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Agriculture Handbook No. 403

Agricultural Research Service
UNITED STATES DEPARTMENT OF AGRICULTURE

Contents

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House Fly Attractants and Arrestants: Screening of Chemicals Possessing Cyanide, Thiocyanate, or Isothiocyanate Radicals

By M. S. Mayer, *Entomology Research Division, Agricultural Research Service* [1]

Few chemicals possessing cyanide (–CN), thiocyanate (–SCN), or isothiocyanate (–NCS) radicals have been tested as attractants for the house fly (*Musca domestica* L.). In fact, chemicals in these groups apparently have received little consideration as attractants or arrestants for any species. The distinction between attractant and arrestant was carefully drawn by Dethier and others (*3*).[2] These authors pointed out that an attractant is a chemical that causes insects to make oriented movements toward its source, but an arrestant is a chemical that causes insects to aggregate in contact with it. Thus, an attractant may work over a distance, but an arrestant must be contacted by the insect to have an effect. Some chemicals possessing these radicals as attractants and arrestants have been reported (Beroza and Green *1*, Green and others *6*, Jacobson *8*) and some of them have been reported as repellents.

Parman and others (*12*) found allyl isothiocyanate had little ability either to arrest or to repel the screw-worm (*Cochliomyia hominivorax* (Coquerel)). In a later publication the same group (Laake and others *9*) reported that allyl isothiocyanate was slightly attractive to *Musca domestica*, but it was considered to be one of the better repellents for *Phormia regina* (Meigen). Gupta and Thorsteinson (*7*) found allyl isothiocyanate to be a weak attractant and arrestant for *Plutella maculipennis* (Curtis), and it was also reported (Dethier *2*) to elicit a biting response by a mustard beetle, *Phaedon cochleariae* (F.).

LaBrecque and Wilson (*10*) found benzhydryl thiocyanate (diphenylmethyl thiocyanate) to be ineffective as a repellent for house flies. Since in this same report dioctylamine and two octyl sulfoxides were promising, Wilson and others (*15*) tested a group of similar or related chemical repellents. Included in these tests were two nitriles, 4-(octylsulfinyl)butyronitrile and 4-(octylthio)-butyronitrile, which appeared to be reasonably good repellents. In my tests these two chemicals failed to arrest a single fly. Ralston and Barrett (*13*) found that aliphatic nitriles containing 10 to 14 carbon atoms were more repellent to flies than oil of citronella. In my tests no aliphatic nitriles of these chain lengths were effective as arrestants.

METHODS

Two methods were used to screen the chemicals. One was to assess the ability of the chemical to attract house flies through olfactory stimulation with an olfactometer. The other was to assess the ability of the chemical to arrest the flies through odor, tarsal chemoreceptor contact, or both with petri-dish tests.

The olfactometer technique has been described by Mayer and Thaggard (*11*). By this technique the flies were confined in the olfactometer, a large cage with two circular ports at the front end. Each port was fitted with a cylindrical trap closed by a screen cover at the end away from the cage and a screen funnel at the end toward the cage. Com-

[1] I thank the following people in this Division: M. W. Abbott, G. S. Asbell, and J. D. James for screening the chemicals, D. J. Guinyard for formulating most of the chemicals, Marie Osborne for assistance with the chemical nomenclature, and C. N. Smith for helpful criticism, guidance, and encouragement.

[2] Italic numbers in parentheses refer to Literature Cited, p. 26.

petitive attractants were exposed in pairs in sleeves attached to the end of the traps farthest from the cage. Air was drawn by a suction fan through the sleeves, over the attractant, through the trap, through the cage of flies, and then exhausted outside the building. After 30 minutes the flies captured in the traps were counted and returned to the cage.

The flies were from the regular laboratory colony and were reared in the usual manner on CSMA medium. All were reared under alternating 12-hour periods of light and darkness. When the adult flies were 1 to 3 days old, they were counted under carbon dioxide narcosis, placed in the olfactometer, and held under constant light. They were not tested within 24 hours after narcosis. Water was provided in the olfactometer at all times. The food was the standard adult diet of powdered egg yolk, milk solids, and sucrose, which was placed in four small paper cups. For tests with ammonia, the food remained in the olfactometer at all times. For tests with the cyanide compounds, the food was removed 2 hours prior to initial testing and returned at the end of the day.

To begin each series of tests, 150 males and 150 females were placed in the olfactometer. During the tests a few flies occasionally escaped. Dead flies were counted daily and the number was subtracted from the computation of flies in the test, but they were not removed from the cage. At the end of each week, when the flies remaining in the olfactometer were 7 to 10 days old and not suitable for further testing, they were killed and counted. When this procedure was used by a capable technician, the final counts never showed more than 8 percent error in the figures previously obtained by subtraction.

The petri-dish technique (Dethier and others *3*) was performed as follows: From 500 to 700 house flies from the regular colony or an insecticide-resistant strain (Cradson-P) were anesthetized with carbon dioxide. Equal numbers of each sex were placed in cylindrical screen holding cages (20.3 cm. long and 6.3 cm. in diameter), provided with a small amount of a 10 percent honey solution on absorbent cotton pads, and held overnight in a room at 27° ± 1° C. and 50 ± 5 percent relative humidity. The next day, 18 hours after anesthesia, the flies were released in the same room into a cubical cage (1.22 meters on a side) and allowed to feed on 10 to 20 grams of sugar for 30 minutes. During this interval all dead flies were removed from the cage and counted so that the number and sex ratio of those in the cage were known. After the 30-minute feeding interval, the sugar was removed; 30 minutes later it was offered to the flies again and testing was begun only after 2 percent of the flies had begun to feed.

In several tests, flies held overnight in a relative humidity of 70 ± 5 percent and tested at 50 percent relative humidity did not approach the food as readily as those held at 50 ± 5 percent. Flies held at the higher relative humidity tended to show much less mortality than those held at the lower humidity. These observations may indicate that the flies at 70 percent relative humidity fed better on the honey than at 50 percent. The percentage of the regular-colony flies that approached the feeding dishes during testing was smaller than that of the Cradson-P strain. Other observations indicated that the percentage of flies feeding was also affected by other factors such as their age and overcrowding of the larvae in the rearing containers, as well as interactions between all these factors. In all tests, however, the 2 percent feeding criterion was strictly followed as the minimum activity for beginning tests, and all chemicals were retested if the number of flies on a sugar standard fell below 2 percent of the total in the cage.

Solutions or suspensions of the test chemicals in acetone or water were mixed thoroughly with white fire-cleaned sand at the rate of 0.2 gram of test chemical to 20 grams of sand. Two uncovered 9-cm. petri dishes, one containing the treated sand and the other containing an equal volume of granulated white sugar (about 13 grams) as a standard, were exposed simultaneously in the cage of flies. After 2 minutes the flies in each dish were counted and disturbed from the dishes by a wave of the hand, the positions of the dishes were reversed, and the test was repeated. Four 2-minute exposure periods constituted a test. The number of flies on the experimental material divided by the number feeding on the standard (T/Std) gave the ratio to the standard. This test was designed primarily to select materials favored as foods, but it may also show the presence of compounds stimulating other responses as well as feeding.

Since these tests were performed with flies fed within 2 hours prior to testing, I assume that the foregut stretch receptor studied by Gelperin (*4*, *5*) could have affected the threshold of response in

such a way as to lower the response of the flies, at least in the petri-dish tests and possibly in the olfactometer tests. However, in such a screening program as this, a chemical that would still be operative under these conditions would be even better if the flies were starved.

Many of the chemicals used in these tests were old and had been held in storage facilities subject to the vagaries of outside temperature conditions. In some instances, the chemical quite possibly had become degraded. However, it was tested on the assumption that all activity may not have been lost. Most of the chemicals were crystalline, and after formulation they were always held under refrigeration.

RESULTS AND DISCUSSION

For many years olfactory attractants specific for the house fly have been sought by screening or testing in glass traps similar to those described by Parman and others (*12*) and LaBrecque and Wilson (*10*). Generally this technique has not been as satisfactory as desired because of its extreme variability. For this and other reasons, the olfactometer technique as described here was developed for testing attractants where olfactory stimulation must be followed by positive anemotactic or klinokinetic movement.

Edamin, a hydrolyzed milk protein solid, was used as the standard, although it has only slight capacity for olfactory stimulation. Where proteinaceous baits such as Edamin are subjected to bacterial decomposition, ammonia or other bacterial metabolic byproducts or both probably account for most of the attractiveness. The results of preliminary tests with Edamin, water, and ammonium hydroxide are shown in table 1. The tests were paired comparisons and analyzed accordingly. Edamin was considered a good standard for comparison because (1) it is slightly more attractive than water; (2) the standard errors of the means were low; (3) little sexual bias existed; (4) the presence or absence of food in the cages failed to produce a marked difference in the response; and (5) Edamin rarely failed to attract some flies during these tests. When Edamin was compared with 1.0 N ammonium hydroxide, the males definitely preferred Edamin, whereas the females, as expected, preferred 1.0 N ammonium hydroxide.

TABLE 1.—*Attractiveness of Edamin, water, and ammonium hydroxide to house flies with and without food in olfactometer tests*

Replications (number)	Attractant [1]		Males trapped [2]		Females trapped [2]	
	Port 1	Port 2	Port 1	Port 2	Port 1	Port 2
			Percent	*Percent*	*Percent*	*Percent*
		WITH FOOD IN CAGE				
7	Dry Edamin	Wet Edamin	8.1	8.5	5.5	3.6
11	do	Water	8.6	3.6	8.7	2.1
	Wet Edamin	do	10.4**	4.9	5.0	3.5
		WITHOUT FOOD IN CAGE				
6	Dry Edamin	Wet Edamin	7.3	6.7	4.1	7.8
	do	Water	9.0	5.5	3.4	3.6
	Wet Edamin	do	5.9	4.9	8.2*	3.6
12	Wet Edamin	1.0 N ammonium hydroxide.	8.3*	4.4	6.0	14.6*

[1] Wet Edamin = 1 gram of Edamin with enough water (about 5 ml.) to give consistency of batter.

[2] Statistical significance in paired comparisons indicated by asterisks (* = 0.05 level, ** = 0.01 level).

Since considerable data existed on the attraction of house flies to ammonia (Richardson *14*, and others), I used ammonia to test the olfactometers, techniques, and flies to determine whether the percent attraction conformed to a logarithmic increase relative to the concentration used. Ammonia was introduced into the cages by placing 2 ml. of solution containing various concentrations of ammonium hydroxide on filter paper in the bottom of Syracuse watch glasses. The solutions were replaced at 10-minute intervals during the 30-minute test period.

The results of tests in which ammonia was introduced in an ascending order of concentration are presented in figure 1. This graph is a compilation of data for flies of several generations and ages. The concentration-response relationship conforms to a straight line over four log units of concentration, with the response decreasing at the two highest concentrations. The method employed for introducing the ammonia is primitive and was meant to test the flies under conditions intended for screening other chemicals. The standard errors were large. However, within most groups of flies of the same generation the line appeared straight over six log units and would then, of course, conform to the Weber-Fechner relationship over the entire range tested.

A true sensory response is evident in the data obtained when the concentrations were tested in descending order, as shown in figure 2. The highest concentration induced a higher response when offered at the beginning of the series than when offered after the lower concentrations (fig. 1). This was followed by an adaptation to all lower concentrations and hence a reduced response. In fact, the concentration that gave the highest response when offered in ascending order produced a response in this series that was not statistically above the threshold (about 5 percent). For these reasons, the olfactometers were presumed to measure accurately the olfactory stimulation of various chemicals that produce behavioral change. Additional data showed no response by females prior to 5 days of age and no response after oviposition, indicating that the olfactory response to ammonia is dependent on ovarian development.

A screening program of potential olfactory attractants for the house fly was undertaken with these olfactometers. Early in this program certain nitriles were observed to stimulate a large number of females to enter the paired control port baited with Edamin. The results of olfactory tests with

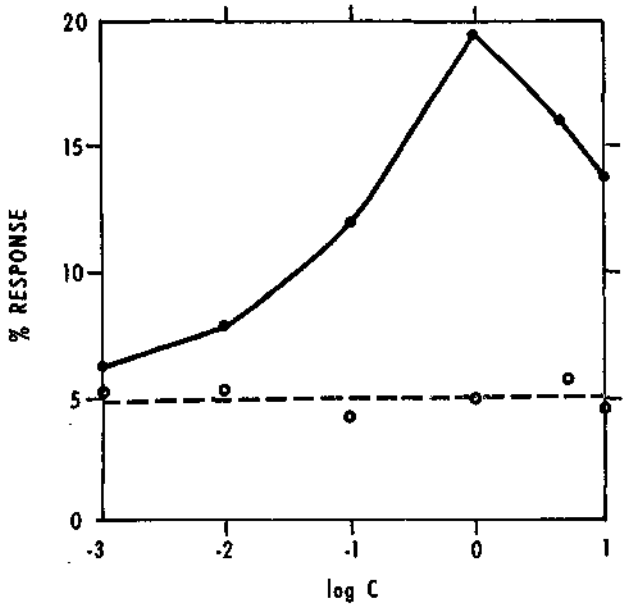


FIGURE 1.—Attraction of 5- to 7-day-old female house flies to various concentrations of ammonium hydroxide when offered in ascending order (solid line) as compared to male and female response to water and male response to ammonium hydroxide (control) (dotted line).

