compared with the other bicyclic systems studied.

The rigid planar nature of this system, combined with the presence of two oxygen atoms, is considered of major importance in determining the biological activity.

Sulfur can replace oxygen in the system with only a slight decrease in activity.

Synergistic activity of the esters of piperonyl alcohol is considerably modified by the nature and relative position of the side chain attached to the alpha-carbon. This apparently results from such factors as lipoid solubility, steric hindrance, and binding on the active surface of the target enzyme(s).

Minimal requirements for synergistic activity are the presence of the methylenedioxyphenyl nucleus in combination with a simple group such as methyl substituted in the phenyl ring. In such simple compounds, nuclear methoxy and nitro groups greatly enhance synergistic activity.

The best synergist studied, α-methylpiperonyl benzoate (XIX), had synergistic ratios of 128, 56, and 3.9 with Sevin, 3,4-dimethoxyphenyl *N*-methylcarbamate, and Zectran. This compared very favorably with the synergistic ratios at 5 to 1 for piperonyl butoxide of 75, 37.5, and 2.6, respectively.

Literature Cited

(1) Adams, R., Levine, I., *J. Am. Chem. Soc.* **45,** 2373 (1923).
(2) Adams, R., Montgomery, E., *Ibid.*, **46,** 1518 (1924).
(3) Adolphi, H., Blum, D., Duffer, P., Hertel, O., Pasedach, H., Stunmeyer, H. (to Badische Anilin und Soda Fabrik), German Patent **1,058,306** (May 27, 1959); *C. A.* **55,** 3916*f* (1961).
(4) Arnold, R. T., *J. Am. Chem. Soc.* **61,** 1405 (1939).
(5) Arnold, R. T., McCool, J., *Ibid.*, **64,** 1315 (1942).
(6) Barthel, W. F., Alexander, B. H., U. S. Dept. Agr. **ARS-33-42** (September 1957).
(7) Barthel, W. F., Gertler, S. I., *Ibid.*, **ARS-33-27** (July 1956).
(8) Beroza, M., Barthel, W. F., J. Agr. Food Chem. **5,** 855 (1957).
(9) Birch, S. F., Dean, R. A., Whitehead, E. V., *J. Inst. Petrol.* **40,** 76 (1954).
(10) Böeseken, J., Greup, J., *Rec. Trav. Chim.* **58,** 528 (1939).
(11) Böeseken, J., Sloof, G., *Proc. Acad. Sci. Amsterdam* **35,** 1250 (1932); *C. A.* **27,** 3457 (1933).
(12) Campbell, K. N., Hopper, P. F., Campbell, B. K., *J. Org. Chem.* **16,** 1736 (1951).
(13) Casida, J. E., *Ann. Rev. Entomol.* **8,** 39 (1963).
(14) Casida, J. E., Report of Conference of International Atomic Energy Agency, Vienna, 1963.
(15) Chatelus, G., Cagniant, P., *Compt. Rend.* **224,** 1777 (1947).
(16) Clark, P. H., Cole, M. M., U. S. Dept. Agr. **ARS-33-62** (October 1960).
(17) Dallacker, F., Binsack, R., *Monatsh.* **92,** 492 (1961); *C. A.* **55,** 27180*d* (1961).
(18) Davidson, D., Weiss, M., *Org. Synthesis*, Coll. Vol. **2,** 590 (1947).
(19) Dorough, H. W., Casida, J. E., J. Agr. Food Chem. **12,** 294 (1964).
(20) Dorough, H. W., Leeling, N. C., Casida, J. E., *Science* **140,** 170 (1963).
(21) Drabek, J., *Chem. Zvesti* **10,** 357 (1956); *C. A.* **50,** 16023 (1956).
(22) Fukuto, T. R., Metcalf, R. L., Winton, M. Y., Roberts, P. A., *J. Econ. Entomol.* **55,** 341 (1962).
(23) Gatterman, L., *Ann. Chem. Justus Liebigs* **347,** 347 (1906).
(24) Georghiou, G. P., Metcalf, R. L., *J. Econ. Entomol.* **55,** 125 (1962).
(25) Georghiou, G. P., Metcalf, R. L., March, R. B., *Ibid.*, **54,** 132 (1961).
(26) Haller, H. L., La Forge, F. B., Sullivan, W. N., *J. Org. Chem.* **7,** 185 (1942).
(27) Haller, H. L., McGovran, E. R., Goodhue, L. D., Sullivan, W. N., *Ibid.*, **7,** 183 (1942).
(28) Hewlett, P. S., *Advan. Pest Control Res.* **3,** 27 (1960).
(29) Hickinbottom, W. J., "Reactions of Organic Compounds," 2nd ed., Longmans, Green, London, New York, and Toronto, 1948.
(30) Howard, J. W., *J. Am. Chem. Soc.* **57,** 2317 (1935).
(31) Kerr, R. W., Bull. Commonwealth Sci. Ind. Res. Org., Australia, No. **261** (1951).
(32) Metcalf, R. L., "Organic Insecticides," Interscience, New York–London, 1955.
(33) Metcalf, R. L., Fukuto, T. R., Winton, M. Y., *J. Econ. Entomol.* **53,** 828 (1960).
(34) *Ibid.*, **55,** 345 (1962).
(35) Metcalf, R. L., March, R. B., *Ibid.*, **46,** 288 (1953).
(36) Miller, E., Read, R. R., *J. Am. Chem. Soc.* **55,** 1224 (1933).
(37) Moore, B. P., Hewlett, P. S., *J. Sci. Food Agr.* **9,** 666 (1958).
(38) Moorefield, H. H., *Contribs. Boyce Thompson Inst.* **19,** 501 (1958).
(39) Moorefield, H. H., *Misc. Publ. Entomol. Soc. Am.* **2,** 145 (1960).
(40) Moorefield, H. H., Weiden, M. H. J., *Contribs. Boyce Thompson Inst.* **22,** 425 (1964).
(41) Mosettig, E., Mozingo, R., *Org. Reactions* **4,** 362 (1948).
(42) Nystrom, R. F., Brown, W. G., *J. Am. Chem. Soc.* **69,** 1197 (1947).
(43) Pasedach, H., Seefelder, M. (to Badische Anilin und Soda Fabrik A. G.), German Patent **1,042,602** (Nov. 6, 1958).
(44) Perkin, W. H., Trikojus, V. M., *J. Chem. Soc.* **128,** 2925 (1926).
(45) Philleo, W. W., Schonbrod, R. A., Terriere, L. C., J. Agr. Food Chem. **13,** 113 (1965).
(46) Prill, E. A., Smith, W. R., *Contribs. Boyce Thompson Inst.* **18,** 187 (1955).
(47) Stoermer, R., Kahlert, B., *Ber. Deut. Chem. Ges.* **34** (2), 1806 (1901).
(48) Wilkinson, C. F., Metcalf, R. L., Fukuto, T. R., unpublished data.

