inflammation, and gastiric ulceration (gastrointestinal syndrome).[34,35] Still larger doses produce, in addition to symptoms of hematopoeitic and gastrointestinal syndromes, damage to the central nervous system leading to tremors and convulsions prior to death (CNS syndrome).[34,35] Copper (complexes) have been shown to be required for immunocompetence.[36,37] Many copper complexes, including $Cu^{II}(3,5\text{-dips})_2$, have been shown to have antiinflammatory activity and promote wound healing.[18] They also have antimicrobial activity,[19] antiulcer activity,[18] and anticonvulsant activity.[38,39] These effects are especially desirable in protecting against the hematopoeitic, gastrointestinal, and central nervous system syndromes induced by progressively increasing doses of ionizing radiation.

Conclusion

Since copper is an essential metalloelement, and as such required by all living cells, and appears to have a physiologic role in homeostasis, it may be possible to synthesize effective and nontoxic copper complexes for use in radioprotection. In toto, their pharmacologic effects are especially desirable in radioprotectants required for the protection of normal tissues in cancer patients undergoing radiotherapy and for those individuals who may be at risk with regard to hazardous effects of exposure to higher doses of ionizing radiation.

Experimental Section

Copper 3,5-diisopropylsalicylate was synthesized according to a published procedure.[12] One group of 22 control and two groups of 24 treated 8–10-week-old female B6CBF1 mice (Cumberland View Farms, Clinton, TN) were used. Control animals were given a subcutaneous (sc) injection of 0.3 mL of vehicle (0.25% Tween 80 in 0.9% pyrogen-free sterile saline) 24 h before irradiation. One treatment group was given a single sc injection of 0.49 mM/kg of $Cu^{II}(3,5\text{-dips})_2$ in 0.3 mL of vehicle 3 h before irradiation and the other group was given the same treatment 24 h before irradiation.

Control and treated mice were placed in Plexiglas cages and irradiated bilaterally with a ^{60}Co source at a rate of 0.4 ± 0.004 Gy/min for 25 min to deliver a projected LD 100/30 dose of 10 ± 0.1 Gy. This radiation dose was measured with an electrometer connected to 0.05-mL NBS-calibrated ion chambers positioned inside wax phantom mice placed in Plexiglas cages. The tissue to air ratio for these phantom mice has been determined to be 97%. These mice were then housed five mice/cage and fed mouse chow and water ad libitum for the 30-day observation period.

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Registry No. $Cu(II)(3,5\text{-dips})_2$, 72841-56-6.

(36) Prohaska, J. R.; Lukasewycz, O. A. *Science* **1981**, *213*, 559.
(37) Kishore, V.; Latman, N.; Roberts, D. W.; Barnett, J. B.; Sorenson, J. R. J. *Agents Actions* **1984**, *14*, 274.
(38) Sorenson, J. R. J.; Rauls, D. O.; Ramakrishna, K.; Stull, R. E.; Voldeng, A. N. In "Trace Substances in Environmental Health–XIII"; Hemphill, D. D., Ed.; University of Missouri Press: Columbia, MO, 1979; p 360.
(39) Sorenson, J. P. J.; Stull, R. E.; Ramakrishna, K.; Riddell, E.; Rolniak, T. M.; Ring, D. S.; Johnson, B. L.; Stewart, D. L. In "Trace Substances in Environmental Health–XIV"; Hemphill, D. D., Ed.; University of Missouri Press: Columbia, MO, 1980; p 252.

Synthesis and Antitumor Activity of Tropolone Derivatives. 1

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Treatment of tropolones with benzaldehyde diethyl acetals gave monotropolone (**12**) and bistropolone (**13**) derivatives at the benzylic position, whereas the related 1-ethoxyisochroman and the diethyl acetals of crotonaldehyde and cinnamaldehyde gave only the monotropolone derivatives (**5**, **10**, or 11). The monotropolone derivatives (**5**, **10**, 11, and **12**) had poor potency against P388 leukemia in mice, but the bistropolone derivatives (**13** and 14) showed significant potency and prolongation of life.

