Summary

A survey was made of the alkaloids contained in the leaves, bark, trunk, and root of *Magnolia liliflora* Desrouss, belonging to the Magnoliaceae, which grows in Japan. The bases identified are: as a tertiary base, colorless prisms, m.p. 260~262° (decomp.) (hydrochloride) from the leaves; as a tertiary base, colorless prisms, m.p. 254° (decomp.) (hydrochloride), and as quaternary bases salicifoline chloride and magnocurarine from the stem bark; and as a quaternary base, salicifoline chloride from the trunk and root.

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9. Takeo Ueda, Tomohiko Kawai, and Tadakazu Tsuji: Studies on Anthelmintics. I. Studies on Hydroxytetralin as an Anthelmintic.

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In the course of investigations on the anthelmintic action of santonin, it was not found to possess such a direct ascaricidal activity as shown by hexylresorcinol *in vitro*[1]. Trendelenburg[2] has suggested that its activity was due to the convulsive action produced in the ascaris by its lactone, while Shirane[3] has claimed that its activity was due to the paralysing action produced in the ascaris by the quinol substance produced from santonin itself. The latter theory has been accepted as an almost established theory in Japan.

Very recently, Kobayashi and Bando[4] explained that the activity of santonin was due to the abnormal kinetic state and the fern-like curling-motion made by the ascaris by santonin.

On the other hand, desmotroposantonin, the isomeric compound of santonin, has been found to possess a slight direct ascaricidal activity *in vitro*.

As to the main skeleton of tetralin ring, santonin possesses one hydroxyl group in the 1-position of tetralin, while desmotroposantonin possesses two hydroxyl groups in the 1,7-positions.

On the whole, the reason why desmotroposantonin has stronger direct ascaricidal properties than santonin might be due to its hydroxyl group in the 7-position.

Judging by the studies of Kobayashi, Bando, or Trendelenburg, and also by Lamson[5], who has studied the activity of the hydroxyl group of alkylbenzene, it seems necessary to investigate not only the behavior of the hydroxyl group in the 7-position of tetralin, but also of that in the 1-position.

In order to confirm this assumption, compounds related to the structure of santonin and desmotroposantonin such as the hydroxytetralin were examined for their ascaricidal activities against *Ascaris lumbricoides* by Lamson-Nakamura method[6] and their curling-motions against *Ascaris lumbricoides* by Kobayashi-Bando method[4].

This paper describes the interesting relationship between the structure and activity of several *ar*- and *al*-hydroxytetralins.

Syntheses of Hydroxytetralins Three series of hydroxytetralins were synthesized, *viz.*

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1) T. Nakamura: Sei-I-Kai Medical Journal, 523, 218 (1933).
2) Trendelenburg: Arch. exp. Pathol. Pharmacol., 79, 190 (1916).
3) A. Shirane: Tokyo Medical Journal, 53, 9, 22 (1949).
4) Y. Kobayashi, T. Bando: Japan J. Pharmacol. 1, 130 (1952).
5) Lamson: J. Pharmacol. Exptl. Therap., 53, 198 (1935).
6) E. Nakamura: Sei-I-Kai Medical Journal, 65, 1816 (1951).

compounds possessing hydroxyl group (A) on the aromatic nucleus, (B) on the aliphatic nucleus, and (C) on both the aromatic and aliphatic nuclei of tetralin.

(A) 7-Hydroxytetralin[7] (I), 5-hydroxytetralin[8] (II), and 5,7-dihydroxytetralin[9] (III) were obtained by the alkali fusion of the corresponding tetralin sulfonic acids, 6-hydroxy-5-methyltetralin (IV) by the Clemmensen reduction of 6-hydroxytetralin-5-aldehyde[10], and 6-nitro-8-hydroxytetralin (V) and 5-nitro-6-hydroxytetralin (VI) were obtained by the decomposition of the diazonium salts from the correspoding nitraminotetralins[7] with copper sulfate solution.

(B) 1-Hydroxytetralin[11] (VII) and 2-hydroxytetralin[12] (VIII) were obtained by the reduction of 1-tetralone or β-naphthol, 3-benzyl-2-hydroxytetralin[13] (IX) and 3-chloro-2-hydroxytetralin[13] (X) by the action of the Grignard reagent upon 2,3-tetralin oxide, and 2,3-tetralin glycol[13] (XI) was obtained by the decomposition of 3-chloro-2-hydroxytetralin with sodium carbonate solution.

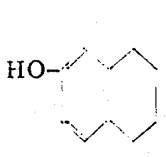
(C) 1,7-Dihydroxytetralin (XII) was obtained by the reduction of 7-hydroxy-1-tetralone[14].

The properties of these compounds are summerised in Table I.

