Action of Substituted Salicylaldehydes on Bacteria and Fungi

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While testing the halogenated and/or alkylated saligenins as gram-negative antiseptics, it was thought desirable to test the corresponding salicylaldehydes. Previous to the work which is described in part in this report, these aldehydes had been only superficially investigated for antiseptic activity (*1*). However, as a result of extensive testing carried out on these compounds, particularly on the dibrom derivative, the salicylaldehydes have been shown to possess marked fungicidal and bactericidal activity.

The main problem to be solved before testing the salicylaldehydes was to find a satisfactory means of dissolving these normally insoluble compounds at a suitable pH (*1*) and in a solution which contributed no antibacterial activity. To this end, two methods were developed.

The first involved mixing the free aldehyde with an excess of borax and making an aqueous solution from this mixture. Thus, a stable preparation is obtained at a satisfactory pH and without the irritating properties associated with solutions of the salicylaldehydes alone. The second method made use of the aldehyde-bisulfite compound in conjunction with an equimolecular amount of sodium hydroxide. The solutions thus obtained are apparently fairly stable and nonirritating. However, on long standing, there is complete decomposition to the parent aldehydes. From a bacteriological standpoint there is no apparent difference on a mole-for-mole basis between the two types of preparation.

Antiseptic testing was carried out by serial tube dilutions, using as test organisms the bacteria listed in Table 1. The results indicate that several of the compounds are promising as antiseptics against both gram-positive and gram-negative bacteria. As gram-negative infections do not generally respond well to the usual gram-positive antiseptics, the latter activity is very significant. This will be reported in detail elsewhere.

The salicylaldehydes prepared were also tested for fungistatic activity against *Trichophyton mentagraphytes* #640, a common pathogenic fungus. The method used was that described previously (*2*). From the results shown in Table 2 it will be noted that several of the compounds exhibit marked fungistatic activity against the fungus strain used. In addition, further studies based on tests described by Schamberg and Kolmer (*4*) show that the salicylaldehydes are fungicidal as well as fungistatic against *T. mentagraphytes*.

TABLE 2

FUNGISTATIC ACTIVITY OF SUBSTITUTED SALICYLALDEHYDES AGAINST *Trichophyton mentagraphytes* #640

Name	Fungistatic effect in mm. of inhibition Concentration of compound				
	5%	0.5%	0.05%	0.005%	0.0005%
Salicylaldehyde	Comp.*	0	0	0	0
5-Chlorsalicylaldehyde	"	Comp.	2	0	0
5-Bromsalicylaldehyde	"	"	1	0	0
5-Iodosalicylaldehyde	"	"	3	0	0
5-tert-Butylsalicylaldehyde	"	"	0	0	0
3,5-Dichlorsalicylaldehyde	"	"	15	2	0
3,5-Dibromsalicylaldehyde	"	21	11	8	0
3-Chlor-5-bromsalicylaldehyde	"	25	14	2	0
3-Chlor-5-tert-butylsalicylaldehyde	"	Comp.	14	0	0
3-Brom-5-tert-butylsalicylaldehyde	"	35	12	0	0

* Indicates complete inhibition on a 90-mm. cup-plate.

TABLE 1

ANTIBACTERIAL EFFECT OF SUBSTITUTED SALICYLALDEHYDES ON CERTAIN BACTERIA

Compound	*Staphylococcus* 209		*Shigella shiga*		*Pseudomonas aeruginosa*		*Streptococcus* C-203
	Dilutions of compounds inhibiting 24-hour cultures						
	With serum	Without serum	With serum	Without serum	With serum	Without serum	With serum
Salicylaldehyde	1: 500	1: 2,000	1:2,000	1:2,000	1: 500	1:1,000	1:1,000
5-Chlorsalicylaldehyde	1:4,000	1: 8,000	1:4,000	1:4,000	<1: 500	<1: 500	1:4,000
5-Bromsalicylaldehyde	1:2,000	1: 8,000	1:4,000	1:8,000	<1: 500	1: 500	1:2,000
5-Iodosalicylaldehyde	1:4,000	1: 4,000	1:2,000	1:2,000	<1:2,000	<1:2,000	1:4,000
5-tert-Butylsalicylaldehyde	1:2,000	1:16,000	1:1,000	1:2,000	<1: 500	<1: 500	1:4,000
3,5-Dichlorsalicylaldehyde	1:4,000	1:64,000	1:8,000	1:8,000	1: 500	1: 500	1:8,000
3,5-Dibromsalicylaldehyde*	1:4,000	1:64,000	1:4,000	1:4,000	1: 500	1: 500	1:4,000
3-Chlor-5-bromsalicylaldehyde	1:4,000	1:32,000	1:2,000	1:8,000	1: 500	1: 500	1:4,000
3-Brom-5-tert-butylsalicylaldehyde	1:4,000	1:64,000	1:1,000	1:2,000	<1: 500	<1: 500	1:8,000

* "Dalyde," H. W. & D. brand of dibromsalicylaldehyde.

