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Mutagenicity and Antibacterial Activity of Hydroxamic Acids

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Hydroxamic acids demonstrated mutagenic and antibacterial activities. These activities appear to be dependent on the hydroxamic acid function and are probably due to the interaction with deoxyribonucleic acid.

Hydroxamic acids have been shown to be effective antifungal and antibacterial agents. Sorbic hydroxamic acid (2) and decanoylhydroxamic acid (3) demonstrated antifungal activities. Salicylhydroxamic acid had in vitro and in vivo antitubercular activity (8). Hase et al. (5) synthesized a series of alkyloxybenzoylhydroxamic acids and fatty acyl hydroxamic acids and found that some of these chemicals possessed antifungal activity. However, none of them was effective against enteric bacteria. Acetohydroxamic acid was an inhibitor of bacterial urease. It also inhibited ammonia and stone formation in the urinary tract during infections (4). The present study investigated the mutagenic and antibacterial activity of several hydroxamic acids with differing acyl groups.

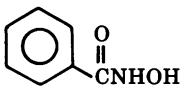
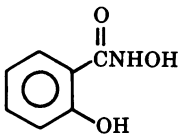
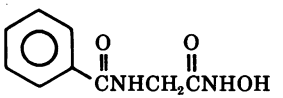
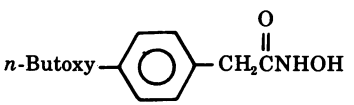
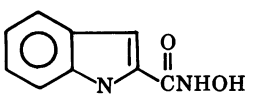
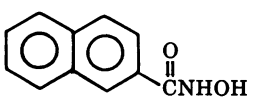
The Ames spot test for chemical mutagenicity (1) was used for the present study. Fifty microliters of sterile dimethyl sulfoxide containing 1 mg of the tested chemical was spotted on the center surface of an agar plate containing *Salmonella typhimurium* strains TA100 or TA98 (7). The control plates were treated with the solvent only. After incubation at 37°C for 2 days, the revertant colonies that appeared were counted, and the clear inhibition zone produced by antibacterial activity was measured. Chemicals inducing more than twice the number of revertants found in the control plate were considered as mutagenic.

In the antibacterial tests, various strains of bacteria (Table 1) were grown in Difco nutrient broth for 6 h at 37°C. The culture was then diluted 100 times with fresh nutrient broth. One-half milliliter of dimethyl sulfoxide containing various amounts of test compounds was added to 4.5 ml of the diluted culture. After incubation at 37°C for 24 h, the minimal concentration for complete growth inhibition was recorded. The concentrations of hydroxamic acids in the medium were 1000, 500, 100, 50, 10, and 1 μg/ml. Minimal inhibitory concentrations of 10 μg/ml or less were considered as "effective," 50 to 100 μg/ml as "slightly effective," and 100 μg/ml or greater as "ineffective."

The results of mutation and antibacterial tests were presented in Table 1. All the hydroxamic acids tested except *p*-butoxyphenylacetohydroxamic acid produced clear antibacterial zones and mutations in both *S. typhimurium* strains TA100 and TA98. It appears that these mutagenic hydroxamic acids may interact with bacterial deoxyribonucleic acid. 2-Naphthoylhydroxamic acid was "effective" against *Streptococcus faecalis* and *Escherichia coli* and was "slightly effective" against *Bacillus cereus* and *Proteus morganii*. Benzoylhydroxamic acid, salicylhydroxamic acid, and indole-2-carbohydroxamic acid were "slightly effective" against some bacterial strains. *p*-Butoxyphenylacetohydroxamic acid lacked mutagenicity for *S. typhimurium* and was virtually ineffective against the tested bacteria.

Thus, hydroxamic acid function appears to be essential for the mutagenic and antibacterial activities of hydroxamic acids, whereas the acyl moiety appears to determine their potency. Although hydroxamic acids have been shown to be effective inhibitors of bacterial and plant urease (6), their antibacterial activity probably is not due to urease inhibition (5). It seems likely that the antibacterial activity is due to their interaction with bacterial deoxyribonucleic acid since hydroxamic acids were shown to have mutagenic and antibacterial effects in this study.

TABLE 1. *Antibacterial and mutagenic activity of hydroxamic acids*

Hydroxamic acid	Structure	Mutagenicity[a]	Minimal inhibitory concentration (μg/ml)							
			I[b]	II	III	IV	V	VI	VII	VIII
Benzoylhydroxamic acid		+	1,000	1,000	NA[c]	500	NA	1,000	100	100
Salicylhydroxamic acid		+	500	1,000	1,000	500	NA	NA	500	50
Benzoylaminoacetohydroxamic acid		+	NA	NA	NA	NA	NA	NA	1,000	10
p-Butoxyphenylacetohydroxamic acid		−	NA	NA	NA	NA	NA	NA	NA	500
Indole-2-carbohydroxamic acid		+	50	500	500	500	1,000	500	500	50
2-Naphthoylhydroxamic acid		+	100	500	500	100	NA	500	10	10

[a] +, Mutagenic for *S. typhimurium* TA98 and TA100; −, not mutagenic.

[b] I, *Bacillus cereus*; II, *Corynebacterium xerosis*; III, *Klebsiella pneumoniae*; IV, *Proteus morganii*; V, *Pseudomonas aeruginosa*; VI, *Staphylococcus aureus*; VII, *Streptococcus faecalis*; VIII, *Escherichia coli*.

[c] NA, Not active at a dose of 500 μg/ml for *p*-butoxyphenylacetohydroxamic acid or 1,000 μg/ml for the other compounds. *p*-Butoxyphenylacetohydroxamic acid was not soluble at 1 mg/ml in the medium.

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