We were interested in the molecular modification of tropolones for the search of new antitumor agents, especially focused on 4-isopropyltropolone (hinokitiol, β-thujaplicin) (**2**), which naturally occurs in the plants of *Chamaecyparis* species.[1]

We found that the reaction of tropolone (**1**) or hinokitiol (**2**) with 1-ethoxyisochroman, considered to be the intramolecular diethyl acetal of benzaldehyde, gives 3-(isochroman-1-yl)- or 3-(isochroman-1-yl)-6-isopropyl tropolone (4 and **5**, respectively).[2] This finding prompted us to study the reactivity of tropolones with acetals.[2] It was found that hinokitiol (**2**) on treatment with benzaldehyde diethyl acetals gives 3-(α-ethoxybenzyl)-6-isopropyltropolones (**12**) and α,α-bis(2-hydroxy-6-isopropyltropon-3-yl)toluenes (**13**). In addition, hinokitiol (**2**) was found to inhibit the growth of KB cells at low concentration (in vitro system) but to be inactive in the survival test of P388 mice (in vivo system)[3] On the other hand, **5** and **13a** were found to be active both in the in vitro and in vivo systems.[3]

These results led us to test for the antitumor activity of hinokitiol derivatives previously prepared[2] and to expand the program to the preparation of compounds related to **5** and **13a**. This paper describes the syntheses of new

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(1) T. Nozoe, *Bull. Chem. Soc. Jpn*, **11**, 295 (1936).
(2) M. Yamato, K. Hashigaki, N. Kokubu, and Y. Nakato, *J. Chem. Soc., Perkin Trans. 1*, 1301 (1984).
(3) The antitumor activities of **2**–**7**, **12a**, and **13a** were communicated: M. Yamato, T. Ishikawa, S. Ishikawa, and K. Hashigaki, *Chem. Pharm. Bull.*, **31**, 2952 (1983).

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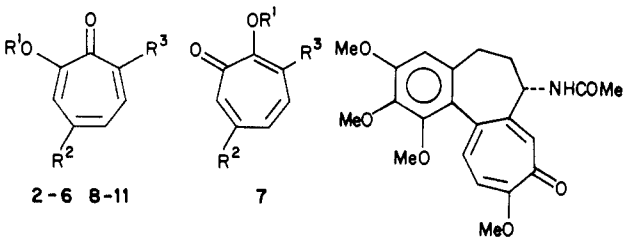
Table I. Antitumor Activities of Tropolone Derivatives 2–11



compd	R^1	R^2	R^3	ref or[a] scheme	inhibtn of KB cells growth ID_{50} μg/mL	inhibtn of KB cells growth ID_{50} nM/mL	antitumor act P388 in mice, ip[b] doses, mg/kg	antitumor act P388 in mice, ip[b] T/C, %
2	H	$CHMe_2$	H	1	0.5	3.6	400	0
							200	62
							100	100
							50	103
3	Me	$CHMe_2$	H	5	49.5	278	200	0
							100	108
							50	106
4	H	H	isochroman[c]	2	0.5	1.6	400	0
							200	96
							100	104
5	H	$CHMe_2$	isochroman	2	0.5	1.7	400	108
							200	126
							100	127
							50	128
6	Me	$CHMe_2$	isochroman	2	29.0	93	400	98
							200	94
							100	92
7	Me	$CHMe_2$	isochroman	2	18.0	58	400	98
							200	88
							100	93
8	H	$CHMe_2$	CH_2Ph	2	0.5	2.0	400	88
							200	97
							100	94
9	H	$CHMe_2$	$CHPh_2$	2	1.4	4.2	400	132
							200	123
							100	119
10	H	$CHMe_2$	CH(OEt)CH=CHMe	I	1.2	4.5	400	115
							200	116
							100	101
11	H	$CHMe_2$	CH(OEt)CH=CHPh	I	NT[d]	NT	400	0
							200	100
							100	112
colchicine					2.2	5,6	1	166
							0.5	160
							0.3	142

[a] The Arabic numerals show reference and the Roman numerals show scheme. [b] The dose listed was given once a day for 1 and 5 days. [c] isochroman = isochroman-1-yl. [d] NT = not tested.

Table II. Antitumor Activity of Monotropolone Derivatives 12

compd	position	R	ref[a]	inhibtn of KB cells growth ID_{50} μg/mL	inhibtn of KB cells growth ID_{50} nM/mL	antitumor act P388 in mice, ip[b] doses, mg/kg	antitumor act P388 in mice, ip[b] T/C, %
12a		H	2	0.3	1.0	400	0
						200	109
						100	102
12b	para	Me	2	6.2	9.9	400	125
						200	105
						100	105
12c	para	OMe	2	0.5	1.5	400	140
						200	128
						100	140
12d	para	NMe_2	2	0.6	1.7	400	0
						200	128
						100	136
12e	para	Cl	2	0.3	0.9	400	0
						200	109
						100	99

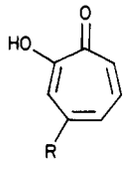
[a] The Arabic numeral shows reference. [b] The dose listed was given once a day for 1 and 5 days.