Received for review March 19, 1965. Accepted September 27, 1965. From a dissertation submitted by the senior author in January 1965 to the Graduate Division, University of California, Riverside, in partial fulfillment of the requirements for the degree doctor of philosophy. Supported in part by a grant from the U. S. Public Health Service, No. CC-00038-08. Paper No. 1638, Citrus Research Center and Agricultural Experiment Station.

STRUCTURE AND ACTIVITY

Effects of Deuteration, Fluorination, and Other Structural Modifications of the Carbamyl Moiety upon the Anticholinesterase and Insecticidal Activities of Phenyl *N*-Methylcarbamates

MOHAMED A. H. FAHMY,[1] R. L. METCALF, T. R. FUKUTO, and D. J. HENNESSY[2]

Department of Entomology, University of California, Riverside, Calif.

The processes of intoxication and detoxication of the aryl *N*-methylcarbamate insecticides are under intensive study in a number of laboratories. There is, however, no general agreement that the ability of these compounds to inhibit cholinesterase (ChE) is either competitive or the result of noncompetitive carbamylation of the esteratic site of the enzyme (*11*) or that detoxication occurs through hydroxylation of the aromatic ring or of the *N*-methyl group, or by hydrolysis (*5, 11*). It appeared that additional evidence regarding both processes might be obtained by investigating the comparative anticholinesterase activity, insecticidal action, and

[1] Present address, University of Assiut, Egypt, U.A.R.
[2] Present address, Fordham University, New York, N. Y.