TABLE I

No.	m. p.	Crystal Form	No.	m. p.	Crystal Form
I	53°	Colorless needles	VII	b.p_{17} 140°	Colorless oil
II	69°	Colorless needles	VIII	b.p_5 116°	Colorless oil
III	122°	Colorless needles	IX	114°	Colorless needles
IV	112°	Colorless needles	X	117°	Colorless needles
V	97°	Yellow needles	XI	44°	Colorless needles
VI	81°	Yellow needles	XII	143°	Colorless crystals

Structural Formula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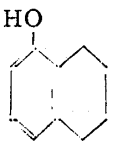
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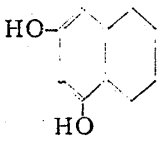
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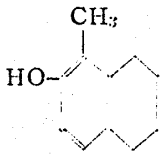
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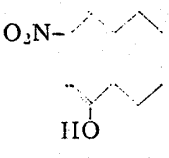
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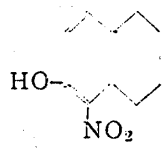
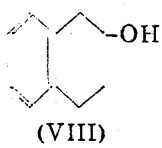
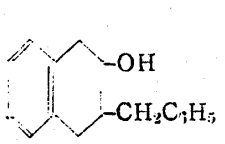

(VI)


(VII)


(VIII)

7) C. Schroeter: Ann., 426, 139 (1922).
8) C. Schroeter: *Ibid.*, 426, 151 (1922).
9) C. Schroeter: Ber., 71, 1052 (1938).
10) R. T. Arnold, H. E. Zangg: J. Am. Chem. Soc., 63, 1314 (1941).
11) C. Schroeter: D. R. P., 346,948 (1921).
12) Bamberger: Ber., 23, 205 (1890).
13) T. Kawai: Japan Pat., 170970 (1943).
14) E. Mosettig, Everette L. May: J. Org. Chem. 5, 533 (1940).



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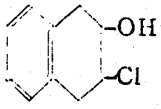
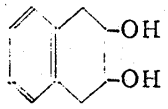
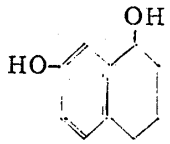


(X)



(XI)



(XII)

Anthelmintic action These hydroxytetralins were examined as to their ascaricidal effects by measuring the time required to kill *Ascaris lumbricoides* by a different length of exposures in dilution of 1:1000 Ringer-Dale's modified solution (pH 6.2) of drugs at 38° by the Lamson-Nakamura method, and examined as to their curling-motions by observing the different length of exposure in dilution of 1:5000 or 1:10000 Ringer-Locke's solution (pH 6.0±0.5) of drugs at 38° by the Kobayashi-Bando method.

The results are given in Tables II and III.

TABLE II

Ascaricidal Rate (%)

No.	Time (mins.)					
	2	5	10	20	30	60
I	0	80	100	100	100	100
II	0	0	40	60	60	100
III	0	20	40	80	80	100
IV	0	40	100	100	100	100
V	0	0	0	20	40	100
VI	0	0	0	20	40	100
VII	0	0	0	0	0	0
VIII	0	0	0	0	0	0
IX	0	0	0	0	0	0
X	0	0	0	0	0	0
XI	0	0	0	0	0	0
XII	0	0	0	0	0	30

TABLE III

Kinetic State and Curling-motion of *Ascaris lumbricoides*

No.	Dilution	State		
		Excitation (hr.)	Supression (hr.)	Curling-motion (hr.)
VII	1:5000	+ (~1)	−	+ (1~2)
	1:10000	−	−	−
VIII	1:5000	+ (~6)	−	++ (0~24)
	1:10000	−	−	−
IX	1:5000	+ (~6)	−	++ (1~24)
	1:10000	−	−	−
X	1:5000	−	± (~7)	−
	1:10000	−	−	−
XI	1:5000	± (~1)	+ (16)	−
	1:10000	−	± (16)	−
XII	1:5000	−	−	+(0.5~24)
	1:10000	−	−	± (1~24)

According to the results of anthelmintic tests, though tetralin itself did not show any anthelmintic action, it was found that *ar*-hydroxytetralins possessed considerable ascaricidal effects, but these compounds did not show any curling-motion. *al*-Hydroxytetralins did not show any ascaricidal action, but all of them showed a little curling-motion. 1,7-Dihydroxytetralin showed a little curling-motion, while it exerted a less ascaricidal action than 7-hydroxytetralin.

