

Substituted Phenyl 2-Propynyl Ethers as Carbamate Synergists

Josef Fellig, J. R. Barnes, A. I. Rachlin, J. P. O'Brien, and Antonino Focella

Thirty-six substituted phenyl 2-propynyl ethers and thioethers were tested for synergistic activity toward carbaryl in the housefly. The most active compounds, namely the 2,3,6-trichloro, 2,4-dibromo, 2-nitro, 3-nitro, and 2-nitro-4-chlorophenyl 2-propynyl ethers lowered the LD₅₀ for carbaryl to

less than 0.1 μg per fly. Substitution with more than one nitro group or more than three halogens decreased activity, as did the introduction of an alkyl, alkoxy, or aryl group or the formation of a thioether.

Synergism of carbamate insecticides was first observed with methylenedioxyphenyl derivatives already known as pyrethrin synergists (Moorefield, 1958) and extensive studies were carried out with this group of compounds (Eldefrawi *et al.*, 1960; Fukuto *et al.*, 1962; Moorefield and Weiden, 1964; Wilkinson *et al.*, 1966). Several other classes of compounds which were also found to exert this synergistic activity are the inhibitors of microsomal oxidation SKF 525A and Lilly 18947, various aryloxyalkylamines related to the latter (Moorefield and Tefft, 1959; Metcalf and Fukuto, 1965; Fahmy and Gordon, 1965), and some organothiocyanates (El-Sebae *et al.*, 1964; Bakry *et al.*, 1968). Recently, we found a new group of carbamate synergists, the phenyl 2-propynyl ethers, which potentiate a variety of carbamate insecticides against several insect species (Fellig and Rachlin, 1968; Barnes and Fellig, 1969). The mode of action of the propynyl synergists has been related to the biochemical level to that of the earlier methylenedioxyphenyl compounds (Sacher *et al.*, 1968). The relation of structure to synergistic activity in the substituted phenyl 2-propynyl ethers forms the subject of this report.

EXPERIMENTAL

Synthesis. The compounds listed in Tables I, II, and III were prepared, as indicated by one of the following general procedures.

GENERAL PROCEDURE 1. To a 500-ml, 3-neck round bottom flask equipped with a stirrer and reflux condenser were charged 0.20 mole of phenol (or thiophenol), 26.2 grams (0.22 mole) of 3-bromopropyne, 30.4 grams (0.22 mole) of potassium carbonate, and 300 ml of acetone. After the reaction mixture was stirred and refluxed for 8 hours, the solids were filtered and the filtrate was evaporated in vacuo at 60°. The residue was purified by crystallization or distillation.

GENERAL PROCEDURE 2. To a 1-liter, 3-neck round bottom flask equipped with a stirrer, dropping funnel, and a thermometer were charged 0.25 mole of the propargyl ether (Table I) and 350 ml of methanol. To the vigorously stirred solution were added dropwise and simultaneously 84 grams (0.33 mole) of iodine in small portions and 240 ml of a 10% aqueous sodium hydroxide solution (0.57 mole) over a period of 15 minutes while the reaction temperature was maintained between 20° and 25°C by means of an ice-water bath. After stirring for 1 hour at room temperature, the reaction mixture was diluted with 100 ml of water. The solids which resulted were collected and recrystallized.

GENERAL PROCEDURE 3. A 2-liter, 3-neck round bottom flask equipped with a stirrer and reflux condenser was charged

with 0.25 mole of phenol (or thiophenol), 0.28 mole of 3-bromopropyne, 22 grams of solid sodium hydroxide, and 350 ml of water. The reaction mixture was stirred and heated on a steam bath for 24 hours after which it was acidified carefully with 6*N* hydrochloric acid and allowed to cool to room temperature. The precipitate was filtered and washed thoroughly with water. (If the precipitate was an oil, it was extracted with ethyl acetate.) The crude product was suspended (or dissolved) in 175 ml of ethyl acetate and washed with two 100-ml portions of a 5% solution of sodium hydroxide and then with two 50-ml portions of water. The resulting organic solution was dried over sodium sulfate and, after the solvent was evaporated in vacuo, the residue was purified by recrystallization or distillation.

