# Antifungal Properties of $n$-Alkanols, $\alpha,\omega$-$n$-Alkanediols, and $\omega$-Chloro-$\alpha$-alkanols

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Received March 6, 1979, from the *Boyce Thompson Institute, Cornell University, Ithaca, NY 14853.* Accepted for publication October 22, 1979.

**Abstract** □ Fourteen $n$-alkanols ($C_1$–$C_{12}$, $C_{14}$, and $C_{16}$), 13 $\alpha,\omega$-$n$-alkanediols ($C_2$–$C_{12}$, $C_{14}$, and $C_{16}$), and 13 $\omega$-chloro-$\alpha$-alkanols ($C_2$–$C_{12}$, $C_{14}$, and $C_{16}$) were tested against *Aspergillus niger*, *Trichoderma viride*, and *Myrothecium verrucaria* in Sabouraud dextrose agar at pH 4.0 and 5.6. Toxicity to *Candida albicans*, *Trichophyton mentagrophytes*, and *Mucor mucedo* was determined in the same medium at pH 5.6 and 7.0 in the absence and presence of 10% beef serum. The fungitoxicity of these alcohols was influenced by chain length and insignificantly by the pH of the medium and the presence of beef serum. The $C_{10}$-member of each series was most active; the order of activity of the three groups was chloroalkanols > alkanols > alkanediols. Compared to the fatty acids, the order of fungitoxicity on a weight basis was 2-alkynoic acids > 2-alkenoic acids > $\omega$-chloroalkanols > alkanoic acids > 2-bromoalkanoic acids > 2-fluoroalkanoic acids > $n$-alkoxyacetic acids > $n$-alkanols > $\alpha,\omega$-$n$-alkanediols.

**Keyphrases** □ Antifungal activity—$n$-alkanols, $\alpha,\omega$-$n$-alkanediols, and $\omega$-chloro-$\alpha$-alkanols, *in vitro*, effect of chain length, pH, and adsorbents □ Structure–activity relationships—$n$-alkanols, $\alpha,\omega$-$n$-alkanediols, and $\omega$-chloro-$\alpha$-alkanols, antifungal activity, *in vitro*, effect of chain length □ $n$-Alkanols—antifungal activity, *in vitro*, effect of chain length, pH, and adsorbents □ $\alpha,\omega$-$n$-Alkanediols—antifungal activity, *in vitro*, effect of chain length, pH, and adsorbents □ $\omega$-Chloro-$\alpha$-alkanols—antifungal activity, *in vitro*, effect of chain length, pH, and adsorbents

In the examination in these laboratories of the effect of structural modification on the antifungal activity of fatty acids, systematic studies were made on the fungitoxicity of alkanoic acids (1), 2-alkenoic acids (2), 2-alkynoic acids (3), 2-fluoroalkanoic acids (1), 2-bromoalkanoic acids (2), $\alpha,\omega$-alkanedicarboxylic acids (4), and alkoxyacetic acids (5). Two major factors that influence the fungitoxicity of fatty acids are the partition coefficient and the absence or presence of adsorbents such as albumin in the growth medium. Among the factors that determine the partition coefficient are chain length, pKa, and pH of the medium (3).

## BACKGROUND

It was established that the intact carboxyl group was not essential for fungitoxicity. The alkyl carboxamides were less toxic than the carboxylic acids at pH 4.0 but were equally toxic at pH 5.6. The pH of the medium had little effect on the activity of the amides, but beef serum had a deactivating effect on both the acids and amides. Chain length was a determining factor for the toxicity of the amides as well as the acids (6).

Esters were reported to be markedly less fungitoxic than the acids (7). This finding was confirmed for the methyl esters of the alkanoic and 2-fluoroalkanoic acids (8) and 2-alkynoic acids (3). An exception to these observations was that *Trichophyton mentagrophytes* was inhibited equally by the esters and free acids. The pH of the medium and the absence or presence of beef serum in the medium did not greatly affect the toxicity of the esters to the fungus.

The antifungal activity of nonionizing compounds is affected only slightly by the pH of the medium. The serum effect on fatty acids, amides, and esters can be rationalized on the basis of hydrogen bonding. Compounds containing carboxyl and carboxamide functions are bound more strongly by beef serum because they possess both donor hydrogen atoms and acceptor oxygen atoms, whereas the esters possess only acceptor oxygen atoms (9).

