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-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

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- (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.

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-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 \pm 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.

Acknowledgment. I am indebted to Cmdr. Brian Gray, Armed Forces Radiobiology Research Institute, for his efforts in obtaining the radioprotectant data with Cu^{II} -(3,5-dips)₂, to Dr. B. H. J. Bielski for his constructive comments on the manuscript, and to the International Copper Research Association, the Arthur Armbrust Cancer Research Foundation, the Denver Roller Corp., the Max and Victoria Dreyfus Foundation, the Kroc Foundation, and the Arkansas Power and Light Co. for financial support.

Registry No. Cu(II)(3,5-dips)₂, 72841-56-6.

Synthesis and Antitumor Activity of Tropolone Derivatives. 1

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Faculty of Pharmaceutical Sciences, Okayama University, Tsushima-naka 1-1-1, Okyama 700, and Cancer Chemotherapy Center, Kami-Ikebukuro 1-37-1, Toshima-Ku, Tokyo 170, Japan. Received May 9, 1984

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 *Cha*maecyparis 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 $3-(\alpha-ethoxybenzyl)-6-isopropyl-$ tropolones (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)⁸ 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 prepared² and to expand the program to the preparation of compounds related to 5 and 13a. This paper describes the syntheses of new

[†]Okayama University.

[‡]Cancer Chemotherapy Center.

⁽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).



					inhibtn of KB cells		antitumor act P388 in mice, ip ^b	
aamnd	ום	D2	D3	ref or ^a	grow	$\frac{1}{10}$	doses,	T/C,
compu	<u></u> .	π- R ²		scheme	µg/mL	nM/mL	mg/kg	%
2	Н	$CHMe_2$	H	1	0.5	3.6	400	0
							200	62
							100	100
		0	**	_			50	103
3	Me	$CHMe_2$	H	5	49.5	278	200	0
							100	108
	**			_			50	106
4	н	н	isochroman ^c	2	0.5	1.6	400	0
							200	96
-		0107					100	104
5	Н	$CHMe_2$	isochroman	2	0.5	1.7	400	108
							200	126
							100	127
<u>^</u>		01114					50	128
6	Me	$CHMe_2$	isochroman	2	29.0	93	400	98
							200	94
-	14	CHIN (2	10.0		100	92
7	Ivie	CHMe ₂	isochroman	2	18.0	58	400	98
							200	88
0	TT	CILLA.		0	0 F	2.0	100	93
8	н	$CHMe_2$	CH ₂ Ph	2	0.5	2.0	400	88
							200	97
٥	ч	OUM	CHDL	9	1.4	4.0	100	94
9	п	Crivie ₂		2	1.4	4.2	400	132
							200	123
10	ч	CHMo	CH(OF+)CH-CHM	т	1.9	4.5	100	119
10	11	Crime ₂	CH(OEt)CH—CHIME	1	1.4	4.0	400	110
							200	101
11	ਸ	CHMe		т	NTT	NT	400	101
11	11	CIIIVIe ₂	On(OEt)On—On h	1	141	141	200	100
							100	119
colchicine					? ?	5.6	1	166
continente					4.4	0,0	0.5	160
							0.3	142

^aThe Arabic numerals show reference and the Roman numerals show scheme. ^bThe dose listed was given once a day for 1 and 5 days. ^c isochroman = isochroman-1-yl. ^dNT = not tested.

compd	position	R	ref°	inhibtn of KB cells growth ${ m ID}_{50}$		antitumor act P388 in mice, ip ^b	
						doses,	T/C,
				$\mu g/mL$	nM/mL	mg/kg	%
12a		Н	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
1 2d	para	NMe ₂	2	0.6	1.7	400	0
	1	-				200	128
						100	136
12e	para	Cl	2	0.3	0.9	400	0
						200	109
						100	99

Table II. Antitumor Activity of Monotropolone Derivatives 12

^aThe Arabic numeral shows reference. ^bThe dose listed was given once a day for 1 and 5 days.

				inhibtn of KB cells		antitumor act P388 in mice, ip^b	
		R	ref or ^a	${ m growth}\;{ m ID}_{50}$		doses,	T/C,
compd	position		scheme	$\mu g/mL$	nM/mL	mg/kg	%
139		Н	2	0.3	0.7	5	188
104						2.5	150
						1.3	132
13b	para	Me	2	1.5	3.4	10	163
100	P					5	147
						2.5	125
13c	para	OMe	2	0.5	1.1	5	173
100	puid	0				2.5	134
						0.6	127
13d	nara	NMe ₂	2	0.7	1.5	10	177
104	Pulu	2				5	173
						2.5	141
13e	para	Cl	2	2.0	4.4	10	144
200	Para	•••				5	141
						2.5	124
13 f	ortho	Me	II	NT^{c}	NT	20	158
201						5	156
						2.5	137
13g	ortho	OMe	II	NT	NT	20	0
8						10	162
						5	151
13h	meta	OMe	II	1.1	2.4	10	134
						5	134
						2.5	142
13i	meta	OMe	II	0.3	0.6	10	158
	para					5	156
	L					2.5	137
14			III	0.3	0.6	10	147
						5	156
						2.5	137

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

^aSee Table I. ^bSee Table I. ^cNT = not tested.