GENERAL PROCEDURE 4. To a 1-liter, 3-neck round bottom flask equipped with a stirrer and reflux condenser was charged 0.2 mole of the phenol, 0.24 mole of 3-bromopropyne, 0.24 mole of potassium bicarbonate, and 600 ml of acetonitrile. After the reaction mixture was stirred and refluxed for 24 hours, the solids were filtered and the filtrate was evaporated in vacuo. The residue was purified by crystallization.

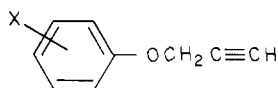
All of the phenols and thiophenols were purchased, except for the following compounds which were prepared by published procedures: 2,3-dibromophenol (Henley and Turner, 1930), *m*-propargyloxyphenol (Haubein, 1965), 2,3-dichlorothiophenol and 2,4,5-trichlorothiophenol (Thompson *et al.*, 1946), 3,4-dichlorothiophenol (Soc. U.S. Chim. Rhône-Poulenc, 1957), 4-chloro-2-nitrothiophenol (Farrington and Warburton, 1956), 2,4-dinitrothiophenol (Zincke and Weisspennig, 1912).

Biological Assay. A susceptible strain, S_{NAIDM}, of the housefly (*Musca domestica* L.), maintained under standard rearing conditions, was used for the insecticide assay. Testing was carried out by topical application of a 1.0- μl drop of acetone, containing carbaryl and synergist, to the thoracic region of 5-day old female houseflies. Three replicates of 10 flies each were treated for each dosage level. Mortality was recorded 24 hours after treatment. Dosage mortality curves were plotted on log-probit paper and LD₅₀ values read from an eye-fitted line. The ratio of carbaryl to synergist was 1 to 5.

Structure-Activity Relationships. The compounds listed in Tables I through III were arbitrarily divided into three groups for the purpose of comparing their synergistic activity. The most active compounds reduced the LD₅₀ for carbaryl in the housefly to less than 0.1 μg per fly. For comparison, the extrapolated LD₅₀ for carbaryl alone exceeded 100 μg per fly. Application, by themselves, of two of the most active synergists, 2-nitro-4-chlorophenyl 2-propynyl ether (XIV) and 2-nitrophenyl 2-propynyl ether (XI) at the same high level produced a kill of 0 and 13%, respectively. The next group, largest among the compounds listed in this report, consists of the synergists that reduced the LD₅₀ of carbaryl to between

Chemical Research Department, Hoffmann-LaRoche Inc., Nutley, N.J. 07110

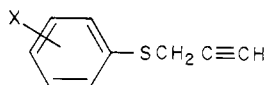
Table I. Synergistic Activity of Substituted Phenyl 2-Propynyl Ethers