The purpose of the present study was to examine the fungitoxic action of the $n$-alkanols, $\alpha,\omega$-$n$-alkanediols, and $\omega$-chloro-$\alpha$-alkanols. These nonionizing compounds would not be expected to undergo strong hydrogen bonding with adsorbents.

It was reported previously that the wood-destroying fungus, Madison 517 on an agar malt extract medium, was inhibited by $n$-alkanols. $n$-Decanol was the most inhibitory of the series (10). The same effect was observed for *Penicillium glaucum* in an inorganic medium containing sucrose or lactose as the carbon source (11). This observation was confirmed in agar media, but $n$-dodecanol was the most effective alcohol for the protection of wood (12). No systematic studies of the $\alpha,\omega$-$n$-alkanediols or $\omega$-chloro-$\alpha$-alkanols have been reported.

The present work concerns the *in vitro* testing of 14 $n$-alkanols ($C_1$–$C_{12}$, $C_{14}$, and $C_{16}$), 13 $\alpha,\omega$-$n$-alkanediols ($C_2$–$C_{12}$, $C_{14}$, and $C_{16}$), and 13 $\omega$-chloro-$\alpha$-alkanols ($C_2$–$C_{12}$, $C_{14}$, and $C_{16}$) against *Aspergillus niger*, *Trichoderma viride*, and *Myrothecium verrucaria* in Sabouraud dextrose agar at pH 4.0 and 5.6. *Candida albicans*, *T. mentagrophytes*, and *Mucor mucedo* also were tested in the same medium at pH 5.6 and 7.0 in the absence or presence of 10% beef serum. Also included in these tests were 11-bromo-1-undecanol for comparison of analogous chloro and bromo compounds and 1,6-dichlorohexane and 1,9-dichlorononane for comparisons with the corresponding chloroalkanols.

## EXPERIMENTAL

Some compounds were obtained from commercial sources[1]. The $\omega$-chloroalkanols [$C_5$ and $C_7$–$C_{10}$ (13), $C_{11}$ (14), and $C_{12}$, $C_{14}$, and $C_{16}$ (15)] were prepared by published methods.

The test fungi included *A. niger* (ATCC 1004), *T. viride* (ATCC 8678), *M. verrucaria* (ATCC 9095C), *C. albicans* (ATCC 10231), *T. mentagrophytes* (ATCC 9129), and *M. mucedo* (ATCC 7941).

The compounds were tested against *A. niger*, *T. viride*, and *M. verrucari* in Sabouraud dextrose agar[2] at pH 4.0 and 5.6 according to published methods (1). Graded levels of test compound dissolved in dimethyl sulfoxide (I) were incorporated into the growth medium, which then was inoculated with the respective fungus. The inoculum consisted of 1 drop of spore suspension delivered from a 5-ml Mohr pipet containing $6 \times 10^6$ spores/ml in 0.85% NaCl solution. Incubation took place at 28° for 5 days.

For *T. mentagrophytes*, *C. albicans*, and *M. mucedo*, the methods described previously were used (16). Graded levels of test compounds dissolved in I were added to Sabouraud dextrose agar at pH 5.6 and 7.0 alone and supplemented with 10% beef serum[3]. The inocula of *T. mentagrophytes* and *M. mucedo* consisted of 1 drop of spore suspension containing $6 \times 10^6$ spores/ml, and the inoculum of *C. albicans* was 1 drop of a suspension obtained from a 20-hr culture in Sabouraud dextrose broth[2] incubated at 37°. The test plates with *T. mentagrophytes* were incubated at 28° for 5 days, and those with *C. albicans* and *M. mucedo* were incubated at 37° for 20 hr.

The results reported are the number of levels of compounds causing 100% inhibition of the test organisms. The compounds were tested at $10^4$, $10^3$, and $10^2$ μg/ml. All tests were carried out in I-plate petri dishes[4].

The results were weighted by calculating the antifungal spectrum index, defined as the sum of the number of levels of complete inhibition multiplied by the number of organisms inhibited within the defined system (17, 18).

