Table II. Biological Activity of Alkyl- and Halo-phenyl–Substituted Carbamates

(% kill of test species)

Compound No.	500 P.P.M. Housefly	Southern armyworm	Mexican bean beetle	Pea aphid	T. atlanticus mite	1000 P.P.M., P. citri mite
1	33	0	100	0	0	0
2	33	35	98	0	8	0
3	0	0	0	0	0	0
4	100	100	100	90	94	100
5	100	0	100	0	24	. .
6	70	0	85	15	0	0
7	95	0	98	5	20	2
8	97	0	100	0	20	58
9	96	30	100	0	0	0
10	0	0	0	0	0	0
11	100	0	100	0	0	. .
12	100	50	100	80	40	90
13	100	0	100	0	34	100
14	45	0	55	0	0	0
15	50	0	100	0	0	0
16	0	0	0	0	0	0
17	17	0	40	0	0	0
18	0	0	0	0	0	0
19	95	35	100	60	0	0

differences in activity caused by changing from 3-methyl to 3-ethyl or from 4-chloro- to 4-bromo- substitution. Very little change in activity was noted.

Compounds 12, 13, 14, and 15 are examples of tetra-substituted phenylcarbamates and were of interest because of the insecticidal properties of compounds 12 and 13. Again, minor changes in structure—e.g., 14 and 15—adversely affected the over-all activity. We concluded from the foregoing discussion that simple relationships among the number, orientation, and variety of alkyl- and halo-substitution in the phenyl carbamic esters and their biological activity are not immediately evident.

However, compound 4 has been used in field studies and is of promise in many areas. The compound was tested under the code U-12,927, and has the tradename Banol, trivial name carbanolate. Field control of several cotton insects, some mite species, and several beetle, mosquito, and lepidopterous larvae species has been demonstrated; details will be published separately.

Acknowledgment

The authors thank R. L. Metcalf and R. E. Kohls for helpful discussions and some laboratory testing data.

Literature Cited

(1) Cole, M. M., Clark, P. H., *J. Econ. Entomol.* **55,** 98 (1962).
(2) Georgiou, G. P., Metcalf, R. L., *Ibid.*, **55,** 125 (1962).
(3) Jacobi, E., Lust, S., Schoer, A., Zima, O., U.S. Patent **2,992,966** (1961).
(4) Kolbezen, M. J., Metcalf, R. L., Fukuto, T. R., J. Agr. Food Chem. **2,** 864 (1954).
(5) Lemin, A. J., U.S. Patent **3,131,215** (1964).
(6) Metcalf, R. L., Fuertes-Polo, C., Fukuto, T. R., *J. Econ. Entomol.* **56,** 862 (1963).
(7) Shorey, L. H., Reynolds, H. T., Anderson, L. O., *Ibid.*, **55,** 5 (1962).

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CARBAMATE INSECTICIDES

Alkyl- and Amino-Substituted Phenyl *N*-Methylcarbamate Insecticides

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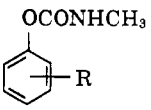
A new series of phenyl-*N*-methylcarbamates has been prepared which contains various combinations of alkyl and alkylamino groups attached to the aromatic ring. Outstanding insecticidal activity has been found in screening tests with Mexican bean beetles and Southern armyworms with derivatives containing the basic group in the para position and the alkyl groups in the meta position.

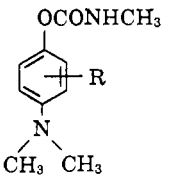
The alkaloid physostigimine (eserine) has long been known to display a complex spectrum of biological activity. The fact that the parent substance eseroline (which is lacking the *N*-methylcarbamate fragment) is biologically inert has led to the study of a large variety of aromatic esters of methylcarbamic acid.