No.	X	M.P. or B.P.	Formula	Calculated		Found		Pro- ce- dure	Yield, %	LD ₅₀ μg carbaryl per fly
				C	H	C	D			
I	2,3,6-Cl ₃	63-65 ^a	C ₉ H ₅ Cl ₃ O	45.90	2.14	46.00	2.24	1	93	0.06
II	2,3,4-Cl ₃	78-80 ^a	C ₉ H ₅ Cl ₃ O	45.90	2.14	46.14	2.53	1	99	0.11
III	3,4,5-Cl ₃	64-65 ^a	C ₉ H ₅ Cl ₃ O	45.90	2.14	45.76	2.55	1	90	0.10
IV	2,4,5-Cl ₃ ^b	63-64 ^a	C ₉ H ₅ Cl ₃ O	45.90	2.14	46.10	2.33	1	95	0.10
V	2,4,6-Cl ₃	99-100 ^a	C ₉ H ₅ Cl ₃ O	45.90	2.14	45.87	2.36	1	90	0.13
VI	2,3,5-Cl ₃	62 ^c	C ₉ H ₅ Cl ₃ O	45.90	2.14	46.18	2.49	1	90	0.41
VII	2,4-Cl ₂	53-54 ^c	C ₉ H ₆ Cl ₂ O	53.76	3.01	53.91	3.33	1	90	0.10
VIII	2,3-Cl ₂	47-49 ^a	C ₉ H ₆ Cl ₂ O	53.76	3.01	53.39	3.05	1	90	0.5
IX	2,4-Br ₂	67-68 ^a	C ₉ H ₆ Br ₂ O	37.27	2.09	37.39	2.31	1	80	0.09
X	2,3-Br ₂	49-50 ^c	C ₉ H ₆ Br ₂ O	37.27	2.09	37.26	2.28	1	85	0.13
XI	2-NO ₂	74-76 ^a	C ₉ H ₇ NO ₂	61.01	3.98	61.34	4.04	1	100	0.06
XII	3-NO ₂	67-69 ^a	C ₉ H ₇ NO ₂	61.01	3.98	61.29	4.12	1	100	0.07
XIII	4-NO ₂ ^b	114-116 ^a	C ₉ H ₇ NO ₂	61.01	3.98	60.96	4.14	1	98	0.16
XIV	2-NO ₂ ,4-Cl	85-86 ^a	C ₉ H ₆ ClNO ₂	51.08	7.86	51.00	7.89	3	45	0.06
XV	2,6-(NO ₂) ₂	76-78 ^a	C ₉ H ₆ N ₂ O ₃	48.66	2.72	48.93	2.72	4	85	0.25
XVI	2,4-(NO ₂) ₂	98-100 ^a	C ₉ H ₆ N ₂ O ₃	48.66	2.72	48.93	2.79	3	34	>0.5
XVII	2,4-NO ₂ ,4Cl.6I	91-93 ^c	C ₉ H ₅ ClINO ₂	32.03	1.69	32.15	1.59	1	70	0.16
XVIII	4-CH ₂ C ₆ H ₅	40-41 ^a	C ₁₆ H ₁₄ O	80.65	5.92	80.52	5.83	1	85	0.12
XIX	2-C ₆ H ₅	100-102 at 0.2mm	C ₁₅ H ₁₂ O	86.51	5.81	86.25	5.55	1	80	0.3
XX	3,4-CH ₂ O ⁻	88 at 0.05mm	C ₁₀ H ₈ O ₂	68.18	4.58	68.51	4.86	1	83	0.10
XXI	4-CCH ₃	118 at 7.0mm	C ₁₀ H ₁₀ O ₂	74.05	6.22	74.65	6.15	1	90	>0.5
XXII	2,6-(OCH ₃) ₂	90 at 0.03mm	C ₁₁ H ₁₂ O ₃	68.73	6.29	68.91	6.39	1	98	>0.5
XXIII	3-CH ₃	60 at 0.06mm	C ₁₀ H ₁₀ O	82.16	6.90	82.30	6.84	1	85	>0.5
XXIV	3-CF ₃	40 at 0.05mm	C ₁₀ H ₇ F ₃ O	60.01	3.53	60.12	3.59	1	95	>0.5
XXV	3-OCH ₂ C≡CH	111 at 0.025mm	C ₁₂ H ₁₀ O ₂	77.40	5.41	77.28	5.55	1	85	0.17

^a Ethanol, ^b Seki *et al.* (1964), ^c petroleum ether (BP 30-60°).

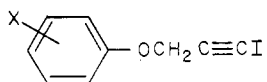
Table II. Synergistic Activity of Substituted Phenyl 2-Propynyl Thioethers