Table III. Antitumor Activity of Binary Tropolone Derivatives 13 and 14

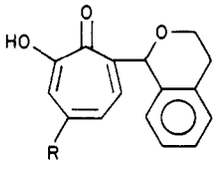
compd	position	R	ref or[a] scheme	inhibtn of KB cells growth ID_{50} μg/mL	inhibtn of KB cells growth ID_{50} nM/mL	antitumor act P388 in mice, ip[b] doses, mg/kg	antitumor act P388 in mice, ip[b] T/C, %
13a		H	2	0.3	0.7	5	188
						2.5	150
						1.3	132
13b	para	Me	2	1.5	3.4	10	163
						5	147
						2.5	125
13c	para	OMe	2	0.5	1.1	5	173
						2.5	134
						0.6	127
13d	para	NMe_2	2	0.7	1.5	10	177
						5	173
						2.5	141
13e	para	Cl	2	2.0	4.4	10	144
						5	141
						2.5	124
13f	ortho	Me	II	NT[c]	NT	20	158
						5	156
						2.5	137
13g	ortho	OMe	II	NT	NT	20	0
						10	162
						5	151
13h	meta	OMe	II	1.1	2.4	10	134
						5	134
						2.5	142
13i	meta para	OMe	II	0.3	0.6	10	158
						5	156
						2.5	137
14			III	0.3	0.6	10	147
						5	156
						2.5	137

[a] See Table I. [b] See Table I. [c] NT = not tested.

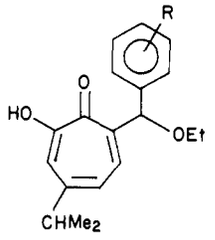
tropolone derivatives, as well as antitumor activity of modified hinokitiol derivatives.



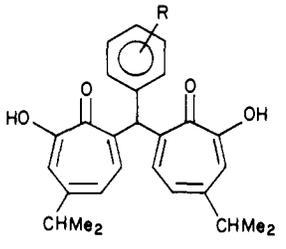
1; R = H
2; R = $CHMe_2$



4; R = H
5; R = $CHMe_2$



12a; R = H



13a; R = H

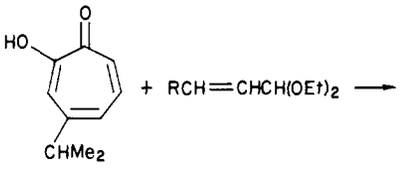
Chemistry. Tables I–III summarize the structures and biological results that were evaluated in this study. We previously reported the syntheses of compounds **4–9**, **12a–e**, and **13a–e**.[2] The syntheses of the remaining compounds are depicted in Schemes I–III.

We[2] found that hinokitiol (**2**) on treatment with benzaldehyde diethyl acetals at 150–160 °C gives monotropolone (**12**) and binary tropolone (**13**) derivatives, but that similar reactions at 180 °C afford only the binary tropolone derivative (**13**).

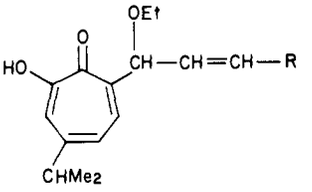
When hinokitiol (**2**) was heated with crotonaldehyde diethyl acetal at 150–160 °C, only monotropolone derivative **10** was formed in 55% yield. When the reaction temperature rose to 180 °C, a binary tropolone derivative was not obtained (Scheme I). Similarly, heating of hinokitiol (**2**) with cinnamaldehyde diethyl acetal at 180 °C afforded only monotropolone derivative **11** in 38% yield.