Discussion and Conclusion The relationship between the chemical structure and anthelmintic action of hydroxytetralin derivatives may be summarized as follows:

It may be said that the aromatic hydroxyl group on tetralin ring showed markedly ascaricidal effect, the hydroxyl group in the 7-position being one of the most active, and the introduction of a hydroxyl, nitro, and alkyl radicals to *ar*-hydroxytetralin led to decrease of the effect. The activity of 7-hydroxytetralin was almost equal to that of isoamylresorcinol. The *al*-hydroxyl groups on tetralin ring showed a little curling-motion. The introduction of chloro, alkyl, and hydroxyl groups to *al*-hydroxytetralin did not show any influence on the effect. The curling-motion by these compounds shown by a dilution of 1:5000 was equal to the activity shown by a dilution of 1:30000–1:40000 of santonin. 1,7-Dihydroxytetralin also showed a slight curling-motion and its activity shown by a dilution of 1:5000 was approximately equal to the activity shown by a dilution of 1:30000 of santonin.

By comparing these compounds with santonin and desmotroposantonin, some interesting criticisms may be raised as to the mode of action of santonin.

Our sincere thanks are due to Prof. Dr. Nakao and Dr. Nakamura of the Jikeikai Medical College for their kind help in testing of anthelmintic activities. This study was supported by a grant from the Ministry of Education, for which we wish to express our gratitudes.

Experimental

6-Hydroxy-5-methyltetralin (IV)—A mixture of 3 g. of 6-hydroxytetralin-5-aldehyde, 6 g. of amalgamated zinc, 6 cc. of toluene, 4.5 cc. of water, and 10 cc. of concentrated hydrochloric acid, was boiled under reflux for 24 hours, with the addition of 3 cc. of concentrated hydrochloric acid every 4 hours. After the solution was decanted from zinc, it was extracted with ether. The organic solvent was removed from the extracted solution. 5-Methyl-6-hydroxytetralin, b.p$_3$ 118° was recrystallized from ligroine to colorless needles, m.p. 112~113°. Yield, 1.5 g. *Anal.* Calcd. for $C_{11}H_{14}O$: C, 81.48; H, 8.64. Found: C, 81.52; H, 9.00.

6-Nitro-8-hydroxytetralin (V)—A solution containing 2 g. of 6-nitro-8-aminotetralin in 100 cc. of 10% sulfuric acid was diazotized at 0° with 1 g. sodium nitrite. The diazotized solution was added dropwise into 150 cc. of boiling 50% copper sulfate solution. Then the reaction mixture was extracted with ether, dried, and ether was removed. 6-Nitro-8-hydroxytetralin, b.p$_3$ 125–130°, was purified from ligroine to yellow needles, m.p. 96~97°. Yield, 1.5 g. *Anal.* Calcd. for $C_{10}H_{11}O_3N$: N, 7.25. Found: N, 7.00.

5-Nitro-6-hydroxyteralin (VI)—This was obtained from 5-nitro-6-aminotetralin by the same method as the synthesis of 6-nitro-8-hydroxytetralin. 5-Nitro-6-hydroxytetralin, b.p$_3$ 118–119°, was recrystallized from petroleum ether to yellow needles, m.p. 80~81°. Yield, 1.5 g. *Anal.* Calcd. for $C_{10}H_{11}O_3N$: N, 7.25. Found: N, 7.18.

1,7-Dihydroxytetralin (XII)—A solution of 3 g. of 7-hydroxy-1-tetralone in 50 cc. of sodium carbonate solution was shaken for 2 days with 70 g. of 3% amalgamated sodium. After the solution was decanted from mercury, it was filtered, acidified, and boiled with hydrochloric acid for 5 minutes. The solution was then extracted with ether, dried, and the solvent was removed. The residue was distilled *in vacuo*. 1,7-Dihydroxytetralin, b.p$_3$ 184~187°, was recrystallized from ethyl acetate to colorless sandy crystals, m.p. 142~143°. Yield, 0.6 g. *Anal.* Calcd. for $C_{10}H_{12}O_2$: C, 73.17; H, 7.32. Found: C, 73.29; H, 7.40.

p-Nitrobenzoate: Colorless prisms, m.p. 179~180°. *Anal.* Calcd. for $C_{24}H_{18}O_8N_2$: N, 6.06. Found: N, 6.04.

Summary

(1) Several hydroxytetralin derivatives, possessing hydroxyl groups on the aromatic and aliphatic nuclei of tetralin, were synthesized and tested as to their ascaricidal activities against *Ascaris lumbricoides* by Lamson-Nakamura method and as to their curling-motion against *Ascaris lumbricoides* by Kobayashi-Bando method.

(2) The aromatic hydroxyl group on tetralin ring showed a marked ascaricidal effect, but did not show any curling-motion effect.

(3) The aliphatic hydroxyl group on tetralin ring showed a little curling-motion, but did not show any ascaricidal effect.

(4) 1,7-Dihydroxytetralin showed an ascaricidal effect and also a little curling-motion.

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