No.	X	M.P. or B.P.	Formula	Calculated		Found		Pro- ce- dure	Yield, %	LD ₅₀ μg carbaryl per fly
				C	H	C	H			
XXVI	2,3-Cl ₂	59-60 ^a	C ₉ H ₆ Cl ₂ S	49.79	2.79	49.77	3.11	1	80	0.34
XXVII	3,4-Cl ₂	98/0.04	C ₉ H ₆ Cl ₂ S	49.79	2.79	49.49	2.96	3	80	>0.5
XXVIII	4-NO ₂	95-97 ^b	C ₉ H ₇ NO ₂ S	55.94	3.65	56.22	3.75	3	90	>0.5
XXIX	2-NO ₂ ,4-Cl	134-136 ^b	C ₉ H ₆ ClNO ₂ S	47.48	2.66	47.64	2.45	3	92	>0.5
XXX	2,4-(NO ₂) ₂	122-124 ^b	C ₉ H ₆ N ₂ O ₂ S	45.39	2.54	45.31	2.47	3	30	>0.5
XXXI	2,4,5-Cl ₃	76-77 ^b	C ₉ H ₅ Cl ₃ S	42.97	2.00	42.84	2.06	1	80	0.51

^a Petroleum ether (BP 30-60°), ^b ethanol.

Table III. Synergistic Activity of Substituted Phenyl 3-Iodo-2-Propynyl Ethers



No.	X	M.P.	Formula	Calculated		Found		Pro- ce- dure	Yield, %	LD ₅₀ μg carbaryl per fly
				C	H	C	H			
XXXII	2,4-Cl ₂ ^a	91-92 ^b	C ₉ H ₅ Cl ₂ IO					2	80	0.12
XXXIII	3,4-Cl ₂ ^a	73-75 ^b	C ₉ H ₅ Cl ₂ IO					2	85	0.17
XXXIV	2,4,5-Cl ₃ ^a	111-113 ^c	C ₉ H ₄ Cl ₃ IO					2	90	0.12
XXXV	2,3,4,6-Cl ₄ ^a	104-105 ^c	C ₉ H ₃ Cl ₄ IO					2	85	0.15
XXXVI	2,3,4,5,6-Cl ₅ ^a	140-141 ^d	C ₉ H ₂ Cl ₅ IO					2	80	0.9

^a Seki *et al.* (1963), ^b petroleum ether (BP 30-60°), ^c ethanol, ^d methylene chloride, petroleum ether (BP 30-60°).

0.1 and 0.5 μg per fly. The least active compounds discussed here are those which produced an LD_{50} for carbaryl equal to or greater than 0.5 μg per fly. While much less active than the previous two groups, all of these compounds still had a measurable synergistic effect.

The most active phenyl 2-propynyl ethers included the 2,3,6-trichloro (I), 2,4-dibromo (IX), 2-nitro (XI), 3-nitro (XII), and 2-nitro-4-chloro (XIV) derivatives. Among the dihalogen-substituted compounds, the 2,4 configuration appeared more active than the 2,3 or 3,4 configurations (VII and VIII, XXXII and XXXIII) and the bromo derivatives slightly more active than the chloro derivatives (IX, X). All of the trichlorophenoxy derivatives (I-VI) had a high level of activity, with one compound (I) being among the most active of this series. Introduction of more than 3 halogens lowered activity (XXXV, XXXVI). The dinitrophenoxy compounds, on the other hand, showed much less activity than the dichlorophenoxy compounds (XV, XVI), even though the mononitro and nitrochloro compounds were among the most active synergists (XI, XII, XIV). A nitro group in the para position seemed to decrease activity more than a nitro group in the ortho position (XV, XVI). Phenyl or benzyl substitution lowered the synergistic activity (XVIII, XIX), as did the introduction of a second propynyl group in the absence of other substituents (XV). Substitution with methyl, methoxy, and trifluoromethyl groups resulted in compounds of low activity (XXI-XXIV). On the other hand, combination of a methylene-dioxyphenyl group and a propynyl group produced a synergist of high activity (XX). Two structural variations affecting the propynyl side chain do not improve the performance of the compounds. Replacement of the terminal hydrogen of the propynyl group by iodine slightly decreased synergistic activity (VII and XXXII, IV and XXXIV) and formation of the phenylthioethers led to compounds of greatly decreased activity (for example, XIV and XXIX).

In conclusion, ring substitution of phenyl 2-propynyl ether with no more than one nitro group or two to three halo-

gens resulted in the most active synergists for carbaryl. Ring substitution by aryl, alkyl, or alkoxy groups decreased activity, as did formation of the thioethers.

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