[1] The $C_1$-, $C_3$–$C_{12}$-, $C_{14}$-, $C_{16}$-, and $C_{18}$-alkanols, the $C_2$–$C_{12}$- and $C_{16}$-$\alpha,\omega$-alkanediols, and 3-chloro-1-propanol, 6-chloro-1-hexanol, 11-bromo-1-undecanol, 1,6-dichlorohexane, and 1,9-dichlorononane were obtained from Aldrich Chemical Co., Milwaukee, Wis. The $C_2$-alkanol was obtained from U.S. Industrial Chemicals Co., New York, N.Y. The $C_{14}$-$\alpha,\omega$-alkanediol was obtained from Eastman Kodak Co., Rochester, N.Y. 2-Chloro-1-ethanol and 4-chloro-1-butanol were obtained from Matheson, Coleman and Bell, Norwood, Ohio.

[2] Difco, Detroit, Mich.

[3] Miles Laboratories, Kankakee, Ill.

[4] Falcon, Oxnard, Calif.

0022-3549/80/0400-0381$01.00/0

Table I—Antifungal Activity [a] of *n*-Alkanols, α,ω-*n*-Alkanediols, and ω-Chloro-α-alkanols at pH 4.0 and 5.6 against *A. niger*, *T. viride*, and *M. verrucaria* in Sabouraud Dextrose Agar

| | Inhibition Levels at pH 4.0 | | | | Inhibition Levels at pH 5.6 | | | |
|---|---|---|---|---|---|---|---|---|
| $n$ [b] | *A. niger* | *T. viride* | *M. verrucaria* | Antifungal Spectrum Index [c] | *A. niger* | *T. viride* | *M. verrucaria* | Antifungal Spectrum Index |
| | | | | $CH_3(CH_2)_nOH$ | | | | |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 |
| 2 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 |
| 3 | 0 | 1 | 1 | 4 | 0 | 1 | 1 | 4 |
| 4 | 1 | 1 | 1 | 9 | 1 | 1 | 1 | 9 |
| 5 | 1 | 1 | 1 | 9 | 1 | 1 | 1 | 9 |
| 6 | 1 | 1 | 1 | 9 | 1 | 1 | 1 | 9 |
| 7 | 1 | 1 | 1 | 9 | 1 | 1 | 1 | 9 |
| 8 | 1 | 3 | 1 | 15 | 1 | 3 | 1 | 15 |
| 9 | 2 | 3 | 3 | 24 | 2 | 3 | 2 | 21 |
| 10 | 2 | 2 | 2 | 18 | 2 | 2 | 2 | 18 |
| 11 | 0 | 2 | 3 | 10 | 0 | 2 | 3 | 10 |
| 13 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 15 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | | $HO(CH_2)_nOH$ | | | | |
| 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7 | 0 | 1 | 1 | 4 | 0 | 1 | 1 | 4 |
| 8 | 1 | 1 | 1 | 9 | 1 | 1 | 1 | 9 |
| 9 | 1 | 1 | 2 | 12 | 1 | 1 | 2 | 12 |
| 10 | 1 | 2 | 2 | 15 | 1 | 2 | 2 | 15 |
| 11 | 1 | 1 | 1 | 9 | 1 | 1 | 1 | 9 |
| 12 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 14 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 16 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | | $Cl(CH_2)_nOH$ | | | | |
| 2 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 |
| 3 | 1 | 1 | 1 | 9 | 1 | 1 | 1 | 9 |
| 4 | 1 | 1 | 1 | 9 | 1 | 1 | 1 | 9 |
| 5 | 1 | 1 | 1 | 9 | 1 | 1 | 1 | 9 |
| 6 | 1 | 1 | 2 | 12 | 1 | 1 | 2 | 12 |
| 7 | 2 | 2 | 2 | 18 | 2 | 2 | 2 | 18 |
| 8 | 2 | 2 | 2 | 18 | 2 | 2 | 2 | 18 |
| 9 | 3 | 3 | 3 | 27 | 3 | 3 | 3 | 27 |
| 10 | 3 | 3 | 3 | 27 | 3 | 3 | 3 | 27 |
| 11 | 1 | 3 | 3 | 21 | 1 | 3 | 3 | 21 |
| 12 | 0 | 2 | 3 | 10 | 0 | 2 | 3 | 10 |
| 14 | 0 | 1 | 2 | 6 | 0 | 1 | 2 | 6 |
| 16 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | | Miscellaneous | | | | |
| $Br(CH_2)_{11}OH$ | 0 | 1 | 0 | 1 | 0 | 1 | 1 | 4 |
| $Cl(CH_2)_6Cl$ | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 |
| $Cl(CH_2)_9Cl$ | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |

[a] Compounds were incorporated in the test medium at $10^4$, $10^3$, and $10^2$ μg/ml. Key to inhibition levels: 3 = inhibition at all levels of the compound, 2 = inhibition at the two highest levels, 1 = inhibition at the highest level only, and 0 = compound inactive at the highest level tested. [b] Number of methylene groups in the chain. [c] Sum of the number of levels of inhibition multiplied by the number of organisms inhibited.

