	8/8	0.4	291
	5 (5.1)	10/10	0.4	154		6.63 (5.8)	8/8	0.4	207
	2.5 (2.6)	10/10	0	119	**1i**	44 (41.8)	10/10	0	114
1c	40 (41.0)	10/10	0.6	218 (2)		22 (20.9)	10/10	0.3	105
	20 (20.5)	10/10	−0.2	201		11 (10.5)	10/10	0.1	124
	10 (10.3)	10/10	0.6	183		5.5 (5.2)	10/10	−0.3	113
	5 (5.1)	10/10	0	166		2.75 (2.6)	10/10	−0.3	109
	2.5 (2.6)	10/10	0.4	159 (1)	**1j**	44 (40.1)	10/10	0	166
1c	40 (41.0)	10/10	−1.3	177		22 (20.1)	10/10	0	109
	20 (20.5)	10/10	−0.4	160		11 (10.0)	10/10	−0.1	149
	10 (10.3)	10/10	0.4	160 (1)		5.5 (5.0)	10/10	0.6	114
	5 (5.1)	10/10	−0.1	131		2.75 (2.5)	10/10	0.6	120
	2.5 (2.6)	10/10	0	125	**1p**	20 (17.5)	10/10	0	352 (6)
	1.25 (1.3)	10/10	0.1	111		10 (8.8)	10/10	−0.1	352 (5)
1d	54 (46.9)	10/10	−0.4	toxic		5 (4.4)	10/10	0.1	188
	27 (23.5)	10/10	−0.8	314 (3)		2.5 (2.2)	10/10	−0.1	129
	13.5 (11.7)	10/10	0.6	264 (1)		1.2 (1.1)	10/10	−0.1	123
	6.75 (5.9)	10/10	0	230 (1)	**2a**	20 (22.7)	10/10	−0.2	98
1e	50 (41.8)	10/10	−0.6	241		10 (11.4)	10/10	−0.1	100
	25 (20.5)	10/10	0.3	176		5 (5.7)	10/10	0	95
	12.5 (10.2)	10/10	0.3	134		2.5 (2.8)	10/10	−0.3	88
	6.25 (5.1)	10/10	−0.2	125		1.25 (1.4)	10/10	−0.2	94
				B. MX-1 Mammary Xenograft System					
1p	40 (35.0)	5/6	−5.9	−100 (5)		5 (4.4)	6/6	0.1	1
	20 (17.5)	5/6	0.3	−100 (5)		2.5 (2.2)	6/6	−0.6	22
	10 (8.8)	6/6	−2.2	1					

[a] Screening was carried out under the auspices of the National Cancer Institute. For detailed explanations of procedures and data, see Instruction 14, Screening Data Summary Interpretation and Outline of Current Screen, Drug Evaluation Branch, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, Bethesda MD 20892. [b] Q01Dx09. Single dose for 9 days, given in milligrams per kilogram body weight per injection. [c] Abbreviations: survivors day 4, live animals on the fourth day of testing/total animals; wt diff, g (T − C), the difference in body weight in grams between test and control animals; cures, number of live animals on the last day of testing (B16 system), or number of tumor-free animals (MX-1 system). T/C for B16 melanoma is the median lifetime of test animals divided by the median lifetime of control animals, times 100. The general protocol for the B16 melanoma system is that 10^6 cell are inoculated ip on day zero of the experiment, and ip treatments are begun on day one. Early deaths, indicative of drug toxicity are evaluated on day four. A T/C value greater than 100 indicates increased survival relative to tumored, untreated controls. T/C for the MX-1 mammary xenograft is 100 times (change in treated tumor wt/change in control tumor wt) if the tumor grows or 100 times (change in treated tumor wt/initial tumor wt) if the tumor regresses. A positive number less than 100 for T/C indicates inhibition of tumor growth. A negative number indicates not only complete inhibition of tumor growth, but actual regression of the implanted tumor or fragment. The protocol used for the MX-1 tumor is that a tumor fragment of known size is surgically implanted underneath the renal capsule of athymic mice. Drug treatment is performed daily on days one through nine of the experiment and tumors are surgically removed and measured on day 11.

