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Overcrowding Factors of Mosquito Larvae. 10. Structure–Activity Relationship of 3-Methylalkanoic Acids and Their Esters against Mosquito Larvae

Yih-Shen Hwang,* H. A. Navvab-Gojrati,[1] and Mir S. Mulla

To study structure–activity relationships, 3-methylalkanoic acids, and methyl, ethyl, and isopropyl 3-methylalkanoates having 14–21 carbon atoms in their main chains were synthesized and evaluated for their larvicidal activity against first-instar larvae of *Culex pipiens quinquefasciatus* Say. Those carboxylic acids and esters having 17–20 carbon atoms in their main chains generally showed a high level of activity. Especially, the C-19 carboxylic acid and esters, i.e., 3-methylnonadecanoic acid and methyl, ethyl, and isopropyl 3-methylnonadecanoates, exhibited the greatest activity. The more active compounds possessed larger slopes of probit regression lines than the less active compounds. In general, alkyl 3-methylalkanoates were less active than their corresponding 3-methylalkanoic acids, and the activity declined in the order of acids, methyl, ethyl, and isopropyl esters.

Previously, we reported that substituted aliphatic carboxylic acids, major components of the overcrowding factors of mosquito larvae, possessed larvicidal activity against several species of mosquitoes (Hwang et al., 1974a; Ikeshoji and Mulla, 1974). Of these acids, some 2-alkylalkanoic acids and 3-methylalkanoic acids showed a high level of activity. Based on these findings, 2-ethyl-, 2-butyl-, and 2-hexylalkanoic acids were synthesized and evaluated for their biological activity against young larvae of the southern house mosquito *Culex pipiens quinquefasciatus* Say (Hwang et al., 1974b). As a result of these studies, it was found that 2-alkyltetradecanoic acids, 2-alkylhexadecanoic acids, and 2-alkyloctadecanoic acids generally exhibited good activity. Their methyl esters also showed a high level of larvicidal activity (Hwang et al., 1976b). As an extension of these investigations, a series of 2-bromoalkanoic acids and methyl 2-bromoalkanoates was evaluated (Hwang and Mulla, 1976). The biological activity of 7-methyloctadecane and 8-methylnonadecane, minor components of the overcrowding factors of mosquito larvae, was studied (Hwang et al. 1976a).

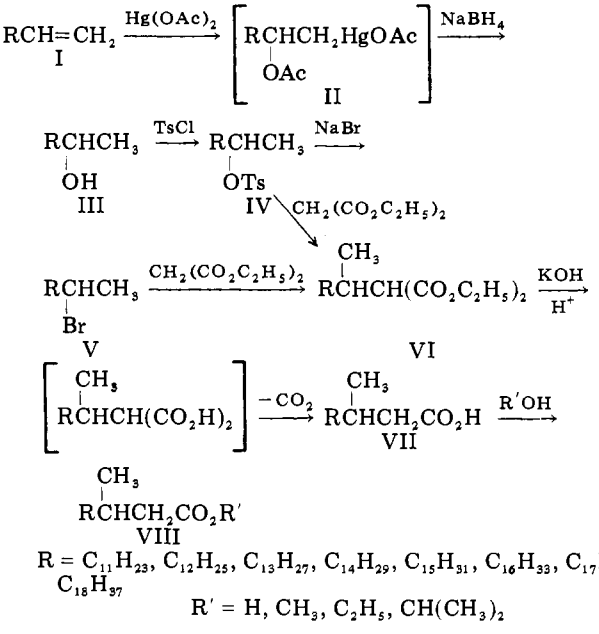
Among the compounds investigated thus far, some 3-methylalkanoic acids, such as 3-methyloctadecanoic acid and 2,3-dimethyloctadecanoic acids, exhibited the greatest larvicidal activity. It therefore became necessary to systematically study this series of compounds. Here we report the synthesis and evaluation of 3-methylalkanoic acids having 14–21 carbon atoms in the main chains and their methyl, ethyl, and isopropyl esters. Based on the evaluation, structure–activity relationships of these acids and their esters are studied and discussed.

