N-Methyl- and *N,N*-Dimethylcarbamates of Hydroxybenzaldehyde Acetals and Mercaptals

Erwin F. Nikles

A series of new *N*-methyl- and *N,N*-dimethylcarbamates of hydroxybenzaldehyde acetals and mercaptals has been prepared. The synthesis of these compounds and their physical, anticholinesterase, and insecticidal properties are reported. Considering over-all insecticidal activity, 2-(1,3-dioxolan-2-yl)phenyl *N*-methylcarbamate has been found outstanding. Furthermore, phenyl *N*-methylcarbamates with the following ortho-substituents show interesting insecticidal properties: 4-methyl-1,3-dioxolan-2-yl, 4,4-dimethyl-1,3-dioxolan-2-yl, 4,5-dimethyl-1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,3-oxathiolan-2-yl, and 1,3-dithiolan-2-yl. Salicylaldehyde dimethyl acetal *N*-methylcarbamate and 2-(1,3-dithiolan-2-yl)phenyl *N,N*-dimethylcarbamate have remarkable selective toxicities. Meta isomers are less active and para compounds show practically no insecticidal properties.

Since carbaryl was successfully introduced as a pest control agent, carbamates with insecticidal properties have become a subject of growing interest. They represent a welcome alternative to the so-called chlorinated hydrocarbons and phosphate type insecticides. However, carbamates will not solve the resistance problem. An example is the difficulties met in the control of cattle tick in Australia, where resistance and cross-resistance have been observed towards DDT, phosphates, and carbaryl (Roulston and Wharton, 1967).

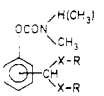
Recently, there have appeared carbamates with a high insecticidal potency and a broad spectrum of activity—e.g., Temik (UC 21149), Lannate (Du Pont 1179) of the oxime type, and Furadan (NIA 10242) of the arylcarbamate type. These insecticidal substances are unfortunately highly toxic to mammals.

The present work is a first report from the author's laboratories on insecticidal carbamates. It refers to *N*-methyl- and *N,N*-dimethylcarbamates derived from acetals and mercaptals of the hydroxybenzaldehydes. These new compounds and their use are the subject of worldwide patent rights. Results were first published in a Belgian patent of April 7, 1966 (Nikles *et al.*, 1966). Subsequently, it was learned that other workers were engaged in research on carbamates of the mercaptal type (Weil and Schlichting, 1967).

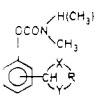
The new carbamates are chemically versatile and easily prepared. They are excellent substances for the study of structure/activity relationships. Their activity range roughly covers that of heterocyclic enolcarbamates—e.g., Isolan—and the ortho and meta substituted arylcarbamates (Weiden and Moorefield, 1964). Field experiments with these compounds showed possibilities for their use in hygiene and plant protection. The most active compound 2-(1,3-dioxolan-2-yl)-phenyl *N*-methylcarbamate shows a favorable acute and chronic mammalian toxicity. Furthermore, crop residues have been found to be of a low order (Geissbühler, 1967).

CHEMISTRY

Structure. Depending on the type of the acetal or mercaptal group, which may be open-chain or cyclic, the structural formulas of the compounds are as follows.

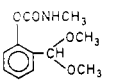


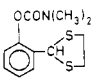
X = O, S
R = lower alkyl radicals



X, Y = O, S
R = lower (substituted) alkylen or alkenylen radicals

For illustration, two typical examples are given.





Starting Materials. It is not intended to deal with all possible methods for the preparation of these carbamates. The discussion will be limited to a few aspects of the syntheses with hydroxybenzaldehydes, methyl isocyanate, or dimethylcarbamoyl chloride as starting materials.

Salicylaldehyde, 5-chlorosalicylaldehyde, 3- and 4-hydroxybenzaldehyde, methyl isocyanate, dimethylcarbamoyl chloride, some of the glycols, and all mercaptans are commercially available.