Compounds **13f–i** were prepared by heating of hinokitiol (**2**) with benzaldehyde diethyl acetals at 180 °C, as pre-

Scheme I

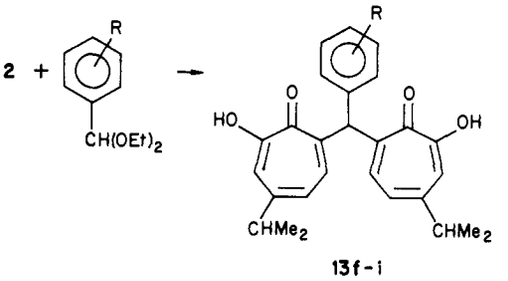


2



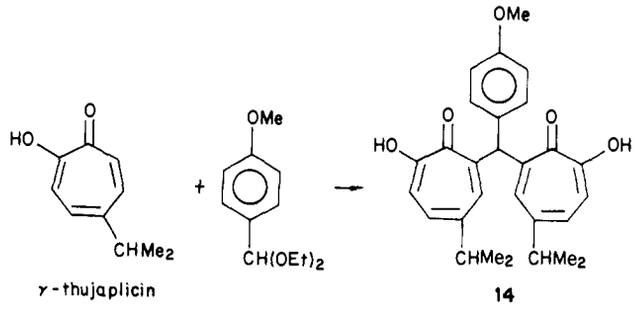
10; R = Me
11; R = Ph

Scheme II



13f–i

Scheme III



viously reported[2] (Scheme II). However, 2-chloro- or 3,4-dichlorobenzaldehyde diethyl acetal gave only monotropolone derivative **12**.

Compound **14** was prepared from γ-thujaplicin[4] and *p*-anisaldehyde diethyl acetal by the similar reaction for **13**.

Biological Results and Discussion

Compounds were tested for antitumor activity in the following in vitro and in vivo systems. In vitro system: the compound was tested for the inhibitory activity of growth of KB cells derived from a human epidermoid carcinoma of the mouth. The IC_{50} (μg/mL) was defined as the concentration of the test compound required to reduce the growth rate to 50% of the control. In vivo system: antitumor effect of the compound was tested against P388 leukemia in mice. The percent of T/C is defined as the medium survival time (MST) of all mice in a drug-treated (T) group divided by MST of the tumor control (C) group × 100.

All tropolone analogues except the methoxytropone analogues (**3**[5], **6**, and **7**) were active in the in vitro system. Needless to say, these methoxytropone analogues were inactive in the in vivo system. These results implied that the hydroxyl group of the tropolone ring is essential for both the antitumor activities in vitro and in vivo. Compound **4**, in which the tropolone moiety was lacking a isopropyl group, was active in the in vitro system but inactive in the in vivo system.

Although the IC_{50} value of hinokitiol (**2**) in the in vitro system was equivalent to that of **5**, it was inactive in the in vivo system. This suggested that the isochromanyl group probably plays a role as a lipophilic moiety in the antitumor action in vivo. For this reason, compounds in which the isochromanyl group in **5** was replaced by an another lipophilic group were prepared. Thus, the benzhydryl analogue **9** has potency comparable to that of **5**, while the benzyl **8** and the ethoxy analogues **10**, **11**, and **12a** were inactive in the in vivo system. however, introduction of substituent at the 4-position of the benzene ring in **12a** caused a variation in potency in the in vivo system. For example, analogues **12b–d** with an electron-releasing group such as methyl, methoxyl, or dimethylamino group were active, but chloro analogue **12e** was inactive.

Interestingly, the activity of the binary tropolone compound **13a** having two hinokitiol moieties in a molecule was about 200 times that of the monotropolone analogue **12a**, almost comparable to that of colchicine, in the in vivo system. The effect of substitution on **13a** was examined next. Substitution of a methoxy or dimethylamino group tends to enhance activity, regardless of the position on the benzene ring. On the other hand, the chloro analogue **13e** was somewhat weaker. Consequently, the 3,4-dimethoxy analogue **13i** was prepared. It showed no improvement of the respective monomethoxy analogues.

The binary γ-thujaplicin analogue **14** has potency comparable to that of **13c**, implying that the substituent position of isopropyl group on the tropolone ring caused no significant variation on the activity.

Colchicine, which is an alkaloid having a tropolone ring, has been known to have potent antitumor activity and to be toxic. In the search for more active and less toxic analogues of colchicine, structure–activity relationships have been studied.[6-8] However, these hinokitiol derivatives do not satisfy the structural requirements for the antitumor activity of colchicine.[6-8] In addition, their structures could not be related to those of any other known antitumor agents.