EXPERIMENTAL SECTION

Synthesis. Previously, a 2-alkanol (III) (Scheme I) was synthesized by treating a methyl alkanoate with methylsulfinyl carbanion, hydrogenolyzing the resultant methylsulfinylmethyl alkyl ketone with aluminum amalgam, and subsequently reducing the 2-alkanone thus formed with lithium aluminum hydride (Hwang et al., 1974a). Despite the high yield, this procedure involved lengthy and laborious operations. A more convenient method using oxymercuration and demercuration of olefins (Brown and Geoghegan, 1967) was adopted for synthesizing the 2-alkanols (III) in the present work. Thus, a 1-alkene (I) was treated with mercuric acetate in aqueous tetrahydrofuran. The intermediary oxymercurial (II), without isolation, was then reduced with sodium borohydride in an alkaline medium to give the desired 2-alkanol (III).

Following the procedures similar to those reported previously (Hwang et al., 1974a), the 2-alkanol (III) was tosylated with *p*-toluenesulfonyl chloride in dry pyridine,

Scheme I. Synthesis of 3-Methylalkanoic Acids and Their Esters



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and the resulting 2-alkyl tosylate (IV) was allowed to react with sodium bromide in *N,N*-dimethylformamide to give a 2-bromoalkane (V). The 2-alkyl bromide (V) or the 2-alkyl tosylate (IV) was condensed with diethyl sodiomalonate in absolute ethanol to yield a diethyl alkylmalonate (VI), which, upon saponification and subsequent decarboxylation, produced a 3-methylalkanoic acid (VII). The acid was allowed to react with thionyl chloride to give a 3-methylalkanoyl chloride, which was then treated with an excess amount of methanol, ethanol, or isopropyl alcohol to yield the methyl, ethyl, or isopropyl ester of the acid (VIII).

All melting points and boiling points are uncorrected. All compounds synthesized were racemates; however, the prefix *dl* is omitted. Elemental analyses were conducted by Chemalytics, Inc., Tempe, Ariz., and the data were within ±0.4% of the theoretical values.

2-Alkanols (III). Mercuric acetate (127.69 g, 0.4 mol) was dissolved in water (400 mL), and tetrahydrofuran (400 mL) was added into the solution. Upon the addition of tetrahydrofuran, the clear aqueous solution became a yellow suspension. Into the stirred suspension, 1-alkene (0.4 mol) was added. As the reaction proceeded, the yellow suspension first became lighter, and then colorless and clear. It took from 5 to 40 min for the yellow color to disappear, depending upon the molecular weight of the 1-alkene. The colorless reaction mixture was further stirred for five times the length of time required for the yellow color to disappear.

Into the mixture, 3 M aqueous sodium hydroxide solution (400 mL) was added, followed by 0.5 M sodium borohydride in 3 M aqueous sodium hydroxide (400 mL). The mercury thus formed was allowed to settle, and sodium chloride was added to saturate the aqueous layer. The upper tetrahydrofuran layer was separated, and the aqueous layer was extracted twice with ether. The combined organic layers were dried and evaporated. The residue was distilled in vacuo or recrystallized from petroleum ether to give a 2-alkanol.

The 2-alkanols synthesized and their melting points and boiling points are as follows: 2-tridecanol, bp 115–116 °C (0.2 mm); 2-tetradecanol, bp 120–122 °C (0.2 mm); 2-pentadecanol, bp 124–126 °C (0.2 mm); 2-hexadecanol, bp 129–132 °C (0.2 mm) [lit. bp 135 °C (1 mm); Asinger and Eckoldt, 1943], mp 42–43 °C (lit. mp 42.2–45 °C; Breusch and Sokullu, 1953); 2-heptadecanol, bp 135–138 °C (0.2 mm), mp 46–47 °C (lit. mp 44–45.5 °C; Breusch and Sokullu, 1953); 2-octadecanol, bp 139–140 °C (0.2 mm), mp 51–53 °C (lit. mp 52–53 °C; Breusch and Sokullu, 1953); 2-nonadecanol, mp 57–58 °C; 2-eicosanol, mp 59–60 °C. The yield was 75–97%. These 2-alkanols showed IR (film or Nujol) at 3350 cm^{-1}.