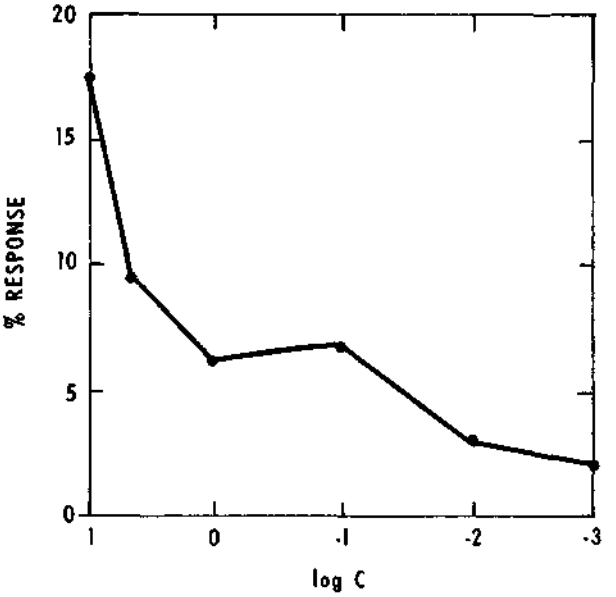
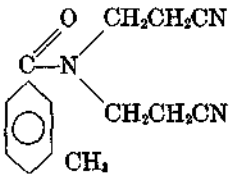


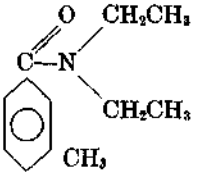
FIGURE 2.—Attraction of 5- to 7-day-old female house flies to various concentrations of ammonium hydroxide when offered in descending order, based on six to eight replications for each point.

52 nitriles are presented in table 2. None of the compounds were highly attractive, but several were associated with unusually high response to Edamin. Two possible behavioral responses could produce these results: (1) The entry of the flies into the Edamin trap could be an avoidance response to the nitrile (repellency), since the Edamin trap was the only part of the olfactometer accessible to the flies that was free of the nitrile odor or (2) the nitrile odor could stimulate a feeding response or a search for food by the females, which then orient to the odor of Edamin. Later tests with the petri-dish technique were to give some indication as to whether the compounds were actually repellents or feeding stimulants.

The first nitrile derivative screened in petri dishes was *N,N*-bis(2-cyanoethyl)-*m*-toluamide (ENT–26949). A high positive response (ratio T/Std = 5.3:1) to this chemical was observed (table 3). The attractiveness or arrestancy of this chemical was apparently due to the presence of the cyano groups, since *N,N*-diethyl-*m*-toluamide (ENT–20219), which is otherwise



ENT–26949



ENT–20219

TABLE 2.—*Attractiveness to house flies of Edamin and various nitriles, listed in order of female response to Edamin, in paired olfactometer tests (3 replications)*

Code No. (ENT–)	Chemical	Attractancy of Edamin to—		Attractancy of chemical to—	
		Males	Females	Males	Females
		Percent	*Percent*	*Percent*	*Percent*
16234	1-Naphthalenepropionitrile, 2-hydroxy-	9.1	42.8	6.8	2.5
16310	Benzonitrile, *m*-nitro-	6.0	37.4	6.6	2.5
17792	Propionitrile, 3-(*p*-chlorobenzoyl)-2-[3,4-(methylenedioxy)phenyl]-	8.4	27.5	7.1	2.4
17128	*o*-Tolunitrile	7.6	26.7	3.6	.9
17129	*m*-Tolunitrile	7.8	25.5	8.6	2.1
17436	Acetonitrile, diphenyl-	11.1	25.0	8.1	2.1
18677	Heptanedinitrile, 4-acetyl-4-phenyl-	7.5	25.0	9.7	2.0
14826	*p*-Tolunitrile	12.9	23.7	4.6	2.8
16034	Heptanedinitrile, 4-(*p*-bromobenzoyl)-4-(2-cyanoethyl)-	4.8	23.6	8.2	4.8
28304	2-Decenenitrile	4.0	22.6	2.6	.2
13188	4-Morpholinepropionitrile	8.7	21.6	5.9	4.4
310	Myristonitrile	17.3	16.6	10.6	3.7
16027	Heptanedinitrile, 4-benzoyl-4-(2-cyanoethyl)-	5.3	16.1	6.4	5.4
28305	2-Nonenenitrile	7.3	14.6	1.1	3.5
14265	4-Morpholinesuccinonitrile	13.3	14.4	10.1	4.0
20145	Mandelonitrile, 3,4-(methylenedioxy)-	3.0	13.8	8.2	2.5
49	Phthalonitrile	12.1	13.0	6.9	1.4
4979	1-Cyclohexene-1-acetonitrile	5.2	12.3	.9	.5
17751	Glycinonitrile, *N*-methylene-	6.6	12.1	9.6	3.1
16033	Heptanedinitrile, 4-(2-cyanoethyl)-4-*p*-toluyl-	4.3	11.4	5.3	13.1
16026	1,1,3,3-Cyclopentanetetrapropionitrile, 2-oxo-	4.9	11.4	4.4	1.9
17359	Acetonitrile, bis[*p*-(dimethylamino)phenyl]phenyl-	6.7	11.1	6.5	2.0
7618	Heptadecanenitrile	10.4	10.9	9.4	3.3
8103	Sebaconitrile	9.1	10.9	8.9	5.8
4981	1-Cyclohexene-1-acetonitrile, 2-allyl-	7.6	9.6	2.4	3.1
234	2-Naphthonitrile	6.4	9.4	7.2	3.5
15766	Nicotinonitrile	4.0	9.3	6.1	3.4

TABLE 2.—*Attractiveness to house flies of Edamin and various nitriles, listed in order of female response to Edamin, in paired olfactometer tests (3 replications)*—Continued

Code No. (ENT–)	Chemical name	Attractancy of Edamin to—		Attractancy of chemical to—	
		Males	Females	Males	Females
		Percent	*Percent*	*Percent*	*Percent*
17661	Cyclopropanecarbonitrile, 2-benzoyl-1,3-diphenyl-	7.9	8.9	13.0	5.1
478	Benzonitrile, *p*-nitro-	4.5	8.8	5.9	1.1
18124	Cyclohexanecarbonitrile, 1-heptyl-	8.2	8.8	5.5	1.3
1547	Nicotinonitrile, 1,2-dihydro-1,4,6-trimethyl-2-oxo-	8.1	8.2	5.3	4.7
16570	Tridecanenitrile	7.6	7.4	4.6	3.3
15707	Lactonitrile, acetate	5.9	7.4	5.9	4.9
16030	Heptanedinitrile, 4-(*p*-chlorobenzoyl)-4-(2-cyanoethyl)-	8.7	7.1	6.6	4.9
13063	Heptanedinitrile, 4-acetyl-4-methyl-	9.2	6.9	7.9	4.9
11234	Palmitonitrile	11.8	6.8	9.2	5.6
7106	Hexanenitrile, 2,4-dihydroxy-3,3,5-trimethyl-	9.3	6.6	8.6	4.3
15930	Butyronitrile, 4-benzoyl-2-(*alpha*-phenacylbenzyl)-2,3-diphenyl-	4.9	6.3	4.7	2.4
16089	Heptanedinitrile, 4-(2-cyanoethyl)-4-(3,4-dichlorobenzoyl)-	3.7	6.0	9.8	2.3
16090	Heptanedinitrile, 4-benzoyl-4-methyl-	6.9	5.8	6.7	.6
4364	Acetonitrile, benzoyl-	10.3	5.7	13.8	4.0
54	Acrylonitrile	6.8	5.7	5.4	2.2
11298	Benzonitrile, 2,4,6-triisopropyl-	8.8	5.3	8.3	3.3
11801	*p*-Anisonitrile	7.1	4.7	7.5	2.1
8777	Propionitrile	8.1	4.5	8.8	4.5
4975	Acetonitrile, phenyl-	9.1	4.4	4.8	2.4
11080	Adiponitrile	8.7	4.3	7.5	2.1
311	Lauronitrile	7.3	4.2	7.0	3.5
28307	2-Furanacrylonitrile	9.2	3.9	3.4	1.0
1651	3-Cyclohexene-1-carbonitrile, 5,5-dimethyl-2-(1-methylpropenyl)-	4.5	3.6	3.3	1.7
28306	2-Octenenitrile, 5,7,7-trimethyl-	5.8	2.9	3.8	1.6
7024	Glutaronitrile	7.5	2.5	7.7	7.4

structurally identical, is one of the best insect repellents. However, I also considered the cyanoethyl radical (I) or propionitrile (ENT–8777) as

$-CH_2CH_2CN$	CH_3CH_2CN
I	ENT–8777

having a potential worth investigating. Thus, early in this program certain known repellents and derivatives were screened to eliminate any likelihood that toluamide and benzamide derivatives were attractive.

The ratios of the numbers of flies on the treated sand to the numbers on granulated sugar were computed (table 3). In addition, from the results with all chemicals tested, five class groupings were assigned, based on the total number of flies arrested on the treated sand, regardless of the numbers found on the sugar standard. This arrangement is highly artificial and not conducive to analytical calculations; however, it was adopted for ease of visualizing all the data. Untreated sand failed to arrest any flies. The chemicals were classified as follows according to their arrestancy to flies:

Class	*Flies (number) arrested by chemical*
1	0
2	1–4
3	5–25
4	26–100
5	Over 100

The toluamides and related compounds that showed some arrestancy are listed in table 3. The completely ineffective compounds were as follows:

Code No. (ENT–)	*Chemical*
26772	*m*-Toluamide, *N,N*-dicyclohexyl-
26774	*m*-Toluamide
30105	*m*-Toluamide, *N,N*-dimethyl-
30033	*o*-Toluamide, *N,N*-dimethyl-
30330	*p*-Toluamide, *N,N*-dimethyl-

Code No. (ENT–)—Con.	*Chemical*
20219	*p*-Toluamide, *N,N*-diethyl-
20218	*m*-Toluamide, *N,N*-diethyl-
20217	*o*-Toluamide, *N,N*-diethyl-
26779	*m*-Toluamide, *N,N*-diethyl-*alpha,alpha,alpha*-trifluoro-
26781	*m*-Toluamide, *N,N*-diethyl-*alpha*-hydroxy-
30126	*m*-Toluamide, *N,N*-dibutyl-
30002	*o*-Toluamide, *N,N*-dibutyl-
30146	*p*-Toluamide, *N,N*-dibutyl-
32948	*m*-Toluamide, *N*-ethyl-*N*-isobutyl-
32952	*m*-Toluamide, *N*-ethyl-*N*-propyl-
26059	*m*-Toluamide, *N*-ethoxy-*N*-ethyl-
30355	*p*-Toluamide, *N*-butyl-
32943	*p*-Toluamide, *N*-butyl-*N*-methyl-
32950	*m*-Toluamide, *N*-butyl-*N*-methyl-
20931	*m*-Toluamide, *N*-isobutyl-
32953	*m*-Toluamide, *N*-isobutyl-*N*-propyl-
19775	Benzamide, *N,N*-dibenzyl-*p*-ethoxy-
19084	Benzamide, *N,N*-dibutyl-*o*-ethoxy-
19710	Benzamide, *N,N*-dibutyl-*p*-ethoxy-
20297	Benzamide, *o*-ethoxy-*N,N*-diethyl-
19708	Benzamide, *N*-butyl-*p*-ethoxy-
20701	Benzamide, *m*-chloro-*N,N*-diethyl-
17586	Benzamide, *o*-chloro-*N,N*-diethyl-
20698	Benzamide, *N,N*-diethyl-3,5-dimethyl-
20490	Benzamide, *N,N*-diethyl-*o*-isopropoxy-
20454	Benzamide, *N,N*-diethyl-*o*-propoxy-
20690	Benzamide, *N,N,o*-triethyl-
22386	Benzamide, *N,N*-dibutyl-*o*-chloro-
30182	Benzamide, *N,N*-dibutyl-*p*-isopropyl-
1016	Benzamide, *N*-pentyl-
19715	Benzamide, *p*-ethoxy-*N*-pentyl-
19716	Benzamide, *p*-ethoxy-*N,N*-dipentyl-
16750	Benzamide, *N*-cyclohexyl-*N*-pentyl-
20596	Phthalamide, *N,N,N',N'*-tetraethyl-
17014	*p*-Anisamide, *N,N*-diisopropyl-

None of the compounds were in class 5 except *N,N*-bis(2-cyanoethyl)-*m*-toluamide (ENT–26949), and only two were in class 4. In addition, ENT–26949 was the only compound with a ratio to sugar in excess of 1.0. Thus, it was reasonable to assume that the cyano or the cyanoethyl moiety was the principal causative agent of the arrestant activity exhibited by ENT–26949. Therefore, a large-scale screening program was accomplished with its ultimate aim to determine which possible combinations of structures carrying the cyanide (–CN), thiocyanate (–SCN), and isothiocyanate (–NCS) radicals could be responsible for the arrestancy of house flies. To date, 390 chemicals have been screened in this program.