In a series of esters derived from aminophenols and either *N*-methyl or *N,N*-dimethylcarbamic acid, Stedman (*18*) observed that a *tert*-amino group ortho, or a quaternary group meta to the phenolic oxygen led to maximum potency as a miotic agent. Subsequently several large series of similar esters were prepared and evaluated (*6*, *19*) to demonstrate relationships between structure and mammalian toxicity. In a study of aromatic *N*-methylcarbamates containing a variety of types of (nonbasic) substituents, Kolbezen, Metcalf, and Fukuto (*11*) demonstrated that both the identity and location of the substituent had a profound effect on its toxicity toward the housefly, *Musca domestica* L., and greenhouse thrip, *Heliothrips haemorrhoidalis* (Bouche). They reported the *N*-methylcarbamate of *m-tert*-butylphenol to be the most active insecticide within the series studied. Very few carbamates have been reported, however, which display both basic and alkyl groups in the aromatic ring (*13*).

Through the development of a process in these laboratories for the conversion of benzoic acids to phenols (*7*, *8*), large samples of isomerically pure *m-tert*-butylphenol were available. This allowed verification of the observations concerning the *N*-methylcarbamate of *m-tert*-butylphenol, and these studies were extended to include nitrogen-containing analogs.

Table I. Insecticidal and Physical Properties of Alkyl-Substituted *N*-Methyl Phenyl Carbamates and Their Corresponding Dimethylamino Analogs





R	M.p., °C.	Molecular formula	Analysis or ref.	LD_{95}, P.P.M.[a] MBB	SAW	M.p., °C.	Molecular formula	Analysis	LD_{95}, P.P.M.[a] MBB	SAW
2,3-$(CH_3)_2$	104–5	$C_{10}H_{13}NO_2$	N = 7.69 Th = 7.82	55	>500	92–4	$C_{12}H_{18}N_2O_2$	N = 12.41 Th = 12.61	100	60
2,6-$(CH_3)_2$	101–5	$C_{10}H_{13}NO_2$	N = 7.84 Th = 7.82	>500	>500	122–3	$C_{12}H_{18}N_2O_2$	N = 12.90 Th = 12.61	>500	>500
3,5-$(CH_3)_2$	99–100.5	$C_{10}H_{13}NO_2$	M.p. = 100.5–102[b]	11	200	85	$C_{12}H_{18}N_2O_2$	N = 12.46 Th = 12.61	3	2.5
2,3,5-$(CH_3)_3$	123–5	$C_{11}H_{15}NO_2$	M.p. = 123–4[b]	15	300	95–7	$C_{13}H_{20}N_2O_2$	N = 11.59 Th = 11.87	4.5	30
3-CH_3-5-C_2H_5	84–5	$C_{11}H_{15}NO_2$	N = 7.47 Th = 7.25	50	>500	65–6	$C_{13}H_{20}N_2O_2$	N = 11.60 Th = 11.87	10	9
3-$CH(CH_3)_2$	69–72	$C_{11}H_{15}NO_2$	N = 7.28 Th = 7.25	140	>500	88–90	$C_{13}H_{20}N_2O_2$	N = 12.40 Th = 11.87	3.1	4
3-$C(CH_3)_3$	144.5	$C_{12}H_{17}NO_2$	M.p. = 144–5[b]	10	>500	122–3	$C_{14}H_{22}N_2O_2$	N = 11.24 Th = 11.19	2.0	15
2,3,5,6-$(CH_3)_4$	167–9	$C_{12}H_{17}NO_2$	N = 6.57 Th = 6.79	>500	>500	133–8	$C_{14}H_{22}N_2O_2$	[c]	>500	>500
3,5-$[C(CH_3)_3]_2$	95–8	$C_{16}H_{25}NO_2$	N = 5.46 Th = 5.31	>500	>500	132–5	$C_{18}H_{30}N_2O_2$	N = 9.58 Th = 9.20	>500	>500

[a] Concentration of insecticide in parts per million to give an LD_{95} with Mexican bean beetle (MBB) and Southern armyworm (SAW).
[b] (*11*). Systemic effectiveness has been described (*4*).
[c] Analysis. Theory for $C_{14}H_{22}N_2O_2$; C = 67.16, H = 8.86; found, C = 66.74, H = 8.44.

