

Insecticidal Properties of 1,3-Indandiones

Effect of Acyl Groups

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The acylated 1,3-indandiones are very toxic to houseflies when tested according to the Peet-Grady insecticide bioassay method. The profound effect of the various acylations upon the insecticidal properties of this series of new compounds provides an opportunity to study the relation between organic chemical structure and insect toxicity.

It was found that the insect toxicity of the acylated indandiones was increased as the number of carbon atoms in the acyl radical was increased from 2 to 5. There-

after the activity toward flies decreased. The isomeric valeryl-1,3-indandiones exhibited powerful insecticidal action approaching that of the pyrethrins. However, their action is not sufficiently rapid for use alone in contact fly sprays. Accordingly, their applications appear to be as a substitute for the major portion of pyrethrum extractives, especially in the more concentrated insecticides. The laboratory preparation of these new compounds is described as well as the details of the biological evaluation against houseflies.

ORGANIC compounds, having an active methylene group positioned between two oxo groups as the dominant functional group, were observed to be toxic toward insects (?). This toxicity can be materially enhanced by certain acylations of the active methylene group. These findings led to attempts to prepare acylated, cyclic 1,3-dioxo compounds by the Claisen condensation between methyl ketones and phthalic esters.

The first Claisen condensation attempted, between mesityl oxide and ethyl phthalate using metallic sodium in benzene as the condensing agent, failed after repeated trials. It was therefore surprising to discover sometime later that the analogous saturated methyl ketone, methyl isobutyl ketone, would condense with ethyl phthalate under the same conditions to produce a tarry residue having strong insecticidal properties. A yellow crystalline substance (melting at

67-68° C.), obtained from the residue by alkali extraction, was found to be very toxic to houseflies when bioassayed by the Peet-Grady method (9) of testing contact insecticides.

Although no reference has been found to the Claisen condensation between ethyl phthalate and methyl isobutyl ketone, analogous reactions have been reported. Wislicenus (12) obtained 2-carbethoxy-1,3-indandione in a similar manner by the condensation of ethyl phthalate with ethyl acetate. Also, Schwerin (10) prepared the 2-acetyl-, 2-propionyl-, and 2-benzoyl-1,3-indandiones by condensing ethyl phthalate with acetone, methyl ethyl ketone, and acetophenone, respectively, using a solution of sodium ethoxide in alcohol as the condensing agent. The above new condensation of ethyl phthalate with methyl isobutyl ketone, would therefore be expected to give the analogous 2-isovaleryl-1,3-indandione according to the reaction,

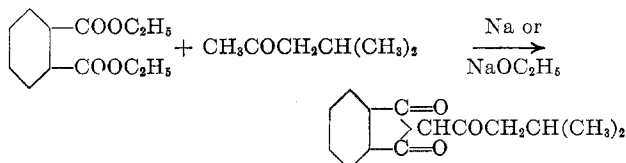


TABLE I. 2-SUBSTITUTED-1,3-INDANDIONES

2-Acyl-1,3-indandione	Melting Point (Uncor.), ° C.	Ketone Used in Claisen Condensation
Acetyl-	109-111 ^a	Acetone
Propionyl-	101 ^a	Methyl ethyl ketone
Butyryl-	29-30	Methyl propyl ketone
Isobutyryl-	96	Methyl isopropyl ketone
Valeryl-	(Oil)	Methyl butyl ketone
Isovaleryl-	67-68	Methyl isobutyl ketone
Pivalyl-	108.5-110.5	Pinacolone
Seneciyl-	135	Mesityl oxide
Caproyl-	37-38	Methyl amyl ketone
Enanthoyl-	(Oil)	Methyl hexyl ketone
Hexahydrobenzoyl-	79-80	Methyl cyclohexyl ketone
β-Phenylpropionyl-	77	4-Phenyl-2-butanone
Benzoyl-	109-110 ^a	Acetophenone
α-Naphthoyl-	193-194	Methyl α-naphthyl ketone
β-Naphthoyl-	140-142	Methyl β-naphthyl ketone
5-Bromo-2-isovaleryl-	122-124	Methyl isobutyl ketone

^a Schwerin (10) reported these values as follows: acetyl-, 110°; propionyl-, 103°; benzoyl-, 108° C.

