

## Muscalure and Related Compounds. I. Response of Houseflies in Olfactometer and Pseudofly Tests

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Muscalure (*cis*-9-tricosene) and related compounds were bioassayed with male *Musca domestica* L. in an olfactometer and in a pseudofly petri dish test to determine the effects of structural variation of the muscalure molecule on activity. Structural variations included double-bond position, *cis-trans* isomerism, substitution of double bond with triple bond, methyl branching at different points in the molecule, carbon chain length, and length of carbon chain linked

to the unsaturated bond. Because muscalure and compounds highly active in the olfactometer were also highly active in the pseudofly test, muscalure may function both as a sex attractant and a sex stimulant. Several of the compounds were about equal to muscalure in activity; the structural requirements for activity appear therefore to be less stringent than those for most other sex pheromones studied thusfar.

Muscalure (*cis*-9-tricosene), a sex attractant pheromone of the housefly *Musca domestica* L. (Diptera: Muscidae), was recently isolated, identified, and synthesized by Carlson *et al.* (1971). Only sexually mature female houseflies produce the pheromone, which attracts males in laboratory olfactometers.

Muscalure was subsequently found by Carlson and Beroza (1973) to be active in field tests in which the addition of the attractant increased the number of flies caught by traps by several times (2.8 to 12.4). Surprisingly, muscalure-baited traps caught about equal numbers of males and females in the field.

Mansingh *et al.* (1972) have recently reported attractant activity for *cis*-9-tricosene and all *cis*-9-alkene homologs from C<sub>19</sub> to C<sub>25</sub> in olfactometer bioassays with male houseflies. A 7:3 mixture of *cis*-9-tricosene and *cis*-9-heneicosene (10 or 15 mg total) was reported as more potent an attractant than muscalure, and *cis*-9-heneicosene was observed to cause orientation.

A series of compounds related to muscalure was synthesized to determine the specificity of muscalure in attracting male houseflies and the structural requirements for biological activity. Compounds were bioassayed for activity two ways—in an olfactometer (Schreck *et al.*, 1967) and by a modification of the pseudofly petri dish test (Rogoff *et al.*, 1964).

### MATERIALS AND METHODS

**Chemicals.** Most of the double-bonded compounds were prepared from available intermediates in accordance with the Wittig synthesis described below for muscalure, which yielded a product containing *ca.* 85% *cis* and 15% *trans* isomers. This mixture was used as the standard because removal of the *trans* isomer of muscalure does not improve activity significantly. Muscalure and several of the compounds were also prepared *via* acetylene intermediates as described in the 2nd muscalure synthesis below. Most chemicals were tested both as synthesized and as the pure *cis* and *trans* isomers. The *cis* and *trans* isomers were separated by silver nitrate-silica gel column chromatography with hexane as the eluent (Carlson *et al.*, 1971).

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Muscalure was prepared by the Wittig reaction as follows. 1-Bromotetradecane (Eastman, 75.4 g, 0.272 mol) and 75 g (0.286 mol) of triphenylphosphine (Aldrich) were dissolved in 300 ml of acetonitrile and refluxed overnight. The acetonitrile was distilled off on a rotating evaporator, and the residue was poured into anhydrous ether. The white solid that precipitated upon stirring was collected and dried thoroughly under vacuum to give 120 g (0.223 mol, 82%) of tetradecyltriphenylphosphonium bromide.

Tetradecyltriphenylphosphonium bromide (19 g, 0.036 mol) was dissolved in 100 ml of anhydrous dimethyl sulfoxide (DMSO) in a dry flask under N<sub>2</sub>. The solution was stirred, cooled in an ice bath, and held between 10 and 20°, while 30 ml of butyllithium (15.16% solution in hexane, Foote Mineral Co.) was added slowly. The dark red solution was held at 15–20° for 1 hr and then cooled to 10°. Freshly distilled nonanal (5.3 g, 0.037 mol, bp 84–85° (16 mm), *n*<sub>D</sub><sup>20</sup> 1.4227) was added dropwise with stirring and then followed by 30 ml of DMSO; the solution was allowed to warm to room temperature overnight. The DMSO solution was extracted directly with pentane several times. The combined pentane extract was treated with charcoal, filtered through Filter-aid (Celite, Johns-Manville), washed with water and brine, and dried over sodium sulfate. Removal of the solvent left a liquid that was taken up in a small volume of hexane and stored overnight in the refrigerator. Any precipitate (triphenylphosphine oxide) was removed by filtration. The filtrate was passed through a short column of Florisil (Floridin Corporation) using hexane as the solvent. This process removes the remaining triphenylphosphine oxide and any remaining aldehyde. Removal of the solvent gave 8.6 g (0.027 mol, 73%) of a clear oil estimated to contain about 85% *cis* isomer of 9-tricosene. The product may be distilled for final purification: bp 157–158° (0.1 mm), *n*<sub>D</sub><sup>25</sup> 1.4507.

