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Effect on Biological Activity of Substituting Sulphur for Oxygen in an Organic Arsenical Compound.

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Voegtlin and his associates[1] have called attention to the significance of sulphur metabolism in connection with arsenic toxicity. It seemed of interest to determine the effect on biological activity of substituting sulphur for oxygen in an organic arsenical compound where this substitution is possible. We approached this problem from our particular standpoint of the chemotherapy of amebiasis, determining toxicity on oral administration to cats and rabbits, and amebacidal activity *in vitro* on *Entameba histolytica,* employing technique described elsewhere,[2] except that we used a Musgrave-Clegg slant and Ringer's solution containing albumen and rice-starch with pH adjusted to lie between 7.4 and 7.6, in an effort to prevent absorption of the drug by the solid medium.

Through the courtesy of the Lilly Research Laboratories, we secured 4-carbaminophenyl-arsonic acid ($H_2O_3As.C_6H_4.NHCONH_2$) and 4-thiocarbamino-phenyl-arsonic acid ($H_2O_3As.C_6H_4.NHCSNH_2$), which differ from each other in that the latter contains sul-

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1 Voegtlin, C., *et al.*, Pub. Health Reports, 1923, xxxviii, 1882.

2 Anderson, H. H., and Leake, C. D., PROC. SOC. EXP. BIOL. AND MED., 1930, xxvii, 267. Koch, D. A., *Univ. Calif. Pub. Zool.*, 1926, xxix, 241.

TABLE I.

Certain comparative physico-chemical and biologic data on carbamino-phenyl-arsonic acid and the corresponding thio compound, with data on sodium acetarsone for use as a standard in calculating therapeutic indices.

Drug	Actual arsenic content	Solubility in water pH=8.0	No. rabbits used	MLD in rabbits mgm./kg.	No. cats used	MLD in cats mgm./kg.	Amebacidal concentration, 48 hr.	Calculated therapeutic index
	%							
Sodium Acetarsone	25.3	1:12	15	150	10	125-150	1:600	1
Carbamino-phenyl-arsonic acid	26.9	1:100 (colloidal)	14	200	11	200-250	1:4000	8.8
Thiocarbamino-phenyl-arsonic acid	18.7	1:500 (colloidal)	8	more than 1000	15	700-800	1:600	5

phur instead of oxygen in the carbamide radicle. The actual arsenic content of the former agreed closely with theory, but there was only 18.7% arsenic in the thio compound instead of the theoretical 27.1%. It seems impossible to prepare this substance with an arsenic content much closer to the theoretical. The comparison of the two drugs was further complicated by the fact that the thio compound was much less soluble than the other even in alkaline solution.

We found, however, that thiocarbaminophenyl-arsonic acid is only about a fourth as toxic on oral administration to rabbits and cats as carbaminophenyl-arsonic acid, and that it is only about one-sixth as powerful an amebacidal agent *in vitro*. A summary of our data, with figures for sodium acetarsone as a standard for calculating therapeutic indices, is given in Table I. Our observations on the amebacidal power of sodium acetarsone agree with those of Sautet.[3]

It is important to determine whether or not a similar marked reduction in biological activity occurs when sulphur is substituted for oxygen in other pentavalent arsenicals, and also in trivalent arseno compounds where the arsenic is more electro-positive. In connection with Voegtlin's suggestion[4] correlating physico-chemical data on compounds like these with their biological activity, in particular that high water solubility leads to rapid excretion, resulting in low toxicity, it should be pointed out again that although carbaminophenyl-arsonic acid is much more soluble than the corresponding thio compound, it is also much more toxic and it seems more generally biologically active.

[3] Sautet, J., *Ann. Parasitol. Hum. Comp.*, 1927, v, 329.

[4] Voegtlin, C., *Physiol. Rev.*, 1925, v, 63.