2-Alkyl *p*-Toluenesulfonates (IV). The procedure of Hwang et al. (1974a) was followed. The 2-alkanols were treated with *p*-toluenesulfonyl chloride in dry pyridine to give the following tosylates: 2-tridecyl tosylate, mp 29–32 °C; 2-tetradecyl tosylate, mp 38–38.5 °C; 2-pentadecyl tosylate, mp 41–42 °C; 2-hexadecyl tosylate, mp 46–47 °C; 2-heptadecyl tosylate, mp 51–53 °C; 2-octadecyl tosylate, mp 54–55.5 °C; 2-nonadecyl tosylate, mp 57–58 °C; 2-eicosyl tosylate, mp 59–59.5 °C. The 2-alkyl tosylates showed IR (Nujol) at 1600, 1350, 1180 cm^{-1}.

2-Bromoalkanes (V). The 2-alkyl tosylates were treated with sodium bromide in *N,N*-dimethylformamide to give the following 2-bromoalkanes: 2-bromotridecane, bp 138–142 °C (26 mm); 2-bromotetradecane, bp 148–155 °C (26 mm); 2-bromopentadecane, bp 135 °C (1.3 mm); 2-bromohexadecane, bp 168–170 °C (2.4 mm); 2-bromoheptadecane, bp 139–142 °C (0.18 mm); 2-bromoeicosane, bp 165–167 °C (0.08 mm). The 2-bromoalkanes showed IR (film) at 2950, 2875, 1470, 1380, 735 cm^{-1}.

3-Methylalkanoic Acids (VII). The 2-bromoalkanes or the 2-alkyl tosylates were condensed with diethyl sodiomalonate in absolute ethanol to give substituted malonic esters which, upon saponification and decarboxylation, yielded the following 3-methylalkanoic acids: 3-methyltetradecanoic acid, bp 138–140 °C (0.2 mm), mp 31–32 °C; 3-methylpentadecanoic acid, bp 142–144 °C (0.3 mm), mp 36–36.5 °C; 3-methylhexadecanoic acid, bp 155–156 °C (0.3 mm), mp 41–42 °C; 3-methylheptadecanoic acid, mp 46–47 °C; 3-methyloctadecanoic acid, mp 52–53 °C; 3-methylnonadecanoic acid, mp 55–56 °C; 3-methyleicosanoic acid, mp 56–57 °C; 3-methylheneicosanoic acid, mp 59–60 °C. The acids showed IR (Nujol) at 3400–2100, 1700, 1420, 1290, 1240, 950 cm^{-1}.