The neutral equivalent, molecular weight, and carbon and hydrogen determinations on the new compound were in close agreement with the values calculated for 2-isovaleryl-1,3-indandione. The chemical properties were also found to be similar to those reported by Schwerin (10) for the acylated indandiones he prepared—namely, solubility in aqueous sodium hydroxide, sodium carbonate, and ammonia to form bright yellow salts. The unusual stability of 2-acetyl-1,3-indandione reported by Dieckmann and Stein (4) was found to be also true of the 2-isovaleryl compound

which could be boiled in a 2 *N* potassium hydroxide solution for 9 hours and be recovered unchanged.

This discovery of the toxicity of 2-isovaleryl-1,3-indandione toward houseflies led to the preparation of the series of 2-substituted-1,3-indandiones shown in Table I, which were found to be similarly toxic to flies in varying degrees. This series of compounds therefore provided an excellent opportunity to correlate insect toxicity with chemical structure. It is fortunate that the unsubstituted 1,3-indandione exhibits little or no insecticidal activity under the same conditions, so that insecticidal activities of the various substituted 1,3-indandiones may be properly ascribed to the respective substituent.

Biological Test Methods

Since most of the acylated indandione compounds were too slow in their paralytic action to be tested by the Peet-Grady method, the following procedure was used. Each of the indandiones was tested in combination with a sublethal dosage of pyrethrum extractives which provided the required rapid paralysis without materially contributing to the kill power of the combination.

Each of the indandiones was dissolved in deodorized kerosene at a concentration of 500 mg. per 100 ml., and pyrethrum extract was added to give a total pyrethrin content of 50 mg. per 100 ml. A few of the members of the series were not sufficiently soluble in the kerosene to give the above concentration; in those cases 10 per cent dioxane was used as cosolvent. The addition of dioxane had no effect upon the results of the bioassays.

The assays were conducted by the large group method of the Peet-Grady test (11); each culture of flies in the pupal stage is divided into groups of approximately five hundred pupae to each test cage to assure random distribution of the sexes. The materially greater resistance of the female flies makes this important.

The resistance of the flies in any individual culture was determined by official test insecticide (O. T. I.) supplied by the National Association of Insecticide and Disinfectant Manufacturers, which was included as the first and last test of each culture. If the results of these two tests did not agree within 10 per cent, the results for the entire culture were discarded.

Inasmuch as it was not practical to use one culture of flies large enough to test the entire series of indandiones, the series was divided into four parts, using four different cultures. Each part consisted of not more than four samples plus two O. T. I. tests, or eight groups of five hundred flies from each culture. Thus, when four members of the series were tested on one culture, each member was tested on approximately two thousand flies.

Since it is impossible to rear houseflies so uniformly that different cultures will always have the same resistance towards a toxicant, the results were statistically adjusted to a common basis of 50 per cent kill for the O. T. I. (δ) included in the respective cultures. However, such a standard evaluates only the specific resistance of the individual cultures toward pyrethrins and does not provide a measure of their resistance toward another insecticidal material. This is especially true if the second material is chemically unrelated to the pyrethrins, which are the sole toxic principles of the official test insecticide. For this reason another standard solution, closely similar to those under test, was used with each culture in addition to the official test insecticide. This secondary standard solution contained 500 mg. of Valone (2-isovaleryl-1,3-indandione), and 50 mg. of total pyrethrins per 100 ml., and was included once in each culture. Valone is manufactured by U. S. Industrial Chemicals, Inc., and was chosen for its efficacy and ready availability.