The results of this system of classification for all chemicals tested except those in table 3 are presented in figure 3. This graph illustrates several

TABLE 3.—*Arrestant activity of various toluamides, benzamides, and other compounds in petri-dish tests*

Code No. (ENT–)	Chemical	Class	Ratio T/Std
26949	*m*-Toluamide, *N,N*-bis-(2-cyanoethyl)	5	5.3:1
26773	*m*-Toluamide, *N,N*-dibenzyl-	4	[1] .431:1
31518	*m*-Toluamide, *N,N*-dioctyl-	4	.2:1
26950	*m*-Toluamide, *N,N*-diethylthio-	3	[1] .205:1
20930	*o*-Toluamide, *N*-isobutyl-	3	.03:1
30079	*o*-Toluamide, *N*-benzyl-	2	[1] .05:1
26804	*m*-Toluamide, *N,N*-di-2-pyridyl-	2	.02:1
32949	*m*-Toluamide, *N*-butyl-*N*-ethyl-	2	.01:1
20946	*p*-Toluamide, *N*-isobutyl-	2	.01:1
20680	Benzamide, *p-tert*-butyl-*N,N*-diisopropyl-	2	.03:1
19714	Benzamide, *N*-benzyl-*p*-ethoxy-	2	.02:1
19204	Benzamide, *N,N*-dibenzyl-*o*-ethoxy-	2	.02:1
28462	*m*-Toluidine, *N,N*-diethyl-	3	.08:1

[1] Two or more tests.

features of the power of arrestancy for this entire group of chemicals. No thiocyanates or isothiocyanates were found that could be included in classes 4 and 5. However, only 61 thiocyanates were tested. If the probability of finding a class

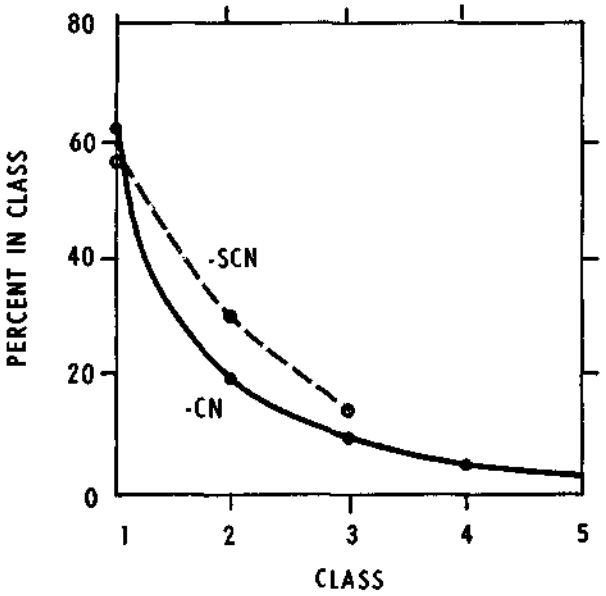


FIGURE 3.—Proportion of all cyanides (–CN) and thiocyanates (–SCN) as arrestants in each class, based on petri-dish tests.

4 or 5 arrestant was the same as for the cyanides, then only two class 5 arrestants could have been expected and four in class 4. Thus, with only six chemicals expected to be class 4 or 5 arrestants, the probability of finding them with this number of chemicals tested may not be too good. Of course, it is possible that no thiocyanate will be a class 4 or 5 arrestant.

Of all cyanides tested, 39.8 percent were considered active; 17.7 percent were in class 2, 10.2 percent in class 3, 5.9 percent in class 4, and 3.7 percent in class 5.

Prior to discussing the organic cyanides, the results with three inorganic cyanides should be noted. Although none of the three were outstanding arrestants, sodium pentacyanonitrosylferrate(*III*) (sodium nitroferricyanide) (ENT–28742) was a class 3 arrestant (ratio 0.25), and even cupric cyanide (ENT–904) was slightly active (ratio 0.01). Sodium cyanide was inactive.

Thiocyanic Acid Esters

Results with various types of thiocyanates that showed some arrestancy are given in table 4. None of the aliphatic esters of thiocyanic acid approached the magnitude of activity shown by certain of the straight-chain cyanides (table 6). Some small activity was observed in those with 2, 16, and 18 carbon chains. The ineffective compounds were as follows:

Code No. (ENT–)	*Chemical*
16178	Thiocyanic acid, methyl ester
18432	Thiocyanic acid, heptyl ester
1125	Thiocyanic acid, octyl ester
1127	Thiocyanic acid, decyl ester
114	Thiocyanic acid, dodecyl ester
1128	Thiocyanic acid, tetradecyl ester

Virtually all of a group of alkyl *p*-hydroxyphenyl thiocyanates were at least slightly active; only 5-*tert*-butyl-4-hydroxy-*m*-tolyl thiocyanate (ENT–19643) was inactive. In certain instances, discussed later (p. 14), hydroxyl groups may have induced great activity in a few chemicals where such a degree of arrestancy was not expected.

Slightly more than half of a group of complex thiocyanates showed some arrestancy. The ineffective compounds were as follows:

Code No. (ENT–)	*Chemical*
15788	Nicotine, compound with cadmium thiocyanate and thiocyanic acid (2:1:2)
17355	Pyrrolidinium, 1-methyl-1-octyl-2-(3-pyridyl)....thiocyanate
15825	Pyrrolidinium, 1-butyl-1-methyl-2-(3-pyridyl)....thiocyanate
15804	Pyrrolidinium, 1-hexadecyl-1-methyl-2-(3-pyridyl)....thiocyanate
17354	Pyrrolidinium, 1-benzyl-1-methyl-2-(3-pyridyl)....thiocyanate
17353	Pyrrolidinium, 1-(o-chlorobenzyl)-1-methyl-2-(3-pyridyl)....thiocyanate
1412	Nicotine, compound with cuprous thiocyanate (2:1)

A few miscellaneous thiocyanates that showed some activity are listed in table 4. Miscellaneous ineffective compounds were as follows:

Code No. (ENT–)	*Chemical*
8887	Thiocyanic acid, benzyl ester
21778	Thiocyanic acid, phenacyl ester
7797	Thiocyanic acid, benzyl pentyl ester
14724	Propionic acid, 3-thiocyanato-, 6-propylpiperonyl ester
14725	Valeric acid, 2-thiocyanato-, 6-propylpiperonyl ester
17008	Thiocyanic acid, pentachlorocyclohexyl ester
19643	Thiocyanic acid, S-*tert*-butyl-4-hydroxy-*m*-tolyl ester
4258-X	Thiocyanic acid, mixed esters with 1-chloro-3-(isobornyloxy)-1,2-propanediol
25370	Acetic acid, thiocyanato-, 2-(isobornyloxy)-ethyl ester
19555	Crotonic acid, 3-thiocyanatopropyl ester
4789	Propionic acid, 2-thiocyanato-, ester with dipentenecarbinol
4788	Propionic acid, 2-thiocyanato-, ester with dipentenecarbinol, hydrogenated
2567	Thiocyanic acid, diester with triethylene glycol
3999	Thiocyanic acid, diester with diethylene glycol (Lethane A-70)
8	Lethane 384 Special (aliphatic thiocyanate)
5	Lauric acid, 2-thiocyanatoethyl ester (Lethane 60)
7	Lethane 384 Special; 50 percent mixture of three parts 2-thiocyanatoethyl esters of aliphatic acids and one part 2-(2-butoxyethoxy) ethyl thiocyanate

Some of these are insecticides (Lethane series).

Only eight isothiocyanates were screened (table 5). Three of these demonstrated some activity, but none were outstanding.

TABLE 4.—*Arrestant activity of various thiocyanates in petri-dish tests*

Code No. (ENT–)	Chemical	Class	Ratio T/Std
	ALIPHATIC THIOCYANATES		
18429	Thiocyanic acid, ethyl ester	2	[1,2] 0.085
1126	Thiocyanic acid, hexadecyl ester	2	.013
1124	Thiocyanic acid, octadecyl ester	2	.033
	ALKYL *p*-HYDROXYPHENYL THIOCYANATES		
19635	Thiocyanic acid, 4-hydroxy-*m*-tolyl ester	3	[1] .12
19636	Thiocyanic acid, 4-hydroxy-*o*-tolyl ester	2	.03
19638	Thiocyanic acid, 4-hydroxy-2,6-xylyl ester	3	.31
19639	Thiocyanic acid, 4-hydroxy-3,5-xylyl ester	2	[1] .05
19637	Thiocyanic acid, 3-ethyl-4-hydroxyphenyl ester	3	.43
19641	Thiocyanic acid, 4-hydroxy-*m*-cumenyl ester	2	[1] .01
19642	Thiocyanic acid, 5-hydroxycarvacryl ester	2	[2] .15
	COMPLEX THIOCYANATES		
15792	Nicotine, compound with cobaltic thiocyanate and thiocyanic acid (2:1:2)	3	[1] .40
15780	Nicotine, compound with manganous thiocyanate and thiocyanic acid (2:1:2)	2	.09
15778	Nicotine, compound with cuprous thiocyanate and thiocyanic acid (1:1:1)	2	[2] .08
15795	Nicotine, compound with cuprous cyanide and thiocyanic acid (1:1:1)	2	[2] .07
1415	Nicotine, compound with cupric thiocyanate (1:1)	3	.07
15784	Nicotine, compound with cupric thiocyanate and thiocyanic acid (2:1:2)	2	[1,2] .03
15837	Nicotinium compound, *N,N'*-didodecyl-dithiocyanate	2	[2] .02
15823	Pyrrolidinium, 1-methyl-1-(*p*-nitrobenzyl)-2-(3-pyridyl) ____thiocyanate	2	.01
	MISCELLANEOUS THIOCYANATES		
14723	Acetic acid, thiocyanato-, 6-propylpiperonyl ester	2	[1] .01
16979	Thiophene, 5-chloro-2-(1,2-dithiocyanatoethyl)-	2	[2] .07
188	Thiocyanic acid, 4-methyl-1-naphthylmethyl ester	2	[1] .11
4784	Thiocyanic acid, tris(*p*-chlorophenyl)methyl ester	2	.03
18233	Thiocyanic acid, diester with *p,p'*-iminodiphenol	3	.12
22371	Propionic acid, 2-thiocyanato-, ethyl ester	2	.02

[1] Seemed to stimulate flies more than ratio would indicate.
[2] Two or more tests.

TABLE 5.—*Arrestant activity of various isothiocyanates in petri-dish tests*

Code No. (ENT–)	Chemical	Class	Ratio T/Std
16038	Isothiocyanic acid, 4-biphenylyl ester	3	0.09
16158	Isothiocyanic acid, *p*-(2-pyrimidylsulfamoyl)phenyl ester	3	.23
23336	Isothiocyanic acid, 1,1,3,3-tetramethylbutyl ester	2	.05
15283	Isothiocyanic acid, allyl ester	1	0
16039	Isothiocyanic acid, *p*-bromophenyl ester	1	0
16040	Isothiocyanic acid, *p*-chlorophenyl ester	1	0
17006	Isothiocyanic acid, 3-methoxy-1-vinylpropyl ester	1	0
17005	Isothiocyanic acid, 3-butoxy-1-vinylpropyl ester	1	0

In consideration of the relatively small number of thiocyanates and isothiocyanates tested for house fly arrestancy, no final conclusion should be drawn of the potential activity of this group of chemicals. However, it does not seem likely that any will compare favorably with the nitriles in activity. However, the thiocyanic acid radical should be synthesized onto the same molecular structures as other class 5 cyanides for a true comparison of activity.

Straight-Chain Nitriles

Twelve nitriles were tested that differed only in the length of the hydrocarbon chain (table 6). None with chains more than five carbon atoms long exhibited any activity, and valeronitrile (ENT–30052) demonstrated only slight activity.