from a coupling reaction using CDI was shown to be the unusual acyl urethane **2a** (uretaxol), which was inactive in the B16 screen. On the basis of the work of Kingston et al.,[13] the urethane group appears to be quite stable, at least to acid hydrolysis, and would not be expected to be a useful prodrug. Another attempt to make a basic prodrug was based on a concept of taking an existing acidic prodrug and coupling it with a dibasic amine to give an amino amide. Thus, 2′-glutaryltaxol (**1f**) was coupled with 3-(dimethylamino)-1-propylamine, using CDI, to form in excellent yield (88% from taxol) the amino amide **1o**. In addition to showing good solubility as the hydrochloride salt (**1p**, up to about 1%), the compound was extremely potent and active. At 10 mg/kg, in the B16 screen, **1p** had a T/C of 352 with 5 out of 10 cures. In the MX-1 breast xenograft assay, this prodrug gave the remarkable values of −100 (complete tumor disappearance) at doses of 40 and 20 mg/kg, with all live animals being tumor free. Further development of this drug is in progress.

Experimental Section

Melting points were taken with a Kofler hot stage microscope and are corrected. NMR spectra were determined with either a Bruker WM-300 or Varian XL-400 spectrometer and are summarized in Table I. Chemical shifts are in ppm relative to TMS (0.00). Mass spectra were recorded on a Varian-Mat 112S or a VG ZAB spectrometer. Preparative centrifugal TLC was done on a Harrison Research Model 7924T (Chromatotron) with plates prepared in our laboratory. All microanalyses were done by Atlantic Microlabs Inc., Atlanta, GA. All solvents and chemicals were used as received. The taxol used in this study was obtained from the National Cancer Institute.

2′-Succinyltaxol (1b). After 3 h at room temperature, a solution of 0.50 g (0.59 mmol) of taxol and 0.90 g (7.6 mmol) of succinic anhydride in 12 mL of pyridine was evaporated to dryness in vacuo. The residue was treated with 20 mL of water, stirred for 20 min, and filtered. The precipitate was dissolved in acetone, water was slowly added, and the fine crystals were collected. This yielded 0.49 g (86%) of **1b**, which showed: mp 178–80 °C; $[\alpha]_D$ −42.1° (*c* 1.1 EtOH). Anal. ($C_{51}H_{55}NO_{17}\cdot H_2O$) C, H, N.

2′,7-Disuccinyltaxol (1i). A solution of 0.30 g (0.35 mmol) of taxol, 0.50 g (4.2 mmol) of succinic anhydride, and 10 mg of DMAP in 4 mL of DMF was heated at 85 °C for 20 h (single spot by TLC with silica, chloroform/acetone, 9:1). With the use of the same procedure as for **1b** above, the crude product was isolated and chromatographed on 5 g of silica with toluene/10–50% acetone. This gave 0.30 g (68%) of crystalline material: mp 180–1 °C; $[\alpha]_D$ −30.1° (*c* 1.05, EtOH). Anal. ($C_{55}H_{59}NO_{20}$) C, H, N.

2'-Glutaryltaxol (1f). With the use of a similar procedure as for **1b**, 0.40 g of taxol gave 0.48 g (94%) of pure **1f** after recrystallization from chloroform/benzene: mp 156–8 °C. Anal. ($C_{52}H_{57}NO_{17}$) C, H, N.

Preparations of Salts 1c–e,g,h,j. General Procedure. The corresponding acids were dissolved in small volumes of MeOH, and these were added to aqueous solutions of equivalent amounts of either sodium bicarbonate, triethanolamine, or *N*-methylglucamine. After evaporation, the gummy solids were dissolved in water and freeze-dried: Anal. **1d** ($C_{57}H_{70}N_2O_{20}\cdot 3H_2O$) C, H, N. Anal. **1e** ($C_{58}H_{72}N_2O_{22}\cdot 4H_2O$) C, H, N. Anal. **1g** ($C_{52}H_{56}NO_{17}Na\cdot 3H_2O$) C, H, N. Anal. **1h** ($C_{58}H_{72}N_2O_{20}\cdot H_2O$) C, H, N.