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



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.

We² 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

HO HO $CHMe_2$ 2



Scheme II

Scheme I



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-





viously reported² (Scheme II). However, 2-chloro- or 3,4-dichlorobenzaldehyde diethyl acetal gave only monotropolone derivative 12.

Compound 14 was prepared from γ -thujaplicin⁴ 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 IC₅₀ (μ g/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 \times 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 Me₄Si 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 (CDCl₃) δ 1.27 (d, 6 H, CHMe₂, J = 7 Hz), 1.05–1.55 (m, 3 H, CH=CHMe), 1.29 (t, 3 H, OCH₂CH₃, J = 7 Hz), 2.63–3.17 (m, 1 H, CHMe₂), 3.82 (q, 2 H, OCH₂CH₃, J = 7 Hz), 4.12–4.52 (m, 1 H, CH=CHMe), 5.12 (dd, 1 H, CH=CHMe, J = 8, 12 Hz), 6.52 (d, 1 H, CHOEt, J =12 Hz), 6.58–7.90 (m, 3 H, tropolone H), 8.80–9.50 (br s, 1 H, OH D₂O exchangeable); MS, m/e 262 (M⁺). Anal. (C₁₆H₂₂O₃) 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 (CDCl₃) δ 1.25 (d, 6 H, CHMe₂, J = 7 Hz), 1.27 (t, 3 H, OCH₂CH₃, J = 7 Hz), 2.56-3.16 (m, 1 H, CHMe₂), 3.80 (q, 2H, OCH₂CH₃, J = 7 Hz), 5.08-5.58 (m, 2 H, CH=CHPh and CHOEt), 6.46 (d, 1 H, CH=CHPh), 6.83-7.76 (m, 8 H, tropolone H and aromatic H), 9.18-9.78 (br s, 1 H, OH D₂O exchangeable); MS, m/e 324 (M⁺). Anal. (C₂₁H₂₄O₃) 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-CH₂Cl₂); NMR (CDCl₃) δ 1.30 (d, 12 H, CHMe₂ × 2, J = 7 Hz), 2.30 (s, 3 H, CH₃), 2.50-3.20 (m, 2 H, CHMe₂ × 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 D₂O exchangeable); MS, m/e 430 (M⁺). Anal. (C₂₈H₃₀O₄) C, H.

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⁽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).

Additions and Corrections

 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–CH₂Cl₂); yield 8%; NMR (CDCl₃) δ 3.76 (s, 3 H, OCH₃); MS, m/e 446 (M⁺). Anal. (C₂₈H₃₀O₅) C, H.

 $\alpha_{,\alpha}$ -Bis(7-hydroxy-5-isopropyltropon-2-yl)-3-methoxytoluene (13h): mp 192–194 °C (from MeOH–CH₂Cl₂); yield 27%; NMR (CDCl₃) δ 3.76 (s, 3 H, OCH₃); MS, m/e 446 (M⁺). Anal. (C₂₈H₃₀O₅) C, H.

α,α-Bis(7-hydroxy-5-isopropyltropon-2-yl)-3,4-dimethoxytoluene (13i): mp 177–178 °C (from MeOH–CH₂Cl₂); yield 36%; NMR (CDCl₃) δ 3.80 (s, 3 H, OCH₃), 3.90 (s, 3 H, OCH₃); MS, m/e 476 (M⁺). Anal. (C₂₉H₃₂O₆) 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-CH₂Cl₂); NMR (CDCl₃) δ 1.25 (d, 12 H, CHMe₂ × 2, J = 7 Hz), 2.58-3.18 (m, 2 H, CHMe₂ × 2), 3.76 (s, 3 H, OCH₃), 6.65 (s, 1 H, CH), 6.68-7.58 (m, 10 H, tropolone H and aromatic H); MS, m/e 446 (M⁺). Anal. (C₂₈H₃₀O₅) 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/cm² growth surface. At 24 h after inoculation, the medium was changed and the cells were treated with graded concentration $(0.3-100 \ \mu\text{g/mL})$ 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 10⁶ 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; CH₃CH=CHCH(OEt)₂, 10602-34-3; PhCH=CHCH(OEt)₂, 7148-78-9; (EtO)₂CH-o-C₆H₄Me, 5469-00-1; (EtO)₂CH-o-C₆H₄OMe, 6314-98-3; (EtO)₂CH-m-C₆H₄OMe, 2403-47-6; 3,4-(MeO)₂C₆H₃CH(OEt)₂, 40527-43-3; (EtO)₂CH-p-C₆H₄OMe, 2403-58-9; γ -thujaplicin, 672-76-4.

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-CH₃-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/

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 μ g of estradiol/day sc in corn oil".

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