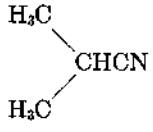
$CH_3(CH_2)_3CN$

ENT–30052

Propionitrile (ENT–8777) was the best of the short-chain nitriles, whereas acetonitrile (ENT–327) and butyronitrile (ENT–8778) were slightly

CH_3CH_2CN	CH_3CN	$CH_3(CH_2)_2CN$
ENT–8777	ENT–327	ENT–8778

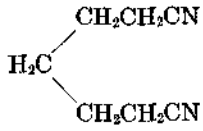
less effective. Isobutyronitrile (ENT–28525) (not a straight-chain compound, see p. 16) was also about equal to acetonitrile and butyronitrile.



ENT-28525

Since these straight-chain nitriles were active, the next logical step was to test derivatives with two cyano groups. The results with this group are also given in table 6. None demonstrated activity greater than class 3.

Since the straight-chain mononitriles that were active had boiling points below 141° C., it is possible that this physical parameter is important for activity. Although pimelonitrile (ENT–28713) was not active, two of its derivatives (table 14) were class 4 arrestants. This structure could be considered as two propionitriles if the fourth carbon atom is considered a common substitution to both chains.



ENT–28713

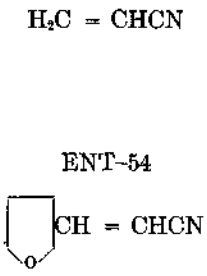
Propionitrile Derivatives

The simplest unsaturated nitrile is acrylonitrile (ENT–54). Although this compound was in class 4 (ratio 0.09), its activity never approached that of propionitrile. A phenyl group on the 2 position (ENT–7248) reduced the activity only slightly (class 3, ratio 0.08), whereas a furan ring (ENT–28307) on the 3 position abolished all activity. An acetylenic bond (ENT–11802) also removed all activity.

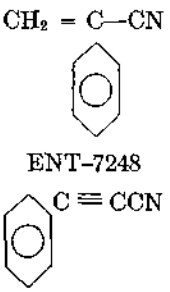
TABLE 6.—*Arrestant activity of various straight-chain aliphatic nitriles and dinitriles in petri-dish tests*

Code No. (ENT–)	Chemical	Boiling point	Carbon atoms	Class	Ratio T/Std
		°C.	*Number*		
	NITRILES				
327	Acetonitrile	81	2	5	0.80
8777	Propionitrile	97	3	5	2.64
8778	Butyronitrile	118	4	5	1.99
30052	Valeronitrile	141	5	2	.02
28396	Hexanenitrile	162	6	1	0
28301	Heptanenitrile	183	7	1	0
11101	Decanenitrile	244	10	1	0
311	Lauronitrile	198	12	1	0
16570	Tridecanenitrile	.....	13	1	0
310	Myristonitrile	226.5	14	1	0
11234	Palmitonitrile	251.5	16	1	0
7618	Heptadecanenitrile	.....	17	1	0
	DINITRILES				
24285	Malononitrile	220	3	2	[1] .04
6591	Succinonitrile	267	4	1	[1] 0
7024	Glutaronitrile	286	5	3	.17
11080	Adiponitrile	295	6	1	0
28713	Pimelonitrile	169	7	1	[1] 0
33237	Suberonitrile	185	8	1	[1] 0
8103	Sebaconitrile	.....	10	1	0

[1] Two or more tests.



ENT-54

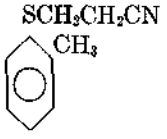


ENT-7248

ENT-28307

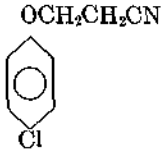
ENT-11802

Most substitutions on the 3 position of propionitrile resulted in a decrease or complete loss of activity (table 7). However, certain relationships can be observed that will be important in further work. Substitution of rings and substitution through ether, ester, and amino linkages generally resulted in virtually total loss of activity. However, substitution through sulfur linkage did not affect the activity as much as the other types and groups. The flies definitely preferred 3-(o-tolylthio)propionitrile (ENT–16985) over the *meta* isomer (ENT–16986).

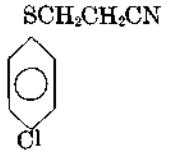


ENT-16985

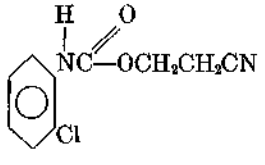
Substitution of *meta*- or *para*-chlorophenyl groups may also enhance activity. It is observed that 3-(*p*-chlorophenoxy)propionitrile (ENT–16700) was the only active ether, and 3-[(*p*-chlorophenyl)thio]propionitrile (ENT–16966) was the best of the thio derivatives. The hydracrylonitrile ester of *m*-chlorocarbanilic acid (ENT–24084) was slightly active. Generally it seems that monosubstitutions on the 2 position of propionitrile will decrease activity unless such substitutions occur through sulfur atoms.



ENT-16700



ENT-16966

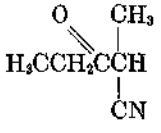


ENT-24084

The following chemicals with single additions to a propionitrile molecule on the 2 position were inactive:

Code No. (ENT–)	*Chemical*
18990	Valeronitrile, 2-methyl-3-oxo-
7461	Propionic acid, 2-cyano-, 4-methylcyclohexyl ester
12066	3-Hexenal, 2-(2-cyanoethyl)-2-ethyl-
15707	Lactonitrile, acetate
23081	Carbanilic acid, *m*-chloro-, ester with lactonitrile
7470b	Propionic acid, 2-cyano, 2-methylcyclohexyl ester
26107	Nonanoic acid, 2-cyanoethyl ester

All but two of these were linked by an ester, which will be shown later to interfere with activity. However, 2-methyl-3-oxo-valeronitrile (ENT–18990), which might be considered as a two-substituted propionitrile, showed some activity (class 2, ratio 0.02). Since no other chemicals with two substitutions on propionitrile were available, it cannot be ascertained whether all such substitutions will adversely affect activity.



ENT-18990

Table 8 presents the results with some active compounds, which are essentially di-substituted propionitrile derivatives. The inactive compounds were as follows:

Code No. (ENT–)	*Chemical*
50880	2-Aziridinecarbonitrile, 1-butyl-
23854	Hydratroponitrile, *beta*-(cyclohexylamino)-, hydrochloride
4924	1-Cyclohexene-1-acetic acid, *alpha*-cyano-*alpha*-methyl-, ethyl ester
17203	2-Furanacrylonitrile, *alpha*-phenyl-
5830	Hydrocinnamic acid, *alpha*-cyano-*alpha*-phenyl-, ethyl ester

Two substitutions on the basic propionitrile molecule superficially may appear to provide more active compounds than only one substitution.

TABLE 7.—*Arrestant activity of propionitrile derivatives substituted on 3 position in petri-dish tests*

Code No. (ENT-)	Chemical	Class	Ratio T/Std
	SINGLE INORGANIC SUBSTITUTION		
17851	Propionitrile, 3-bromo-	3	0.07
	SINGLE ORGANIC SUBSTITUTION		
5926	Butyraldehyde, 2-(2-cyanoethyl)-2-ethyl-	1	0
	RING SUBSTITUTION		
23733	Hydrocinnamonitrile	1	0
14830	Cyclohexanepropionitrile, 1-nitro-	1	0
18069	Propionitrile, 3-isobornyl-	1	0
13188	4-Morpholinepropionitrile	1	0
17124	*L*-Pyroglutamic acid, 1-(2-cyanoethyl)-	2	[1].08
	SUBSTITUTION THROUGH ETHER LINKAGE		
25449	Propionitrile, 3-methoxy-	1	0
25450	Propionitrile, 3-ethoxy-	1	0
24894	Propionitrile, 3,3′-oxydi-	1	[1]0
13078	Propionitrile, 3-(allyloxy)	1	[1]0
17772	Propionitrile, 3-isopropoxy-	1	0
8628	Propionitrile, 3-butoxy-	1	[1]0
17914	Propionitrile, (hexyloxy)-	1	0
8290	Propionitrile, 3-[(2-ethylhexyl)oxy]-	1	[1]0
5764	Propionitrile, 3-(cyclohexyloxy)-	1	0
5935	Propionitrile, 3-[(2-methylcyclohexyl)oxy]-	1	[1]0
16700	Propionitrile, 3-(*p*-chlorophenoxy)-	4	.55
14827	Propionitrile, 3-(2-phenoxyethoxy)-	1	0
	SUBSTITUTION THROUGH SULFUR LINKAGE		
14259	Propionitrile, 3-(phenylsulfonyl)-	4	.12
16966	Propionitrile, 3-[(*p*-chlorophenyl)thio]-	5	1.05
16986	Propionitrile, 3-(*m*-tolylthio)-	1	0
16985	Propionitrile, 3-(*o*-tolylthio)-	3	.13
16840	Propionitrile, 3,3′-thiodi-	1	0
	SUBSTITUTION THROUGH ESTER LINKAGE		
2885	Acrylic acid, 2-cyanoethyl ester	1	0
16824	Cinnamic acid, 2-cyanoethyl ester	1	0
24084	Carbanilic acid, *m*-chloro-, ester with hydracrylonitrile	2	.02
	SUBSTITUTION THROUGH AMINO LINKAGE		
23632	Propionitrile, 3-hydrazino-, monosulfate	1	0
26057	Propionitrile, 3-(methylamino)-	1	0
25451	Propionitrile, 3-(dimethylamino)-	3	.04
23944	1-Aziridinepropionitrile	1	0
13185a	Propionitrile, 3-(diethylamino)-	3	[1].06
32938	Propionitrile, 3-(dipropylamino)-	1	0
32937	Propionitrile, 3-(dibutylamino)-	1	0

See footnotes at end of table.

TABLE 7.—*Arrestant activity of propionitrile derivatives substituted on 3 position in petri-dish tests*—Con.

Code No. (ENT–)	Chemical	Class	Ratio T/Std
	SUBSTITUTION THROUGH AMINO LINKAGE—Con.		
20446	Propionitrile, 3-(dipentylamino)-	3	.03
24580	Propionitrile, 3-(octadecylamino)-	2	[1] .01
24579	Propionitrile, 3-[(3,5,5-trimethylhexyl)amino]-	1	[1] 0
16612	Glycine, *N*-(2-cyanoethyl)-	2	[1] .04
17126	*DL*-Alanine, *N*-(2-cyanoethyl)-	2	.02
17125	*DL*-Aspartic acid, *N*-(2-cyanoethyl)-	1	0
20448	Propionitrile, 3-(benzylamino)-	3	.04
	SUBSTITUTION THROUGH KETONE LINKAGE		
11714	Propionitrile, 2-benzoyl-	2	.01

[1] Two or more tests.

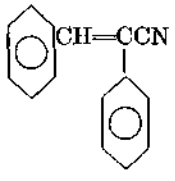
TABLE 8.—*Arrestant activity of various chemicals with two or more substitutions on propionitrile molecule in petri-dish tests*

Code No. (ENT–)	Chemical	Class	Ratio T/Std
22936	Lactonitrile, 2-methyl-, carbanilate	2	0.04
17792	Propionitrile, 3-(*p*-chlorobenzoyl)-2-2-[(3,4-methylenedioxy)phenyl]-	3	.11
23889	1-Piperidinepropionitrile, *alpha*-phenyl-, hydrochloride	2	[1] .02
23855	Hydratroponitrile, *beta*-(benzylamino)-, hydrochloride	2	[1 2] .05
23852	Hydratroponitrile, *beta*-(dimethylamino)-, hydrochloride	4	.30
16816	Acrylonitrile, 2,3-diphenyl-	2	.06
20206	Δ^{3},*alpha*-Indoleacetamide, *alpha*-cyano-2-oxo-	3	.25

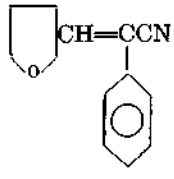
[1] Two or more tests.
[2] Seemed to stimulate flies more than ratio would indicate.

However, the compounds in this heterogeneous group cannot properly be compared with those chemicals having one substitution. Four chemicals (ENT–23854, ENT–23889, ENT–23855, ENT–23852) are hydrochloride salts bound *para* to the phenyl moieties. One of these compounds was in class 4, whereas the others showed little or no activity. It will be remembered that three of the compounds in table 7, which incorporated chlorine in the *para* or *meta* position, were active.

2,3-Diphenylacrylonitrile (ENT–16816) exhibited a small amount of activity but was less active than 2-phenylacrylonitrile (ENT–7248), which in turn was less active than acrylonitrile, whether rated by ratio or class grouping. *alpha*-Phenyl-2-furanacrylonitrile (ENT–17203) differs from ENT–16816 only in the presence of a furan ring replacing a phenyl. With this addition all activity was lost, as was true for 2-furanacrylonitrile (ENT–28307). Thus at least for acrylonitrile and its derivatives, furan rings eliminate all attractiveness.