Muscalure was also prepared by the following route, which yielded a product containing *ca.* 95% *cis* isomer. Anhydrous tetrahydrofuran (40 ml) was added under a N<sub>2</sub> atmosphere to 1-pentadecyne (10.42 g, 0.05 mol, Chemical Samples Co. or Farchan Research Laboratories) in a 250-ml, four-necked flask fitted with a magnetic stirrer, thermometer, two dropping funnels, and a N<sub>2</sub> inlet. After the mixture was cooled with stirring to 5°, butyllithium (40 ml of 15.16% solution, 0.055 mol) was added dropwise from one dropping funnel, while the temperature of the mixture was kept below 15°. The mixture was then stirred at ice bath temperature for 1 hr. A mixture of octyl bromide (10.62 g, 0.055 mol, Eastman) and 40 ml of hexamethylphosphoramide (hempa, Aldrich or Eastman, distilled from calcium hydride) in the second funnel was

**Table I. Relative Activity of 9-Tricosene (85% Cis Isomer) and Its Analogs<sup>a</sup> as Housefly Attractants in Olfactometer Tests**

Compound	Flies attracted, % <sup>b</sup>	Activity score
2-Methyl-8-docosyne	20.7 (ab)	97
10-Methyl-9-docosene	18.9 (abc)	88
9-Tricosyne	14.0 (d)	65
10-Methyl-9-tricosene	13.8 (de)	65
10-Tetracosene	13.7 (def)	64
9-Docosene	13.4 (fg)	63
10-Tricosene	10.9 (gh)	51
9-Methyl-9-tricosene	8.3 (ghi)	39
8-Docosene	8.2 (hij)	38
22-Methyl-9-tricosene	8.2 (hij)	38
9-Tetracosene	4.4	21
8-Tricosene	4.0	19
11-Tricosene	3.2	15
7-Tricosene	3.1	14
8-Methyl-8-docosene	2.8	13
9-Tricosene (85% cis isomer)	21.4 <sup>c</sup> (a)	100

<sup>a</sup> Compounds were tested as synthesized; i.e., cis-trans isomers were not separated. <sup>b</sup> Average of five replicates. Means not followed by the same letter are significant at the 1% level by Duncan's multiple range test. Singly underlined activity score =  $p < 0.01$  from muscalure. <sup>c</sup> Average of flies attracted in 75 tests. This value used in calculating activity scores of analogs.

added dropwise to the stirred slurry of lithium pentadecylacetylide, which was held below 20°. After overnight stirring at room temperature, the mixture was poured onto ice and extracted with pentane. The pentane extract was washed with water and brine and dried over sodium sulfate. The solvent was removed in a rotating evaporator and the residual oil was distilled to give 13.78 g (86%) of 9-tricosyne as a clear oil, bp 145° (0.05 mm).

Six-tenths gram of 5% palladium on barium sulfate (Engelhard) and 0.130 ml of pure synthetic quinoline were added to 6.41 g of the 9-tricosyne in 70 ml of hexane. This mixture was magnetically stirred in the presence of hydrogen at atmospheric pressure until 1 M equivalent of hydrogen was absorbed. The catalyst was filtered off, and the filtrate was washed successively with 5% hydrochloric acid, saturated aqueous sodium carbonate, water, and brine. After the hexane solution was dried over sodium sulfate and the solvent was removed, the product was vacuum distilled to give 9-tricosene (95% cis isomer) in essentially quantitative yield.