To establish the general utility of this combination, a considerable number of compounds of this type was synthesized and tested for insecticidal activity (*15*, *16*). When a *p*-dimethylamino group was added to the above-mentioned ester to produce 3-*tert*-butyl-4-dimethylaminophenyl *N*-methylcarbamate, a dramatic increase in potency and in the spectrum of insects effected was observed. A comparison of insecticidal activity and physical properties of a series of alkyl phenyl carbamates with their corresponding dialkylamino analogs is shown in Table I. Outstanding activity was observed with two structural features, a *p*-amino group and *m*-alkyl substituents. The basic group could be substituted with a variety of alkyl substituents up to a total of ten carbon atoms without loss of activity (Tables II and III). The ring-substituted alkyl groups were most effective when small (up to four carbon atoms) and located so as to hinder the free rotation of the amine group. By contrast, however, ortho substituents which severely restricted rotation of the carbamate group appeared to reduce insecticidal activity drastically.

One of these compounds, 4-dimethylamino-3,5-xylyl *N*-methylcarbamate (trade-mark Zectran for the technical grade material), has undergone extensive laboratory and field trials (*1*, *10*, *12*, *14*, *20*) and is now a commercial product.

Experimental

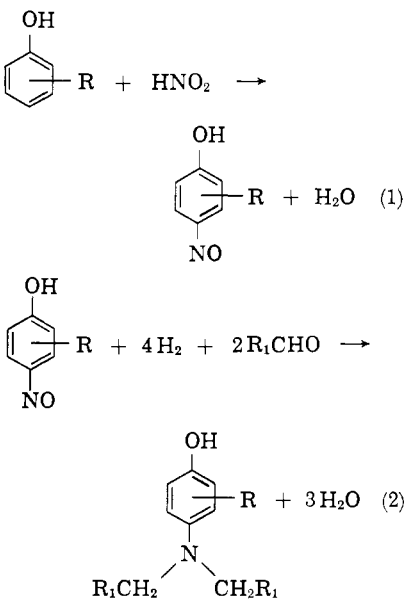
Insecticidal Test Methods. Primary leaves of Cranberry bean plants, *Phaseoleus vulgaris* L. (var. Cran.), were dipped in aqueous dilutions containing carbamates. The leaves when dry were infested with third instar larvae of the Mexican bean beetle (MBB), *Epilachna varivestis* Muls., or third instar larvae of the Southern armyworm (SAW), *Prodenia eridania* (Cran). The infested plants were caged and held at greenhouse temperatures of about 80° F. for 6 days before mortality counts were made. These counts were corrected for natural mortality by the use of Abbotts' formula.

The LD_{95} figures shown in Tables I, II, and III are extrapolated from insecticidal data plotted on logarithmic probability paper.

Synthesis of Compounds

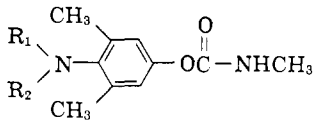
Methyl Isocyanate. The methyl isocyanate was prepared by combining methylamine and phosgene in a hot tube according to the method of Slocombe and coworkers (*17*).

Alkyl Phenols. Phenols with alkyl groups located in the desired positions were the starting materials for synthesis. Pure *m*-*tert*-butylphenol (melting point, 43° C.) was prepared from *p*-*tert*-butylbenzoic acid (*7*, *8*). 3,5-Di-*tert*-butylphenol (melting point, 91–92° C.) was prepared from 3,5-di-*tert*-butylaniline (*2*) by the hydrolysis of its diazonium salt. *m*-Isopropylphenol was obtained from the Hercules Powder Co., Wilmington, Del. The other compounds were readily available and were purified, if necessary, to provide physical properties agreeing with those described in the literature.



R = *o*- or *m*-alkyl groups
R_1 = primary or secondary alkyl groups

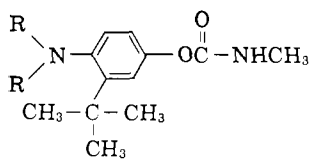
Table II. Properties and Insecticidal Activity