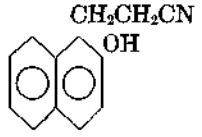
ENT–16816



ENT–17203

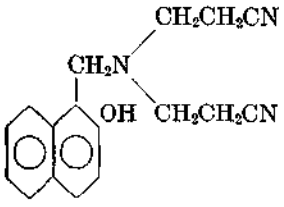
It is difficult to evaluate the overall effect of substituent groups on a propionitrile molecule. In general, it seems that the more complex the substituent groups, the less the activity that can be expected. However, a compound in which the substitution included both a naphthalene group and a

hydroxyl group, 2-hydroxy-1-naphthalene propionitrile (ENT–16234), was a class 5 arrestant (ratio 0.83).

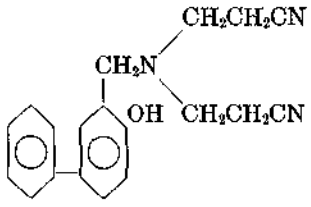


ENT–16234

Twenty-two chemicals were available that had two or more propionitrile moieties bound to larger molecules. This group of chemicals is listed in table 9. The relation of structure to activity of the chemicals containing two propionitrile moieties is unclear. For example, 3,3′-[[(2-hydroxy-1-naphthyl)methyl]imino]dipropionitrile (ENT–22646) differs from 3,3′-[(5-phenylsalicyl)imino]-dipropionitrile (ENT–22307) only in the type of

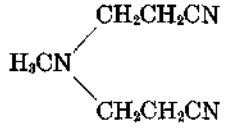


ENT–22646



ENT–22307

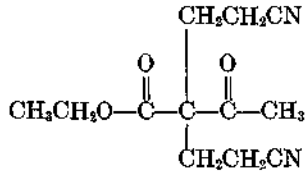
cyclic moiety, yet one is class 5 and the other class 1, and 3,3′-(methylimino)dipropionitrile (ENT–26303), which has no cyclic moiety, has no



ENT–26303

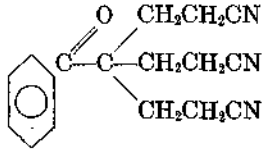
activity. It seems that a hydroxyl group in combination with a naphthalene ring may induce some activity not entirely attributable to the iminodipropionitrile moiety (ENT–16234 and ENT–22646). The imino linkage per se does not appear to confer activity.

Four chemicals having two propionitrile moieties not bound by an imino-type linkage were tested and all had class 4 or 5 activity. Included in this highly active group are *N,N*-bis(2-cyanoethyl)-*m*-toluamide (ENT–26949), which binds the two propionitrile moieties through an amide nitrogen, and the ethyl ester of 2,2-bis(2-cyanoethyl) acetoacetic acid (ENT–16032), where they are bound through an acyl carbon and may be considered a derivative of pimelonitrile.

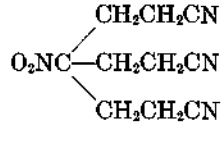


ENT–16032

The data concerning the activity of those chemicals with three or four propionitrile moieties are more clear. 4-Benzoyl-4-(2-cyanoethyl)heptanedinitrile (ENT–16027) exhibits strong arrestancy; however, any *para* addition to the phenyl, whether a methyl, bromine, or chlorine, removes much of the activity. This is in contrast to the effect of the *para*-chlorine additions discussed earlier in connection with other chemicals. The addition of two chlorine atoms in the *meta* and *para* positions further decreases the arrestancy of this group of chemicals. Activity in this group is not dependent on a cyclic moiety, since 4-nitro-4-(2-cyanoethyl)-heptanedinitrile (ENT–23096) was active. The two chemicals containing four propionitrile moieties demonstrated only a weak ability to arrest the flies even though they possess cyclic moieties.



ENT–16027



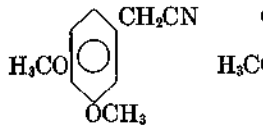
ENT–23096

Derivatives of acetonitrile, butyronitrile, and valeronitrile also demonstrated an ability to arrest flies; however, not as many derivatives of these chemicals were available for testing. The results of tests with active derivatives of acetonitrile are presented in table 10. The inactive compounds were as follows:

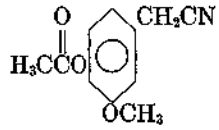
Code No. (ENT–)	*Chemical*
23725	Acetonitrile, (4-hydroxy-3-methoxyphenyl)-, acetate
23875	Acetonitrile, (*p*-nitrophenyl)-
4979	1-Cyclohexene-1-acetonitrile
4980	Δ^1, *alpha*-Cyclohexaneacetonitrile, 2-allyl-
26061	1-Naphthaleneacetonitrile
16855	Acetonitrile, (phenylsulfonyl)-
23764	1-Pyrrolidineacetonitrile
23766	Glycinonitrile, *N*-(1,1,3,3-tetramethylbutyl)-, hydrochloride
4364	Acetonitrile, benzoyl-
7187a	Acetic acid, cyano-, cyclohexyl ester

Code No. (ENT–)—Con.	*Chemical*
4983	[1], *alpha*-Cyclohexaneacetonitrile, *alpha*-phenyl-
16132	Acetonitrile, 2-phenyl-
19354	Acetonitrile, benzoylphenyl-
2754	Glycinonitrile, *N*-(*p*-bromophenyl)-2-phenyl-
20145	Mandelonitrile, 3,4-(methylenedioxy)-
16855	Cyanomethyl phenyl sulfone

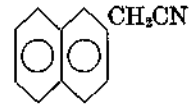
Only one single-substituted derivative of acetonitrile that contained a phenyl group, (3,4-dimethoxyphenyl)acetonitrile (ENT–23882), showed relatively strong activity. However, (4-hydroxy-3-methoxyphenyl)acetonitrile acetate (ENT–23725) differs only in one acetate group and exhibits complete lack of stimulation. Although 1-naphthaleneacetonitrile (ENT–26061) was not active, 2-hydroxy-1-naphthalenepropionitrile (ENT–16234) exhibited marked stimulation. Another interesting relationship was noted. Although cyanomethyl phenyl sulfone (ENT–16855) demonstrated no activity, its close relative, 2-cyanoethyl phenyl sulfone (ENT–14259) (table 7), was strongly active. From the evidence presented so far it appears that not only chain length of the cyanide parent is involved in activity but also derivatives on the substituent groups.



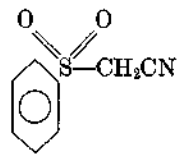
ENT–23882



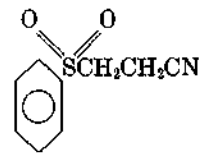
ENT–23725



ENT–26061



ENT–16855



ENT–14259

TABLE 9.—*Arrestant activity of various chemicals containing two or more propionitrile moieties in petri-dish tests*

Code No. (ENT–)	Chemical	Class	Ratio T/Std
	TWO PROPIONITRILE MOIETIES		
26949	*m*-Toluamide, *N,N*-bis(2-cyanoethyl)-	5	5.34
16032	Acetoacetic acid, 2,2-bis(2-cyanoethyl)-, ethyl ester	5	1.29
22646	Propionitrile, 3,3′-[[(2-hydroxy-1-naphthyl)methyl]imino]di-	5	.79
17133	*DL*-Methionine, *N,N*-bis(2-cyanoethyl)-	3	.15
15102	Carbamic acid, (2-cyanoethyl)ethyldithio-, zinc salt	2	[1] .05
16825	Carbamic acid, ethylenebis[(2-cyanoethyl)dithio-, disodium salt	2	.03
16878	Carbamic acid, ethylenebis[(2-cyanoethyl)dithio-, zinc salt	2	.02
17122	*DL*-Alanine, *N,N*-bis(2-cyanoethyl)-	2	[2] .02
13041	Malonic acid, bis(2-cyanoethyl)-, diethyl ester	2	.02
26303	Propionitrile, 3,3′-(methylimino)di-	1	0
24647	Propionitrile, 3,3′-[(3,5-dichlorosalicyl)imino]di-	1	0
22307	Propionitrile, 3,3′-[(5-phenylsalicyl)imino]di-	1	0
17121	*DL*-Aspartic acid, *N,N*-bis(2-cyanoethyl)-	1	0
17237	Disulfide, bis[(2-cyanoethyl)ethylthiocarbamoyl]-	1	[1] 0
	MORE THAN TWO PROPIONITRILE MOIETIES		
16027	Heptanedinitrile, 4-benzoyl-4-(2-cyanoethyl)-	5	3.18
16033	Heptanedinitrile, 4-(2-cyanoethyl)-4-*p*-toluoyl-	4	.52
16030	Heptanedinitrile, 4-(*p*-chlorobenzoyl)-4-(2-cyanoethyl)-	4	.45
16034	Heptanedinitrile, 4-(*p*-bromobenzoyl)-4-(2-cyanoethyl)-	4	.25
16089	Heptanedinitrile, 4-(2-cyanoethyl)-4-(3,4-dichlorobenzoyl)-	4	.18
23096	Heptanedinitrile, 4-(2-cyanoethyl)-4-nitro-	4	.19
16026	1,1,3,3-Cyclopentanetetrapropionitrile, 2-oxo-	4	.09
16028	1,1,3,3-Cyclohexanetetrapropionitrile, 2-oxo-	3	.07

[1] Seemed to stimulate flies more than ratio would indicate.
[2] Two or more tests.

TABLE 10.—*Arrestant activity of various substituted acetonitrile derivatives in petri-dish tests*

Code No. (ENT–)	Chemical	Class	Ratio T/Std
	SINGLE SUBSTITUTIONS		
23882	Acetonitrile, (3,4-dimethoxyphenyl)-	4	[1] 0.25
4975	Acetonitrile, phenyl-	2	[1] .01
17751	Glycinonitrile, *N*-methylene-	4	.45
23466	Acetic acid, cyano-, hydrazide	3	.11
2755	Glycinonitrile, *N*-phenyl-	2	.01
2824	Glycinonitrile, *N*-(*o*-methoxyphenyl)-	2	[2] .05
	MORE THAN ONE SUBSTITUTION		
17436	Acetonitrile, diphenyl-	[3] 3	([1] [3])
2757	Glycinonitrile, *N*-1-naphthyl-2-phenyl-	3	.18
2753	Glycinonitrile, *N*,2-diphenyl-	2	.03
17359	Acetonitrile, bis[*p*-(dimethylamino)phenyl]phenyl-	3	.31
28712	Acetonitrile, iminodi-	2	.01
23663	Acetonitrile, (ethylenedinitrilo)tetra-	3	[2] .56
20205	3,3-Indolediacetic acid, *alpha,alpha'* dicyano-2-oxo-, diethyl ester	2	[2] .14

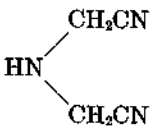
[1] Two or more tests.
[2] Seemed to stimulate flies more than ratio would indicate.
[3] Induced greatly different activities in two tests: 0:27; 38:292.

Certain substitutions linked through nitrogen seemed to possess activity, although not strongly. The most potent arrestant among this group was *N*-methyleneglycinonitrile (ENT–20150). This chemical resembles, and was as effective as, acrylonitrile (ENT–54). Other members of this group demonstrated a consistent but low activity. Two other chemicals were placed arbitrarily in this series, benzoylacetonitrile (ENT–4364) and cyclohexyl cyanoacetate (ENT–7187a). Neither of these exhibited any activity.

$$H_2C = NCH_2CN$$

ENT–20150

Several double- and triple-substituted derivatives of acetonitrile were relatively good arrestants, but none were good enough to be rated in class 4 or 5. Iminodiacetonitrile (ENT–60248) exhibited very slight activity, even though two acetonitrile moieties were present.



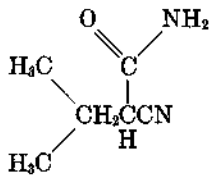
ENT–60248

Isobutyronitrile (ENT–28525) was a class 4 arrestant of great variability with a ratio of 0.04. Only one of the single-substituted derivatives of butyronitrile that was tested, 2-cyanobutyramide (ENT–20170), showed any arrestancy (class 2, ratio 0.08). The inactive compounds were as follows:

Code No. (ENT–)	*Chemical*
19356	Butyronitrile, 4-(diethylamino)-
16701	Butyronitrile, 4-(2,4-dichlorophenoxy)-
7451	Butyric acid, 2-cyano-, cyclohexyl ester
7464	Butyric acid, 2-cyano-, 2-methylcyclohexyl ester
7467	Butyric acid, 2-cyano-, 3-methylcyclohexyl ester
7468	Butyric acid, 2-cyano-, 4-methylcyclohexyl ester
26028	Butyronitrile, 4-(octylthio)-
26029	Butyronitrile, 4-(octylsulfinyl)-
23765	Propionitrile, 2,2'-(ethylenediimino)bis[2-methyl-

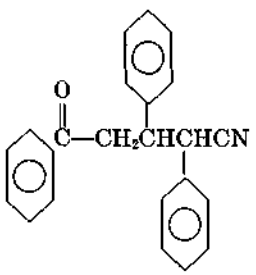
A few of these derivatives were similar to propionitrile derivatives, which showed no activity (cf. 4-(diethylamino)butyronitrile (ENT–19356) with 3-(diethylamino)propionitrile (ENT–13185)). Although tests of these single-substituted derivatives failed to provide much information, tests of those with double-, triple-, and quadruple-substituted molecules provided some meaningful in-

formation. These are presented in table 11. Isopropylcyanoacetamide (=2-cyano-3-methylbutyramide) (ENT–20149) was a strong arrestant. Some activity might have been expected from 4-(*p*-chlorobenzoyl) - 2 - cyano - 3 - phenylbutyrate (ENT–16067) because of the chlorine in the *para* position. However, the close proximity of the carboxyl group to the cyanide radical probably eliminated this expected activity.



