Note

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Seigorō Hayashi, Hiroshi Ueki, Yōko Ueki, Hiroyuki Aoki, Kanji Tanaka, Junjirō Fujimoto, Kōzō Katsukawa, and Masahiro Mori : Studies on the Relationship between the Antitumor and the Antibacterial Activities of Quinone Derivatives.

(*Faculty of Pharmaceutical Sciences, University of Kumamoto*[*1])

The antibacterial activities of quinone derivatives have been reported by Cooper, *et al.*[1,2] and Hayashi, *et al*[3] and the mechanisms of the activity are attributed to the binding of protein with quinones.[4] Raciborski,[5] Fischer,[6] Cecil[7] and Hayashi, *et al.*[8] have reported that the bindings occur between glycine, cysteine, or ribonucleic acid in bacterial cell and quinones.

On the antitumor activity of ethyleneimino quinones, Gauss, *et al.*[9,10] Hayashi and Ueki[11,12] reported that glycolytic systems of tumor cell were affected by ethyleneimino group of the quinones and suggested that the activity of quinones were attributable to the reaction of alkyl group with the enzymes that were essential to the life of tumor cell. In this paper, the relationship between the antitumor and the antibacterial activities was discussed for the introduction of ethyleneimino or 2-chloroethylamino groups in quinoid nucleus. The cylinder agar plate method was used for the antitumor cell effects against Ehrlich ascites tumor and the antibacterial effects against *Staphylococcus aureus* TERASHIMA and *Escherichia coli* were shown.

Experimental

Substances tested——The quinone derivatives were synthesized in this laboratory. Substances tested, insoluble in water, were dissolved in 5% propyleneglycol solution.

Tumor Cells——A mouse of *dd* strain was transplanted intraperitoneally with Ehrlich ascites tumor cells. On the 7th day after the transplantation cells were harvested and the number of the cell was adjusted to five million per ml. by phosphate buffer saline.

Bacteria used——*Staphylococcus aureus* TERASHIMA and *Esherichia coli* strains.

Assay Method——1) Antitumor test was performed by the cylinder agar plate method (CAP method)[13] using Ehrlich ascites tumor cells. 2) Antibacterial test was performed by a multiple dilution method using normal bouillon. One-fifth ml. of the serially diluted test solution was mixed with 1.8 ml. of normal bouillon and the mixture was sterilized in boiling water for 30 min. Then one platinum loop of the bacterial suspension was inoculated in the mixture and incubated at 37° for 48 hr.

*1 Kuhonji, Ōe-machi, Kumamoto (林 清五郎, 植木 寛, 植木洋子, 青木弘行, 田中完二, 藤本準次郎, 勝川浩三, 森 昌弘).

1) E. A. Cooper : Biochem. J., **7**, 186 (1913).
2) *Idem* : J. Soc. Chem. Ind., **46**, 59 (1927).
3) S. Hayashi, *et al.* : Kumamoto Pharm. Bull., **I**, 93 (1954).
4) E. A. Cooper : Biochem. J., **22**, 317 (1928).
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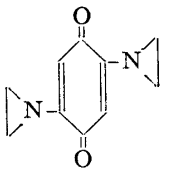
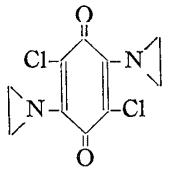
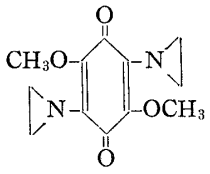
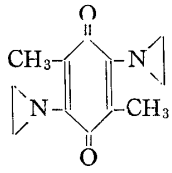
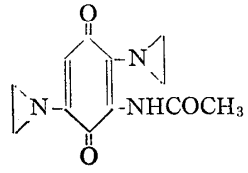
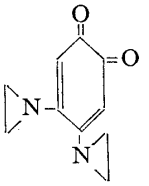
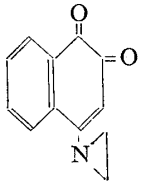
8) S. Hayashi, *et al.* : Kumamoto Pharm. Bull., **II**, 62 (1955).
9) W. Gauss : Angew. Chemie, **69**, 252 (1957).
10) *Idem* : Chem. Ber., **91**, 2216 (1958).
11) S. Hayashi, H. Ueki : Paper presented at the 19th General Meeting of the Japanese Cancer Association.
12) *Idem* : Paper presented at the 21st General Meeting of the Japanese Cancer Association.
13) S. Yamazaki, *et al.* : J. Antibiotics, **9A**, 135 (1956).

