4) It may be concluded that arsonoso radical might be favorable for the antibacterial property, compared with arsono radical.

(Received October 18, 1952)

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6. Kiyoshi Takahashi, Shigeshi Toyoshima, and Takeo Ueda: Arsenical Chemotherapeutic Drugs. XI.[1] Antibacterial Properties of Diarylarsinic Acids and Diarylarsinous Acids.

(*Pharmaceutical Institute, Keio-Gijuku University**)

As described in the previous paper[1], the authors could not find any drug possessing a remarkable antibacterial activity and a low toxicity among primary arsenical compounds. As described in the previous papers[2], the authors synthesized many compounds belonging to the diarylarsinous acid series.

These types of arsenical compounds, although of interest for chemotherapeutic use, have scarcely been investigated as to their antibacterial activities. Only three compounds of dihydroxydiphenylarsinic acid were examined as to their effects on tuberculosis[3].

This paper describes the antibacterial activities of diarylarsinic acids and diarylarsinous acids.

Experimental Procedures Twenty-three compounds of the diarylarsinic acid series and 17 compounds of the diarylarsinous acid series were prepared according to the methods described in the previous papers[2]. These compounds, as shown in Tables I and II, were examined for their antibacterial activities.

Bacteriological procedures were the same as described in the foregoing paper[1].

Escherichia coli, *Shigella dysenteriae* (Komagome BIII), *Eberthella typhosa* (Kyodai strain) and *Staphylococcus aureus* (Terashima strain) were employed. The maximum dilution in molar concentration necessary for bacteriostasis after 48 hours were measured in media containing complete buillon by the serial dilution methods.

Antibacterial Activities of the Arsenical Compounds The antibacterial activities of the diarylarsinic acids are given in Table I by the maximum dilution in molar concentration required to inhibit the growths of bacteria.

It is evident from Table I that none of the diarylarsinic acids exerted a positive antibacterial activity *in vitro*.

The antibacterial activities of the diarylarsinous acids are given in Table II by the maximum dilution in molar concentration required to inhibit the growths of bacteria.

It is seen from Table II that among the diarylarsinous acids three compounds of diphenylarsinous oxide, 4-hydroxydiphenylarsinous acid, and 3-amino-4-hydroxydiphenylarsinous acid hydrochloride possessed more marked activities than sulfathiazole, seven compounds of 2-carboxydiphenylarsinous acid anhydride, 4-carboxydiphenylarsinous acid, 4-aminodiphenylarsinous acid, 4-nitrodiphenylarsinous acid, 4,4′-dihydroxydiphenylarsinous acid, 4,4′-diaminodiphenylarsinous acid, and 3-nitro-4-hydroxydiphenylarsinous acid posses-

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1) Part X: T. Ueda, K. Takahashi, S. Toyoshima, S. Kano: This Bulletin, 1, 17 (1953).
2) K. Takahashi: J. Pharm. Soc. Japan, 72, 529, 533, 1144 (1952).
3) M. Matsui, N. Hirano: Saikingaku-zasshi, 567 (1943), (Japan).

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sed activities approximately equal to that of sulfanilamide, and all the other compounds did not show any positive activity.