Alkyl 3-Methylalkanoates (VIII). A 3-methylalkanoic acid (3 g) was refluxed with thionyl chloride (20 mL) for 2 h. The excess thionyl chloride was removed by evaporation. The residual 3-methylalkanoyl chloride was poured into an excess amount of methanol, ethanol, or isopropyl alcohol (50 mL). The mixture was stirred at room temperature for 30 min and the excess alcohol was removed by evaporation. The residue was distilled in vacuo to give nearly theoretical yields of the following esters: methyl 3-methyltetradecanoate, bp 95–98 °C (0.1 mm); ethyl 3-methyltetradecanoate, bp 98–100 °C (0.15 mm); isopropyl 3-methyltetradecanoate, bp 128–129 °C (0.3 mm); methyl 3-methylpentadecanoate, bp 98–100 °C (0.2 mm); ethyl 3-methylpentadecanoate, bp 116–117 °C (0.3 mm); isopropyl 3-methylpentadecanoate, bp 117–118 °C (0.3 mm); methyl 3-methylhexadecanoate, bp 121–122 °C (0.3 mm); ethyl 3-methylhexadecanoate, bp 123–125 °C (0.3 mm); isopropyl 3-methylhexadecanoate, bp 126–127 °C (0.3 mm); methyl 3-methylheptadecanoate, bp 140 °C (0.2 mm); ethyl 3-methylheptadecanoate, bp 142 °C (0.2 mm); isopropyl 3-methylheptadecanoate, bp 153 °C (0.1 mm); methyl 3-methyloctadecanoate, bp 142 °C (0.05 mm); ethyl 3-methyloctadecanoate, bp 150 °C (0.2 mm); isopropyl 3-methyloctadecanoate, bp 151 °C (0.2 mm); methyl 3-methylnonadecanoate, bp 155 °C (0.2 mm); ethyl 3-methylnonadecanoate, bp 165 °C (0.3 mm); isopropyl 3-methylnonadecanoate, bp 155 °C (0.2 mm); methyl 3-methyleicosanoate, bp 156 °C (0.2 mm); ethyl 3-methyleicosanoate, bp 166–168 °C (0.25 mm); isopropyl 3-methyleicosanoate, bp 157–158 °C (0.2 mm); methyl 3-methylheneicosanoate, bp 168–170 °C (0.05 mm); ethyl 3-methylheneicosanoate, bp 177 °C (0.1 mm); isopropyl 3-methylheneicosanoate, bp 178–180 °C (0.07 mm). The esters showed IR (film) at 1740 cm^{-1}.

Bioassays. First-instar larvae of *C. p. quinquefasciatus* were used in assessing the biological activity of the 3-methylalkanoic acids and their methyl, ethyl, and isopropyl esters. Details of the bioassay procedures were reported elsewhere (Hwang et al., 1974a,b). The bioassay data in terms of percent mortalities under various concentrations were analyzed by the log-probit regression analysis using Compucorp Model 145E computer. The biological activity of the test compounds was expressed by means of lethal concentrations in part per million inhibiting the emergence of 50 and 90% of the population (LC_{50} and LC_{90}).

RESULTS AND DISCUSSION

Table I shows the biological activity of the synthesized compounds against first-instar larvae of *C. p. quinquefasciatus*. Among the carboxylic acids studied, 3-methylheptadecanoic acid (**4**), 3-methyloctadecanoic acid (**5**), 3-methylnonadecanoic acid (**6**), and 3-methyleicosanoic

Table I. Biological Activity in ppm of 3-Methylalkanoic Acids and Methyl, Ethyl, and Isopropyl 3-Methylalkanoates against Mosquito Larvae

$$R\text{-}CH(CH_3)CH_2CO_2R'$$

	R′ = H			R′ = CH_3			R′ = C_2H_5			R′ = $CH(CH_3)_2$		
R	No.	LC_{50}	LC_{90}	No.	LC_{50}	LC_{90}	No.	LC_{50}	LC_{90}	No.	LC_{50}	LC_{90}
n-$C_{11}H_{23}$	1	6.51	>10.00	1-A	5.94	>10.00	1-B	1.30	1.87	1-C	>10.00	>10.00
n-$C_{12}H_{25}$	2	4.87	>10.00	2-A	1.15	1.32	2-B	8.21	>10.00	2-C	4.30	>10.00
n-$C_{13}H_{27}$	3	1.25	1.57	3-A	3.50	8.76	3-B	9.33	>10.00	3-C	4.46	9.24
n-$C_{14}H_{29}$	4	0.09	0.25	4-A	1.13	1.67	4-B	0.54	1.37	4-C	1.23	2.90
n-$C_{15}H_{31}$	5	0.47	0.64	5-A	0.15	0.38	5-B	0.48	1.63	5-C	1.02	1.85
n-$C_{16}H_{33}$	6	0.06	0.11	6-A	0.17	0.32	6-B	0.11	0.21	6-C	0.32	0.91
n-$C_{17}H_{35}$	7	0.26	0.38	7-A	0.38	0.58	7-B	0.97	1.75	7-C	0.70	1.72
n-$C_{18}H_{37}$	8	1.25	9.87	8-A	3.38	>10.00	8-B	4.42	>10.00	8-C	>10.00	>10.00