The anticholinesterase and insecticidal activity of aryl $NHCD_3$, $NHCF_3$, NH_2, $NHSi(CH_3)_3$, and $N<^{CH_2}_{CH_2}$ carbamates are described. These alterations of the normal $NHCH_3$ carbamate insecticides resulted in both decreased anticholinesterase and insecticidal activity to the housefly and mosquito larva, except for the $NHCD_3$ carbamate which showed no deuterium isotope effect in either cholinesterase inhibition or toxicity. The $NHCF_3$ and NH_2 carbamates showed substantial synergism when evaluated in admixture with piperonyl butoxide. Since these compounds cannot be detoxified by $NHCH_2OH$ formation, this synergism suggests that the primary attack is hydroxylation of the aromatic ring followed by hydrolysis of the carbamate ester.

synergism by piperonyl butoxide of carbamates with modified *N*-substituents such as 3-isopropylphenyl $NHCD_3$ carbamate and 3-isopropylphenyl $NHCF_3$ carbamate. These are isosteres of the highly insecticidal 3-isopropylphenyl $NHCH_3$ carbamate but differ in the stability of the C—X bonds of the *N*-methyl group. Thus, if conversion of $NHCH_3$ to $NHCH_2OH$ is the primary pathway of detoxication by microsomal oxidation, which can be inhibited by piperonyl butoxide, then both the toxicity and degree of synergism of the three compounds should be measurably different.

Other alterations in the groups attached to the carbamate *N*-atom are known to affect activity greatly. For example, the *N,N*-dimethylcarbamates are only about 0.01 to 0.1 as active as the corresponding *N* - methylcarbamates either as anticholinesterases and as insecticides (*13*) and *N*-ethyl, *N*-benzyl, and *N*-phenylcarbamates are virtually inactive (*9*). To obtain additional information on the role of the *N*-methyl group in biological activity, a series of substituted phenyl carbamates and phenyl *N*-trimethylsilylcarbamates was prepared and evaluated along with *m*-isopropylphenyl aziridinylcarbamate which has a cyclic ethyleneimine ring. Additional data are included on a corresponding group of *N*-acylcarbamates.

Experimental

Materials and Methods. Deuterated 3-isopropylphenyl *N-d,d,d,*-methylcarbamate was prepared from nitromethane interchanged with heavy water and reduced to methylamine hydrochloride which was added to *m*-isopropylphenylchloroformate prepared from the sodium salt of the phenol and phosgene. The deuterocarbamate was recrystallized several times from petroleum ether and had a m.p. of 69–72° C. as compared with 72–3° for *m*-isopropylphenyl *N*-methylcarbamate. NMR spectra of the two compounds in carbon tetrachloride with tetramethylsilane as an internal standard were identical except for the absence in the deutero-compound of the doublet at τ values of 2.6 to 2.8 p.p.m. (*N*-methyl protons) and showed the isopropyl protons at 1.1 to 1.3 p.p.m., NH proton at 2.05 p.p.m., and isopropyl proton at 3.3 to 3.5 p.p.m. The spectra indicated a purity of >95% for the deutero-compound.

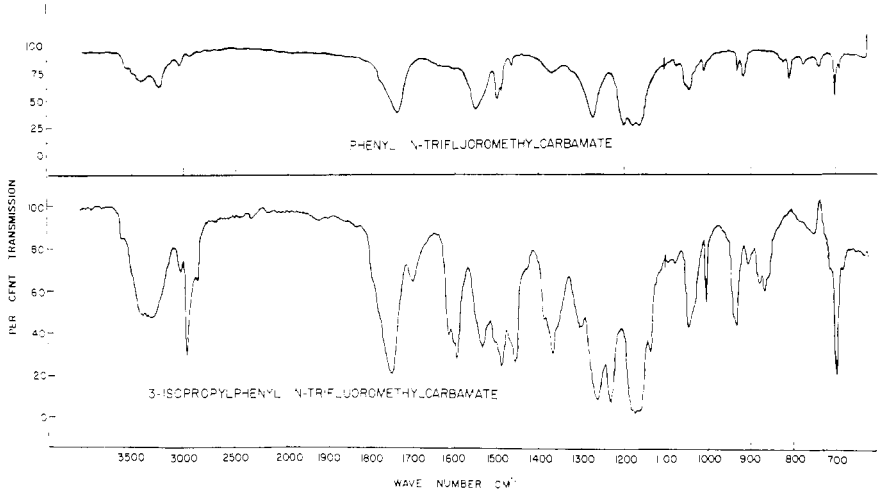

Figure 1. Infrared spectra of phenyl *N*-trifluoromethylcarbamate in KBr and 3-isopropylphenyl *N*-trifluoromethylcarbamate in CCl_4

Table I. Properties and Biological Activities of Deuterated and Fluorinated Carbamates