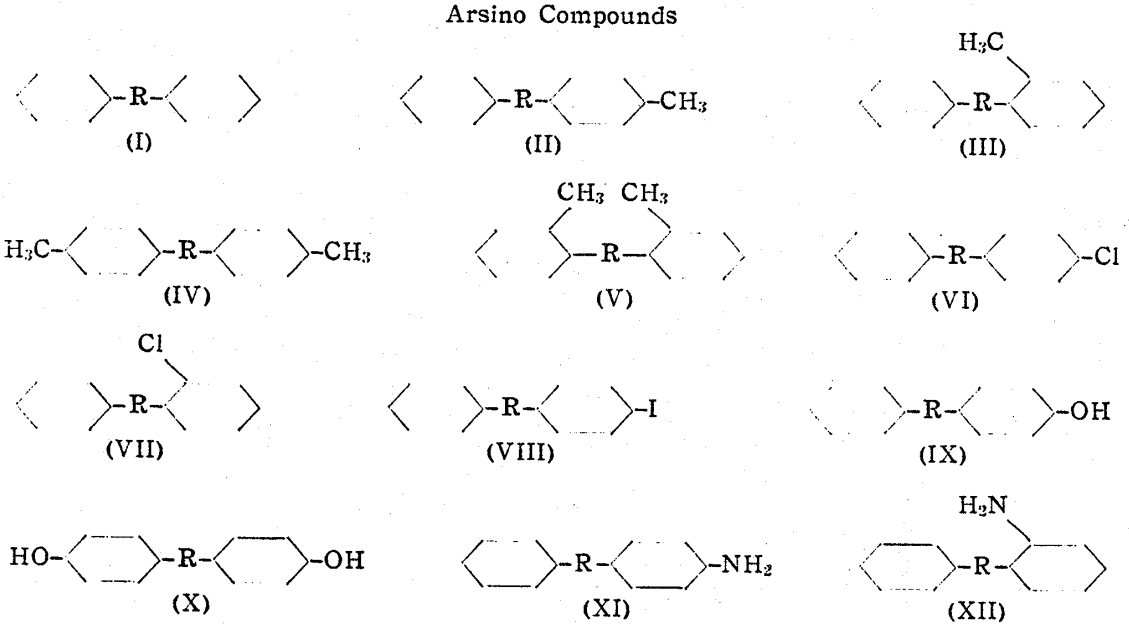
Discussion and Conclusion The observations with the diarylarsinic acids as described above show that none of these compounds exerted any antibacterial activity. Therefore, it may be said that arsino radical combined with two aryl residues did not take part in exerting any antibacterial activity.

According to the observations with diarylarsinous acids, these compounds could be divided into three groups. Diphenylarsinous oxide, 4-hydroxydiphenylarsinous acid, and 3-amino-4-hydroxydiphenylarsinous acid hydrochloride belong to the first group, which was more active than sulfathiazole, 2-carboxydiphenylarsinous acid anhydride, 4-carboxydiphenylarsinous acid, 4-aminodiphenylarsinous acid, 4-nitrodiphenylarsinous acid, 4,4'-dihydroxydiphenylarsinous acid, 4,4'-diaminodiphenylarsinous acid, and 3-nitro-4-hydroxydiphenylarsinous acid belong to the second group, which was as active as sulfanilamide, and all the other compounds belong to the third group which was almost inactive.

TABLE I R= -AsO(OH)-

Arsino Compounds	Bacteria *Esch. coli*	Bacteria *Staph. aur.*	Arsino Compounds	Bacteria *Esch. coli*	Bacteria *Staph. aur.*
(I)	$>10^{-3}$	10^{-3}	(XIII)	$>10^{-3}$	$>10^{-3}$
(II)	$>10^{-3}$	$>10^{-3}$	(XIV)	$>10^{-4}$	10^{-3}
(III)	$>10^{-3}$	$>10^{-3}$	(XV)	$>10^{-3}$	$>10^{-3}$
(IV)	$>10^{-3}$	$>10^{-3}$	(XVI)	$>10^{-3}$	$>10^{-4}$
(V)	$>10^{-3}$	$>10^{-3}$	(XVII)	$>10^{-3}$	$>10^{-3}$
(VI)	$>10^{-3}$	10^{-3}	(XVIII)	$>10^{-3}$	$>10^{-3}$
(VII)	$>10^{-3}$	$>10^{-3}$	(XIX)	$>10^{-3}$	$>10^{-3}$
(VIII)	$>10^{-3}$	$>10^{-3}$	(XX)	$>10^{-3}$	$>10^{-3}$
(IX)	$>10^{-3}$	$>10^{-3}$	(XXI)	10^{-4}	10^{-3}
(X)	$>10^{-3}$	$>10^{-3}$	(XXII)	10^{-3}	10^{-3}
(XI)	$>10^{-3}$	$>10^{-3}$	(XXIII)	10^{-3}	10^{-3}
(XII)	$>10^{-3}$	$>10^{-3}$			

