killing the ascarid as rapidly as alkylresorcinols, they paralyse the ascarid after a shorter interval. This property of the diarylarsinous acids is a distinguishing characteristic of their mode of action, in contrast with those of santonin and alkylresorcinols. From this finding, it may be requisite to obtain more appropriate methods for evaluating anthelmintic properties of arsenicals. Further work on this problem will be reported in this Bulletin in the future.

Our sincere thanks are due to Prof. Dr. T. Nakao and Dr. E. Nakamura of Jikei-Kai Medical College for their kind help in testing the anthelmintic action.

Summary

(1) Three series of arsenical compounds, viz. the diarylarsinic acids, arylarsenous acids, and diarylarsinous acids were examined as to their anthelmintic activities against *Ascaris lumbricoides* by the Lamson-Nakamura method.

(2) Diarylarsinic acids did not show any anthelmintic effect.

(3) Some of the arylarsenous acids and diarylarsinous acid exerted considerable effects against the ascarid but did not produce any curling-motion effect.

(Received November 5, 1953)

6. Takeo Ueda and Tadakazu Tsuji: Studies on Anthelmintics.

II. Studies on Anthelmintic Compounds Related to Santonin.

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These studies were undertaken with the aim of establishing the relationship between the chemical constitution and the activity of santonin as well as its analogs. As described in the previous paper,¹⁾ *al*-hydroxytetralins have been found to possess weak anthelmintic activity against *Ascaris lumbricoides*.

On the basis of these results, it has been assumed that the activity of santonin might be due, at least partially, to the hydroxyl group in its 1-position. That is, the lactone-ring of santonin might contribute to the increase of anthelmintic activity as well as the hydroxyl group in the 1-position.

Though numerous studies²⁻⁵⁾ on the mode of action of santonin have been conducted, conclusions obtained from them have not always coincided with one another, and are contrary to our assumption.

This paper describes the relationship between the chemical structure and anthelmintic activity of several compounds possessing a lactone-ring.

Compounds Used to Test Anthelmintic Action 1-Hydroxytetralin-2-propionic acid lactone derivatives (I), 4-methyl coumarin derivatives (II), 2-methylchromone derivatives (III), 2-methylchromane derivatives (IV), and phenylbutyrolactone derivatives (V), as shown in the following tables, were employed to test their curling-motion

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1) T. Ueda, T. Tsuji: This Bulletin, 1, 32 (1953).

2) T. Nakamura: Sei-I-Kai Med. J., 52, 218 (1933).

3) A. Shirane: Tokyo Med. J., 53, 9, 122 (1949).

4) K. Mineshita: Folia Pharmacol. Japonica, 44, 3, 26 (1948).

5) K. Matsuda: Ibid., 44, 3, 26 (1948).

by the Kobayashi-Bando method. In addition to these compounds, tetralin peroxide-(1) (VI) and 9-substituted-6-keto- $\Delta^{7,8,5,10}$ hexahydronaphthalenes (VII) were also examined by the same method.

Anthelmintic Activity Anthelmintic activities of the compounds described above were tested by observing the kinetic state of *Ascaris lumbricoides* exposed to Ringer-Locke's solution of the chemicals in dilution of 1:5,000 or 1:10,000, adjusted to pH 6.8 at 38°, according to the Kobayashi-Bando method.

Results obtained are summarized in Tables I and II. In the tables, "Paralysis" denotes the time after which the ascarid showed no movement without outside stimulus, and "Death", the time which the ascarid showed no movement under any stimulus.

TABLE I.
Kinetic State of *Ascaris lumbricoides*

No.	Compound	Dilution	Curling-motion (hr.)	Excitation (hr.)	Paralysis (hr.)	Death (hr.)
I a	1-Hydroxytetralin-2-propionic acid lactone	1: 5,000	+ (5~7) (43~48)	+ (7~8)	+ (67)	72
I b	Desmotroposantonin	1: 5,000	+ (0.5~8)	+ (0~2)	+ (60)	78
II a	6-Hydroxy-4-methylcoumarin	1: 5,000 1: 10,000	— —	+ (0~6) + (0~6)	+ (24) + (27)	72 78
II b	7-Hydroxy-4-methylcoumarin	1: 5,000 1: 10,000	— —	+ (0~8) + (0~4)	+ (72) + (72)	95 95
II c	6,7-Dihydroxy-4-methylcoumarin	1: 5,000 1: 10,000	± (0~24) —	+ (0~2) + (0~1)	+ (72) + (84)	100 100
II d	7,8-Dihydroxy-4-methylcoumarin	1: 5,000 1: 10,000	± (0~8) ± (0~20)	+ (0~4) + (0~20)	+ (72) + (72)	78 98
II e	7-Hydroxy-4-methyl-dihydrocoumarin	1: 5,000 1: 10,000	± (0.5~1) —	+ (0~6) + (0~5)	+ (72) + (72)	78 95
II f	6,7-Dihydroxy-4-methyl-dihydrocoumarin	1: 10,000	—	—	+ (60)	78
II g	7,8-Dihydroxy-4-methyl-dihydrocoumarin	1: 5,000 1: 10,000	— —	— —	+ (15) + (27)	44 90
III a	6-Hydroxy-2-methylchromone	1: 5,000 1: 10,000	± (0~48) ± (0~44)	+ (0~6) + (0~5)	+ (64) —	96 96
III b	7,8-Dihydroxy-2-methylchromone	1: 5,000 1: 10,000	± (0~3) —	+ (0~3) + (0~6)	+ (64) —	114 126
IV a	7-Hydroxy-2-methylchromane	1: 5,000	—	+ (2~4)	+ (24)	72
IV b	7,8-Dihydroxy-2-methylchromane	1: 5,000 1: 10,000	± (16) ± (16)	— —	+ (64) + (64)	96 96