	Compound	M.P., ° C.	Analysis Theory	Analysis Found	I_{50} Fly ChE	Affinity	*Musca domestica* LD_{50}, μg./Gram Fly A (alone)	*Musca domestica* LD_{50}, μg./Gram Fly B(1 : 5 p.b.)[a]	Degree of Synergism A/B	LC_{50} *Culex pipiens 5-fasciatus* I., P.P.M.
I	3-Isopropylphenyl *N*-methylcarbamate	72–3	(*14*)		4.5×10^{-7}	450	90	9.5	9.5	0.038
II	3-Isopropylphenyl *N-d,d,d*-methylcarbamate	69–72	...	...	4.5×10^{-7}	450	90	9.5	9.5	0.045
III	3-Isopropylphenyl *N*-trifluoromethylcarbamate	b.p. 88–90/3 mm.	C = 53.44 H = 4.85	C = 63.5 H = 6.73	3×10^{-4}[b]	0.66	>500	160[b]	>3.1	>10
IV	Phenyl *N*-methylcarbamate	85–6	(*14*)		2×10^{-4}	1	500	38	13	>10
V	Phenyl *N*-trifluoromethylcarbamate	84–8	C = 46.83 H = 2.93	C = 46.67 H = 2.71	$>1.6 \times 10^{-3}$ (10%)	<0.1	>500	>500	1.0	>10

[a] Piperonyl butoxide synergist.
[b] Calculated for 60% carbamate.

Table II. Properties and Biological Activities of Carbamates, *N*-Trimethylsilylcarbamates, and Other Modifications

	Compound	M.P., ° C.	Analysis Theory	Analysis Found	I_{50} Fly ChE	Affinity	*Musca domestica* LD_{50}, μg./Gram Fly A (olone)	*Musca domestica* LD_{50}, μg./Gram Fly B(1 : 5 p.b.)	Degree of Synergism A/B	LC_{50} *Culex pipiens fasciatus* l., P.P.M.
VI	Phenylcarbamate	135–9			$>1.0 \times 10^{-3}$	<0.2	>500	>500	10	>10
VII	3-Isopropylphenylcarbamate	126–7	C = 67.04 H = 7.25	C = 67.39 H = 7.15	3.7×10^{-4}	0.6	>500	77.5	> 6.4	1.17
VIII	3-Isopropylphenyl *N*,*N*-dimethylcarbamate		(*13*)		5.0×10^{-5}	4	450	90	5.0	0.25
IX	3-Isopropylphenylaziridinylcarbamate	[a]	C = 70.24 H = 7.28	C = 70.00 H = 7.43	$>1.1 \times 10^{-3}$ (10%)	<0.2	>500	>500	1.0	>10
X	3-Isopropylphenyl *N*,*N*-diethylcarbamate	b.p., 100°/0.3 mm.	C = 71.49 H = 8.94	C = 71.86 H = 8.93	$>1 \times 10^{-3}$	<0.2	>500	>500	1.0	8.2
XI	2-Isopropoxyphenyl *N*-methylcarbamate		(*14*)		6.9×10^{-7}	290	25.5	7.0	3.6	0.3
XII	2-Isopropoxyphenylcarbamate	113–18	C = 61.54 H = 6.65	C = 61.94 H = 6.53	1.0×10^{-3}	0.2	>500	27.0	>18.5	>10
XIII	4-Methylthio-3,5-xylenyl *N*-methylcarbamate	118–20	Mesurol (Bayer 37344)[b]		1.2×10^{-6}	165	24	12.5	2.1	0.23
XIV	4-Methylthio-3,5-xylenylcarbamate	117–21	C = 56.87 H = 6.15	C = 57.33 H = 6.27	$>1.6 \times 10^{-3}$ (20%)	<0.1	>500	135	3.7	>10
XV	1-Naphthyl *N*-methylcarbamate	142	Carbaryl or Sevin		9.0×10^{-7}	220	900	12.5	72	1.0
XVI	1-Naphthylcarbamate	175–7	C = 70.59 H = 4.80	C = 70.72 H = 5.07	5×10^{-3} (ext)	0.04	>500	>500	1.0	10
XVII	3-Ethoxyphenyl *N*-methylcarbamate	55–6	(*14*)		6.0×10^{-6}	33	75	14.5	5.2	3
XVIII	3-Ethoxyphenylcarbamate	113–115	C = 59.67 H = 6.08	C = 60.03 H = 5.8	$>1 \times 10^{-3}$	<0.2	>500	>500	1.0	>10
XIX	3-Isopropylphenyl *N*-trimethylsilylcarbamate	55–7	C = 62.15 H = 8.36	C = 62.49 H = 7.55	2.3×10^{-4}	0.88	120	40	3.0	>10
XX	2-Isopropoxyphenyl *N*-trimethylsilylcarbamate	64–70	C = 58.43 H = 7.86	C = 57.99 H = 7.48	1.2×10^{-3}	0.17	500	44	11.5	>10
XXI	1-Naphthyl *N*-trimethylsilylcarbamate	93–6	C = 64.86 H = 6.56	C = 65.31 H = 6.47	$>1.2 \times 10^{-3}$	<0.17	>500	ca. 500	> 1.0	>10
XXII	4-Methylthio-3,5-xylenyl *N*-trimethylsilylcarbamate	84–9	C = 55.12 H = 7.43	C = 55.56 H = 7.76	$>1.1 \times 10^{-3}$	<0.18	>500	190	2.6	>10
XXIII	Phenyl *N*-trimethylsilylcarbamate	54–9	C = 57.42 H = 7.17	C = 57.93 H = 7.07	$>1 \times 10^{-3}$	<0.05	>500	>500	1.0	>10
XXIV	3-Ethoxyphenyl *N*-trimethylsilylcarbamate	55–8	C = 56.92 H = 7.51	C = 57.17 H = 7.60	$>1 \times 10^{-3}$	<0.05	>500	>500	1.0	>10
XXV	3-Isopropylphenyl *N*-methyl, *N*-acetylcarbamate	b.p. 136–40/2 mm. (Boots R.D. 14838)	(*19*)		4.0×10^{-5}	5	235	21	11.2	0.028
XXVI	3-Isopropylphenyl *N*-methyl, *N*-propionylcarbamate	b.p. 146–8/2 mm. (Boots R.D. 14990)	(*19*)		1.1×10^{-4}	1.8	150	14	10.7	0.034
XXVII	3-Isopropylphenyl *N*-methyl *N*-butyrylcarbamate	b.p. 140–4/1.5 mm. (Boots R.D. 15914[c])	(*19*)		4.4×10^{-5}	4.5	85	14	6.1	0.018