**Olfactometer Bioassay.** These tests were conducted essentially as described previously (Carlson *et al.*, 1971). Filtered, humidified outside air was conducted through two ports in the front face of a Plexiglas cage (90 × 45 × 54 cm) and out through a screen that formed the rear face of the cage. A horizontal glass cylindrical trap fitted with a vertical screen at its midpoint and an inverted screen funnel at its inner end was inserted into each port. A hexane solution containing 50 μg of the test compound was applied to filter paper positioned in the outer end of one of the cylindrical traps, while 50 μg of muscalure on filter paper was similarly placed in the other trap (Tables I and II). Incoming air passed sequentially over the samples, through the traps, and past 300 male, 24- to 36-hr-old Cradson-P houseflies in the cage before exiting. Counts were made of flies entering the traps in 30 min. The flies were allowed 30 min for recovery between tests and were used for 2 days. The activity score for each analog was calculated by dividing the percentage of flies trapped by the analog by the percentage of flies trapped by muscalure (85% cis, 15% trans) and multiplying by 100. It therefore

**Table II. Relative Activity of 9-Tricosene (85% Cis Isomer) and Its Isomerically Pure Analogs as Housefly Attractants in Olfactometer Tests**

Compound	Flies attracted, % <sup>a</sup>	Activity score <sup>b</sup>
<i>cis</i> -2-Methyl-8-docosene <sup>c</sup>	19.3 (b)	83
<i>cis</i> -9-Docosene	19.2 (bc)	82
<i>cis</i> -8-Docosene	17.1 (bcd)	73
<i>cis</i> -10-Tricosene	14.6 (de)	62
<i>cis</i> -10-Tetracosene	11.4 (ef)	49
<i>cis</i> -9-Heneicosene	8.4 (f)	36
<i>trans</i> -22-Methyl-9-tricosene	7.8 (f)	33
<i>cis</i> -11-Tricosene	6.9 (g)	30
<i>cis</i> -22-Methyl-9-tricosene	6.8 (g)	29
<i>trans</i> -21-Methyl-9-docosene	6.4 (g)	27
<i>trans</i> -9-Tricosene	6.5 (g)	28
<i>trans</i> -10-Tetracosene	5.3 (g)	23
<i>cis</i> -21-Methyl-9-docosene	5.3 (g)	23
<i>trans</i> -9-Tetracosene	5.1 (g)	22
<i>cis</i> -9-Tetracosene	5.0 (g)	21
<i>trans</i> -9-Docosene	5.0 (g)	21
<i>trans</i> -2-Methyl-8-docosene	4.8 (g)	21
<i>trans</i> -8-Tricosene	4.7 (g)	20
<i>trans</i> -7-Tricosene	4.4 (g)	19
<i>cis</i> -7-Tricosene	3.8 (g)	16
<i>cis</i> -8-Tricosene	3.7 (g)	16
<i>trans</i> -8-Docosene	3.7 (g)	16
<i>trans</i> -10-Tricosene	3.6 (g)	15
<i>trans</i> -11-Tricosene	2.9 (g)	12
9-Tricosene (85% cis isomer) <sup>d</sup>	23.4 <sup>b</sup> (a)	100

<sup>a</sup> Average of five replicates. Means not followed by the same letter are significant at the 1% level by Duncan's multiple range test. Singly underlined activity score =  $p < 0.01$  from muscalure. <sup>b</sup> Average % flies attracted in 110 tests. This value used in calculating activity scores of analogs. <sup>c</sup> Data on yields, properties, and cis-trans ratios of synthesized compounds are available from the authors on request. <sup>d</sup> *cis*-9-Tricosene: CH<sub>3</sub>(CH<sub>2</sub>)<sub>7</sub>CH=CH(CH<sub>2</sub>)<sub>12</sub>CH<sub>3</sub>.

represents activity relative to that of muscalure, which was assigned an activity score of 100.

In another series, each chemical in one trap was tested against a blank trap (no chemical) and captures were compared with those made by muscalure identically tested (Table III).

**Pseudofly Petri Dish Bioassay.** These tests (Rogoff *et al.*, 1964, 1973) are based on the mating behavior of houseflies. Provided with the proper stimuli, males leap onto the backs of other flies or fly models and exhibit a behavioral sequence typical of that observed in their normal mating. The fly model in the pseudofly petri dish test was a fly-sized knot cut from a black shoelace and cemented to the center of a 9-cm plastic petri dish. The knot (pseudofly) was then treated with 0.03 ml of a hexane solution containing 30 μg of the test chemical or with 0.03 ml of hexane alone. After the solvent evaporated, two male houseflies (Orlando regular strain), 3 to 10 days old, were introduced into the dish which was covered. In any single session, six dishes were used for each test material to minimize variations in behavior of individual flies. Light (35 footcandles, incident) and temperature (25°) were controlled in the observation room, and dishes were arrayed in groups and observed sequentially for six 3-min periods, with data being recorded for each period. Observations on each test material at any one session were pooled, and the numbers were converted to strikes/fly/hr. The test array permitted comparison of 12 variants during any observation session. Data from three to four such sessions were fully amenable to statistical treatment. Data

