

OVERCROWDING FACTORS OF MOSQUITO LARVAE.

IX. 2-BROMOALKANOIC ACIDS AND THEIR METHYL ESTERS AS MOSQUITO LARVICIDES

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ABSTRACT. 2-Bromoalkanoic acids and methyl 2-bromoalkanoates from C₁₀ to C₂₂ with even numbers of carbon atoms were bioassayed for their biological activity against 1st instars of *Culex pipiens quinquefasciatus* Say. 2-Bromoalkanoic acids from C₁₄ to C₁₈ and methyl 2-bromoalkano-

ates from C₁₀ to C₁₈ showed moderate or potent activity, whereas the others exhibited little or no activity. The biological activity was, in general, dependent upon the number of carbon atoms in the acids and in the acid moieties of the esters.

INTRODUCTION. Recently, considerable success has been achieved in developing new insecticides by structural modifications of existing bioactive compounds. By replacing the isobutenyl methyl groups of chrysanthemic acid moiety in bioresmethrin with halogen atoms; Brown et al. (1973, 1975) and Elliott et al. (1973) synthesized halogenated pyrethroids which showed increased insecticidal activity.

2-Ethyl-substituted carboxylic acids were identified as active components of the overcrowding factors of mosquito larvae by Ikeshoji and Mulla (1974a). Subsequent studies showed that various alkanolic acids with 1 or 2 lower alkyl substituents at the C-2 and/or C-3 positions in the carbon chain manifested considerable activity against *Culex pipiens quinquefasciatus* Say (Ikeshoji and Mulla 1974b, Hwang et al. 1974a, b). Methyl esters of these 2- or 3-alkylalkanoic acids also exhibited larvicidal activity (Hwang 1976, Hwang et al. 1976).

In searching for more active analogs of the overcrowding factors, we have synthesized and evaluated a number of compounds with various structural characteristics. In view of the successful replacement of methyl groups with halogen atoms in the synthesis of bioactive organic compounds, we have prepared some halogen analogs of the overcrowding factors. We now report the biological activity of 2-bromoalkanoic acids and their methyl esters against larvae of *C. p. quinquefasciatus*.

MATERIALS AND METHODS. 2-Bromodecanoic, 2-bromododecanoic, 2-bromotetradecanoic, and 2-bromohexadecanoic acids were obtained from Pfaltz and Bauer, Inc., Flushing, N.Y. 2-Bromooctadecanoic, 2-bromicosanoic, and 2-bromodocosanoic acids were prepared by the modified Hell-Volhard-Zelinsky reaction (Cason et al. 1953) from their corresponding alkanolic acids.

Thus, a mixture of an alkanolic acid (0.15 mol) and phosphorus tribromide (0.165 mol) was heated on a steam-bath with stirring. Bromine (0.165 mol) was added rapidly to the mixture. More bromine (0.17 mol) was then added dropwise. The resulting reaction mixture was heated on a steam bath for 8 hr, during which time a 2-bromoalkanoyl bromide was formed. The mixture was poured into water (500 ml) and stirred for 1 hr. The 2-bromoalkanoic acid which separated as white solids was collected by filtration. Recrystallization of the crude product from petroleum ether yielded the pure 2-bromoalkanoic acid.

Methyl 2-bromoalkanoates were prepared by adding an ethereal solution of diazomethane into an ethereal solution of 2-bromoalkanoic acids. Removal of the solvent and the excess diazomethane gave crude products which, upon distillation or recrystallization, yielded pure methyl 2-bromoalkanoates. Alternatively, methanolysis of 2-bromoalkanoyl bromides also gave methyl 2-bromoalkanoates.

All 2-bromoalkanoic acids and methyl

2-bromoalkanoates are racemates. The prefix *dl* is omitted. Physical properties and spectrometric data of these compounds agreed with those in the literature. The purity of the compounds was determined by gas-liquid chromatographic analysis on a silicon gum rubber UCC-W 982 column. All 2-bromoalkanoic acids and methyl 2-bromoalkanoates were more than 95% pure.