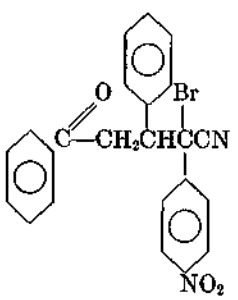
ENT–20149

The most interesting information and perhaps the most significant concerns the different isomers of butyronitrile derivatives separated by differences in melting points. Two isomers of 4-benzoyl-2,3-diphenyl butyronitrile (ENT–17780) were tested, one of which melted at 109° C. (ENT–17779) and the other at 117° (ENT–17780). The isomer melting at the lower temperature was a class 5 arrestant, whereas the isomer melting at 117° was in class 3.



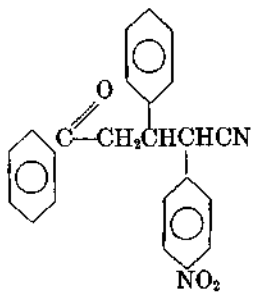
ENT–17779

Another rather close relative of this chemical is 4-benzoyl-2-bromo-2-(*p*-nitrophenyl)-3-phenylbutyronitrile (ENT–17794). Two isomers were tested, one with a melting point at 151° C. (ENT–17793) and the other at 191° (ENT–17794). Again the isomer melting at the lower temperature was included in class 5, whereas the isomer melting at the higher temperature was a class 1 arrestant.



ENT–17794

A reversal seemed to occur when two isomers of 4-benzoyl-2-(*p*-nitrophenyl)-3-phenyl butyronitrile (ENT–17777 and ENT–17778) were tested. The chemical did not prove to be a good arrestant, although lacking only the bromine of ENT–17793. However, the isomer with the 170° C. melting point (ENT–17777) was a weak class 3 arrestant, whereas the isomer with the 144° melting point (ENT–17778) was in class 1.



ENT–17777

These few data do not prove that arrestancy is dependent on low melting or boiling points. However, these three chemicals do definitely illustrate that stereochemical configuration is important to activity as arrestants.

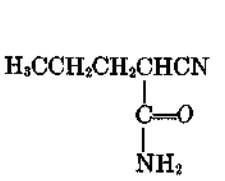
A small number of valeronitrile derivatives were available for screening. Since the parent chemical was ineffective (table 6), little activity was expected from this group of chemicals. However, the three chemicals having an amide group were effective—2-cyanovaleramide (ENT–20148, class 5, ratio 1.18), 2-cyano-4-methyl-2-propylvaleramide (ENT–20209, class 3, ratio 0.07), and 2-cyano-2-isopropylvaleramide (ENT–20210, class 2, ratio 0.02). The inactive compounds were as follows:

Code No. (ENT–)	*Chemical*
20151	Valeronitrile, 5-chloro-
11712	Valeronitrile, 2-benzoyl-
16512	Valeronitrile, 5,5'-oxydi-
23095	Valeronitrile, 4-methyl-4-nitro-
22305	Heptanedioic acid, 4,4-dicyano-, diallyl ester
7351	Valeronitrile, 4-hydroxy-2-phenyl-
13167	Glutaric acid, 2-cyano-3-methyl-, diethyl ester
13172	Glutaric acid, 2-cyano-3-methyl-, allyl ethyl ester
17776	Hydrocinnamic acid, 2-cyano-3-phenacyl-, methyl ester
4981	1-Cyclohexene-1-acetonitrile, 2-allyl-

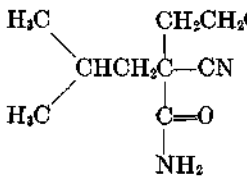
TABLE 11.—*Arrestant activity of multiple-substituted derivatives of butyronitrile in petri-dish tests*

Code No. (ENT–)	Chemical	Class	Ratio T/Std
	TWO SUBSTITUTIONS		
20149	Butyramide, 2-cyano-3-methyl-	5	0.70
9216	Butyronitrile, 2-hydroxy-2-methyl-, acetate	1	0
	THREE SUBSTITUTIONS		
16067	Butyric acid, 4-(*p*-chlorobenzoyl)-2-cyano-3-phenyl-	1	0
17663	Butyronitrile, 4-(*p*-methoxybenzoyl)-2,3-diphenyl-	1	0
17779	Butyronitrile, 4-benzoyl-2,3-diphenyl- (isomer m.p. 109° C.)	5	.67
17780	Butyronitrile, 4-benzoyl-2,3-diphenyl- (isomer m.p. 117° C.)	3	.05
17778	Butyronitrile, 4-benzoyl-2-(*p*-nitrophenyl)-3-phenyl- (isomer m.p. 144° C.)	1	0
17777	Butyronitrile, 4-benzoyl-2-(*p*-nitrophenyl)-3-phenyl- (isomer m.p. 170° C.)	3	.05
5611	Succinic acid, 2-cyano-3-methyl-, diethyl ester	1	0
5645	Succinic acid, 2-cyano-2,3-dimethyl-, diethyl ester	3	[1] .10
	FOUR SUBSTITUTIONS		
17672	Butyronitrile, 4-benzoyl-2-bromo-2,3-diphenyl-	4	.29
17793	Butyronitrile, 4-benzoyl-2-bromo-2-(*p*-nitrophenyl)-3-phenyl- (isomer m.p. 151° C.)	5	.60
17794	Butyronitrile, 4-benzoyl-2-bromo-2-(*p*-nitrophenyl)-3-phenyl- (isomer m.p. 191° C.)	1	0

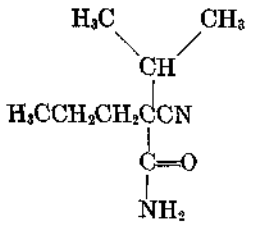
[1] Two or more tests.



ENT–20148



ENT–20209



ENT–20210

The next large group of chemicals that were screened were those having one or more cyano groups bound directly to a cyclic moiety. Results with the active compounds are given in table 12. The inactive compounds were as follows:

Code No. (ENT–)	*Chemical*
24184	Benzonitrile
492	Benzonitrile, *p*-chloro-
33363	Benzonitrile, 2,3-dichloro-
17128	*o*-Tolunitrile
17129	*m*-Tolunitrile
14826	*p*-Tolunitrile
488a	Benzonitrile, *p*-bromo-
11801	*p*-Anisonitrile
11298	Benzonitrile, 2,4,6-triisopropyl-
25034	Isophthalonitrile
234	2-Naphthonitrile
22124	9-Phenanthrenecarbonitrile
23919	9-Fluorenecarbonitrile, 9-amino-
5928	5-Norbornene-2-carbonitrile
16843	5-Norbornene-2,3-dicarbonitrile
26364	7-Oxabicyclo[4.1.0]heptane-3-carbonitrile
5832	Butyric acid, 2-cyano-2-phenyl-
17235	Nicotinonitrile, 1,2-dihydro-4,6-dimethyl-2-oxo-
1547	Nicotinonitrile, 1,2-dihydro-1,4,6-trimethyl-2-oxo-
8635	3-Cyclohexene-1-carbonitrile
3957	Cyclohexanecarbonitrile, 1-hydroxy-*x*-methyl
1651	3-Cyclohexene-1-carbonitrile, 5,5-dimethyl-2-(1-methylpropenyl)-
21026	Butyramide, *N*-(1-cyanocyclohexyl)-*N*-methyl-

TABLE 12.—*Arrestant activity of chemicals having one or more cyanide radicals bound directly to cyclic moieties in petri-dish tests*

Code No. (ENT–)	Chemical	Class	Ratio T/Std
33327	Benzonitrile, 2,4,5-trichloro-	3	[1] 0.07
33325	Benzonitrile, 2,4,6-trichloro-	2	[1] .02
478	Benzonitrile, *p*-nitro-	3	.02
49	Phthalonitrile	4	.13
16842	5-Norbornene-2,3-dicarbonitrile, 2-methyl-	2	[1] .10
16848	7-Oxabicyclo[2.2.1]hept-5-ene, 2,3-dicarbonitrile, 1-(hydroxymethyl)-, acetate	2	[1] .08
16983	2,3-Norbornanedicarbonitrile, 5,6-dichloro-, *alpha*-isomer	2	[1 2] .05
25962	2-Norbornanecarbonitrile, *exo*-5-chloro-6-oxo-, *O*-(methylcarbamoyl)oxime, *endo*-	4	.17
18124	Cyclohexanecarbonitrile, 1-heptyl-	4	.23
21025	Propionamide, *N*-(1-cyanocyclohexyl)-*N*-methyl-	3	.27
16844	4-Cyclohexene-1,2-dicarbonitrile, 3,3-dimethyl-6-(1-methylpropenyl)-	2	[1] .02

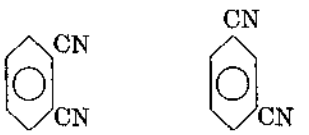
[1] Two or more tests.

[2] Seemed to stimulate flies more than ratio would indicate.

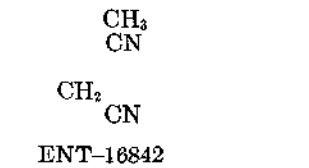
The least complex member of this group was benzonitrile (ENT–24184), which evoked no response from the flies. Since it was earlier hypothesized that a chlorine in the *para* position seemed to enhance activity, *p*-chlorobenzonitrile (ENT–492) and 2,3-dichlorobenzonitrile (ENT–33363) were screened and found inactive. However, two trichlorobenzonitrile derivatives evoked a small positive response. Methyl groups in any position did not confer any activity, but a *para*-nitro addition evoked a class 3 response.

ENT–24184

Phthalonitrile (ENT–49) was active, but isophthalonitrile (ENT–25034) was totally inactive. 5-Norbornene-2,3-dicarbonitrile (ENT–16843) was inactive, but the addition of a methyl group in 2-methyl-5-norbornene-2,3-dicarbonitrile (ENT–16842) restored some of the activity. Although chlorine substitution conferred no activity to benzonitrile, two chlorine additions to the norbornene ring to produce 5,6-dichloro-2,3-norbornanedicarbonitrile (ENT–16983) restored some activity to the inactive molecule. 1-Heptylcyclohexanecarbonitrile (ENT–18124) evoked a class 4 response, even with the attachment of a seven carbon chain as did *exo*-5-chloro-6-oxo-*endo*-2-norbornanecarbonitrile *O*-(methylcarbamoyl)oxime (ENT–25962).



ENT–49 ENT–25034 ENT–16843



ENT–16842 ENT–16983

Table 13 lists some effective long carbon-chain nitriles. Generally these chemicals demonstrated little to no activity. The inactive compounds were as follows:

Code No. (ENT–)	*Chemical*
4913	3-Pentenoic acid, 2-cyano-3-ethyl-2-propyl-, ethyl ester
4912	3-Pentenoic acid, 2-cyano-2,3-diethyl-, ethyl ester
4965	3-Pentenoic acid, 2-butyl-2-cyano-3-methyl-, ethyl ester
4916	2-Hexenoic acid, 2-cyano-3-methyl-, ethyl ester
4915	2-Hexenoic acid, 2-cyano-3,5-dimethyl-, methyl ester
4914	2-Hexenoic acid, 2-cyano-3-isobutyl-5-methyl-, ethyl ester
4963	3-Heptenoic acid, 2-cyano-2,3-dimethyl-, ethyl ester
28306	2-Octenenitrile, 5,7,7-trimethyl-
4918	2-Octenoic acid, 2-cyano-3-methyl-, methyl ester
4920	2-Octenoic acid, 2-cyano-3-pentyl-, ethyl ester
4911	3-Octenoic acid, 2-cyano-2,3-dimethyl-, ethyl ester
28305	2-Nonenenitrile
22306	Octadecanenitrile, 9,10-epoxy-
22318	Octadecanenitrile, *p*-tolyl-

TABLE 13.—*Arrestant activity of various long-chain nitriles in petri-dish tests*

Code No. (ENT–)	Chemical	Class	Ratio T/Std
7106	Hexanenitrile, 2,4-dihydroxy-3,3,5-trimethyl-	3	[1] 0.11
20211	Hexanamide, 2-cyano-5-methyl-2-propyl-	3	[1] .19
4957	3-Pentenoic acid, 2-cyano-3-methyl-2-propyl-, ethyl ester	2	.01
23623	Heptanenitrile, 2-hydroxy-4,6,6-trimethyl-, carbanilate	2	[1] .01
28304	2-Decenenitrile	3	.08
22317	Octadecanenitrile, 10-phenyl-	2	[1] .08
22319	Octadecanenitrile, tolylene, di-	2	[1] .05

[1] Two or more tests.