Amino Amide Derivative 1o and Salt 1p. To a well-stirred solution of 4.00 g (4.13 mmol) of **1f** in 40 mL of acetonitrile was added 0.88 g (5.43 mmol) of CDI, and the mixture was heated to 45 °C for 5 min. After the mixture was cooled to room temperature, a solution of 0.47 g (4.61 mmol) of 3-(dimethylamino)-1-propylamine in 3 mL of acetonitrile was added over a period of 20 min. After 30 min, the solvent was evaporated, and the residue was treated with 150 mL of water and 40 mL chloroform. The organic layer was washed five times with 150 mL of water, dried with K_2CO_3, and evaporated. Recrystallization from methylene chloride/ethyl acetate gave 3.6 g (83%) of **1o**. An additional 0.50 g (11%) of **1o** could be recovered by the preparation of an oxalate salt and conversion back to the free base: mp 135–7 °C; MS-FAB$^+$, m/z 1052.4 ($M^+ + 1$, 100), calcd 1052.5. Anal. ($C_{57}H_{69}N_3O_{16}\cdot H_2O$) C, H, N.

The hydrochloride salt **1p** was prepared by slow addition of 0.50 g of **1o**, dissolved in about 1 mL of warm EtOH, to 1 equiv of HCl in 50 mL of water followed by freeze-drying: ^{1}H NMR ($CDCl_3$) δ 2.76 and 2.85 (d, J = 4.9, $HN^+(CH_3)_2$). Anal. ($C_{57}H_{70}ClN_3O_{16}\cdot 3H_2O$) C, H, Cl, N.

2'-t-BOC-glycyltaxol (1k). Tosyl chloride, 0.27 g (1.4 mmol), was added to a solution of 0.12 g (0.72 mmol) of t-BOC-glycine in 5 mL of pyridine, and the mixture was stirred for 5 min in an ice bath. Then, 0.15 g (0.18 mmol) of taxol was added, and stirring was continued for about 1.5 h, until the bath had reached room temperature. The solution was poured into 60 mL of cold water, and the solid was collected and washed with water. After drying, the product was purified by preparative TLC (alumina, chloroform/acetone, 1:1, with 2% methanol). This yielded 136 mg (75%) of an amorphous white power.

2'-t-BOC-L-phenylalanyltaxol (1l). In a similar manner to that described for **1k**, 498 mg (1.88 mmol) of t-BOC-L-phenylalanine, 714 mg (3.76 mmol) of tosyl chloride, and 400 mg (0.469 mmol) of taxol yielded 760 mg of crude material. A 150-mg portion was purified with the use of centrifugal TLC with methylene chloride/0–3% methanol. This gave 65 mg (64%) of pure **1l**.

Deprotection of 1k and 1l. Method 1. With rapid stirring, 5 mL of freshly prepared 3 M HCl in ethyl acetate was added to 100 mg of **1k** or **1l**. After 5 min at room temperature, the solvent was removed in vacuo to give a white foam that was treated with water. The aqueous solution was filtered, and the filtrate was evaporated to yield 60–70 mg of white foam. Analysis of this material by ^{1}H NMR and HPLC (reverse phase) indicated a complex mixture, containing no t-BOC groups and no taxol.

Method 2. With good stirring, 3 mL of 20% TFA in methylene chloride was added to 0.20 g of **1k** or **1l**. After 30 min at room stirring the solvent was removed in vacuo to give a white foam that was treated with water. Filtration gave a white solid. Analysis of this material by ^{1}H NMR and HPLC (reverse phase) indicated a complex mixture, containing no t-BOC groups and no taxol.

Method 3. To a solution of 10 mg of **1k** in 0.5 mL of chloroform was added 0.05 μL of TMS iodide. After 10 min at room temperature the solvent was removed in vacuo to give a white foam that was treated with water. The resulting solid was analyzed by ^{1}H NMR and HPLC (reverse phase), which indicated a complex mixture.

2'-CBZ-glycyltaxol (1m). A solution of 660 mg (0.774 mmol) of taxol, 195 mg (0.933 mmol) of CBZ-glycine, and 175 mg (1.08 mmol) of CDI in 7 mL of DMF was heated for 19 h at 90 °C. The solvent was evaporated in vacuo; the residue was triturated with water, dissolved in 10 mL of chloroform, and extracted repeatedly with water. After drying and evaporation, the residue was subjected to centrifugal TLC with silica and 2% methanol in methylene chloride. The following were isolated: uretaxol (**2a**), 147 mg; compound **1m**, 384 mg (43.7%); taxol, 43 mg.