R_1	R_2	R.I. or M.P., °C.	Molecular Formula	Analysis	LD_{95}, P.P.M.[a] MBB	SAW
H	H	113–4	$C_{10}H_{14}N_2O_2$	N = 14.49 Th = 14.42	3.0	2.5
CH_3	CH_3	85	$C_{12}H_{18}N_2O_2$	N = 12.46 Th = 12.60	3.0	2.5
C_2H_5	C_2H_5	62–3	$C_{14}H_{22}N_2O_2$	N = 11.14 Th = 11.19	1.0	4.0
n-C_3H_7	n-C_3H_7	80–2	$C_{16}H_{26}N_2O_2$	N = 10.21 Th = 10.07	1.0	6.0
n-C_4H_9	n-C_4H_9	60	$C_{18}H_{30}N_2O_2$	N = 8.88 Th = 9.14	3.0	12.5
iso-C_4H_9	iso-C_4H_9	95–6	$C_{18}H_{30}N_2O_2$	N = 8.91 Th = 9.14	8.0	6.0
n-C_5H_{11}	n-C_5H_{11}	n_D^{22} = 1.5055	$C_{20}H_{34}N_2O_2$	N = 8.52 Th = 8.37	10.0	65.0
H-	iso-C_4H_9	97–9	$C_{14}H_{22}N_2O_2$	N = 11.26 Th = 11.19	3.0	3.0
CH_3	n-C_4H_9	78	$C_{15}H_{24}N_2O_2$	N = 10.53 Th = 10.60	3.0	8.0
CH_3	n-C_5H_{11}	n_D^{21} = 1.5100	$C_{16}H_{26}N_2O_2$	N = 9.44 Th = 10.07	3.0	12.0
C_2H_5	iso-C_4H_9	n_D^{21} = 1.5168	$C_{16}H_{26}N_2O_2$	N = 10.56 Th = 10.07	11.0	4.5
n-C_4H_9	iso-C_4H_9	69–70	$C_{18}H_{30}N_2O_2$	N = 9.02 Th = 9.14	1.3	5.0

[a] Approximate concentration of insecticides in parts per million to give LD_{95} for Mexican bean beetle (MBB) and Southern armyworm (SAW).

Table III. Properties and Insecticidal Activity



R	M.P., °C.	Molecular Formula	Analysis	LD_{95}, P.P.M.[a] MBB	SAW
H	161–2	$C_{12}H_{18}N_2O_2$	N = 12.74 Th = 12.60	0.6	30.0
CH_3	122–3	$C_{14}H_{22}N_2O_2$	N = 11.24 Th = 11.19	6.0	35.0
C_2H_5	86–7	$C_{16}H_{26}N_2O_2$	N = 10.12 Th = 10.07	3.5	15.0
n-C_3H_7	82–4	$C_{18}H_{30}N_2O_2$	N = 9.36 Th = 9.14	<6.0	250.0
n-C_4H_9	82–4	$C_{20}H_{34}N_2O_2$	N = 8.21 Th = 8.35	3.5	>500

[a] Approximate concentration of insecticides in parts per million to give LD_{95} for Mexican bean beetle (MBB) and Southern armyworm (SAW).

The preferred method patterned after the procedure of Karrer and Schläpfer (*9*) is illustrated by the synthesis of 4-nitroso-3,5-xylenol.

Twenty-four grams of 3,5-xylenol were dissolved in 160 ml. of methanol and diluted with 170 ml. of concentrated HCl. The solution was cooled and maintained at 0° to 5° C. Twenty-two grams of solid sodium nitrite was added in small portions, with agitation, over a 3-hour period. After standing overnight at 5° to 10° C., the heavy slurry was diluted threefold with ice and water, filtered, washed with water and finally pentane, and dried to give 25 grams of yellow solid which melted at 175° C. with decomposition. Recrystallization from ethanol-water did not appreciably increase the decomposition temperature.

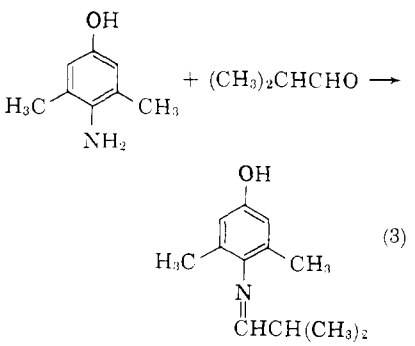
A variety of reducing agents was successfully used to convert the intermediate to the corresponding aminophenol, including zinc and acetic acid, sodium hydrosulfite, sodium sulfide, and hydrogen. Most of the products were stable in air. However, *o*- or *p*-aminophenols, without alkyl groups adjacent to the basic group, darkened rapidly in air. It was necessary to alkylate these materials immediately or store them as their acid salts in a nitrogen atmosphere.