The most important finding of the present study was the development of the binary tropolone analogues **13** and **14**, which have potent antitumor activity in vivo. Synthesis of other binary type of compounds and study on their mechanism of antitumor action are in progress.

Experimental Section

Melting points were determined on a Yanagimoto micromelting apparatus and are uncorrected. NMR spectra were run on a Hitachi R-24 spectrometer at 60 MHz, with Me_4Si as an internal standard. Mass spectra were recorded on a Shimadzu LKB-9000 spectrometer. The elemental analyses were within 0.4% of the theoretical values. Column chromatographic separations were performed by flash technique on 200–300-mesh silic gel (Wako C-300).

3-Isopropyl-6-(1-ethoxy-2-butenyl)tropolone (10). A mixture of crotonaldehyde diethyl acetal (8 g, 52 mmol) and hinokitiol (4 g, 24 mmol) was heated at 160 °C for 5 h under an argon atmosphere. The reaction mixture was chromatographed on silica gel with petroleum ether–AcOEt (15:1) to give **10** (3.5 g, 55% based on hinokitiol) as a viscous oil: NMR ($CDCl_3$) δ 1.27 (d, 6 H, $CHMe_2$, J = 7 Hz), 1.05–1.55 (m, 3 H, CH=CH*Me*), 1.29 (t, 3 H, OCH_2CH_3, J = 7 Hz), 2.63–3.17 (m, 1 H, $CHMe_2$), 3.82 (q, 2 H, OCH_2CH_3, J = 7 Hz), 4.12–4.52 (m, 1 H, CH=C*H*Me), 5.12 (dd, 1 H, C*H*=CHMe, J = 8, 12 Hz), 6.52 (d, 1 H, C*H*OEt, J = 12 Hz), 6.58–7.90 (m, 3 H, tropolone H), 8.80–9.50 (br s, 1 H, OH D_2O exchangeable); MS, m/e 262 (M^+). Anal. ($C_{16}H_{22}O_3$) C, H.

3-Isopropyl-6-(1-ethoxy-3-phenylpropenyl)tropolone (11). A mixture of cinnamaldehyde diethyl acetal (10 g, 48 mmol) and hinokitiol (4 g, 24 mmol) was heated at 180 °C for 6 h under an argon atmosphere. The reaction mixture was chromatographed on silica gel with petroleum ether–AcOEt (15:1) to give **11** (3 g, 38% based on hinokitiol) as a viscous oil: NMR ($CDCl_3$) δ 1.25 (d, 6 H, $CHMe_2$, J = 7 Hz), 1.27 (t, 3 H, OCH_2CH_3, J = 7 Hz), 2.56–3.16 (m, 1 H, C*H*Me_2), 3.80 (q, 2H, OCH_2CH_3, J = 7 Hz), 5.08–5.58 (m, 2 H, C*H*=CHPh and C*H*OEt), 6.46 (d, 1 H, CH=C*H*Ph), 6.83–7.76 (m, 8 H, tropolone H and aromatic H), 9.18–9.78 (br s, 1 H, OH D_2O exchangeable); MS, m/e 324 (M^+). Anal. ($C_{21}H_{24}O_3$) C, H.

α,α-Bis(7-hydroxy-5-isopropyltropon-2-yl)-2-methyltoluene (13f). A mixture of *o*-tolualdehyde diethyl acetal (2.4 g, 12 mmol) and hinokitiol (4 g, 24 mmol) was heated at 180 °C for 2 h under an argon atmosphere. The reaction mixture as chromatographed on silica gel with petroleum ether–AcOEt (10:1) to give **13f** (1.2 g, 22% based on hinokitiol): mp 188–189 °C (from MeOH–CH_2Cl_2); NMR ($CDCl_3$) δ 1.30 (d, 12 H, $CHMe_2$ × 2, J = 7 Hz), 2.30 (s, 3 H, CH_3), 2.50–3.20 (m, 2 H, C*H*Me_2 × 2), 6.82 (s, 1 H, CH), 6.90–7.70 (m, 10 H, tropolone H and aromatic H), 8.50–9.50 (br s, 1 H, OH D_2O exchangeable); MS, m/e 430 (M^+). Anal. ($C_{28}H_{30}O_4$) C, H.

