Summary

(1) The antibacterial action of organic arsenical compounds was inhibited by thiol compounds but not by sulfanilamide-antagonists.

(2) The activity of succinic dehydrogenase of various bacteria was inhibited by organic arsenical compounds. This inhibitory effect was considered parallel to the bacteriostatic activities of organic arsenical compounds.

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5. Takeo Ueda and Tadakazu Tsuji: Arsenical Chemotherapeutic Drugs. XV. Studies on Arsenical Compounds as Anthelmintics.

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Many informations, regarding the trypanocidal, spirocidal, and antibacterial activities of the arsenical drugs, have been gained, but up to date no observations have been reported regarding their anthelmintic activities.

Studies to determine the most suitable type of chemical structure among the arsenical compounds and the most appropriate method of the anthelmintic tests for them were undertaken before proceeding with their detailed studies. Several arsenical compounds were examined as to their anthelmintic properties by the usual method. This paper describes the anthelmintic activities of several arsenical compounds against *Ascaris lumbricoides.*

Compounds Used to Test Anthelmintic Action Three series of arsenical compounds, viz. the diarylarsinic acids, the arylarsenous acids and the diarylarsinous acids, as shown in the following tables, were tested for their anthelmintic properties . All of the compounds are known. Among them, the diarylarsinic acids and the diarylarsinous acids were prepared by Ueda-Takahashi method[1].

Anthelmintic Action According to the Lamson-Nakamura method[2], these arsenical compounds were examined as to their anthelmintic activities by observing the kinetic state of *Ascaris lumbricoides* exposed in dilution of 1 : 1,000 Bunge's solution of the chemicals at 38°.

Results are given in Tables I, II, and III. Numbers under the heading "Paralysis" denote the time after which the ascarid showed no movement without outside stimulus, and under "Death", the time after which the ascarid showed no movement under any stimulus.

As shown in the tables, none of the diarylarsinic acids showed any action, though some of the arylarsenous acids and the diarylarsinous acids exerted considerable effect: Phenylarsenous acid (No. 16), 4-tolylarsenous acid (No. 17), 4-hydroxyphenylarsenous acid (No. 18), and 4-hydroxydiphenylarsinous acid (No. 22) showed marked ascaricidal effect and 3-nitro-4-hydroxyphenylarsenous acid (No. 19), 3-amino-4-hydroxyphenylarsenous acid (No. 20), diphenylarsinous acid (No. 21), 4-nitrodiphenylarsinous acid (No. 23), 4-chlorodiphenylarsinous acid (No. 24), 2-carboxydiphenylarsinous acid

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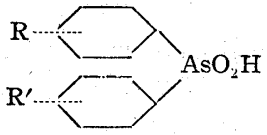
1) K. Takahashi: J. Pharm. Soc. Japan, 72, 533 (1952).
2) E. Nakamura: Sei-I-Kai Med. J., 65, 3, 181 (1951).

TABLE I.

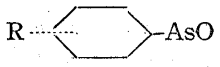
Anthelmintic Action of Diarylarsinic Acids



No.	Structural formula		State	
	R	R′	Paralysis (hr.)	Death (hr.)
1	H	H	65	72
2	H	4′-NO_2	72	84
3	H	4′-NH_2	42	68
4	H	4′-CH_3	65	72
5	H	2′-CH_3	39	65
6	H	4′-COOH	72	84
7	H	2′-COOH	42	68
8	H	4′-OH, 3′-NO_2	39	78
9	H	4′-OH, 3′-NH_2	72	84
10	H	4′-CH_3, 3′-NO_2	69	84
11	4-NH_2	4′-NH_2	72	84
12	4-CH_3	4′-CH_3	72	84
13	2-CH_3	2′-CH_3	24	65
14	4-COOH	4′-COOH	72	84
15	4-NO_2	4′-OH, 3′-NO_2	72	84

TABLE II.