Symmetrical alkylation of the aminophenol was accomplished by means of the corresponding dialkyl sulfate, prepared from the appropriate alcohol by the method of Suter and Gerhart (*21*). The phenol was suspended in water containing a large excess of sodium bicarbonate. A threefold molar excess of the alkyl sulfate was added to the hot (75° to 100° C.) slurry over a 1- to 3-hour period with heating. The stirring was continued for 3 to 4 hours after cooling. The crude product was extracted from the slurry and crystallized from an appropriate solvent. Lower temperatures were used (20° to 35° C.) with methyl and ethyl sulfate.

An alternative procedure involved the conversion of the nitrosophenol to the dialkylamino derivative in one sequence (*5*) (Equation 2). The nitrosophenol (15 parts by weight) was suspended in methanol (50 parts) along with 5% palladium on charcoal catalyst (1 part) and hydrogenated at 25° to 50° C. at a pressure of 25 to 50 p.s.i.g. When the theoretical amount of hydrogen had been absorbed to produce the aminophenol, the appropriate aldehyde, diluted with methanol, was added in several portions at various intervals during the final reductive alkylation.

When the reaction was complete, as indicated by the volume of hydrogen absorbed, the reaction mixture was filtered to remove the catalyst and the volume of solvent was reduced by vacuum distillation. Dilution of the final concentrate with ice and water usually induced crystallization of the dialkylaminophenol product.

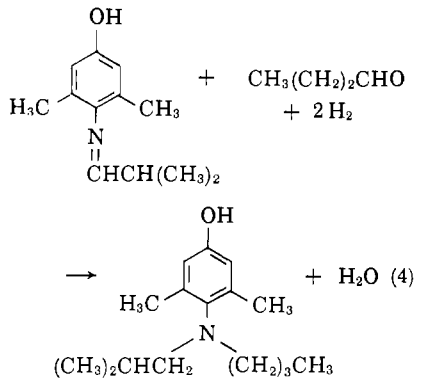
The unsymmetrical dialkylaminophenols were prepared from the corresponding aminophenols by means of an intermediate Schiff base. The synthesis of 4(*n*-butylisobutylamino)-3,5-xylyl *N*-methylcarbamate will be used as an example to illustrate the method. The intermediate Schiff base was prepared from 4-amino-3,5-xylenol and isobutyraldehyde by the method of Clarkson (*3*) (melting point, 110–14° C., Equation 3).



(3)

The base was treated with a slight molar excess of *n*-butyraldehyde in methanol solution containing 5% palladium on charcoal catalyst, and hydro-

genated at a pressure of 25 to 50 p.s.i.g. at a temperature of 25° to 50° C. (Equation 4). When the theoretical amount of hydrogen was absorbed, the catalyst was removed by filtration, and the solu-



tion was poured over crushed ice. The tan, crude 4-(*n*-butylisobutylamino)-3,5-xylenol was recrystallized twice from pentane to give white needles (melting point, 89–90° C.).

Analysis. Theory for $C_{16}H_{27}NO$: C, 77.05; H, 10.91; N, 5.62. Found: C, 76.60; H, 10.57; H, 5.73.

***N*-Methylcarbamates.** The specific phenol used for preparing each carbamate was dissolved in dry hexane, ether, or methylene chloride to give a solution approaching saturation at room temperature and treated with a 10 to 100% molar excess of methyl isocyanate and a trace of triethylamine catalyst. An exothermic reaction usually took place, and if amounts of phenol in excess of 50 grams were used, an ice bath was necessary to control the temperature. The crude product was purified by recrystallization from an appropriate solvent such as hexane, carbon tetrachloride, or chloroform.

The structures were established by elemental analysis, as summarized in Tables I, II, and III, and by an examination of their infrared spectra. All of the carbamates had characteristic absorption bands at 3300 to 3500 cm.$^{-1}$ (N—H stretching frequency) and 1675 to 1750 cm.$^{-1}$ (carbonyl group) and other distinctive bands for various individual compounds.