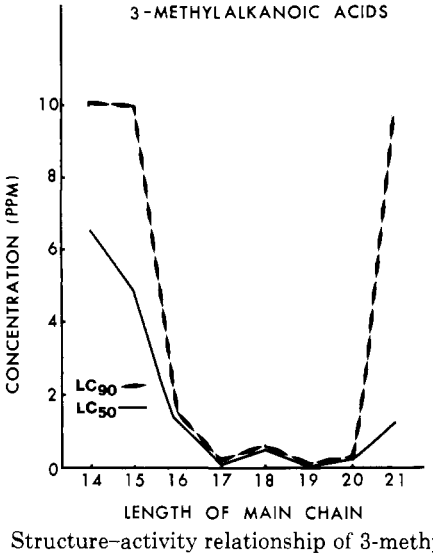

Figure 1. Structure–activity relationship of 3-methylalkanoic acids.

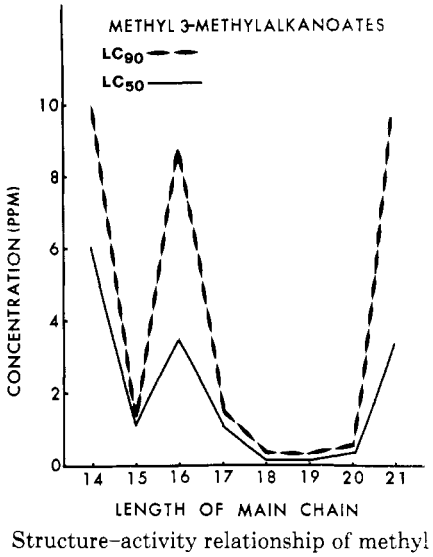

Figure 2. Structure–activity relationship of methyl 3-methylalkanoates.

acid (7) were the most active with LC_{50} and LC_{90} both below 1 ppm. Methyl 3-methyloctadecanoate (5-A), methyl 3-methylnonadecanoate (6-A), and methyl 3-methyleicosanoate (7-A) were the most effective methyl esters, their LC_{50} and LC_{90} being less than 1 ppm. Ethyl 3-methylnonadecanoate (6-B) and isopropyl 3-methylnonadecanoate (6-C) were the most active ethyl and isopropyl esters, respectively. Of all acids and esters investigated, 3-methylnonadecanoic acid (6) was the most potent with LC_{50} at 0.06 ppm and LC_{90} at 0.11 ppm.

The structure–activity relationships of these compounds are shown in Figures 1–4, in which the biological activity in terms of LC_{50} and LC_{90} in ppm is plotted against the length of the main chains in the acids and the esters. In the 3-methylalkanoic acid series (Figure 1), 3-methyltetradecanoic acid (1) showed weak activity with LC_{50} and LC_{90} both larger than 6 ppm. As the main-chain length increased to 3-methylpentadecanoic acid (2) and 3-methylhexadecanoic acid (3), the activity gradually increased. The activity reached the greatest when the main chain length increased to 3-methylheptadecanoic acid (4), 3-methyloctadecanoic acid (5), 3-methylnonadecanoic acid (6), and 3-methyleicosanoic acid (7). These carboxylic acids showed about the same level of activity; however, the C-19 acid (6) exhibited the lowest LC_{50} and LC_{90} among the acids and esters studied. The highest homologue of this series, 3-methylheneicosanoic acid (8), showed lower activity. The slopes of probit regression lines of the more active C-16, C-17, C-18, C-19, and C-20 acids (13.2, 3.0, 9.2, 4.4, and 7.8, respectively) were generally greater than those of the less active C-14, C-15, and C-21 acids (1.7, 3.8, and 1.4, respectively).