First-instar larvae of *C. p. quinquefasciatus* were used in assessing the biological activity of the 2-bromoalkanoic acids and methyl 2-bromoalkanoates. The bioassay procedure was reported by Hwang et al. (1974a,b). In brief, 20 larvae were placed in 200 ml of water in 11-cm diameter glass custard dishes and fed with a mixture of ground rabbit pellets and yeast (3:1). Serially diluted acetone solutions of the testing materials were added to the dishes which were then kept at $27 \pm 1^\circ\text{C}$ under a photoperiod of 14 h. The bioassays were continued until adult emergence. The tests were run in duplicate and repeated at least twice. Controls were run in duplicate in each experiment. The biological activity of the test compounds was expressed in terms of lethal concentrations in ppm inhibiting the emergence of 50 and 90% of the population (LC_{50} and LC_{90}).

RESULTS AND DISCUSSION. Table 1 shows the biological activity of the testing compounds in terms of LC_{50} and LC_{90} .

These compounds include seven 2-bromoalkanoic acids and seven methyl 2-bromoalkanoates.

2-Bromodecanoic acid (**1**) and 2-bromododecanoic acid (**2**) did not show good activity. However, the activity gradually increased in 2-bromotetradecanoic acid (**3**) and greatly increased in 2-bromohexadecanoic acid (**4**) and 2-bromooctadecanoic acid (**5**). The latter two acids were the most active among all acids tested. Thereafter, the activity drastically decreased in 2-bromoeicosanoic acid (**6**) and 2-bromodocosanoic acid (**7**).

Methyl 2-bromodecanoate (**8**) showed moderate activity. The activity increased steadily in methyl 2-bromododecanoate (**9**), methyl 2-bromotetradecanoate (**10**), and methyl 2-bromohexadecanoate (**11**) and reached to the greatest in methyl 2-bromooctadecanoate (**12**). The last 2 homologs, methyl 2-bromoeicosanoate (**13**) and methyl 2-bromodocosanoate (**14**), showed almost no activity.

Changes in activity by esterification of acids to esters were estimated by the ratios $LC_{50}(\text{acid})/LC_{50}(\text{ester})$ and $LC_{90}(\text{acid})/LC_{90}(\text{ester})$. If the ratios equal to 1, there is no change in activity by esterification. If the ratios are larger than 1, the activity is increased by esterification, and vice versa (Table 1). The activity of acids, **1**, **2**, and **3** was greatly increased by transforming them into esters **8**, **9**, and **10**. On the contrary, activity decreased

Table 1. Biological activity of 2-bromoalkanoic acids and methyl 2-bromoalkanoates against 1st instars of *C. p. quinquefasciatus*.

R =	No.	R' = H		No.	R' = CH ₃		$LC_{50}(\text{acid})/$ $LC_{50}(\text{ester})$	$LC_{90}(\text{acid})/$ $LC_{90}(\text{ester})$
		LC_{50}	LC_{90}		LC_{50}	LC_{90}		
<i>n</i> -C ₉ H ₁₇	1	>40.0	>40.0	8	3.3	18.7	>12.1	>2.1
<i>n</i> -C ₁₀ H ₂₁	2	25.6	>40.0	9	2.4	5.9	10.7	>6.8
<i>n</i> -C ₁₂ H ₂₅	3	11.0	>20.0	10	2.0	14.5	5.5	>1.4
<i>n</i> -C ₁₄ H ₂₉	4	0.7	3.1	11	1.4	3.2	0.5	0.97
<i>n</i> -C ₁₆ H ₃₃	5	0.6	2.7	12	0.9	1.5	0.7	1.8
<i>n</i> -C ₁₈ H ₃₇	6	>10.0	>10.0	13	>10.0	>10.0	-	-
<i>n</i> -C ₂₀ H ₄₁	7	>20.0	>20.0	14	>40.0	>40.0	-	-