Arsino Compounds



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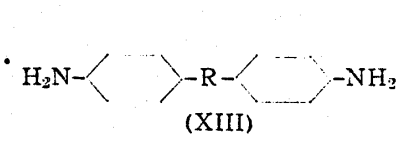
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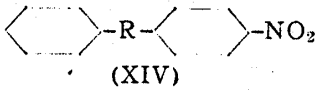
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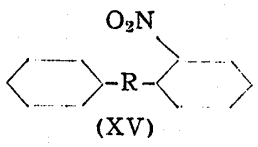
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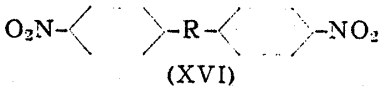
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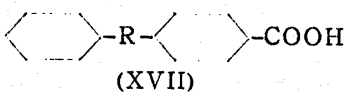
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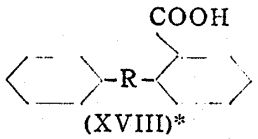
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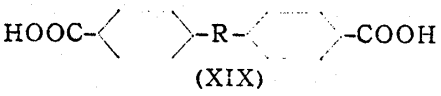
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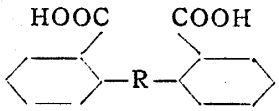
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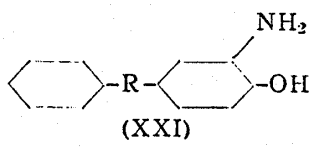
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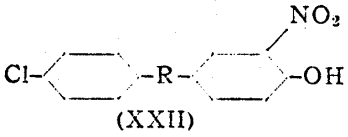
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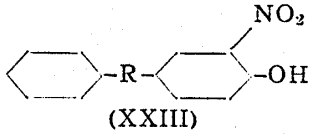
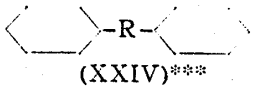

(XXIII)

TABLE II R= -As(OH)-

Arsinoso Compounds	Bacteria			
	Esch. coli	*Staph. aur.*	*S. dysenteriae*	*Eber. typhosa*
(XXIV)	10^{-3}	10^{-3}	10^{-7}	10^{-3}
(XXV)	10^{-3}	10^{-7}	10^{-3}	10^{-3}
(XXVI)	10^{-3}	10^{-5}	10^{-3}	10^{-3}
(XXVII)	10^{-3}	10^{-4}	10^{-3}	10^{-3}
(XXVIII)	10^{-3}	10^{-5}	10^{-3}	10^{-3}
(XXIX)	$>10^{-3}$	$>10^{-3}$	—	—
(XXX)	$>10^{-3}$	$>10^{-3}$	—	—
(XXXI)	10^{-4}	10^{-3}	10^{-4}	10^{-4}
(XXXII)	10^{-4}	10^{-4}	10^{-4}	10^{-4}
(XXXIII)	10^{-5}	10^{-3}	10^{-5}	10^{-5}
(XXXIV)	$>10^{-3}$	$>10^{-3}$	—	—
(XXXV)	$>10^{-3}$	$>10^{-3}$	—	—
(XXXVI)	$>10^{-3}$	$>10^{-3}$	—	—
(XXXVII)	$>10^{-3}$	$>10^{-3}$	—	—
(XXXVIII)	10^{-4}	10^{-7}	10^{-4}	10^{-4}
(XXXIX)	10^{-4}	10^{-3}	10^{-4}	10^{-4}
(XL)	10^{-5}	10^{-8}	10^{-8}	10^{-3}