TABLE II. RESULTS OF PEET-GRADY BIOASSAYS OF ACYL INDANDIONES

2-Acyl-1,3-indandione ^a	% Kill in 24 Hr.	% Kill Adjusted	2-Acylated-1,3-indandione ^a	% Kill in 24 Hr.	% Kill Adjusted
Series 1			Series 2		
Acetyl-	32	43	Pyrethrins only	24	29
Propionyl-	43	55	Pivalyl-	84	87
Butyryl-	56	68	Caproyl-	53	59
Isobutyryl-	52	64	Enanthoyl-	41	47
Isovaleryl- ^b	75	84	Hexahydrobenzoyl-	60	66
O. T. I.	38	50	Isovaleryl- ^b	72	77
			O. T. I.	44	50
Series 3			Series 4		
Senecieryl-	37	40	1,3-Indandione (not acylated)	42	35
Benzoyl-	54	57	β -Naphthoyl-	48	40
5-Bromo-2-benzoyl-	55	58	Isovaleryl- ^b	85	80
Isovaleryl- ^b	83	85	O. T. I.	57	50
O. T. I.	47	50			

^a Each sample contains 50 mg. pyrethrins + 500 mg. of the acylated indandione per 100 ml.; 50 mg. pyrethrins are equivalent to 2.5% of commercial pyrethrum 20:1 extract.

^b Secondary standard.

In order to calculate the adjusted results for each of the indandiones in the four cultures to one basis, the adjusted value for the secondary standard was fixed at 80 per cent. The values for the other indandiones were then readjusted to this new base.

Table II gives the results obtained on each of the acyl 1,3-indandiones severally adjusted within each culture. These values have again been adjusted in Table III, to the base of 80 per cent for the secondary standard, so that the four cultures are now directly comparable. Although the toxicity ratio of pyrethrins (as shown by the official test insecticide) to indandiones varies from one culture to another, the relation between the samples containing an indandione remained fairly constant.

The 2-valeryl- and the 2-(β -phenylpropionyl)-1,3-indandiones were not tested on sufficient numbers of flies to ensure the accuracy of the other tests and were not included in Table III. The results obtained on these two compounds, however, indicate that the former was approximately equivalent to 2-isovaleryl- and the latter to 2-enanthoyl-1,3-indandione.

Since this new series of insecticides appears to complement the pyrethrins, it is interesting to evaluate their insecticidal activity in terms of the pyrethrins as occurring in pyrethrum extract. However, to make these calculations, it is necessary to take into account the fact that as the kill percentage approaches 100, each successive increase in killing

TABLE III. TOXICITY OF ACYLATED INDANDIONES TOWARD HOUSEFLIES IN TERMS OF PYRETHRINS

50 Mg. Pyrethrins + 500 Mg. 2-Acyl-1,3-indandione	Readjusted % Kill (Isovaleryl = 80%)	Pyrethrin Equivalent ^a , Mg./100 Ml.	% Activity Compared with Pyrethrins
Acetyl-	37	23	5
Propionyl-	49	43	10
Butyryl-	63	80	16
Isobutyryl-	58	66	13
Isovaleryl-	80	140	28
Pivalyl-	89	210	42
Caproyl-	63	80	16
Enanthoyl-	51	52	10
Hexahydrobenzoyl-	70	100	20
Benzoyl-	50	50	10
β -Naphthoyl-	40	30	6
Senecieryl-	33	13	3
No acyl group	35	20	4
50 mg. pyrethrins only	80

^a The amount of pyrethrins which would have to be added to the 50 mg./100 ml. solution to produce the kill obtained by the respective corresponding acylated indandione-pyrethrum combination.

