Communications to the Editor

[Chem. Pharm. Bull. 31(8)2952—2954(1983)]

ANTITUMOR ACTIVITY OF ISOCHROMANYLTROPOLONES

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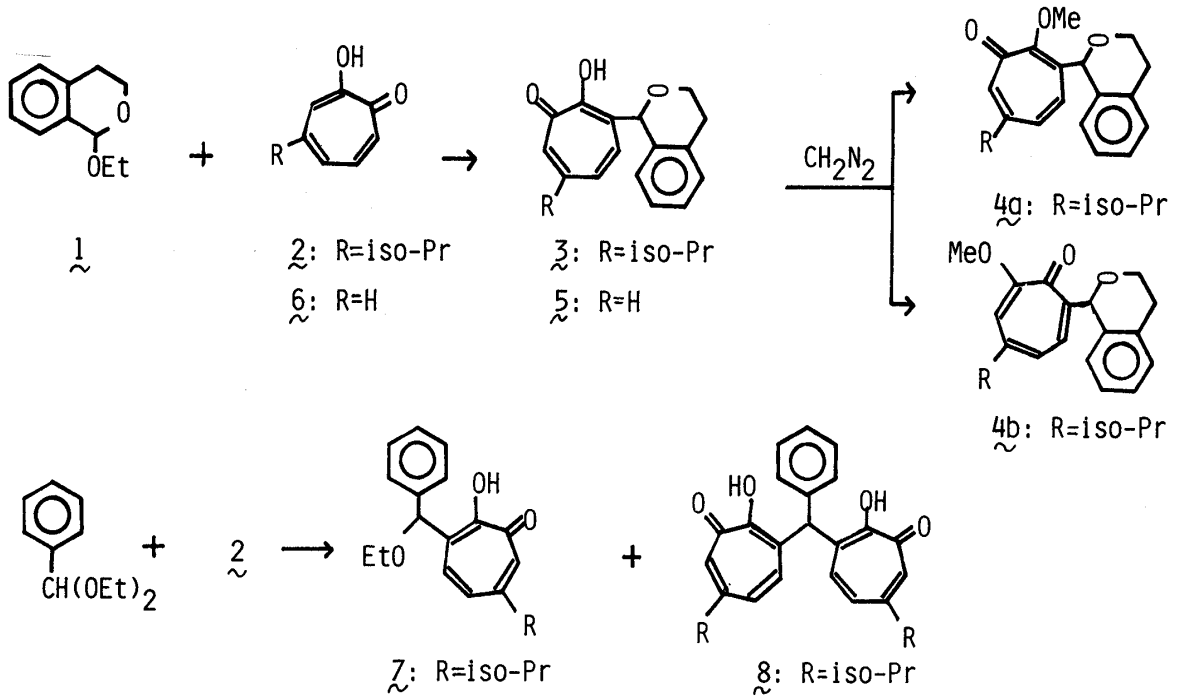
The reaction of 1-ethoxyisochroman (1) with 4-isopropyltropolone (2) (hinokitiol, β-thujaplicin) afforded 3-(1-isochromanyl)-6-isopropyltropolone (3). Compound 3 exhibited a potent inhibitory property against KB cell multiplication in vitro and antitumor activity against mouse leukemia P388 in vivo. On the other hand, 2 did not exhibit the antitumor activity in the in vivo system.

In analogy with 1, the reaction of benzaldehyde diethyl acetal with 2 afforded 3-(α-ethoxybenzyl)-6-isopropyltropolone (7) and α,α-bis(6-isopropyltropolon-3-yl)toluene (8). Compound 8 exhibited very potent antitumor activity.

KEYWORDS——— isochroman; hinokitiol; tropolone; acetal; KB cell; leukemia P388; antitumor activity

On the basis of the previous information about the reactivity of 1-ethoxyisochroman (1) with nucleophilic reagent,[1] 4-isopropyltropolone (2) (hinokitiol, β-



1 2: R=iso-Pr 3: R=iso-Pr 4a: R=iso-Pr 4b: R=iso-Pr
6: R=H 5: R=H

7: R=iso-Pr 8: R=iso-Pr

thujaplicin) which naturally occurs in some plants of Chamaecyparis species[2] was heated with 1. 3-(1-Isochromanyl)-6-isopropyltropolone (3) was obtained. Treatment of 3 with diazomethane afforded 3-(1-isochromanyl)-6-isopropyl-2-methoxytropone (4a) and 7-(1-isochromanyl)-4-isopropyl-2-methoxytropone (4b).

Similarly, 3-(1-isochromanyl)tropolone (5) was prepared by heating of 1 with tropolone (6).

These compounds (2-8) were screened for antotumor activity by tests in in vitro and in vivo systems. In the in vitro system, growth inhibition against KB cells was tested in cultures in each of two dishes per dose of drug at concentrations of 100, 30, 10, 3 and 1 μg/ml. In the in vivo system, the survival of mice bearing leukemia P388 was tested. In this test, 6 mice per group were used and a multiple dose assay was used with one injection (i.p.) per day for 9 days. Antitumor activity was evaluated in terms of ED_{50} (μg/ml) in the in vitro system and T/C (%) in the in vivo system.

Though 2 was not effective in the in vivo system, 3 gave considerable response to both antitumor activity screens (ED_{50}=0.52 μg/ml, T/C (%)=126). On the other hand, 4a and 4b were not effective even in the in vitro system. Compound 5 was not effective in the in vitro system, although it exhibited antitumor efficasy in the in vitro

Table I. Antitumor Activity of 2-8

Compd. No.	mp (°C)	Inhibition of KB cells multiplication ED_{50} (μg/ml)	in vivo Antitumor act. P388 in mice Dose (mg/Kg)	T/C (%)
2	52-53	0.58	400	0
			200	62
			100	100
			50	103
3	135-138	0.52	400	108
			200	126
			100	112
4a	130-132	18.6	400	98
			200	88
			100	93
4b	96-97	29.0	400	98
			200	94
			100	92
5	175-178	0.50	400	0
			200	96
			100	104
7	oil[a)]	<0.30	400	0
			200	109
			100	102
8	199-200	<0.30	5	188
			2.5	150
			1.25	132

a) bp 140°C (0.05 mmHg).

system (ED_{50}=0.50 μg/ml).

Compond 1, considered to be the intramolecular acetal of benzaldehyde, seemed to have characteristics like benzaldehyde diethyl acetal. Consequently, the reaction of benzaldehyde diethyl acetal with 2 was undertaken. Heating of 2 with benzaldehyde diethyl acetal fforded 3-(α-ethoxybenzyl)-6-isopropyltropolone (7) and α,α-bis(6-isochromanyltropolon-3-yl)toluene (8). Compond 7 was not effective in the in vivo system, though it was effective in the in vitro system (ED_{50}=<0.3 μg/ml). Compound 8 was found to be remarkably effective in both systems (ED_{50}=<0.3 μg/ml, T/C (%)=132 at 1.25 mg/Kg, 188 at 5 mg/Kg).

The structural requirement for the antitumor activity in this series is being studied.

ACKNOWLEDGEMENT We are gratful to Dr. Tazuko Tashiro and Dr. Takashi Tsuruo, Cancer Chemotherapy Center, Tokyo, for screening the antitumor activity.

REFERENCES AND NOTES

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(Received June 20, 1983)