Arsinoso Compounds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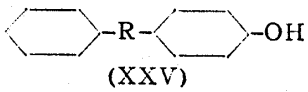
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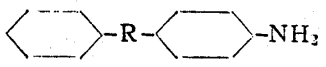
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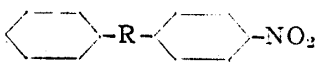
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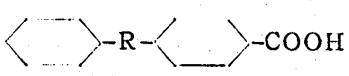
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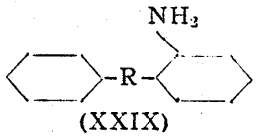
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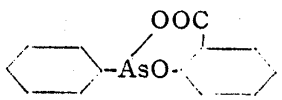
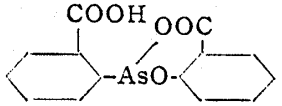
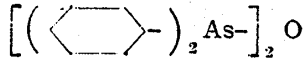
* 

** 

*** 

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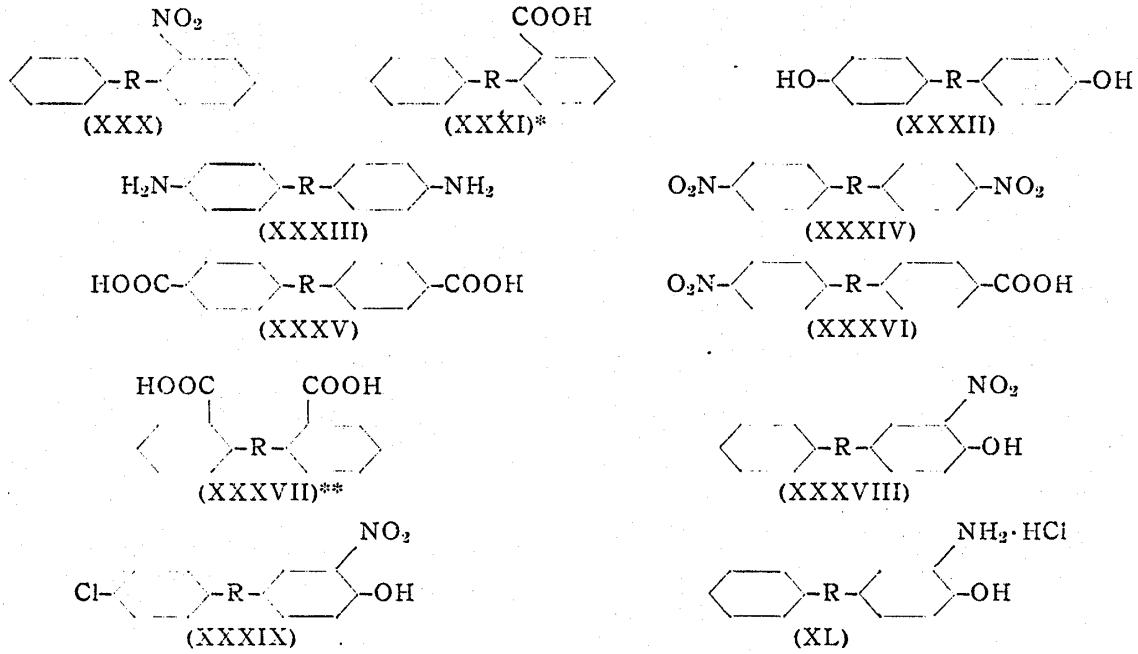


It may be noteworthy that the compounds of the first group showed extremely strong activities, especially against gram-negative bacteria, and was hardly antagonized by complete bouillon. Moreover, it may be expected that the compounds would exert activities against resistant strains of bacteria unsusceptible to known drugs, and the arsenical drug might be considered to act against bacteria by a mode different from other chemotherapeutic drugs. On the other hand, it must be remembered that the compounds would show strong toxic effects due to arsinoso radical.

The toxicities of the compounds of the first group were determined by the single injection method in mice. The results are given in Table III. The toxicities of the compounds were comparatively high, as expected.