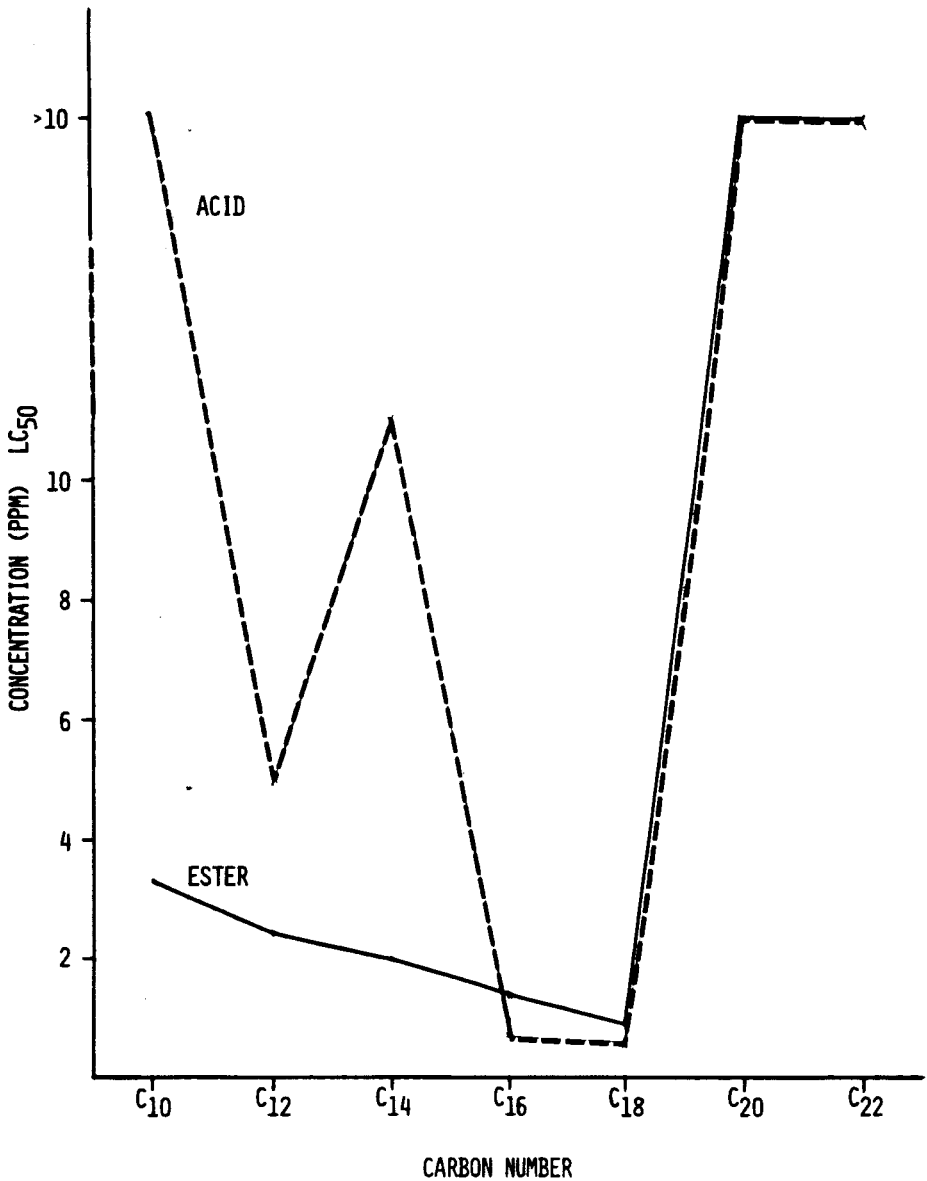


Fig. 1. Structure-activity relationship of 2-bromoalkanoic acids and methyl 2-bromoalkanoates against 1st instars of *C. p. quinquefasciatus*.

on esterifying acids **4** and **5** into esters **11** and **12**, although there was a decrease in LC₉₀ value from acid **5** to ester **12**. Acids **6** and **7** and esters **13** and **14** were so inactive that estimation of activity changes was not feasible. The activity of less active acids increased greatly by esterification, whereas the activity of more active acids did not increase by the process.