Acknowledgment

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Literature Cited

(1) Arnold, W. J., *Abstracts, Pacific Branch, Entomol. Soc. Am.* **1** (1), 10 (1961).
(2) Burgers, J., *Rec. Trav. Chim.* **75,** 1327 (1956).
(3) Clarkson, R. G., U. S. Patent **2,220,065** (Nov. 5, 1940).
(4) David, W. A. L., Metcalf, R. L., Winton, M., *J. Econ. Entomol.* **53,** 1021 (1960).
(5) Emerson, W. S., U. S. Patent **2,380,420** (July 31, 1945).
(6) Haworth, R. D., Camberton, A. H., Woodcock, D., *J. Chem. Soc.* **1947,** p. 182.
(7) Kaeding, W. W., *J. Org. Chem.* **26,** 3144 (1961).
(8) Kaeding, W. W., Lindblom, R. O., Temple, R. G., *Ind. Eng. Chem.* **53,** 805 (1961).
(9) Karrer, P., Schläpfer, R., *Helv. Chim. Acta* **24,** 298 (1941).
(10) Kenaga, E. E., Doty, A. E., Hardy, J. L., *J. Econ. Entomol.* **55** (4), 466 (1962).
(11) Kolbezen, M. J., Metcalf, R. C., Fukuto, T. R., J. AGR. FOOD CHEM. **2,** 864 (1954).
(12) Metcalf, R. L., *Agr. Chem.* **16** (6), 20 (1961).
(13) Metcalf, R. L., "Organic Insecticides," p. 317, Interscience, New York, 1955.
(14) Shorey, H. H., Reynolds, H. T., Anderson, L. D., *J. Econ. Entomol.* **55** (1), 5 (1962).
(15) Shulgin, A. T., U. S. Patent **3,060,225** (Oct. 23, 1962).
(16) *Ibid.*, **3,084,098** (April 2, 1963).
(17) Slocombe, R. J., Hardy, E. E., Saunders, J. A., Jenkins, R. L., *J. Am. Chem. Soc.* **72,** 1888 (1950).
(18) Stedman, E., *J. Biol. Chem.* **20,** 719 (1926).
(19) Stevens, J. R., Bentel, R. H., *J. Am. Chem. Soc.* **63,** 308 (1941).
(20) Stewart, D., Evans, E. M., Arnold, W. J., *Abstracts, Pacific Branch, Entomol. Soc. Am.* **1** (1), 9 (1961).
(21) Suter, C. M., Gerhart, H. L., *Org. Syn.* **19,** 27 (1939).

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CARBAMATE INSECTICIDES

Hydride-Transferring Ability of Methylenedioxybenzenes as a Basis of Synergistic Activity

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An explanation of the inhibition of the metabolism of carbamates and other pesticides by methylenedioxybenzenes is proposed. Oxidative metabolism of the methylenedioxybenzene with transfer of hydride from the methylenedioxy group is postulated. If the resulting electrophilic benzodioxolium ion were to react with a nucleophilic group in a component of the pesticide-metabolizing enzyme, irreversible inhibition could result. Catechol derivatives as possible products of this process may also compete with the pesticide at some limiting stage of metabolism.

CERTAIN substituted methylenedioxybenzenes are synergists for a number of classes of pesticides of different structural types (*5, 14, 18, 19, 32, 38*), among which are the carbamates (*34, 37*). These same compounds are antagonists (*39, 44*) for a few pesticides and are synergists for some and antagonists for other structurally similar phosphorothioates (*44, 48*). Of the action of these methylenedioxybenzenes, Moorefield (*37*) has said, "This group of compounds must possess a polyvalent and nonspecific potential for blocking enzyme catalysis, or act independently at a less critical site in the insect, or influence the efficiency of an essential property common to the reactivity of all successful insecticides, such as aiding transport." When the antagonistic effect of these same compounds is also considered, the first alternative offered by Moorefield seems most attractive. Inhibition of metabolism as a satisfactory explanation for the synergistic and antagonistic action of the methylenedioxybenzenes has received a measure of experimental support (*4–6, 8, 9, 13, 16, 20, 28, 29, 34, 37, 40, 50, 51*). In higher animals the liver microsomes