Only two phosphorus esters with various nitriles demonstrated even slight activity. These two were *O,O*-dimethyl *O*-phosphorothioate, *O*-ester with 4-hydroxy-*m*-anisonitrile (ENT–27230, class 2, ratio 0.08) and *O,O*-dimethylphosphorothioate, *O*-ester with 5-chlorosalicylonitrile (ENT–27235, class 2, ratio 0.02). The inactive compounds were as follows:

Code No. (ENT–)	*Chemical*
16155	Phosphonic acid, (2-cyanoethyl)-, diethyl ester
16156	Phosphonic acid, (2-cyanoethyl)-, dibutyl ester
27175	Phosphonic acid, (4-cyanobutyl)-, diethyl ester
27174	Phosphonic acid, (4-cyanobutyl)-, ethyl-*p*-nitrophenyl ester
25869	Phosphonothioic acid, ethyl-, *O*-2-chloroethyl ester, *O*-ester with *p*-hydroxybenzonitrile
27033	Phosphonothioic acid, methyl-, *O*-ethyl ester, *O*-ester with *p*-hydroxybenzonitrile
25832	Phosphonothioic acid, phenyl-, *O*-ethyl ester, *O*-ester with *p*-hydroxybenzonitrile
27227	Phosphonothioic acid, (chloromethyl)-, *O*-ethyl ester, *O*-ester with 4-hydroxy-*m*-anisonitrile
27028	Phosphonothioic acid, (chloromethyl)-, *O*-ethyl ester, *O*-ester with *p*-hydroxybenzonitrile

The chemicals listed in table 14 are derivatives of various dicyano compounds given in table 6. Only one of the malononitrile derivatives, [4-[bis-(2 - chloroethyl)amino] - 2 - methylbenzylidene]-malononitrile (ENT–50199), exhibited unquestionable arrestancy.

Several related derivatives of succinonitrile were available that provide some insight into the effect of slight molecular changes on arrestancy. Although phenyl succinonitrile (ENT–16982) was a class 2 arrestant, 2,3-diphenyl succinonitrile (ENT–25341) was a class 5 arrestant. The addition of a methylenedioxy (ENT–25343) or methoxy (ENT–25346) group to one of the phenyl rings of ENT–25341 diminished the activity to class 4. The addition of chlorine in the *para* position caused a further reduction in activity to class 3 (ENT–25342 and ENT–25344). Two *para* chlorine atoms (ENT–25340) eliminated most of the activity. A *para* isopropyl group (ENT–25345) was about as active as a chlorine substitution.

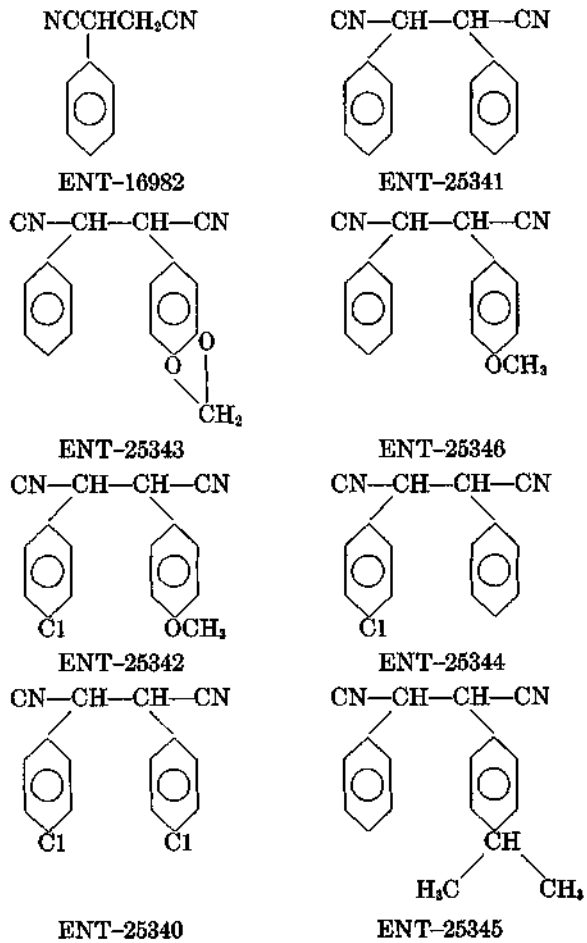
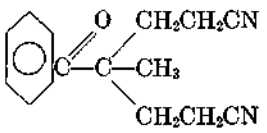


TABLE 14.—*Arrestant activity of 4 chemicals with 2 cyano radicals in petri-dish tests*

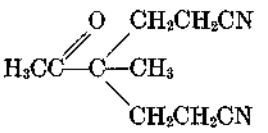
Code No. (ENT–)	Chemical	Class	Ratio T/Std
16838	Malononitrile, 1-cyclopropylethylidene-	1	0
19689	Malononitrile, benzylidene-	1	0
16815	Malononitrile, (*alpha*-methylbenzylidene)-	2	.09
16819	Malononitrile, (*p-alpha*-dimethylbenzylidene)-	1	[1] 0
16820	Malononitrile, (*m*-ethyl-*alpha*-methylbenzylidene)-	2	.01
16821	Malononitrile, (*alpha*-methyl-*p*-phenylbenzylidene)-	2	[1] .06
50199	Malononitrile, [4-[bis(2-chloroethyl)amino]-2-methylbenzylidene]-	3	.12
24628	Tartrononitrile, methyl-, acetate	1	0
23333	Succinonitrile, tetramethyl-	1	0
16982	Succinonitrile, phenyl-	2	.02
25341	Succinonitrile, 2,3-diphenyl-	5	[1] .54
25344	Succinonitrile, 2-(*p*-chlorophenyl)-3-phenyl-	3	[1] .06
25340	Succinonitrile, 2,3-bis(*p*-chlorophenyl)-	2	[1] .03
25342	Succinonitrile, 2-(*p*-chlorophenyl)-3-(*p*-methoxyphenyl)-	3	[1] .15
25346	Succinonitrile, 2-(*p*-methoxyphenyl)-3-phenyl-	4	[1] .19
25345	Succinonitrile, 2-*p*-cumenyl-3-phenyl-	3	[1] .09
25343	Succinonitrile, 2-[3,4-(methylenedioxy)phenyl]-3-phenyl-	4	[1] .59
14265	4-Morpholinesuccinonitrile	3	.05
13063	Heptanedinitrile, 4-acetyl-4-methyl-	4	[1] .28
16090	Heptanedinitrile, 4-benzoyl-4-methyl-	4	.89

[1] Two or more tests.

The best arrestancy for this entire group was exhibited by 4-benzoyl-4-methyl-heptanedinitrile (ENT–16090) and 4-acetyl-4-methyl-heptanedinitrile (ENT–13063). This is an interesting phenomenon in view of the fact that heptanedinitrile (ENT–28713) by itself was inactive. However, by comparing these two chemicals with



ENT–16090



ENT–13063

some of those in table 9, the similarity apparent in the heptanedinitrile molecule per se becomes less important than the structural similarity to the dipropionitrile derivatives. This similarity then most probably explains the activity of these two heptanedinitrile derivatives although the parent chemical was inactive.

Nine miscellaneous compounds were also tested. Cyanoguanidine (ENT–14632) was a class 3 compound (ratio 0.34). The following compounds were either ineffective (class 1) or slightly effective (class 2, ratios 0.02–0.03):

Code No. (ENT–)	*Chemical*
22316	Cyanamide, dibenzyl-
22314	Cyanamide, bis(2-methylallyl)-
17789	Cyanamide, diallyl-
8193	*s*-Triazine, 2,4,6-trimethoxy-
8192	*s*-Triazine, 2,4,6-tributoxy-
24917	1,3,5,2,4,6-Triazatriphosphorine, 2,2,4,4,6,6-hexachloride
16307	Urea, 1-acetyl-3-cyano-
22927	Acetamide, *N*-(cyanoamidino)-

The data and chemical information previously discussed are indicative of only general trends. No absolute rule on the structural relationship to activity could be obtained with the limited number of similar chemicals available for testing. However, an abbreviated form of "nearest neighbor" or active-group-position analysis was obtained for most of the chemicals tested excluding the thiocyanate compounds. One such analysis was made of compounds containing a cyano radical in various positions with respect to a carboxyl or ester group. The number of compounds in each class at each position was as follows:

	Position				
Class	*alpha*	*beta*	*gamma*	*delta*	*epsilon*
1.....	60	2	7	6	2
2.....	7	0	2	3	0
3.....	3	1	0	1	0

Although none of the relationships were productive of compounds with a high activity, the percentage of slightly active compounds was a little higher at the greater distances between the two radicals.

Fifty of these compounds not included in previous tables are listed below. All were ineffective or only slightly effective, with ratios of 0.01 to 0.05.

Code No. (ENT–)	*Chemical*
5599	Acetic acid, cyano-, methyl ester
19027	Acetic acid, cyano-, ethyl ester
32563	Acetic acid, cyano-, propyl ester
7427	Acetic acid, cyano-, hexyl ester
7380	Acetic acid, cyano-, 2-ethylhexyl ester
7221	Acetic acid, cyano-, 2-ethoxyethyl ester
13014	Acetic acid, cyano-, 2-(2-butoxyethoxy) ethyl ester
7370b	Acetic acid, cyano-, 3-methylcyclohexyl ester
7371	Acetic acid, cyano-, 4-methylcyclohexyl ester
19051	Acetic acid, cyano (2,4,6-trimethylphenyl)-
23778	Acrylic acid, 2-cyano-3-ethoxy-, ethyl ester
7457	Propionic acid, 2-cyano-, cyclohexyl ester
4908	2-Pentenoic acid, 2-cyano-3-methyl-, ethyl ester
4909	2-Pentenoic acid, 2-cyano-3-ethyl-, ethyl ester
11617	Valeric acid, 2-cyano-, ethyl ester [1]
11064	Butyric acid, 2-cyano-4-methyl-, ethyl ester
4910	Hexanoic acid, 2-cyano-, ethyl ester
7489	Hexanoic acid, 2-cyano-3,3-dimethyl-4-oxo-, ethyl ester [1]
13044	Hexanoic acid, 2-cyano-3,3-dimethyl-4-oxo-, allyl ester
13010	Hexanoic acid, 2-cyano-3,3-dimethyl-4-oxo-, 2-methoxyethyl ester
4907	Hexanoic acid, 2-cyano-2-isopropyl-, ethyl ester
4931	Sorbic acid, 2-cyano-3,5-dimethyl-, methyl ester
4960	3-Hexenoic acid, 2-cyano-2,3,5-trimethyl-, methyl ester
4964	3-Hexenoic acid, 2-cyano-2-ethyl-3,5-dimethyl-, methyl ester [1]
4962	3-Hexenoic acid, 2-cyano-3-methyl-2-propyl-, ethyl ester
4959	3-Hexenoic acid, 2-cyano-2-ethyl-3-propyl-, ethyl ester
7224	Octanoic acid, 2-cyano-4-ethyl-, methyl ester
4995	Octanoic acid, 2-cyano-3-methyl-, ethyl ester
4997	Nonanoic acid, 2-cyano-, ethyl ester
4996	Nonanoic acid, 2-cyano-3-methyl-, ethyl ester
4999	Cyclohexaneacetic acid, *alpha*-cyano-, ethyl ester
7622	Cyclohexaneacetic acid, *alpha*-cyano-4-methoxy-, ethyl ester
7020	Δ [1], *alpha*-Cyclohexaneacetic acid, *alpha*-cyano-, ethyl ester
7170	Cyclohexaneacetic acid, *alpha*-cyano-, propyl ester
7184	Cyclohexaneacetic acid, *alpha*-cyano-, allyl ester
7175	Cyclohexaneacetic acid, *alpha*-cyano-, isopropyl ester
7226	Cyclohexaneacetic acid, *alpha*-cyano-, 2-ethoxyethyl ester
7185	Cyclohexaneacetic acid, *alpha*-cyano-, cyclohexyl ester
7240	Cyclohexaneacetic acid, *alpha*-cyano-, benzyl ester
24083	Cinnamic acid, *p*-chloro-*alpha*-cyano- [1]
10525	Cinnamic acid, *alpha*-cyano-, ethyl ester
4998	Hydrocinnamic acid, *alpha*-cyano-, ethyl ester
4925	Cinnamic acid, *alpha*-cyano-*beta*-methyl-, ethyl ester
4928	Cinnamic acid, *alpha*-cyano-*beta*-ethyl-, ethyl ester
4934	Cinnamic acid, *alpha*-cyano-*beta*-propyl-, ethyl ester
4926	Cinnamic acid, *alpha*-cyano-*beta*-pentyl-, ethyl ester
20317	Cinnamic acid, *alpha*-cyano-*o*-methoxy-, ethyl ester [1]
8518	Cinnamic acid, *alpha*-cyano-*p*-methoxy-, ethyl ester [1]
20318	Cinnamic acid, *alpha*-cyano-3,4-(methylenedioxy)-, ethyl ester [1]
15927	Pyruvic acid, 3-cyano-3-phenyl-, ethyl ester [1]

[1] Class 2 or 3.