Figure 1 shows the structural-activity relationship of the 2-bromoalkanoic acids and the methyl 2-bromoalkanoates using LC₅₀ values for expressing the biological activity. The acids from C₁₄ to C₁₈ and the esters from C₁₀ to C₁₈ showed moderate to good activity. The biological activity of the 2-bromoalkanoic acids and the methyl 2-bromoalkanoate was, in general, dependent upon the number of carbon atoms in the acids and in the acid moieties of the esters.

Ikeshoji and Mulla (1974b) and Hwang et al. (1974a) reported that 2-methylhexadecanoic acid and 2-methyloctadecanoic acid showed weak activity against mosquito larvae. Replacement of the methyl group in the methyl-substituted carboxylic acids with a bromine atom should not alter the spatial arrangement, the steric hindrance, and ultimately the biological activity of these 2 types of acids too much. This is because the van der Waals radius of a bromine atom attached to a carbon atom is 1.95 Å, which is almost equivalent to that of a methyl group (2.0 Å) (Pauling 1960). In fact, 2-bromohexadecanoic acid and 2-bromooctadecanoic acid are much more active than their methyl analogs. The reason for the increase in activity by substituting methyl group for bromine atom is still unknown.

By structural modification of inactive compounds, we have been able to obtain bioactive compounds. Replacement of the methyl group of 2-methylalkanoic acids

with bromine atom produced more active 2-bromoalkanoic acids and their methyl esters.

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References Cited

- Brown, D. G., O. F. Bodenstern and S. J. Norton. 1973. New potent pyrethroid, bromethrin. *J. Agr. Food Chem.* 21:767-9.
- Brown, D. G., O. F. Bodenstern and S. J. Norton. 1975. Halopyrethroids. II. A difluoropyrethroid. *J. Agr. Food Chem.* 23:115-7.
- Cason, J., N. L. Allinger and G. Sumrell. 1953. Branched-chain fatty acids. XXV. Methods of synthesis of 2-alkanoic acids. *J. Org. Chem.* 18:850-6.
- Elliott, M., A. W. Farnham, N. F. Janes, P. H. Needham and D. A. Pulman. 1973. Potent pyrethroid insecticides from modified cyclopropane acid. *Nature.* 244:456-7.
- Hwang, Y.-S. 1976. Overcrowding factors of mosquito larvae—Active analogs obtained by structural modifications. *Proc. and Papers, Calif. Mosq. Contr. Assoc.* 44:93-4.
- Hwang, Y.-S., M. S. Mulla and J. R. Arias. 1974a. Overcrowding factors of mosquito larvae. V. Synthesis and evaluation of some branched-chain fatty acids against mosquito larvae. *J. Agr. Food Chem.* 22:400-3.
- Hwang, Y.-S., M. S. Mulla and J. R. Arias. 1974b. Overcrowding factors of mosquito larvae. VI. Structure-activity relationships of 2 substituted aliphatic carboxylic acids against mosquito larvae. *J. Agr. Food Chem.* 22:1004-6.
- Hwang, Y.-S., M. S. Mulla and G. Majori. 1976. Overcrowding factors of mosquito larvae. VIII. Structure-activity relationship of methyl 2-alkylalkanoates against mosquito larvae. *J. Agr. Food Chem.* 24:649-51.
- Ikeshoji, T. and M. S. Mulla. 1974a. Overcrowding factors of mosquito larvae. Isolation and chemical identification. *Environ. Entomol.* 3:482-6.
- Ikeshoji, T. and M. S. Mulla. 1974b. Overcrowding factors of mosquito larvae. Activity of branched fatty acids against mosquito larvae. *Environ. Entomol.* 3:487-91.
- Pauling, L. 1960. *The nature of the chemical bond*, 3rd ed., Cornell University Press, Ithaca, New York, 257 pp.