2'-CBZ-L-phenylalanyltaxol (1n). With the use of a similar procedure as for **1m**, 100 mg (0.12 mmol) of taxol, 50 mg (0.17 mmol) of CBZ-L-phenylalanine, and 30 mg (0.19 mmol) of CDI yielded: uretaxol, 8 mg; compound **1n**, 90 mg (68%).

Uretaxol (2a). From the reactions used to produce **1m** and **1n**, the less polar byproduct uretaxol (**2a**) was isolated by centrifugal preparative TLC (see above) and showed: mp 230–1 °C; MS-FAB$^+$, m/z 880.4 ($M^+ + 1$, 17), 119 (100), calcd for ($C_{48}H_{50}NO_{15}$) 880.3.

Mixtures of **2a**, acetic anhydride, and pyridine yielded after standard workup a product with one extra acetyl group (^{1}H NMR analysis).

Deprotection of 1m or 1n. A solution of 25 mg of ester **1m** or **1n** in 10 mL of ethyl acetate was hydrogenated for 2 h at atmospheric pressure in the presence of 25 mg of 5% Pd/C. Filtration and evaporation gave 23 mg of a solid. Analysis by TLC and ^{1}H NMR showed a mixture of taxol and 2'-mono ester. This later component decomposed within 1–12 h.

Reaction of Taxol with Betaine Chloride Acid Chloride. A mixture of 75 mg (0.44 mmol) of betaine chloride acid chloride,[17] 50 mg of taxol (0.060 mmol), and 3 mg of DMAP in 2.5 mL of pyridine was stirred at room temperature for 2 h. The solvent was evaporated, and the residue was treated with water. The isolated solid material (45 mg) was shown to be taxol by TLC analysis. The aqueous solution did not contain any taxol-related compounds (^{1}H NMR analysis).

Reaction of Taxol with Dimethylglycine. By use of a procedure similar to that described above for **1k**, 13 mg (0.13 mmol) of dimethylglycine, 36 mg (0.19 mmol) of tosyl chloride, and 20 mg (0.023 mmol) of taxol yielded 16.5 mg of crude product. The ^{1}H NMR spectrum of this material was consistant with the formation of an ester derivative. Attempts to purify this material by preparative TLC (silica, chloroform/acetone, 3:1) led to decomposition; the isolated material appeared to be taxol by TLC and ^{1}H NMR analyses.

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Registry No. **1a**, 33069-62-4; **1b**, 117527-50-1; **1c**, 117605-12-6; **1d**, 117604-55-4; **1e**, 117604-56-5; **1f**, 117527-51-2; **1g**, 117605-13-7; **1h**, 117604-57-6; **1i**, 117527-52-3; **1j**, 117605-14-8; **1k**, 117527-53-4; **1l**, 117527-54-5; **1m**, 117527-55-6; **1n**, 117527-56-7; **1o**, 117527-57-8; **1o**·oxalate, 117605-11-5; **1p**, 117604-58-7; 1 (R_1 = $COCH_2NH_2$, R_2 = H), 117527-59-0; 1 (R_1 = $COCH_2N(CH_3)_2$, R_2 = H), 117527-60-3; 1 (R_1 = L-(OCH(CH_2Ph)NH_2, R_2 = H), 117527-61-4; **2a**, 115441-21-9; **2** (R = $COCH_3$), 117527-58-9; $(CH_3)_3N^+CH_2COCl$ Cl^-, 53684-57-4.

(17) Vassel, B.; Skelly, W. G. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 154.

(18) **Note Added in Proof.** After this paper was submitted for publication, a related paper appeared (Magri, N. F.; Kingston, D. G. I. *J. Nat. Prod.* 1988, *51*, 298) in which the authors also reported the synthesis of compounds **1b** and **2a**. The ^{1}H NMR data reported for these compounds is in general agreement with our results except for one of the C-7 proton coupling constants in compound **2a** (compound **13** of Kingston paper), where we observed a value of J = 6.6 Hz as compared to a reported value of J = 4 Hz. Kingston reported a value of J = 7 Hz for a closely related compound (compound **12** of Kingston paper).