In the methyl 3-methylalkanoate series (Figure 2), the lowest homologue, methyl 3-methyltetradecanoate (1-A), had weak activity. The activity increased in methyl 3-methylpentadecanoate (2-A) but decreased in methyl 3-methylhexadecanoate (3-A). The greatest activity was achieved when the main-chain length extended from methyl 3-methylheptadecanoate (4-A) to methyl 3-methyloctadecanoate (5-A), methyl 3-methylnonadecanoate (6-A), and methyl 3-methyleicosanoate (7-A). The C-18 (5-A) and C-19 (6-A) methyl esters were the most effective in this series with LC_{50} at 0.15–0.17 and LC_{90} at 0.32–0.38 ppm. Thereafter, the activity diminished in methyl 3-methylheneicosanoate (8-A). The more active C-15, C-17, C-18, C-19, and C-20 methyl esters had greater slopes of probit regression lines than the less active C-14, C-16, and C-21 methyl esters (21.3, 7.6, 3.0, 4.9, and 7.0, respectively, as compared to 2.2, 3.2, and 1.5, respectively).

The first homologue of the ethyl 3-methylalkanoate series (Figure 3), ethyl 3-methyltetradecanoate (1-B), exhibited considerable activity. The activity, however, decreased in the next two higher homologues, ethyl 3-methylpentadecanoate (2-B) and ethyl 3-methylhexadecanoate (3-B) and increased thereafter in ethyl 3-methylheptadecanoate (4-B) and ethyl 3-methyloctadecanoate (5-B). The greatest activity was attained in ethyl 3-methylnonadecanoate (6-B), having LC_{50} and LC_{90} at 0.11 and 0.21 ppm, respectively. The last two ethyl esters, ethyl 3-methyleicosanoate (7-B) and ethyl 3-methylheneicosanoate (8-B) showed diminished activity. Similar to the previous two series, the slopes of probit regression lines were greater in the more active C-14, C-17, C-18, C-19, and C-20 ethyl esters (8.1, 3.2, 2.4, 4.7, and 5.0, respectively)

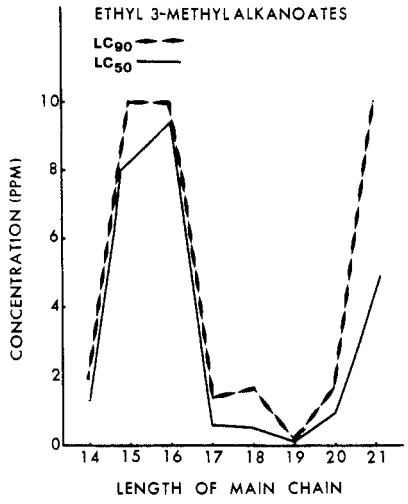

Figure 3. Structure–activity relationship of ethyl 3-methylalkanoates.

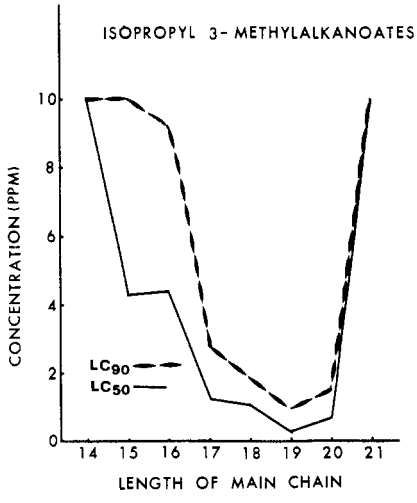

Figure 4. Structure–activity relationship of isopropyl 3-methylalkanoates.

than in the less active C-15, C-16, and C-21 ethyl esters (1.4, 1.2, and 1.3, respectively).