TABLE II.
Kinetic State of *Ascaris lumbricoides*

No.	Compound	Dilution (hr.)	Curling-motion (hr.)	Excitation (hr.)	Paralysis (hr.)	Death (hr.)
V a	4-Hydroxyphenyl- butyrolactone	1:5,000	± (0~45)	—	+ (20)	80
V b	4-Anisoylbutyro- lactone	1:5,000	± (0~2)	+ (2~4)	+ (9)	43
VI	Tetralin peroxide- (1)	1:5,000 1:10,000	+ (18~72)	+ (1~3) + (1~2)	+ (3~12) + (18~54)	40 78
VII a	9-Dichloromethyl- 6-keto- $\Delta^{7,8;5,10}$ -hexa- hydronaphthalene	1:5,000	+ (0.1~0.5)	—	+ (10)	20
VII b	9-Methyl-6-keto- $\Delta^{7,8;5,10}$ -hexahydro- naphthalene	1:5,000	+ (0.5~1)	—	+ (20)	25

From the results, as shown in the tables, it was observed that the compounds of (I) showed typical but weak curling-motion. Some of the compounds of (II), (III) and (IV) showed weak and untypical curling-motion. The compounds of (V) also showed weak and untypical curling-motion, and paralyzed ascarid at comparatively shorter interval. Furthermore, the compounds of (VI) and (VII) showed typical but weak curling-motion, and paralyzed ascarid at comparatively shorter interval.

Discussion and Conclusion Various criticisms may be raised on the significance of the Kobayashi-Bando method. However, this method is considered valuable for the examination of santonin and its analogs.

Observations with the above compounds, as described in the experimental part, show that the compounds of (I), (VI) and (VII), exerted a weak but typical curling-motion, which was assumed by Kobayashi and Bando⁶⁾ to be characteristic of santonin. Similar effect was also produced by *al*-hydroxytetralins. None of the compounds of (II), (III), (IV), and (V) were observed to show the typical curling-motion. From these findings, it seems that the lactone-ring on tetralin contributes slightly to the curling-motion and that the *al*-hydroxyl group may take the place of the lactone-ring to produce this effect.

It is assumed that lactone derivatives other than tetralin lactone derivatives, might exert a different type of effect from that of santonin and its analogs. According to the results, it seems that there might exist none of the drug substituted for santonin among the lactone derivatives possessing structure essentially different from santonin.

9-Substituted-6-keto- $\Delta^{7,8;5,10}$ -hexahydronaphthalene was observed to effect the curling-motion nearly equal to that of 1-hydroxytetralin. It is supposed that the dienone structure from tetralin might contribute to the curling-motion, though further study is necessary in order to verify this.

From the above, it is thought that santonin may be strengthened synergically with its lactone structure, neglecting the influence of possible stereoisomerism.

Above is only an assumption requiring further study, but it is hoped that it will be valuable to the synthesis of santonin analogs possessing anthelmintic effects.

The authors wish to express their acknowledgement to Prof. Dr. Nakao and Dr. Nakamura of Jikei-Kai Medical College.

Summary

1) A number of compounds possessing the lactone-ring were prepared and tested

6) Y. Kobayashi, T. Bando: *Folia Pharmacol. Japonica*, 44, 5, 24 (1948).

for their curling-motion against *Ascaris lumbricoides* by the Kobayashi-Bando method.

2) The compounds derived from *al*-hydroxytetralin showed a weak but typical curling-motion.

3) The compounds possessing lactone structure but not tetralin ring, showed untypical curling-motion.

4) An assumption of value to the synthesis of santonin analogs was made.

(Received November 5, 1953)

7. Itiro Yosioka: Studies on Phenazines. V.¹⁾ Synthesis of Iodinin Isomers. (2). Synthesis of 1,7-Dihydroxyphenazine Di-N-oxide.

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In the previous papers of this series^{1,2)}, the synthesis of iodinin and two of its isomers, 1,8- and 2,7-dihydroxyphenazine di-N-oxides have been reported. In the present paper, the synthesis of another isomer of iodinin, 1,7-dihydroxyphenazine di-N-oxide is reported.

The synthesis of dihydroxyphenazines, the starting materials of di-N-oxides is first described.

Following the improved Wohl-Aue reaction, *o*-nitroanisole was condensed with *m*-anisidine in the presence of potassium hydroxide. In this reaction 1,9- and 1,7-dimethoxyphenazines were expected as the condensation products, which were chromatographed on alumina and separated into three crystalline substances, m.p. 254°, 176° and a small amount of m.p. 122°.

The crystalline product of m.p. 254° showed the same properties and analytical values as that of 1,9-dimethoxyphenazine (I), previously synthesized by Clemo and Daglish³⁾. Accordingly, the substance having m.p. 176° must be 1,7-dimethoxyphenazine (II)⁴⁾. The crystals with m.p. 122° were found to be identical with 2-methoxyphenazine (III) by mixed melting point determination with authentic specimen.

(I) and (II) were demethylated with hydrobromic acid in glacial acetic acid to 1,9- (IV) and 1,7-dihydroxyphenazines (V), respectively.

* Motofuji-cho, Bunkyo-ku, Tokyo (吉岡一郎).

1) Part IV: This Bulletin, 1, 66 (1953).

2) I. Yosioka, Y. Kidani: J. Pharm. Soc. Japan, 72, 1128 (1952).

3) G. R. Clemo, A. F. Daglish: J. Chem. Soc., 1950, 1481.

4) Recently it was learned that A. I. Kiprianov and S. B. Serebryani (C. A., 46, 4010 (1952)) carried out the same reaction and obtained 1,9- (m.p. 260°) and 1,7-dimethoxyphenazines (m.p. 174°).