(4) H. Erdtman and J. Gripenberg, *Nature (London)*, **161**, 719 (1948).
(5) T. Nozoe and S. Katsura, *Yakugaku Zasshi*, 64, 181 (1944).
(6) M. Rösner, H-G. Capraro, A. E. Jacobson, L. Atwell, A. Brossi, M. A. Iorio, T. H. Williams, R. H. Sik, and C. F. Chignell, *J. Med. Chem.*, **24**, 257 (1981).
(7) F. R. Quinn and J. A. Beisler, *J. Med. Chem.*, **24**, 251 (1981).
(8) A. Brossi, P. N. Sharma, L. Atwell, A. E. Jacobson, M. A. Iorio, M. Molinari, and C. F. Chignell, *J. Med. Chem.*, **26**, 1365 (1983).

α,α-Bis(2-hydroxy-6-isopropyltropon-3-yl)toluenes (**13g–i**) were prepared in the same manner.

α,α-Bis(7-hydroxy-5-isopropyltropon-2-yl)-2-methoxytoluene (13g): mp 148–151 °C (from MeOH–CH_2Cl_2); yield 8%; NMR ($CDCl_3$) δ 3.76 (s, 3 H, OCH_3); MS, *m/e* 446 (M^+). Anal. ($C_{28}H_{30}O_5$) C, H.

α,α-Bis(7-hydroxy-5-isopropyltropon-2-yl)-3-methoxytoluene (13h): mp 192–194 °C (from MeOH–CH_2Cl_2); yield 27%; NMR ($CDCl_3$) δ 3.76 (s, 3 H, OCH_3); MS, *m/e* 446 (M^+). Anal. ($C_{28}H_{30}O_5$) C, H.

α,α-Bis(7-hydroxy-5-isopropyltropon-2-yl)-3,4-dimethoxytoluene (13i): mp 177–178 °C (from MeOH–CH_2Cl_2); yield 36%; NMR ($CDCl_3$) δ 3.80 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3); MS, *m/e* 476 (M^+). Anal. ($C_{29}H_{32}O_6$) C, H.

α,α-Bis(7-hydroxy-4-isopropyltropon-2-yl)-4-methoxytoluene (14). A mixture of *p*-anisaldehyde diethyl acetal (3.5 g, 17 mmol) and 5-isopropyltropolone (γ-thujaplicin)[4] (4.9 g, 30 mmol) was heated at 180 °C for 2 h under an argon atmosphere. The reaction mixture was column chromatographed on silica gel with petroleum ether–AcOEt (10:1) to give 14 (0.7 g, 13% based on γ-thujaplicin): mp 186–188 °C (from MeOH–CH_2Cl_2); NMR ($CDCl_3$) δ 1.25 (d, 12 H, $CHMe_2 \times 2$, J = 7 Hz), 2.58–3.18 (m, 2 H, $CHMe_2 \times 2$), 3.76 (s, 3 H, OCH_3), 6.65 (s, 1 H, CH), 6.68–7.58 (m, 10 H, tropolone H and aromatic H); MS, *m/e* 446 (M^+). Anal. ($C_{28}H_{30}O_5$) C, H.

Culture of KB Cells and Determination of ED_{50} of the Drugs. A clonal KB cell line, established by Dr. M. Green, St. Louis University, and kindly supplied by Dr. K. Fujinaga, Sapporo Medical College, was grown in Eagle's minimal essential medium containing 10% calf serum (Grand Island Biological).[9] Cells were grown in plastic dishes (Lux Scientific) at 37 °C in 5% CO_2–95% air. The cells grew exponentially for at least 72 h under these cell densities, and the doubling time of the KB cell populations was about 20 h.

The cytotoxic activity of the drugs on cultured KB cells was measured by determining the IC_{50}.[9] KB cells were seeded in plastic dishes (diameter, 60 min; Lux Scientific) at a density of 2100 cells/cm^2 growth surface. At 24 h after inoculation, the medium was changed and the cells were treated with graded concentration (0.3–100 μg/mL) of the drugs. Two dishes were used for each drug concentration. The cells were cultivated for 48 h in the presence of drugs. The medium was removed and the cell layer was washed with phosphate buffered saline (PBS) and trypsinized with an aliquot of 0.25% trypsin–EDTA (Grand Island Biological). PBS containing 2% fetal calf serum was added to neutralize the trypsin. The cells were suspended by pipeting and enumerated with a Coulter counter. The IC_{50} of each drug was obtained by plotting the logarithm of the drug concentration vs. the growth rate (percentage of control) of the treated cells.