An analysis was also made of compounds containing a cyano radical separated by various numbers of carbon atoms from a carbon-carbon double bond. The number of compounds in each class at each distance was as follows:

	Distance			
Class	*0*	*1*	*2*	*3*
1.....	22	5	5	1
2.....	5	0	1	0
3.....	2	0	0	0
4.....	1	1	0	0

The group included only four compounds in classes

3 and 4, and these were all within one carbon of the double bond.

The following results were obtained with compounds in which a nitrogen atom was located in various positions relative to a cyano radical:

	Position			
Class	[1] *0*	*alpha*	*beta*	*gamma*
1.....	4	6	14	4
2.....	2	4	11	0
3.....	1	4	10	0
4.....	0	0	2	1
5.....	0	0	4	0

[1] Cyanide radical bonded directly to nitrogen.

Thirty-nine, or 58 percent, of these 67 chemicals exhibited some degree of activity (class 2 or better); 27 of the 41 with the nitrogen in the *beta* position, or 66 percent, were active, and these included six of the seven most effective compounds (classes 4 and 5). These proportions indicate that a nitrogen in the *beta* position is at least conducive to activity.

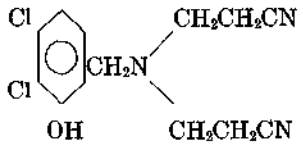
Of five chemicals tested with a sulfur located on the *beta* carbon from the cyanide, three were active; two of these had activity above class 3.

Evaluation of the effect of acyl and amide groups was also made, with the following results:

	Position		
Class	*alpha*	*beta*	*gamma*
1.....	4	1	2
2.....	4	0	2
3.....	4	4	3
4.....	0	0	7
5.....	2	0	5

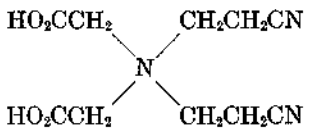
As seen from these data, almost all compounds with an acyl or amide group in the *gamma* position were active. Of course, the fact that most of these are dipropionitrile derivatives must not be overlooked. Even those chemicals with *alpha* and *beta* acyl or amide groups showed consistent if slightly lower activity on the average. It seems safe to say, then, that chemicals that possess *gamma* acyl or amide links are the most promising.

The importance of this linkage is further supported by the results with 3,3′-[(3,5-dichlorosalicyl)imino]dipropionitrile (ENT–24647), which has two propionitrile groups, but no acyl or amide linkage and no activity. This is also true of ENT–



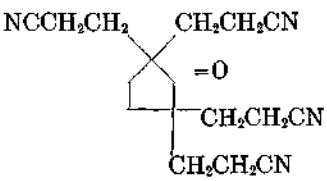
ENT–24647

22307, ENT–17121, and a few others. Only moderate activity was obtained from two tetra-

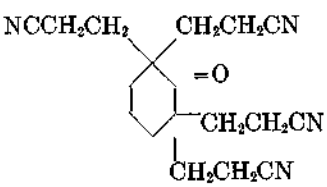


ENT–17121

propionitrile derivatives, ENT–16026 and ENT–16028. These also contain a saturated ring, which was usually not associated with high activity.



ENT–16026



ENT–16028

Except among the straight-chain hydrocarbons, only three chemicals with no acyl or amide linkage produced a high degree of arrestancy (class 5). These three chemicals are ENT–16966, ENT–16234, and ENT–22646, which are slightly different from similar chemicals showing activity. Two are naphthalene derivatives containing hydroxyl groups in different locations. The third is a *para*-chloro substituted phenyl derivative with a thio linkage. None of the other class 5 chemicals are closely related to any of these three chemicals, and it is possible that the mode of stimulation by these chemicals is somehow different from the rest.

Only 39 chemicals were available in which the cyano radical was attached directly to a cyclic structure, and only 11 had activity ranging from class 2 to class 4 (28.2 percent). This percentage is lower than that calculated for all chemicals, and it is thus not unreasonable to consider that these types of cyanide derivatives will not be as stimulatory to the house fly as other types.

An analysis was also made of a group of compounds in which a cyano radical was situated at various distances from a cyclic moiety, i.e., separated by various numbers of carbon, nitrogen, or (in a few compounds) oxygen atoms. The number of compounds in each class at each distance was as follows:

	Distance (carbon atoms)			
Class	*1*	*2*	*3*	*4*
1.....	33	26	2	9
2.....	11	11	1	1
3.....	6	9	1	3
4.....	4	3	1	6
5.....	2	3	0	5

Of 56 chemicals having a cyano radical separated from the cyclic moiety by one atom, 23 were active (41 percent) with all classes represented, almost identical with the percentages among all compounds tested. All the 13 cyclohexyl compounds were in class 1. If only the phenyl compounds are considered, the proportion of active compounds was 56 percent, substantially higher than the general average.

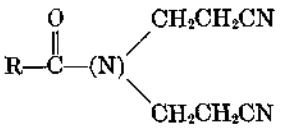
The next group to be considered was that where the cyanide is located two atoms from the cyclic moiety. In this group, 50 percent of the chemicals were active with all groups represented, again higher than the general average, but still slightly disappointing since this group includes most of the simple propionitrile derivatives.

The largest proportion of active compounds was found among those with cyanides located four atoms from a phenyl ring, 63 percent of which were in class 2 or higher and 46 percent of which were in classes 4 and 5. Of course, many compounds in this group had acyl and amide linkages as discussed previously. Unfortunately few chemicals were available to adequately assess the importance of the phenyl group compared with the amides.

CONCLUSIONS

The importance of the foregoing results lies not only in the demonstration of arrestant activity in certain compounds but in the indication that certain molecular configurations possessing this action can possibly be combined with moieties having other properties without destroying either arrestant or other properties. The limited research with this generic group of chemicals has already indicated that different members may elicit one or more of the following behavioral responses: (1) Attraction, (2) arrestancy, (3) stimulation of feeding, or (4) repellency. These chemicals should be more thoroughly studied, since it is conceivable that any member of the group might affect different species of insects in different ways.

Acetonitrile, propionitrile, butyronitrile, and isobutyronitrile are relatively potent arrestants, and certain derivatives of these basic groups still retain this activity. It has been shown that the acyl or amide group, in combination with propionitrile (II), can be used with some chemical

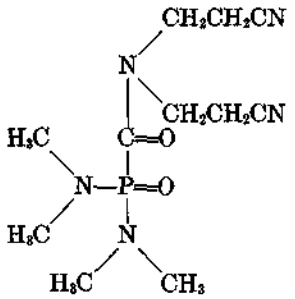


II

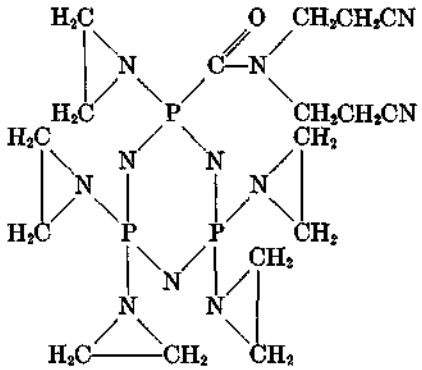
groups to produce arrestancy in house flies. If a chemosterilant moiety could be combined in the same molecule without impairment of either the arresting or the sterilizing action, the single compound would be more effective in practical application than the chemosterilant alone, since the insects would remain in contact with it for longer periods and ingest more of the compound if it is a feeding stimulant as well as an arrestant.

For example, a combination with hempa (III) or its relatives such as tepa, metepa, or thiotepa might prove active in both respects. With apholate several combinations might be possible, e.g., IV. However, the activity of the nitriles could be impaired by proximity to phosphorus. The III

and IV structures have been used here only to illustrate a point. More and better nitrile derivatives may be found.



III



IV

SUMMARY

Tests were made in an olfactometer to determine the attractiveness of ammonia and various nitriles to house flies (*Musca domestica* L.). Petridish tests were made to determine the arrestancy of these and related compounds. The olfactometer tests with ammonia showed that the attraction conformed to the Weber-Fechner relationship over four log units of concentration. Olfactory tests with 52 nitriles were not indicative of attraction.

A total of 53 toluamide and benzamide derivatives and 390 cyanides, thiocyanates, or isothiocyanates were screened as arrestants on white sand in competition with granulated sugar. The compounds were placed in classes 1 to 5 according to the number of flies arrested by the test chemical, irrespective of the number on the sugar.

N,N-Bis(2-cyanoethyl)-*m*-toluamide (ENT–26949) exerted a strong degree of arrestancy. However, the overall results with the 53 toluamide and benzamide derivatives indicated these structures were not responsible for the degree of arrestancy of this chemical.

Three inorganic cyanides were tested. Two of them were slightly active as arrestants, indicating that a cyano radical was responsible for at least some of the arrestant activity.

Fifty-four thiocyanates were tested to determine the activity of this radical, since the literature suggested that some effect might be expected. No thiocyanate was found that could be placed in class 4 or 5. This was also true of eight isothiocyanate compounds.

The activity of *N,N*-bis(2-cyanoethyl)-*m*-toluamide (ENT–26949) and tests with the toluamide and benzamide derivatives suggested that the propionitrile moiety (ENT–8777) might have been responsible for the arrestant activity of this chemical. A series of straight-chain aliphatic nitriles was tested, and three of these—acetonitrile (ENT–327), propionitrile (ENT–8777), and butyronitrile (ENT–8778)—were shown to be strong arrestants, with propionitrile the best. Activity decreased abruptly after chain lengths of four carbon atoms.

Seven straight-chain aliphatic compounds having two cyanide radicals demonstrated poor activity. Acrylonitrile (ENT–54), a single unsaturated 3-carbon cyanide, showed a definite but weaker activity than propionitrile.

Generally all substitutions on the 2 position of propionitrile were less effective than the parent chemical. Only one chemical with an *alpha* substitution on a propionitrile molecule had even a low order of activity. Thirteen chemicals considered to be multiple substitutions on a basic propionitrile molecule were tested, and four of these were active.

Fourteen chemicals were tested that had two propionitrile moieties attached to a single molecule. Generally more of these were active than any other group, especially those linked through an amide or acyl group. Only eight chemicals were tested that had more than two propionitrile moieties on a single molecule. All of these were active. The best were those with acyl linkages.

Only six single-substituted acetonitrile derivatives were active out of 16 tested, and only three were class 3 or higher. Only 13 other acetonitrile derivatives were available for testing, and none showed activity greater than class 3.

Eleven single-substituted derivatives of butyronitrile were available for testing. One of these, isobutyronitrile, possesses definite activity (class 4). Thirteen multiple-substituted butyronitrile derivatives were tested. Seven of these exerted strong arrestant activity.

Thirteen derivatives of valeronitrile were tested, three of which were active. These were the only ones with amide groups near the cyanide radical.

Thirty-four chemicals were tested that had one or more cyano radicals bound directly to a cyclic moiety. These were generally inactive, except three, which were class 4 arrestants. None of these three possessed other similar structural similarities.

Tests were made with 23 nitriles with chain lengths greater than five carbon atoms, many of which had the cyanide radical in the *alpha* position relative to an ester linkage. None were better than class 3 arrestants. Tests with 50 shorter chain chemicals where the cyano radical was in the *alpha* position relative to an ester linkage did not indicate activity greater than class 2 or 3.

Tests with 11 phosphorus esters with various nitriles produced only two chemicals in class 2.

Tests with 18 derivatives of malononitrile and succinonitrile indicated no activity above class 3 except ENT–25341, ENT–25343, and ENT–25346. Two pimelonitrile derivatives were class 4 arrestants. Both of these may be considered as dipropionitriles joined near an acyl group.

It was concluded that three aliphatic nitriles were highly active as house fly arrestants and that two or more propionitrile molecules could be bound to other molecules and at least retain activity as long as the bond was through an acyl or amide linkage. Certain combinations with cyano radicals seemed directly responsible for lack of activity. The predominant one of these was in proximity to an ester linkage.

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