[a] Purification of this compound was effected by several washings with ligroin (*15*).
[b] Sample provided by Farbenfabriken Bayer, Leverkusen, Germany.
[c] Samples provided by Boots Pure Drug, Nottingham, England.

Trifluoromethyl isocyanate, b.p. −35°, was prepared according to Motornyi, Kirenskaya, and Yarovenko (*16*). With phenol this gave phenyl *N*-trifluoromethylcarbamate, m.p. 84–8° (lit. 88°). With 3-isopropylphenol a product was obtained, b.p. 88–90° at 3 mm. This did not give a satisfactory analysis; however, comparisons of the infrared spectra of this and the pure phenyl *N*-trifluoromethylcarbamate (Figure 1) showed that the product contained 60% of the desired carbamate, and the remainder was unreacted *m*-isopropylphenol. An attempt to wash out the phenol with 0.1% sodium hydroxide solution almost completely hydrolyzed the carbamate within 1 minute.

The other carbamates with altered *N*-methyl groups were prepared from the appropriate phenylchloroformate (*20*) by reaction with ammonia (*2*), ethyleneimine (*8*), or other amines and are shown in Table II. *N*-trimethylsilylcarbamates were prepared according to the method of Pump and Wannagut from the appropriate phenylchloroformate and hexamethyldisilazane (Table II).

These carbamates were evaluated for activity as inhibitors of fly head cholinesterase (ChE) and as toxicants to the female housefly (*Musca domestica* NAIDM strain) and to *Culex pipiens quinquefasciatus* mosquito larvae by methods previously described (*10*).

Discussion of Results

$NHCD_3$ Carbamate. The anticholinesterase and insecticidal activity of 3-isopropylphenyl *N*-methylcarbamate (I) and 3-isopropylphenyl *N*-*d*,*d*,*d*,-methylcarbamate (II) are shown in Table I. The two compounds had identical activities, and the values obtained for the former were consistent with those previously reported (*14*). These data show the lack of any deuterium isotope effect in regard to reaction with ChE, intoxication of and detoxication in insects, or effect of methylenedioxyphenyl synergist on detoxication. Neither I nor II was toxic at 500 μg. per gram to the resistant strain of houseflies, R_{MIP}, selected with (I) (*6*). Both I and II were equally toxic to the larvae of the salt marsh caterpillar, *Estigimene acrea*.