Antitumor Assays in Vivo. Groups of six CDF_1 mice were inoculated ip with 10^6 P388 leukemia cells. Drug treatment was (ip) initiated 24 h after inoculation of leukemia cells. Compounds tested were dissolved in dimethyl sulfoxide.

Acknowledgment. We express appreciation to the late Professor Ryuzo Hirohata and Kanto Ishi Seiyaku Co., Ltd., for supplying hinokitiol and γ-thujaplcin.

Registry No. **2**, 499-44-5; **10**, 92397-04-1; **11**, 92397-05-2; **13f**, 92397-06-3; **13g**, 92397-07-4; **13h**, 92397-08-5; **13i**, 92397-09-6; **14**, 92397-10-9; $CH_3CH{=}CHCH(OEt)_2$, 10602-34-3; $PhCH{=}CHCH(OEt)_2$, 7148-78-9; $(EtO)_2CH$-*o*-C_6H_4Me, 5469-00-1; $(EtO)_2CH$-*o*-C_6H_4OMe, 6314-98-3; $(EtO)_2CH$-*m*-C_6H_4OMe, 2403-47-6; 3,4-$(MeO)_2C_6H_3CH(OEt)_2$, 40527-43-3; $(EtO)_2CH$-*p*-C_6H_4OMe, 2403-58-9; γ-thujaplicin, 672-76-4.

(9) T. Tsuruo, H. Iida, S. Tsukagoshi, and Y. Sakurai, *Cancer Res.*, **39**, 1063 (1979).

Additions and Corrections

1983, Volume 26

Kam-Sing Cheung, Steven A. Wasserman, Edward Dudek, Stephen A. Lerner, and Michael Johnston*: Chloroalanyl and Propargylglycyl Dipeptides. Suicide Substrate Containing Antibacterials.

Page 1740. In the acknowledgment, Merrell Dow Pharmaceuticals should read Dow Chemical Co.

1984, Volume 27

J. B. Hynes,* Y. C. S. Yang, J. E. McGill, S. J. Harmon, and W. L. Washtien: Improved Synthesis and Antitumor Evaluation of 5,8-Dideazaisofolic Acid and Closely Related Analogues.

Page 233. In Table I, the following footnote should be added for IAHQ[a]: [a] The sample of IAHQ tested was derived by the route described in ref 13; the 9-CHO-IAHQ and 9-CH_3-IAHQ tested were prepared from this sample of IAHQ.

Book Review: The Peptides: Analysis, Synthesis, Biology. Volume 5. Special Methods in Peptide Synthesis, Part B.

Page 553. The correct price for Volume 5 is $79.50.

Herbert T. Nagasawa,* David J. W. Goon, William P. Muldoon, and Richard T. Zera: 2-Substituted Thiazolidine-4(*R*)-carboxylic Acids as Prodrugs of L-Cysteine. Protection of Mice against Acetaminophen Hepatotoxicity.

Page 592. In Table I, the data for compound **10** should read as follows (column heading/correction): survival/17/18, 4+/1, 3+/1, 1+/3, 0/13.

R. M. DeMarinis,* A. J. Krog, D. H. Shah, J. Lafferty, K. G. Holden, J. P. Hieble, W. D. Matthews, J. W. Regan, R. J. Lefkowitz, and M. G. Caron: Development of an Affinity Ligand for Purification of α_2-Adrenoceptors from Human Platelet Membranes.

Page 918. The correct author list should read: R. M. DeMarinis,* H. Oh, A. J. Krog, D. H. Shah, J. Lafferty, K. G. Holden, J. P. Hieble, W. D. Matthews, J. W. Regan, R. J. Lefkowitz, and M. G. Caron. In the paper as published H. Oh had been inadvertently omitted.

Charles D. Jones,* Mary G. Jevnikar, Andrew J. Pike, Mary K. Peters, Larry J. Black, Allen R. Thompson, Julie F. Falcone, and James A. Clemens: Antiestrogens. 2. Structure–Activity Studies in a Series of 3-Aroyl-2-arylbenzo[*b*]thiophene Derivatives Leading to [6-Hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone Hydrochloride (LY156758), a Remarkably Effective Estrogen Antagonist with Only Minimal Intrinsic Estrogenicity.

Page 1061. In Table III, footnote *c* should read "Every rat received 0.1 μg of estradiol/day sc in corn oil".