**Table III. Relative Activity of 9-Tricosene (85% Cis Isomer) and Its Analogs as Housefly Attractants in Olfactometer Tests (Chemicals Tested Against Blanks)**

Compound	Flies attracted, % <sup>a</sup>	Activity score
<i>cis</i> -2-Methyl-8-docosene	34.3 (a)	134
<i>cis</i> -9-Docosene	29.2 (ab)	115
<i>cis</i> -10-Tetracosene	25.6 (bcd)	100
<i>cis</i> -8-Docosene	24.3 (bcde)	95
10-Methyl-9-docosene <sup>b</sup>	23.8 (bcdef)	93
2-Methyl-8-docosyne	23.1 (bcdefg)	91
10-Methyl-9-tricosene <sup>b</sup>	17.5 (h)	69
9-Tricosyne	17.0 (hi)	67
<i>trans</i> -2-Methyl-8-docosene	14.6 (ij)	58
<i>trans</i> -21-Methyl-9-docosene	10.6 (j)	42
9-Methyl-9-tricosene <sup>b</sup>	10.7 (j)	42
<i>trans</i> -22-Methyl-9-tricosene	9.7 (k)	38
<i>cis</i> -9-Heneicosene	7.2 (l)	28
<i>cis</i> -22-Methyl-9-tricosene	7.0 (l)	27
<i>cis</i> -21-Methyl-9-docosene	5.6 (m)	22
22-Methyl-9-tricosyne	5.3 (m)	21
9-Tricosene (85% cis isomer)	25.5 <sup>c</sup> (bc)	100
Blank	4.5 <sup>d</sup> (mn)	17

<sup>a</sup> Average of three replicates. Means not followed by the same letter are significant at the 1% level by Duncan's multiple range test. Singly underlined activity score =  $p < 0.01$  from muscalure. <sup>b</sup> Isomers not separated. <sup>c</sup> Average of 12 tests. This value used in calculating activity scores of analogs. <sup>d</sup> Average % flies captured by blank traps in 51 tests *vs.* test compounds.

from each test session were converted to a ratio to the mean of all data taken to remove variation normally found between sessions. Analysis of variance and the Dunnett "t" separation of means test (Dunnett, 1964) were used to determine the significance of differences between test materials and muscalure. Individual test means were corrected by subtracting values for the blanks (Snedecor and Cochran, 1967) and converting such corrected means to a percentage of the values for muscalure (=100).

## RESULTS AND DISCUSSION

In general, unbranched compounds which had high activity as pure *cis* isomers (Table II) also rated high as the *cis-trans* mixtures (Table I), from which one may conclude that the presence of *ca.* 15% *trans* isomer in the unbranched compounds did not greatly affect attraction, though the score of the active *cis-trans* mixture was generally less than that of the corresponding pure *cis* isomer. None of the analogs scored as high as muscalure in direct competition.

When selected compounds from Tables I and II were tested individually with a blank (Table III), the most attractive compounds again rated highest in this test. Although the activity score of 2 of the compounds exceeded that of muscalure, the difference, if any, is not considered sufficient to recommend use of either analog over muscalure. Furthermore, the *cis*-2-methyl-8-docosene would be more costly to synthesize than muscalure.

Compounds were synthesized with double bonds in the 7, 8, 9, 10, and 11 positions and in the *cis* and *trans* configuration. Compounds structurally most different from muscalure rated poorly, *i.e.*, those with double bonds in the 7 and 11 positions and those in the *trans* configuration. Compounds with a triple bond in place of a double bond were highly attractive but provided no significant advantage over muscalure. Relative to unsaturation, activity was generally as follows: *cis*  $\geq$  *trans*.

When the length of the carbon chain was varied between C<sub>21</sub> and C<sub>24</sub>, the C<sub>23</sub> compound was most effective.