The chemical reactivity of carbon-deuterium (C—D) bonds is generally lower than that of carbon-hydrogen (C—H) bonds, and the ratio of $k_{C—H}/k_{C—D}$ or the deuterium isotope effect has become an important tool for investigations of chemical mechanisms. This isotope effect, which is primarily the result of a difference in the zero-point energy between C—D and C—H, is maximal when the bond to hydrogen or deuterium is cleaved in the formation of the activated complex, and decreases to a limiting value, $\sqrt{2}$ or 1.4, with increasing binding in the activated complex (*23*). Thus, studies of the comparative toxicity of DDT and α-deutero DDT to the housefly have shown deuterium isotope effects of 1.25 to 1.5 (*1*, *15*), and this is in accord with the well known detoxication pathway for DDT of dehydrochlorination, an E_2-type elimination (*3*), mediated by the enzyme DDT-dehydrochlorinase. The data obtained here with the $NHCD_3$ carbamate suggest that the N—CH_3 group is not directly involved in reaction with ChE and that the formation of $NHCH_2OH$ is not the primary mechanism in the detoxication of 3-isopropylphenyl *N*-methylcarbamate by the housefly. Alternatively, it may be that slow *N*-oxide formation is the rate-determining step in detoxication with rapid rearrangement to $NHCH_2OH$, in which case no isotope effect would be observed.

$NHCF_3$ Carbamates. As shown in Table I, neither phenyl (V) nor 3-isopropylphenyl (III) *N*-trifluoromethylcarbamates were highly active. Compound III had an affinity for ChE of <0.001 that of 3-isopropylphenyl *N*-methylcarbamate (I) and was noninsecticidal, although it was substantially synergized by piperonyl butoxide. The two compounds are isosteres as the Van der Waals radius of F is 1.35 compared with 1.2 A. for H. However, the C—F bond (energy 107 kcal. per mole) is substantially more stable than the C—H bond (energy 87.3 kcal. per mole) (*17*). The degree of synergism observed with the CF_3 compound (III) again suggests that the main detoxication pathway is not through the formation of a $NHCH_2OH$ derivative, since the greater stability of the C—F bond should markedly decrease the rate at which this type of detoxication could occur. The lack of activity in anticholinesterase and insecticidal activity may be attributed to the hydrolytic instability of the $NHCF_3$ carbamate (III, $\sigma^* = -0.92$) over the $NHCH_3$ carbamate (I, $\sigma^* = -0.10$). The modified Hammett equation, $\log (k/k_o) = \sigma^*\rho$ (*21*) indicates through the proportionality of polar effects, that the $NHCF_3$ compound hydrolyzes about 2×10^3 times faster than the $NHCH_3$ analog, where $\rho = 2.32$ and $\log k_o = 2.4$, as calculated from the hydrolysis data of Kolbezen, Metcalf, and Fukuto (*9*).

NH_2 Carbamates. The results obtained with several aryl carbamates (*N*-unsubstituted) are shown in Table II. These compounds (VI, VII, XII, XIV, XVI, and XVIII) are only about 0.001 as active anticholinesterases as their biologically active *N*-methyl analogs (I, IV, XI, XIII, XV, and XVII) and of the order of 0.1 as active as insecticides, even with the substantial synergism resulting from combination with piperonyl butoxide. The information suggests that the *N*-methyl group is especially complementary to the esteratic site of ChE, since 3-isopropylphenyl *N*-methylcarbamate (I), for example, has an affinity for the enzyme of about 100 times that of the *N*,*N*-dimethylcarbamate (VIII) and about 1000 times that of the carbamate (VII). Similar effects were shown by the other pairs of carbamates in Table II. The appreciable toxicity to houseflies shown by the synergized unmethylated carbamates VII, XII, and XIV—while not approaching that of the corresponding *N*-methylcarbamates I, XI, and XIII—again suggests that the major detoxication pathway is not through formation of $NHCH_2OH$. The hydrolytic instability of the NH_2 carbamates may be a factor in their low activity, as phenylcarbamate ($K = 2.2 \times 10^4$) hydrolyzes about 100 times faster than phenyl *N*-methylcarbamate ($K = 1.9 \times 10^2$ liters/mole/minute) (*4*). The possibility that these unmethylated substituted phenylcarbamates may have a direct action upon the acetyl choline receptor protein (*22*) cannot be overlooked. The complete inactivity of 3-isopropylphenyl aziridinyl carbamate (IX) as compared with the moderately active 3-isopropylphenyl *N*,*N*-dimethylcarbamate (VIII) may be due to the rigidity of the three-membered ethyleneimine ring. However, this compound is very unstable in aqueous media.