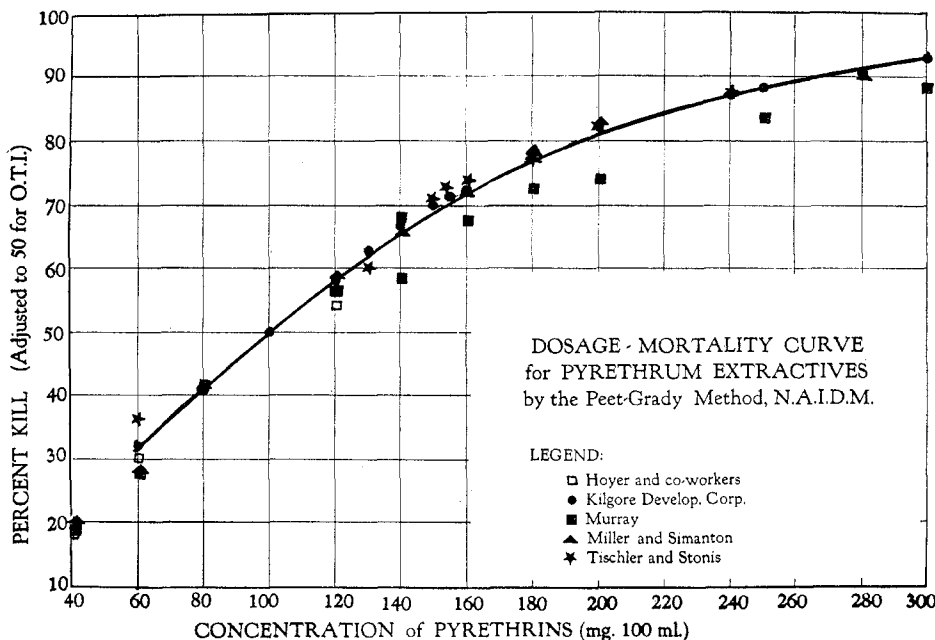


Figure 1

power becomes more significant. This can be readily appreciated by inspection of the dosage-mortality curve for the pyrethrins shown in Figure 1. This curve is based upon data obtained in this laboratory and appears to be in close agreement with other published data (8). The value reported for 100 mg. per 100 ml. pyrethrins was used in lieu of the official test insecticide whenever the latter was not given in the literature. All data were accordingly adjusted to the same basis of 50 per cent kill for the official test insecticide.

The adjusted kill for 50 mg. per 100 ml. pyrethrins, as shown in Figure 1, is 30 per cent. This concentration of pyrethrins, a check, was included in culture 2, Table II, and gave a 29 per cent kill. Since this concentration of pyrethrins was used in combination with each of the indandiones, any resulting kill in excess of 30 per cent is regarded as due to the concomitant indandione. The concentrations of pyrethrins alone required to produce the kills corresponding to each of the pyrethrin-indandione combination results, are determined from Figure 1. For example, 150 mg. per 100 ml. pyrethrins alone are required to effect the kill produced by 50 mg. pyrethrins + 500 mg. 2-hexahydrobenzoyl-1,3-indandione. Therefore, 500 mg. of the indandione have replaced the insecticidal activity of 100 mg. of pyrethrins and may be considered as having 20 per cent of the insecticidal activity of pyrethrins in this range. The values shown in Table III were calculated in a similar manner.

Discussion of Results

While all of the 2-acyl-1,3-indandiones appeared to have some insecticidal activity, the size and structure of the acyl group have a pronounced effect upon the toxicity toward insects. As the number of carbon atoms in the acyl group increases from 2 to 5, the corresponding effectiveness increases rapidly; then it falls off rapidly.

Bousquet and co-workers (2) showed that the most effective alkyl thiocyanates of their work contained 10 to 14 carbon atoms. Recently Dahm and Kearns (3) reported that the most active aliphatic secondary amines studied in a comprehensive series contained 11 to 15 carbon atoms.

If the total number of carbon atoms in the acylated indandiones is considered here instead of the acyl group alone, it is apparent that the most effective members of this series of new insecticides likewise contain a total of 11 to 14 carbon atoms.

The substitution of a bromine atom for one of the hydrogens of the benzene ring of the 2-isovaleryl-1,3-indandione caused a marked decrease in the insecticidal activity. Similarly, methylation of the acidic hydrogen also destroyed the major part of the activity.

The only member of the series having greater toxicity to houseflies than the first discovered isovaleryl derivative is the pivalyl acylated 1,3-indandione. Since it is prepared from the expensive pinacolone, its commercial production is not so feasible as the slightly less active isovaleryl compound now being used.