**Table IV. Activity of Muscalure and Its Analogs in Pseudofly and Olfactometer Tests**

Compound	Activity score in test indicated	
	Pseudofly <sup>a</sup>	Olfactometer <sup>b</sup>
9-Tricosyne	107** (I)	67
10-Methyl-9-tricosene	102** (I)	69
<i>cis</i> -9-Tricosene (muscalure)	100** (A-I)	100 <sup>c</sup>
<i>cis</i> -2-Methyl-8-docosene	96** (G)	83
<i>cis</i> -8-Docosene	77** (D)	73
2-Methyl-8-docosyne	76** (A)	97
<i>cis</i> -9-Docosene	72** (D)	82
<i>cis</i> -10-Tetracosene	68** (F)	49
<i>trans</i> -2-Methyl-8-docosene	66** (G)	21
<i>cis</i> -10-Tricosene	65** (E)	62
<i>cis</i> -22-Methyl-9-tricosene	64** (H)	29
<i>trans</i> -8-Docosene	62** (D)	16
10-Methyl-9-docosene	56** (D)	88
<i>trans</i> -10-Tetracosene	47** (C)	23
<i>trans</i> -22-Methyl-9-tricosene	45** (H)	33
<i>cis</i> -21-Methyl-9-docosene	38* (D)	23
8-Methyl-8-docosene	31 (D)	13
<i>trans</i> -9-Tricosene	27 (B)	28
<i>cis</i> -11-Tricosene	25** (E)	30
<i>trans</i> -9-Tetracosene	24* (C)	22
<i>trans</i> -8-Tricosene	22 (B)	20
<i>trans</i> -11-Tricosene	21 (B)	12
<i>trans</i> -7-Tricosene	14 (B)	19
<i>cis</i> -7-Tricosene	9 (B)	16
<i>trans</i> -10-Tricosene	7 (B)	15
<i>trans</i> -9-Docosene	6 (A)	21
9-Methyl-9-tricosene	5 (H)	42
<i>cis</i> -8-Tricosene	4 (B)	16
22-Methyl-9-tricosyne	-2 (H)	21
<i>cis</i> -9-Tetracosene	-5 (C)	21
<i>trans</i> -21-Methyl-9-docosene	-7 (A)	27

<sup>a</sup> From three to ten replicate tests, computed from corrected ratios to means. \*\*  $p < 0.01$  from blank; \*  $p < 0.05$  from blank; doubly underlined activity score =  $p < 0.01$  from muscalure; single underline =  $p < 0.05$  from muscalure. Comparisons were derived from several sets of statistical analyses. Sets (comparisons of compounds tested at the same time) are identified by letter in parentheses. <sup>b</sup> From Tables I and II, except for 22-methyl-9-tricosyne from Table III. <sup>c</sup> 85% *cis* isomer.

The length of the longer chain on the unsaturated bond, which varied between C<sub>12</sub> and C<sub>16</sub>, seemed to be crucial (*e.g.*, muscalure has C<sub>9</sub> and C<sub>14</sub> chains on its double bond). Thus, the most active compounds had for their longer chains mostly C<sub>14</sub> and some C<sub>13</sub> groups. *cis*-9-Heneicosene, which has a C<sub>12</sub> chain, showed low activity in olfactometer tests and moderate activity in the pseudofly test. We could not confirm the findings of Mansingh *et al.* (1972) in olfactometer and pseudofly tests with 50 and 30  $\mu$ g, respectively, of the improved attractancy of a 7:3 mixture of *cis*-9-tricosene and *cis*-9-heneicosene.

In addition to experimental variation, it is possible that geological variation between strains of flies could be responsible for the lack of attraction or activation observed.

Compounds were synthesized with a methyl branch in the 2- and in the penultimate position (iso branching) and on the double-bonded carbon atoms. Activity was high with the methyl in the 2 position (on the short chain) but decreased sharply with iso branching on the long chain. (Compare activities of *cis*-2-methyl-8-docosene and *cis*-21-methyl-9-docosene.) The low activity of *cis*-22-methyl-9-tricosene verified the deleterious effect of iso branching

on the long chain. The activity of compounds with methyl branching on the double-bonded carbon atoms of the long chain exhibited higher activity than compounds with a similar branch on the short chain. Thus, 10-methyl-9-docosene and 10-methyl-9-tricosene were much more active than 8-methyl-8-docosene and 9-methyl-9-tricosene.