N—$Si(CH_3)_3$ Carbamates. The biological activity of the isomeric trimethylsilylphenyl *N*-methylcarbamates has been described recently (*12*) as comparable to that of the familiar carbon analogs. Therefore, it appeared to be equally interesting to investigate the activity of the *N*-trimethylsilylcarbamates. Silicon is more electropositive than carbon and introduces more ionic character when bonded to carbon or nitrogen. An approximate measure of such bond polarity (as % ionic character) is given by the expression

$$\% \text{ ionic character} = 100[1 - e^{-1/4(x_1 - x_2)^2}]$$

where $x_1 - x_2$ represents the electronegative difference (*17*). For the N—Si bond this value is 30% compared with 12% for the C—Si bond. Even more ionization of the N—Si bond should be expected in the structure $RCONHSiR_3$ because of the electron-withdrawing properties of the carbamyl moiety.

The significance of the N—Si bond polarity relates to the manner in which it invites and directs reactions with suitable ions and molecules. Goubeau and Paulin (*7*) suggested that *N*-trimethylsilylcarbamate can be rapidly cleaved by water or alcohol to produce the corresponding carbamate and $(CH_3)_3SiOH$ or $(CH_3)_3SiOCH_3$, depending on whether the reactant is water or methyl alcohol. Therefore, it should be expected that the anticholinesterase activities of the *N*-trimethylsilylcarbamates in aqueous systems are really due to the corresponding carbamates, with the corollary that the activities for the two types of compounds are similar. The data in Table II show that this is the case for all the

carbamates and trimethylsilylcarbamates investigated.

The *N*-trimethylsilylcarbamates were toxic only when the corresponding carbamate showed activity, suggesting that in vivo hydrolysis of the former to the latter occurs in the fly. The initial hydrolysis step might protect the remainder of the molecule from the action of other detoxication mechanisms before reaching the site of action. Indeed, as shown in Table II, 3-isopropylphenyl *N*-trimethylsilylcarbamate (XIX) is several times as toxic as 3-isopropylphenylcarbamate (XII). If this hypothesis is valid, it would be expected that the degree of synergism of the *N*-trimethylsilylcarbamate by piperonyl butoxide would be less than that for the corresponding carbamates and this is true for all the synergizable compounds of this nature in Table II.

It is interesting to compare the activities of the *N*-trimethylsilylcarbamates with the *N*-acylcarbamates of 3-isopropylphenol (*19*) (XXV–XXVII, Table II). These compounds have affinities for fly ChE of about 0.001 to 0.002 that of 3-isopropylphenyl *N*-methylcarbamate (I) yet retain much of the insecticidal activity of the parent carbamate. This suggests that, like the trimethylsilylcarbamates, they must undergo in vivo hydrolysis, forming, in the case of acyl compounds, *N*-methylcarbamates and the corresponding carboxylic acid.

Acknowledgment

The *N*-acylcarbamates were supplied through the kindness of D. J. Higgins, Boots Pure Drug Co., Ltd., Nottingham, England.