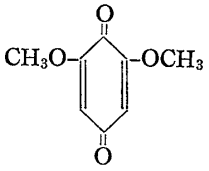
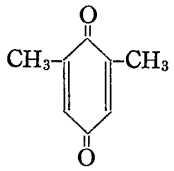
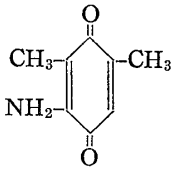
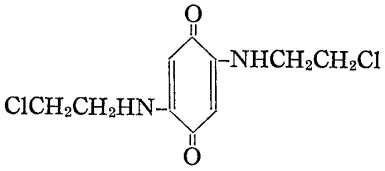
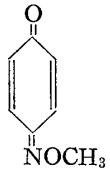
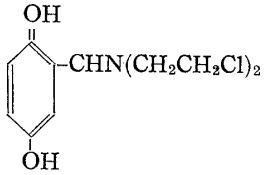
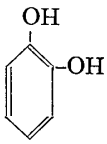
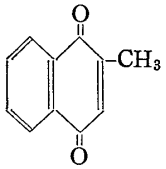
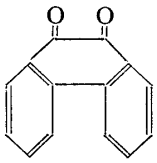
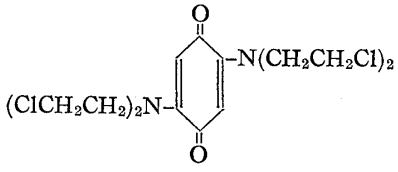
Results and Discussion

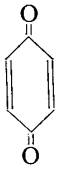
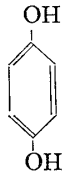
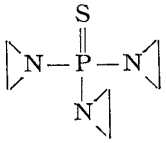
Table I shows the results of antitumor and antibacterial activities of quinone derivatives. As compared with commercially available antitumor agent, thio-TEPA, all the quinone derivatives showed potent inhibition of dehydrogenase activity of tumor cells, except Nos. 11, 15 and 17, but the compounds having 2-chloroethylamino (Nos. 11 and 17) or ethyleneimino group (No. 1) were less effective than the mother substance (No. 20).

On the antibacterial effect, six compounds, Nos. 4, 5, 8, 14, 15 and 16 were effective against gram positive bacteria and especially No. 16 was also effective against gram negative bacteria. The differences on the antibacterial effect were found little between

Table I. Antitumor and Antibacterial Effects of Quinone Derivatives

No.	Compounds	Effect (mm.)	M.E.C.	
			Staphy.	*Coli*
1		35	$10^{-3} \times 1/2$	10^{-3}
2		20	10^{-3}	—
3		47	10^{-3}	—
4		48	$10^{-3} \times 1/8$	$10^{-3} \times 1/4$
5		36	$10^{-3} \times 1/16$	$10^{-3} \times 1/2$
6		35	—	—
7		46	$10^{-3} \times 1/4$	$10^{-3} \times 1/2$

8		50	$10^{-3} \times 1/16$	10^{-3}
9		35	10^{-3}	—
10		20	—	—
11		7	—	—
12		60	$10^{-3} \times 1/4$	10^{-3}
13		28	—	—
14		23	10^{-4}	—
15		0	$10^{-3} \times 1/32$	10^{-3}
16		35	$10^{-5} \times 1/2$	10^{-5}
17		12	—	—

18		60	10^{-3}	—
19		45	—	—
20		17	—	—

Effect : mm. of diameter of inhibition zone
Staphy. : *Staphylococcus aureus* TERASHIMA
Coli : *Escherichia coli*
M.E.C. : Minimum effective concentration (mole)
— : below 10^{-3} mole

the quinones substituted with 2-chloroethylamino or ethyleneimino groups and other quinones, that is, the alkylating groups did not show any activity against bacteria.

Also No. 6, 4,5-bis(ethyleneimino)-1,2-benzoquionone, which has a marked activity for prolongation of the survival time of mice bearing Ehrlich ascites tumor,[11] did not show antibacterial activity against both gram positive and negative bacteria.

From these results, it was thought that any relationship between the antitumor and the antibacterial activity might not exist in quinone derivatives.

Summary

Sixteen of the quinone derivatives were examined for the antitumor activity against Ehrlich ascites tumor cell by the cylinder agar plate method and for the antibacterial activity against *Staphylococcus aureus* TERASHIMA and *Esherichia coli*. Any relationship were not found between the antitumor and the antibacterial activity.

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