Chemical Procedures

With the single exception of the 2-seneciroyl derivative prepared from mesityl oxide, all of the acylated 1,3-indandiones are suitably prepared by Claisen condensations in benzene solution, using alcohol-free sodium methoxide or ethoxide as the condensing agent. Experiments made with metallic sodium lowered the yields as did the use of alcohol as a solvent for the reaction. Under these conditions mesityl oxide tended to polymerize rather than enter into a Claisen reaction. However, by adding powdered sodium methoxide to a mixture of the reactants in the absence of a solvent, it was possible to obtain the desired 2-seneciroyl-1,3-indandione. All of the acylated indandiones gave an intense yellow-red color test with ferric chloride.

The series of acylated 1,3-indandiones thus prepared, together with their melting points and the methyl ketones used in their preparation, are given in Table I.

2-ISOVALERYL-1,3-INDANDIONE. Twenty-three grams (one atom) of metallic sodium, powdered under 50 ml. of toluene and cooled, were covered with 450 ml. of dry benzene; 33.6 grams (one mole) of dry methanol were added and refluxed about 5 hours until all of the sodium had been converted to the alkoxide. A mixture of 194 grams (one mole) of methyl phthalate and 105 grams (one mole) of dry methyl isobutyl ketone was added and refluxed for 8 hours. The toluene and benzene were then removed by steam distillation at 0.5 atmosphere, and the residue was thrown into 2 liters of water and leached for 12 hours. When the water layer was separated and acidified, the product separated as an oil and quickly solidified. The crude triketone was recrystallized from 85 per cent aqueous methanol, using about 3 ml. per gram of product. The yield was 109 grams (47 per cent).

Analysis. Calculated $C_{11}H_{14}O_3$, C 73.01 per cent, H 6.13; observed, C 73.00 per cent, H 6.24. Molecular weight: calculated, 230; observed, 207 (Rast). Neutral equivalent: calculated 230; observed 229, 225.

PREPARATION OF 2-ACYL-1,3-INDANDIONES. The Claisen condensations, in general, were conducted in approximately

the same manner as described above. Commercial sodium methoxide was used with about the same results.

In cases where the products failed to crystallize readily, they were first purified by recrystallizing the sodium salts. For this purpose the sodium salts could be leached from the condensation residues using about 300 to 500 ml. per mole. Some of the sodium salts as naphthoyl compounds required large volumes of water since their solubility was in the neighborhood of only one per cent.

KETONES. The ketones used in preparing the compounds listed in Table I were obtained from the following sources:

Pinacolone was prepared by the method described by Gilman (6).

4-Phenyl-2-butanone was prepared by the reduction of benzalacetone with hydrogen at atmospheric pressure, using Raney nickel catalyst; it was purified by the bisulfite addition product. Its boiling point was 65–67° C. at 2 mm., with a yield of 84 per cent.

Methyl cyclohexyl ketone was made by oxidation of methylcyclohexylcarbinol with acid dichromate solution according to the method of Beckmann (1).

Methyl butyl and methyl α -naphthyl ketones were used as obtained from Eastman Kodak Company.

The other methyl ketones were technical products from the following sources: methyl ethyl and methyl propyl ketones

from Shell Development Corporation, methyl isopropyl ketone from Sharples Solvents Corporation, methyl isobutyl and methyl amyl ketones from Carbide and Carbon Chemicals Corporation, mesityl oxide from Commercial Solvents Corporation, methyl hexyl ketone, acetophenone, and methyl β -naphthyl ketone from Fritzsche Brothers. Those boiling below 100° C. were dried over calcium chloride; those boiling above 100° C. were distilled to dry.