In the isopropyl 3-methylalkanoate series (Figure 4), the lowest homologue, isopropyl 3-methyltetradecanoate (**1-C**), was inactive. The activity slightly increased in isopropyl 3-methylpentadecanoate (**2-C**) and isopropyl 3-methylhexadecanoate (**3-C**). The next two higher homologues, isopropyl 3-methylheptadecanoate (**4-C**) and isopropyl 3-methyloctadecanoate (**5-C**), showed moderate activity. Isopropyl 3-methylnonadecanoate (**6-C**) exhibited the greatest activity in the series with LC_{50} and LC_{90} at 0.32 and 0.91 ppm, respectively. Thereafter, the activity slightly decreased in isopropyl 3-methyleicosanoate (**7-C**) and almost completely diminished in isopropyl 3-methylheneicosanoate (**8-C**). The slopes of probit regression lines of the more active C-17, C-18, C-19, and C-20 isopropyl esters (3.4, 5.0, 2.8, and 3.3, respectively) were again generally larger than those of the less active C-14, C-15, C-16, and C-21 isopropyl esters (1.3, 0.9, 4.0, and 0.5, respectively).

We previously reported that esterification of 2-alkylalkanoic acids produced more active methyl 2-alkylalkanoates (Hwang et al., 1976b). We also reported that esterification of less active 2-bromoalkanoic acids yielded more active methyl 2-bromoalkanoates but esterification of more active 2-bromoalkanoic acids did not produce more active methyl 2-bromoalkanoates (Hwang and Mulla, 1976). In the present studies, with a few exceptions, esterification of 3-methylalkanoic acids generally produced less active alkyl 3-methylalkanoates. The exceptions were ethyl 3-methyltetradecanoate (**1-B**) and methyl 3-methylpentadecanoate (**2-A**) which were more active than their corresponding carboxylic acids. The present studies also revealed that the activity of the esters showed a general tendency of decline as the size of alcohol moieties increased. Typical examples were shown in Figure 5. Although there were some deviations, the overall trend was such that the activity gradually declined as the R′ group changed from H to methyl, ethyl, and isopropyl groups in the C-17, C-18, C-19, and C-20 compounds.

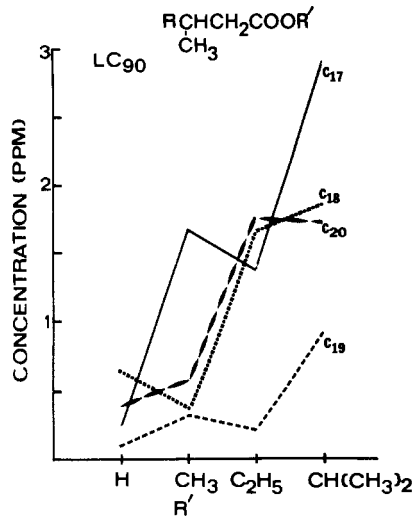

Figure 5. Relationship between the biological activity and the size of H and alcohol moieties in 3-methylalkanoic acids and their esters.

In studying the structure–activity relationship of 3-methylalkanoic acids and methyl, ethyl, and isopropyl 3-methylalkanoates having 14–21 carbon atoms in the main chains, we found that acids and esters having 17–20 carbon atoms in the main chains showed a high level of larvicidal activity. Especially, the C-19 acid and esters, i.e., 3-methylnonadecanoic acid (**6**) and methyl, ethyl, and isopropyl 3-methylnonadecanoates (**6-A**, **6-B**, **6-C**), exhibited the greatest biological activity. We also found that esters were, in general, less active than their corresponding carboxylic acids, and the activity declined in the order of carboxylic acids, methyl, ethyl, and isopropyl esters.

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