Syntheses and Antimicrobial Properties of the Related Compounds of Decanoylacetaldehyde. VIII. On the Relationship between the Chemical Structure and Antifungal Property.

The chemical nature of the effective substance isolated from *Houttuynia cordata* Thunb. ("*dokudami*" in Japanese) was determined as decanoylacetaldehyde, by the present writer.[1]

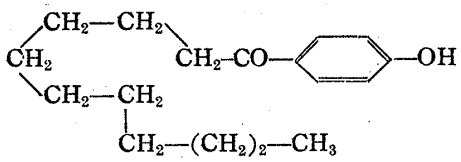
Based on this finding, an extensive research for more effective antimicrobial substances has been made by synthesizing a large number of related compounds in cooperation with Okeda.[2] As a result, strong antifungal substances have been found such as nonylpyrazole and decanoylphenol but they were still unsatisfactory in some respects and required further examinations.

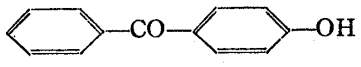
In dealing with the problem of an improvement, it was felt that it would be of interest to call attention to the following facts. That is, as reported in the previous paper,[3] derivatives of decanoylphenol were the only effective ones among the compounds of benzene series having a decanoyl radical. This indicates that decanoyl or nonyl radical had no toxicity against fungi, but posessed the capacity to strengthen that of the parent substance, phenol. Consequently it was assumed that in order to find a new effective antifungal substance, the introduction of a nonyl or decanoyl radical into a parent substance toxic against fungi might give good results, but it is difficult to find substances toxic against fungi other than phenol, β-ketoaldehyde, or pyrazole.

Search for a new toxic substance was postponed in favor of finding a solution to the problem as to why decanoyl or nonyl radical possessed supplementary action in toxicity against fungi.

The affinity of such a radical as nonyl is too poor to modify the structure by introducing further any radical which plays an auxiliary part and is chemically reactive.

To date some unsatisfactory explanations have been proposed concerning the mode of the action of nonyl radical. The writer presumed that an unknown important factor must be found and in order to attack the problem, the first step was to search for a radical capable of substituting the nonyl radical. The benzene nucleus was thought to satisfy the conditions of equivalency and chemical reactivity. Although there seems to be no apparent similarity between the nonyl radical and the benzene nucleus, a configurational one does exist in the case where the nonyl radical has a hexagonal arrangement instead of a straight one.



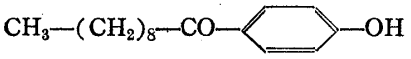
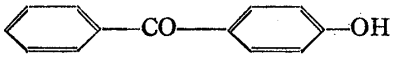
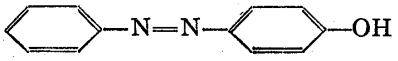
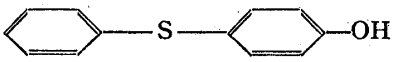
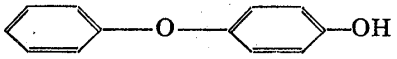


Benzoylphenol synthesized on trial prevented the growth of *Trichophyton interdigitale* in the minimum concentration of 1:80,000 *in vitro*. This activity was no more than one-half of that of decanoylphenol, but when compared with that of phenol a remarkable increase was noted, giving rise to the conclusion that the nonyl radical and benzene nucleus had much resemblance in antimicrobial actions. In order to explain the fact that two substances belonging to different systems had a similar bacteriological

1) Kosuge : J. Pharm. Soc. Japan, **72**, 1227(1952).
2) Kosuge, Okeda : J. Biochem. (Japan), **41**, 183(1954).
3) Kosuge, Sato : J. Pharm. Soc. Japan, **74**, 1139(1954).

action, a new concept had to be brought forward that the configuration of a supplementary molecule was a very important factor in the relationship between chemical structure and antimicrobial property. A question as to whether the benzene nucleus in benzoylphenol influences the antimicrobial effect primarily in a configurational way or not, would be answered by observing a variation of the effect on substituting –CO– bond in benzoylphenol with other radicals (cf. Table I). If factors other than the configurational one have an influence on their antifungal properties, different results would be expected in accordance with variations of electronic configuration of benzene nucleus. Various bonds, –N:N–, –S–, –O–, —, $-CH_2-$, –NH–, –NNO–, $-SO_2-$, were introduced and the antifungal properties of these substances were examined. The results are shown in Table I.

Table I.

Substance	Antifungal activity against *Trichophyton interdigitale* (×1,000)
	200
	80
	100
	400
	100
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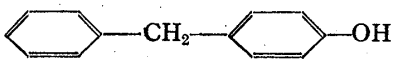
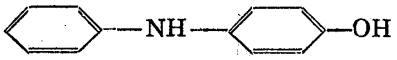
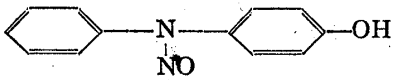
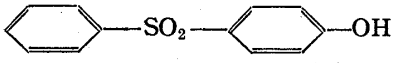
	100
	40
	100
	1<

From the results shown in Table I, it is seen that the antifungal effect of each substance was almost of the same order as that of decanylphenol, that is, in spite of the variation in the nature of the bonds, antifungal power did not vary, showing that the configurational factor had a great influence on it. It may be concluded that the action of a nonyl or decanoyl radical is a result of its configuration.

By summarizing the results concerning the relationship between chemical structure and antimicrobial property, it can be concluded that a condition which some substances must satisfy to possess an antimicrobial activity, i.e. a criterion for the search of an effective antimicrobial substance, would be as follows : First, a group toxic against the microörganism is necessary. Second, an auxiliary radical to increase the toxicity of the basic group is necessary and it works mainly in a configurational way. Third, both type and nature of the bond between the basic group and the auxiliary radical will be of no consequence so long as the bond itself does not reduce the antimicrobial activity.

Toxic Group ····· Bond ····· Auxiliary radical

The present writer's conclusion may not explain all the relationships between the chemical structure and antimicrobial properties, but the new concept that a radical having

a definite configuration is necessary as an auxiliary one, seems to be valid.

Whether the concept is applicable or not to the understanding of the mode of action of agents against other microörganisms is reserved for further study.

The substances descrived above haye been examined for the first time as antifungal agents but they are already well known in literatures.

The discovery of a number of new antifungal substances may be expected by the improvement of each substance and by the substitution of a toxic radical with others. For example, 2,4-dichlorobenzene-azophenol prevented the growth of *Trichophyton interdigitale* in the minimum concentration of 1:2,000,000 *in vitro*.

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