Thus, on the basis of the preliminary experiments reported here, it can be seen that the series of compounds in question shows activity against both fungi and gram-negative and

gram-positive bacteria. The preparation of dibromsalicylaldehyde solubilized with borax was singled out for extensive *in vitro* and *in vivo* testing against both bacterial and fungal infections. The reports of these studies will be the subject of subsequent publications by our collaborators (*3*).

References

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Prediction of Speed of Performance by Muscle Action Potentials[1]

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By the use of a new electronic counting technique a rather remarkable relationship has been found between reaction time to aperiodic stimuli in a monotonous situation and frequency of muscle action potentials (recorded from bipolar electrodes placed above the eyes) during a 6-second interval before the onset of the stimuli.

The task was to respond by pressing a key as quickly as possible when occasional stimuli (simultaneous flash of light and sound of a buzzer) were presented. The subject was comfortably seated in an electrically shielded, sound-reduced darkroom. The schematic diagram (Fig. 1) shows the general relationships between the various electronic amplifying and recording units used in this study.

Presentation of the stimulus, occurrence of the response, frequency of action potentials from surface electrodes placed over the supraorbital muscles, low-frequency potentials from the same supraorbital electrodes, and muscle action potential rate from electrodes on the hand while responding were all simultaneously recorded on a Grass ink-writing oscillograph.

The electrodes were small solder discs attached to the surface of the skin with adhesive tape. Washing the skin with ether and applying a small amount of electrode jelly between skin and electrode served to make a satisfactory low-resistance contact (R = approximately 20,000 ohms). A ground electrode was attached to the subject's cheek.

Fig. 2 shows graphically the gradual transition from sleep to a condition of normal alertness as measured by the reaction time, associated muscle spike frequency, and low-frequency potentials from the supraorbital placement. At the point in the record indicated by the arrow, the experimenter knocked vigorously on the door of the shielded room. The stimulus before the knock had elicited no response, line № 2 had shown no muscle activity for the previous 40 seconds, and line № 3 showed alpha spindles at low amplitude only for the previous 5 minutes. The knock produced a "startle" reaction, with the immediate resumption of muscle spike activity, low-frequency activity, and a pressing of the response key in the absence of a stimulus. The second stimulus produced a response slower than normal, while the third stimulus, 6 seconds later, produced a normal reaction time. Both responses are shown on line № 4 as active contractions of the finger muscles.

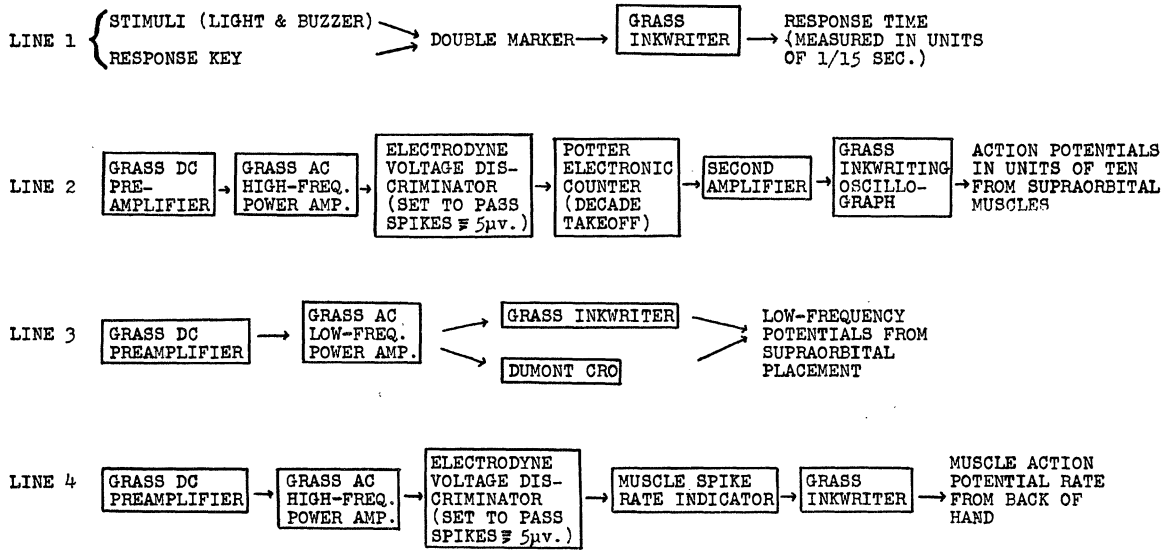

FIG. 1

It is feasible with this arrangement to achieve considerable versatility in studying a variety of muscle contraction problems under a variety of conditions of effort and work. Some specific data on one of these problems—the course of events in certain muscles only remotely involved in a long-continued task as the individual approaches a state of boredom and sleepiness—are presented here.

Fig. 3 shows the relationship between frequency of action potentials from electrodes placed over the supraorbital muscles and response time to a combined light and buzzer stimulus. The solid line represents the mean values; the vertical lines, the standard deviation above and below the mean. These data

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