## RESULTS

The results of the tests of the *n*-alkanols, α,ω-*n*-alkanediols, and ω-chloro-α-alkanols against *A. niger*, *T. viride*, and *M. verrucaria* are given in Table I; the results of the tests against *C. albicans*, *T. mentagrophytes*, and *M. mucedo* are given in Table II.

A comparison of the fungitoxicity of the alkanols based on the combined antifungal spectrum indexes at pH 4.0 and 5.6 (Table I) reveals that the homologs of chain length $C_5$–$C_{12}$ were most active against *A. niger*, *T. viride*, and *M. verrucaria*. The order of activity of the compounds tested was $C_{10} > C_{11} > C_9 > C_{12} > C_8 = C_7 = C_6 = C_5 > C_4 > C_3 = C_2$. Similarly, for the alkanediols, the most active members of the series were the $C_7$–$C_{11}$-compounds; the order of activity was $C_{10} > C_9 > C_{11} = C_8 > C_7$. For the ω-chloro-α-alkanols, the most fungitoxic compounds were between $C_8$ and $C_{14}$; the order of activity was $C_{10} = C_9 > C_{11} > C_8 = C_7 > C_6 > C_{12} > C_5 = C_4 = C_3 > C_{14} > C_2$. Varying the pH between 4.0 and 5.6 did not affect the fungitoxicity of the three classes of compounds significantly.

The most fungitoxic alkanols against *C. albicans*, *T. mentagrophytes*, and *M. mucedo* were the $C_5$–$C_{12}$-compounds; the overall order of toxicity was $C_{11} = C_{10} > C_{12} > C_9 = C_8 > C_7 > C_6 = C_5 > C_4 > C_{14} = C_3$. For the alkanediols, the $C_7$–$C_{12}$-compounds were the most toxic; the order of toxicity was $C_{10} > C_{11} > C_9 = C_8 = C_7 > C_{12}$. The chloroalkanols were most fungitoxic at chain lengths between $C_2$ and $C_{11}$ in the order $C_{10} = C_9 > C_{11} = C_8 = C_7 > C_6 = C_5 = C_2 > C_4 = C_3 > C_{12}$. Raising the pH from 5.6 to 7.0 and adding beef serum to the growth medium caused no significant deactivation of the antifungal activity of the three classes of compounds.

11-Bromo-1-undecanol was less fungitoxic than the analogous alkanol, chloroalkanol, and alkanediol. 1,6-Dichlorohexane and 1,9-dichlorononane were markedly less toxic than the analogous alkanols, chloroalkanols, and alkanediols, with the 6-carbon compound being more active than the 9-carbon compound.

## DISCUSSION

It is apparent (Tables I and II) that the chain length influences antifungal activity in each homologous series of compounds. A chain length of 10 carbon atoms seems to be optimal for maximal fungitoxicity. This result was observed previously for the alkanols (10–12). The relationship between the chain length and the partition coefficient with respect to the antifungal activity of fatty acids was discussed previously (3). This constant was employed in the application of regression analysis to fungitoxicity (19).

**Table II—Antifungal Activity of *n*-Alkanols, α,ω-*n*-Alkanediols, and ω-Chloro-α-alkanols at pH 5.6 and 7.0 against *C. albicans*, *T. mentagrophytes*, and *M. mucedo* in Sabouraud Dextrose Agar in the Absence and Presence of Beef Serum [a]**