Literature Cited

(1) Barker, R. J., *J. Econ. Entomol.* **53,** 35 (1960).
(2) Carter, H. E., Frank, R. L., Johnson, H. W., *Org. Syn.* **23,** 14 (1943).
(3) Cristol, S. J., *J. Am. Chem. Soc.* **67,** 1494 (1945).
(4) Dittert, L. W., Higuchi, T., *J. Pharmacol. Sci.* **52,** 852 (1963).
(5) Dorough, H. W., Casida, J. E., J. AGR. FOOD CHEM. **12,** 294 (1964).
(6) Georghiou, G. P., Metcalf, R. L., March, R. B., *J. Econ. Entomol.* **54,** 132 (1961).
(7) Goubeau, J., Paulin, D., *Chem. Ber.* **93,** 1111 (1960).
(8) Iwakura, Y., Nabeye, A., *J. Org. Chem.* **25,** 1118 (1960).
(9) Kolbezen, M. M., Metcalf, R. L., Fukuto, T. R., J. AGR. FOOD CHEM. **2,** 864 (1954).
(10) Metcalf, R. L., Fuertes-Polo, C., Fukuto, T. R., *J. Econ. Entomol.* **56,** 862 (1963).
(11) Metcalf, R. L., Fukuto, T. R., J. AGR. FOOD CHEM. **13,** 220 (1965).
(12) Metcalf, R. L., Fukuto, T. R., *J. Econ. Entomol.*, in press, 1965.
(13) Metcalf, R. L., Fukuto, T. R., Winton, M. Y., *Ibid.*, **55,** 345 (1962).
(14) *Ibid.*, p. 889.
(15) Moorefield, H. H., Weiden, M. H. J., Hennessy, D. J., *Contribs. Boyce Thompson Inst.* **21,** 481 (1962).
(16) Motornyi, S. P., Kirenskaya, L. I., Yarovenko, N. N., *J. Gen. Chem. (Engl. Transl.) U.S.S.R.* **29,** 2122 (1959).
(17) Pauling, L., "The Nature of the Chemical Bond," Cornell Univ. Press, Ithaca, N. Y., 1944.
(18) Pump, J., Wannagut, U., *Monatsh. Chem.* **93,** 352 (1962).
(19) Robertson, W. A. A., Fraser, J., Clinch, P. G., Brit. Patent **982,235** (Feb. 3, 1965).
(20) Strain, F., Bissinger, W. E., Dial, H. W. R., Budoff, H., DeWitt, B. J., Stevens, H. C., Langston, J. H., *J. Am. Chem. Soc.* **72,** 1254–63 (1950).
(21) Taft, R. W., Jr., Chap. 13 in "Steric Effects in Organic Chemistry," M. S. Newman, ed., Wiley, New York, 1956.
(22) Weiden, M. H. J., Moorefield, H. H., J. AGR. FOOD CHEM. **13,** 200 (1965).
(23) Wiberg, K. B., *Chem. Revs.* **55,** 713 (1955).

Received for review July 20, 1965. Accepted September 29, 1965. Supported in part by U. S. Public Health Service grant No. CC00038-07. University of California Citrus Research Center and Agricultural Experiment Station, paper No. 1642.

METABOLIC STUDIES

Metabolism of *N*-(Mercaptomethyl)-phthalimide-carbonyl-C^{14}-*S*-(*O*,*O*-dimethyl-phosphorodithioate) (Imidan-C^{14}): Balance Study in the Rat

I. M. FORD, J. J. MENN, and G. D. MEYDING[1]

Stauffer Chemical Co., Agricultural Research Center, Mountain View, Calif.

The fate of Imidan-C^{14} labeled in the carbonyl carbon was determined following administration of a single oral dose to rats. Ninety-eight per cent of the radioactive material was accounted for in studies with three male and two female rats. Of that recovered, 79% was excreted in the urine and 19% in the feces at the time of sacrifice, either 72 or 120 hours after treatment. Less than 1% of the administered compound appeared in the urine as Imidan or its phosphorothiolate analog, *N*-(mercaptomethyl)phthalimide-*S*-(O,O-dimethylphosphorothiolate)(Imidoxon). Tissue residues accounted for 2.6% of the administered radioactivity with no selective storage in any tissue. Little, if any (<0.04%), radioactivity was detected in the expired CO_2.

THE FATE of the insecticide, *N*-(mercaptomethyl) phthalimide-*S*-(*O*, *O*-dimethylphosphorodithioate) (Imidan, Stauffer Chemical Co.), has been determined in the cotton plant (*15*) and in a steer (*10*). Imidan-C^{14} is absorbed and metabolized primarily to phthalamic and/or phthalic acids and possibly to benzoic acid or its derivatives following surface application to cotton leaves (*15*). Approximately 10% of a dermally applied dose of Imidan-C^{14} appeared in the urine and feces of a hereford steer within seven days after treatment. The primary degradation products in the urine of the steer were considered to be phthalic and phthalamic acids (*10*).

Metabolism of several other phosphorodithioate insecticides in mammals has also been studied using phosphorus-32–labeled materials (*1, 8, 9, 17*). Rapid degradation, extensive excretion in the urine and feces, and incorporation of trace amounts of P^{32} into normal biological constituents has usually been noted. With only a few exceptions (*5, 8, 10, 14, 16*), the fate of nonphosphorus-

[1] Present address, Stauffer Chemical Co., Research Center, Richmond, Calif.