The results of the pseudofly petri dish test showed a high degree of similarity (correlation coefficient 0.76) with those of olfactometer tests (Table IV). The few discrepancies (e.g., 10-methyl-9-docosene ranked second in the olfactometer and thirteenth in the pseudofly test) did not negate the general agreement. The similarity of data derived by the two testing procedures on muscalure and its trans isomer was noted by Rogoff *et al.* (1973). Since the mating-type behavior elicited by muscalure and many of its analogs was accompanied by increased rates of capture (*i.e.*, greater attraction) in the olfactometer, our data are consistent with the hypothesis that muscalure is the compound that produced the sex stimulant and attractant action reported by Rogoff *et al.* (1964).

Structural requirements for activity of insect sex pheromones have been investigated only for a few insect species. Generally, any variation in structure causes a great loss in activity. In the case of muscalure, a number of structural variations have produced active compounds,

some of which equal or even slightly exceed the activity of muscalure. Accordingly, requirements in chemical structure for activity of the muscalure molecule are not considered to be highly specific. This lower specificity may be characteristic of sex pheromones that, like muscalure, are not highly potent (*e.g.*, compared with the sex pheromones of many Lepidoptera).

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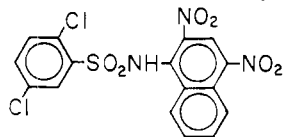
## Insect Chemosterilants. Sulfonamides

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Seven *N*-(2,4-dinitro-1-naphthyl)benzenesulfonamides were more active as chemosterilants in *Musca domestica* L. (oral administration) than the 2,5-dichloro analog (ENT 52766) reported

previously. As a male sterlant, 2,5-dichloro-2',4'-dinitrobenzenesulfonanilide was ten times more effective than ENT 52766.

Most chemosterilants effective in male insects are biological alkylating agents but other classes of male chemosterilants have been discovered in the past 10 years (Bořkovec, 1972). When Fye *et al.* (1973) reported the activity of 2,5-dichloro-*N*-(2,4-dinitro-1-naphthyl)benzenesulfonamide (ENT 52766) in the male house fly, *Musca domestica* L., no other structurally similar sulfonamide was known to sterilize male insects. Sterilants effective in both sexes are of special importance for practical application but a much higher activity than that shown by ENT 52766 would be desirable. Consequently, our efforts were directed toward synthesizing related sulfonamides with high sterilizing activity and toward determining which parts of the molecule exemplified by ENT 52766 were essential for activity. Herein we describe the results of this study.



ENT 52766

*ca* L., no other structurally similar sulfonamide was known to sterilize male insects. Sterilants effective in both sexes are of special importance for practical application but a much higher activity than that shown by ENT 52766 would be desirable. Consequently, our efforts were directed toward synthesizing related sulfonamides with high sterilizing activity and toward determining which parts of the molecule exemplified by ENT 52766 were essential for activity. Herein we describe the results of this study.

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#### EXPERIMENTAL SECTION

**Synthesis of Chemicals.** The melting points are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Tables of complete analytical data for the sulfonamides not mentioned in this section will appear in the microfilm edition; see paragraph at end of paper regarding supplementary material.

The majority of the *N*-(1-naphthyl)arylsulfonamide precursors were prepared by the procedure of Witt and Schmitt (1894). Alkylsulfonamides were prepared by condensing the appropriate sulfonyl chloride with 1-naphthylamine in pyridine solvent. Melting points of new compounds are listed in Table I.

*N*-(1-Naphthyl)aryl(or alkyl)sulfonamides were nitrated by a slightly modified method of Morgan and Godden (1910) and Morgan and Evens (1919). The general procedure which we have used for the preparation of a wide variety of *N*-(2,4-dinitro-1-naphthyl) derivatives, in yields ranging from 28 to 82%, follows.

*N*-(2,4-Dinitro-1-naphthyl)aryl(or alkyl)sulfonamides. To a solution or suspension of finely pulverized *N*-(1-naphthyl)aryl(or alkyl)sulfonamide (0.01 mol) in glacial acetic acid (20–30 ml) was rapidly added 70% nitric acid (0.021–0.022 mol). Usually the mixture was heated to 70–75° for 5–15 min but for exothermic reactions the initial temperature was allowed to subside prior to heating. In vigorous reactions, when the induction temperature exceeded 55°, no external heating was necessary. If the product did not precipitate during the reaction, cooling was used to induce