| | Inhibition Levels [b] | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *C. albicans* | | | | *T. mentagrophytes* | | | | *M. mucedo* | | | | |
| | pH 5.6 | | pH 7.0 | | pH 5.6 | | pH 7.0 | | pH 5.6 | | pH 7.0 | | Antifungal |
| $n$ [c] | Without Serum | With Serum | Without Serum | With Serum | Without Serum | With Serum | Without Serum | With Serum | Without Serum | With Serum | Without Serum | With Serum | Spectrum Index [d] |
| | | | | | | $CH_3(CH_2)_nOH$ | | | | | | | |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 4 |
| 3 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 16 |
| 4 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 36 |
| 5 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 36 |
| 6 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 48 |
| 7 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 60 |
| 8 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 60 |
| 9 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 72 |
| 10 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 1 | 1 | 1 | 1 | 72 |
| 11 | 2 | 2 | 2 | 2 | 3 | 2 | 3 | 2 | 1 | 1 | 1 | 1 | 66 |
| 13 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 4 |
| 15 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 17 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | | | | $HO(CH_2)_nOH$ | | | | | | | |
| 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 6 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 4 |
| 7 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 36 |
| 8 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 36 |
| 9 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 36 |
| 10 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 54 |
| 11 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 48 |
| 12 | 0 | 0 | 0 | 0 | 3 | 3 | 3 | 3 | 0 | 0 | 0 | 0 | 12 |
| 14 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 4 |
| 16 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | | | | $Cl(CH_2)_nOH$ | | | | | | | |
| 2 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 48 |
| 3 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 36 |
| 4 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 36 |
| 5 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 48 |
| 6 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 48 |
| 7 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 72 |
| 8 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 72 |
| 9 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 2 | 2 | 2 | 2 | 84 |
| 10 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 2 | 2 | 2 | 2 | 84 |
| 11 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 1 | 1 | 1 | 1 | 72 |
| 12 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 |
| 14 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 16 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | | | | Miscellaneous | | | | | | | |
| $Br(CH_2)_{11}OH$ | 1 | 1 | 1 | 1 | 3 | 3 | 3 | 3 | 1 | 1 | 1 | 1 | 60 |
| $Cl(CH_2)_6Cl$ | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 16 |
| $Cl(CH_2)_9Cl$ | 0 | 0 | 0 | 0 | 2 | 2 | 1 | 1 | 0 | 0 | 0 | 0 | 6 |

[a] *C. albicans* and *M. mucedo* were incubated at 37° for 30 hr, and *T. mentagrophytes* was incubated at 28° for 5 days. [b] Compounds were incorporated in the test medium at $10^4$, $10^3$, and $10^2$ μg/ml. Key to inhibition levels: 3 = inhibition at all levels of the compound, 2 = inhibition at the two highest levels, 1 = inhibition at the highest level only, and 0 = compound inactive at the highest level tested. [c] Number of methylene groups in the chain. [d] Sum of the number of levels of inhibition multiplied by the number of organisms inhibited.

The order of fungitoxicity of the three classes of compounds was chloroalkanols > alkanols > alkanediols. This finding suggests that, in addition to possessing a certain degree of amphiphilicity, each compound also should have a lipophilic and a hydrophilic end. These concepts are consistent with the results obtained with the fatty acids and derivatives (1–6, 8).

Although these data do not indicate a mechanism of action for the alkanols and related compounds, it is clear that alkylation plays no part in the fungitoxic reaction. The bromoalkanol, which is a better alkylating agent than the corresponding chloro compound, is a poorer antifungal agent.

The antifungal activity of alkanols can be modified by altering the ω-end of the molecule. Conceivably, an ω-substituted alkanol could be prepared with superior antifungal activity. Such a compound also would have the advantage of its activity not being affected significantly by a pH change or the presence of serum.

Since an attempt is being made at generalizing the antifungal activity of the substituted straight-chain alkanes, it is not unreasonable to compare the activity of the alkanols with the carboxylic acids. Totaling the antifungal spectrum indexes of the seven most active members of each series of compounds at pH 4.0 and 5.6 for *A. niger*, *T. viride*, and *M. verrucaria* gives the order of fungitoxicity for six types of fatty acids and three types of alcohols, on a weight basis, as 2-alkynoic acids (336) > 2-alkenoic acids (288) > ω-chloroalkanols (266) > alkanoic acids (264) > 2-bromoalkanoic acids (253) > 2-fluoroalkanoic acids (228) > *n*-alkoxyacetic acids (220) > alkanols (205) > α,ω-alkanediols (98) (3, 5).

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# New Instrumentation for Determining Flexure Breaking Strength of Capsule-Shaped Tablets

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Received June 14, 1978, from the *Applied Pharmaceutics Laboratory, Miles Laboratories, Inc., Elkhart, IN 46514.* Accepted for publication October 22, 1979.