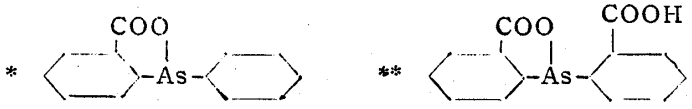
TABLE III

Compound	Toxicity M.T.D. (mg/kg, i.v., with mouse)
Diphenylarsinous oxide	5
4-Hydroxydiphenylarsinous acid	2.5
3-Amino-4-hydroxidiphenylarsinous acid hydrochloride	20

It is apparent, therefore, that the toxicity of these compounds must be reduced in order to utilize them clinically. The authors succeeded in reducing their toxicities by their condensation with SH-compounds, the results of which will be described in the next paper.

Though the compounds of the second group showed moderate activities, they were not of promise for chemotherapeutic use, because they might possess considerable toxicities due to the arsinoso radical.

The relationship between the antibacterial properties and chemical structures of the diarylarsinous acids are complicated, compared with those of arylarsinous acids. Diphenyl-



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arsinous oxide containing no substituent was the most active among these compounds. At the present stage, it cannot be explained sufficiently why diphenylarsinous oxide exerts a strong activity and possesses a high toxicity. However, when diphenylarsinous oxide was compared with the other acids, it may be assumed that the former acid would combine more easily with important SH-enzyme in bacteria and hosts, that the products resulting from the acid and the SH-enzyme would be more stable, and that the acid would be less antagonized by antagonists in bouillon (detailed discussions on this problem will be described in the future paper).

Moreover, it was observed that the introduction of a substituent on the benzene ring of diphenylarsinous acid more or less weakened activities of its substitute. Therefore, any substituent on the benzene ring should be considered to be more or less antagonized by antagonists in bouillon; less antagonized substituents were the hydroxyl radical and both hydroxyl and amino radicals in the ortho position, while more antagonized ones were the amino, nitro, carboxyl, and sulfonic radicals. It may be said, therefore, that the activity and the toxicity due to arsinoso radical were influenced by the kind and number of substituents on the benzene ring. These assumptions may be supported by the analogous fact which was already observed by Ueda and Toyoshima[4] in the course of their studies on antibacterial actions of arylarsonous acids against *Escherichia coli* and *Staphylococcus aureus*. In these studies, it was made clear that 4-hydroxyphenylarsonous acid and 3-amino-4-hydroxyphenylarsonous acid were not antagonized in media added with bouillon, while 4-aminophenylarsonous acid was strongly antagonized in the same medium, and it was assumed that both amino and hydroxyl radicals on 3-amino-4-hydroxyphenylarsonous acid might not be free, by interfering with each other.

As discussed above, it may be concluded that the compounds of the first group in toxicity-lowering form are of promise for the chemotherapeutic use.

The authors wish to acknowledge with thanks that a part of the expenses for this research was furnished by the Scientific Research Fund provided by the Ministry of Edudation.

Summary

1) Twenty-three compounds of the diarylarsinic acid series and seventeen compounds of diarylarsinous acid series were examined as to their antibacterial activities.

2) Among these compounds, diphenylarsinous oxide, 4-hydroxydiphenylarsinous acid, and 3-amino-4-hydroxydiphenylarsinous acid hydrochloride exerted marked antibacterial activities *in vitro* and comparatively high toxicities.

3) It may be concluded that the three compounds were of promise for the chemotherapeutic use if their toxicities could be lowered by some appropriate methods.

4) The relationship between antibacterial properties and chemical structures of diarylarsinous acids were discussed and the assumption was made as to their relationship. Arsinoso radical might be favorable for an antibacterial property, compared with arsino radical, and the activity and the toxicity due to arsinoso radical might be influenced intensively by the kind and number of substituents on the benzene ring.

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4) T. Ueda, S. Toyoshima: Papers read before the Annual Meeting of the Pharmaceutical Society of Japan (1951).

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