Literature Cited

- (1) Beckmann, E., *Ann.*, **250**, 325 (1889).
- (2) Bousquet, E. W., Salzberg, P. L., and Dietz, H. F., *IND. ENG. CHEM.*, **27**, 1342 (1935).
- (3) Dahm, P. A., and Kearns, C. W., *J. Econ. Entomol.*, **34**, 462 (1941).
- (4) Dieckmann, W., and Stein, R., *Ber.*, **37**, 3384 (1904).
- (5) Ford, J. H., *Soap*, **13**, No. 6, 116 (1937).
- (6) Gilman, "Organic Synthesis", collective Vol., p. 451, 1932.
- (7) Kilgore, L. B., U. S. Patents 2,070,603 (1937), 2,107,298 (1938), 2,228,170 (1941).
- (8) Miller, A. C., and Simanton, W. A., *Soap*, **14**, No. 5, 103 (1938); Tischler, N., and Stonis, J. E., *Ibid.*, **14**, No. 10, 97 (1938); Murray, C. A., *Ibid.*, **14**, No. 2, 99 (1938); Hoyer, D. G. Schmidt, S. Z. von, and Weed, A., *J. Econ. Entomol.*, **29**, 598 (1936).
- (9) Peet, C. H., and Grady, A. G., *J. Econ. Entomol.*, **21**, 612–17 (1928); "Soap Blue Book", New York, MacNair-Dorland Co.
- (10) Schwerin, E., *Ber.*, **27**, 104–14 (1894).
- (11) Simanton, W. A., and Miller, A. C., *Soap*, **14**, No. 4, 115 (1938).
- (12) Wislicenus, W., *Ber.*, **20**, 593 (1887).

Substitutes for Copper and Zinc in Fungicidal Sprays

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FOR many years Bordeaux mixture has been the standard spray for the control of plant diseases. Except on plants to which it causes serious injury, it is still the standard. It is cheap, easily handled, and practically noninjurious to operators, adheres well, and is active over relatively long periods. Other copper sprays are also used to a limited extent. The so-called insoluble coppers are used either on varieties sensitive to Bordeaux mixture or at times when a mild copper fungicide is sufficiently effective to give adequate control. As a killer of fungi, Bordeaux mixture ranks so high that except for use on plants that it injures severely, little work has been done on the development of fungicides to take its place.

Because Bordeaux mixture and most copper sprays may, under certain conditions, cause severe injury to peaches, plums, cherries, apples, and other fruit trees, most of the substitutes for copper fungicides have been developed and are being developed for use on these trees. Since the turn of the century lime-sulfur solution and sprays containing finely divided sulfur have supplanted Bordeaux mixture and other copper sprays in spring applications for the control of apple scab, but in summer in the warmer sections Bordeaux mixture is still used because in hot weather it is less injurious than sulfur and lime-sulfur solution. In sections where apple blotch and bitter rot are prevalent, Bordeaux mixture is used because it is the only known spray that will control these diseases. Except where blotch and bitter rot are present, apple growers can use lime-sulfur solution or sulfur

somewhat later than is the practice at present and thus save one or perhaps two applications of copper.

Comparatively little copper is used on peach trees. It is employed to some extent on the Pacific Coast for the control of peach blight and brown-rot blossom blight, but it is mostly used throughout the country as a dormant spray for the control of leaf curl. Lime-sulfur solution has been used successfully against this disease. At present Bordeaux mixture is employed because it can be combined with the oil sprays applied for the control of San Jose scale. Lime-sulfur solution combined with these oil sprays would be apt to cause serious injury to peach trees. Liquid lime-sulfur, dormant strength, is a practicable substitute.

For the spraying of cherry and plum trees lime-sulfur solution and the sulfur sprays are successfully used, although in some sections copper sprays are preferred for the control of leaf spot on sour cherries.

For pears copper sprays are much less apt to cause injury and are generally more effective than lime-sulfur solution and sulfur. The tendency of the lime-sulfur and sulfur sprays to cause stunting when applied during the growing season almost entirely prevents their use on grapes, small fruits, nut crops, potatoes, tomatoes, and vegetable crops in general. For the control of such diseases as grape black rot and potato late blight, Bordeaux mixture is a necessity. There is no substitute for it. Bordeaux mixture and other copper sprays are also essential in the control of such diseases as pecan scab, walnut