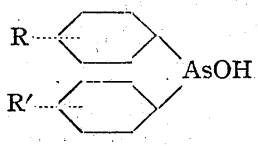
Anthelmintic Action of Arylarsenous Acids (Arylarsene Oxides)

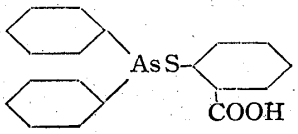


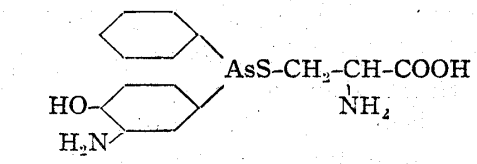
No.	Structural formula	State	
	R	Paralysis (hr.)	Death (hr.)
16	H	1	2
17	4-CH_3	1.5	2
18	4-OH	9	15
19	4-OH, 3-NO_2	16	39
20	4-OH, 3-NH_2	16	65

TABLE III.

Anthelmintic Action of Diarylarsinous Acids



No.	Structural formula		State	
	R	R′	Paralysis (hr.)	Death (hr.)
21	H	H	4	39
22	H	4′-OH	7	12
23	H	4′-NO_2	16	39
24	H	4′-Cl	16	36
25	H	2′-COOH	16	42
26	H	3′-NH_2·HCl, 4′-OH	72	84
27	4-NO_2	4′-NO_2	16	39
28	4-COOH	4′-NO_2	16	39
29			12	60

30  39 72

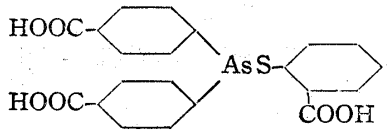
31  65 72

Table IV.

Toxicity of Arsenical Compounds in Mice

No.	M.T.D (*i.v.*) (mg./kg.)
16	1.57
17	1.72
18	2.0
19	7.5
20	40.0
21	10.0
22	2.5
25	10.0
26	20.0
29	20.0
30	40.0

(No. 25), 4,4'-dinitrodiphenylarsinous acid (No. 27), 4-carboxy-4'-nitrodiphenylarsinous acid (No. 28) and diphenyl-2-carboxyphenylthioarsinite (No. 29) showed marked paralysing effect. However, none of them showed any excitation and curling-motion.

Discussion Although the arsenicals are of interest as invaders against SH-ferments in various kinds of living bodies, their anthelmintic properties have not yet been discussed.

This is the first paper to show that arsenicals possess activity against the ascarid, as described in the experimental part.

Relationship between chemical structure and anthelmintic property of the arsenicals is deduced by the fact that the quinquevalent arsenicals did not show any anthelmintic activity, while the trivalent arsenicals exerted considerable effect against the ascarid. This coincides with findings that the trivalent arsenicals possess, in general, far stronger microbial effects than the quinquevalent arsenicals.

The effects of the trivalent arsenicals were observed to depend on their substituent groups. It was observed that the arylarsenous series were, in general, more effective than the diarylarsinous series. From Tables II and III, compounds No. 16, 17, 18, and 22 showed remarkable ascaricidal activity, while compounds No. 19, 20, 21, 23, 24, 25, 27, and 28, showed only moderate activity. Effectivity was observed to be qualitatively parallel to their toxicity. Their effectivity was lowered by introduction of thiol-residue into the arsinous acids for the purpose of reducing toxicity. A good balance of effectivity and toxicity, among the diarylarsinous acid series, seems to be the basis of a promising drug.

At the present stage, it is impossible to conclude what type of the compound is of promise. Additional studies are necessary to determine compounds possessing higher effectivity and lower toxicity.

In view of the mode of anthelmintic action of the diarylarsinous acids against *Ascaris lumbricoides*, it is of interest that, though these arsenicals are not capable of

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.

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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 studies[2~5] 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

* Shinano-machi, Shinjuku-ku, Tokyo (上田武雄, 辻 忠和).

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).