**Abstract** □ New instrumentation to measure the flexure breaking strength of capsule-shaped tablets was developed. It consisted of a mechanical linkage to apply the breaking load at a uniform rate and a strain-gauge instrumented cantilever beam to convert the load to a proportional millivolt response on a recorder. A recorder tracing was obtained of increasing load with time, with a break in the tracing denoting the tablet's flexure breaking strength. Measurements were made for different tablet hardnesses, and a plot of tablet hardness *versus* flexure breaking strength yielded a profile of the mechanical strength of the tablet. The instrumentation was shown to have application for determining the effects of tablet thicknesses, tablet ingredients, tablet sizes, cup depths, and bisect dimensions on tablet strength.

**Keyphrases** □ Flexure breaking strength—determination for capsule-shaped tablets, new instrumentation □ Tablet breakage—capsule-shaped tablets, determination of flexure breaking strength, new instrumentation □ Hardness, tablets—flexure breaking strength, determination for capsule-shaped tablets, new instrumentation

Although tablet breakage is a problem often encountered in the manufacture, packaging, and distribution of capsule-shaped tablets, little information is available on the subject. Several factors that need to be studied for their effects on breakage are the ingredients, size, shape, and dimensions of the tablets. To evaluate these factors, the flexure breaking strength of the tablet must be determined. At present, there is no generally accepted mechanical method to measure the flexure breaking strength of tablets with sufficient accuracy and precision.

## BACKGROUND

A widely used but subjective flexure test employed in practice is to break the tablet between the thumb and fingers and to evaluate both the force necessary to break the tablet and the sharpness of the snap. An instrument constructed to simulate the manual method was described (1) in which a pneumatic tablet hardness tester was modified by the addition of two auxiliary pieces, one attached to the plunger and the other to the anvil. Increasing pressure is applied through the plunger on the center of the tablet face until it breaks to measure the fracture resistance. These investigators found that the fracture resistance was directly proportional to tablet thickness and pointed out the importance of this finding for reducing tablet breakage. They also indicated that additional research was necessary to design an instrument that would be more versatile and accurate.

In another study, a flexure tester was constructed by attaching a knife edge and two fulcrums to the platens of a motorized tablet hardness tester (2). The flexure tester was found to be a rapid, reproducible instrument for determining the tablet tensile strength of very strong tablets but could not be used for very weak tablets.

Two related procedures have been developed to measure resistance to bending. In one procedure, mercury is added to provide the weight to break the tablet (3). In the other procedure, a special tablet form is used that is unrelated to the manufactured product (4). Both procedures, however, are impractical for use in industry.

The objective of this study was to develop new instrumentation that can be calibrated readily for increased accuracy, measure a wide range of tablet strengths, and be of practical use in a product development laboratory. This paper describes the instrument developed and indicates

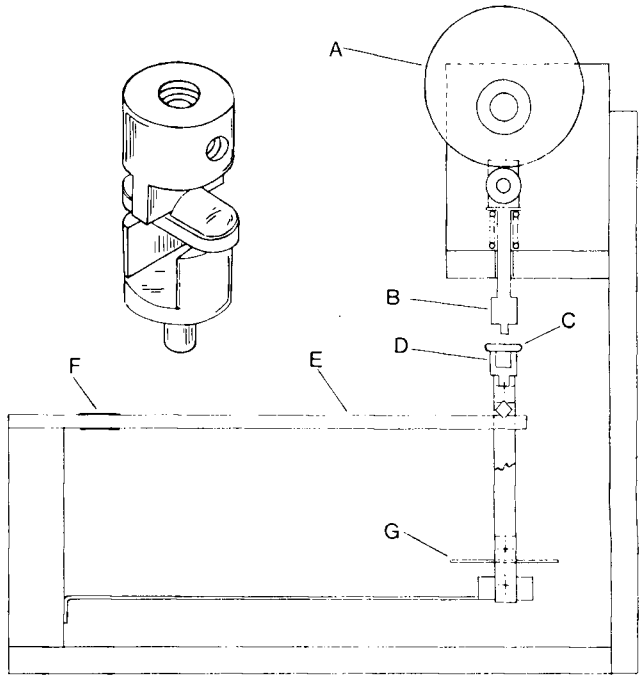


**Figure 1**—*Instrumentation for measuring flexure breaking strength. Key: A, motor-driven cam; B, plunger; C, capsule-shaped tablet; D, anvil; E, cantilever beam; F, strain gauges; and G, weight platform for calibration.*



*0022-3549/80/0400-0384$01.00/0*