The substituted salicylaldehydes needed for the preparation of compounds **38** and **39** (Table II) were obtained using the method of Reimer-Tiemann (Duff, 1941), and 4- and 5-methylsalicylaldehyde using a modified Duff method (Liggett and Diehl, 1945) starting with *m*- and *p*-cresol. 3,5-Dimethylsalicylaldehyde for compound **41** was easily prepared following the method described by Berres (1959). The Gattermann's synthesis gave 2,6-dimethyl-4-hydroxybenzaldehyde with 65% yield using 3,5-xylenol and hydrogen cyanide as starting materials (Dakshinamurty and Santappa, 1962).

2-Methyl-1,2-propanediol (isobutylene glycol) was prepared by hydration of methallyl alcohol via the cyclic acetal with isobutyraldehyde as intermediate (Groll and Hearne, 1937). The isomeric 2,3-butanediols (*dl*- and *meso*-) were obtained from *cis*- and *trans*-2,3-epoxybutane by the procedure of Wilson and Lucas (1936). Catalytic hydrogenation of commercial 3-hydroxy-3-methyl-2-butanone gave *dl*-2-methyl-2,3-butanediol (Bergmann and Herman, 1953). 3-Butene-1,2-diol (erythrol) was obtained by hydration of butadiene monoxide according to the method of Whitmore and Krems (1949), and 3-methoxy-1,2-propanediol (glycerol-1-methyl-

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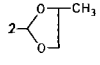
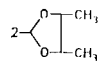
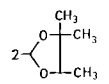
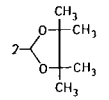
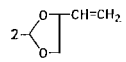
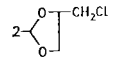
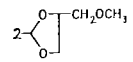
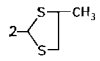
Table I. Physical and Analytical Data of *N*-Methylcarbamates and Phenols

No.	R	M.p., ° C. (solvent used for crystallization)	Solubility (25° C.), p.p.m. Hexane	Solubility (25° C.), p.p.m. Water	Molecular formula	Analysis Calcd., %	Analysis Found, %	B.p., ° C. (m.p.)	Molecular formula	Analysis Calcd., %	Analysis Found, %
1	2-CH(OCH$_3$)$_2$	67–8 (benzene-hexane)	2830	15000	$C_{11}H_{15}NO_4$	C, 58.65 H, 6.71 N, 6.22	C, 58.52 H, 6.68 N, 6.30	77/0.06 mm.	$C_9H_{12}O_3$	C, 64.27 H, 7.19	C, 64.41 H, 7.31
2	3-CH(OCH$_3$)$_2$	Oily residue			$C_{11}H_{15}NO_4$	C, 58.65 H, 6.71 N, 6.22	C, 58.43 H, 6.72 N, 6.2	Oily residue	$C_9H_{12}O_3$	C, 64.27 H, 7.19	C, 64.18 H, 7.15
3	2-CH(OC$_2$H$_5$)$_2$	92–3 toluene	2220	2300	$C_{13}H_{19}NO_4$	C, 61.64 H, 7.56 N, 5.53	C, 61.76 H, 7.43 N, 5.6	80/0.15 mm.	$C_{11}H_{16}O_3$	C, 67.32 H, 8.22	C, 67.2 H, 8.3
4	2-CH(SCH$_3$)$_2$	50–2 (methanol)	4720	<50	$C_{11}H_{15}NO_2S_2$	N, 5.44 S, 24.92	N, 5.34 S, 24.59	Oily residue	$C_9H_{12}OS_2$	C, 53.96 H, 6.04	C, 54.0 H, 5.9
5	3-CH(SCH$_3$)$_2$	69–70 (methanol at −10°)	1120	120	$C_{11}H_{15}NO_2S_2$	N, 5.44 S, 24.92	N, 5.61 S, 24.9	Oily residue	$C_9H_{12}OS_2$	S, 32.01	S, 31.8
6	4-CH(SCH$_3$)$_2$	126–7 (methanol)			$C_{11}H_{15}NO_2S_2$	N, 5.44 S, 24.92	N, 5.37 S, 25.2	(74–5, toluene)	$C_9H_{12}OS_2$	C, 53.96 H, 6.04	C, 54.0 H, 6.0
7	2-CH(SC$_2$H$_5$)$_2$	55–6 (cyclohexane)			$C_{13}H_{19}NO_2S_2$	N, 4.91 S, 22.47	N, 4.70 S, 22.52	Oily residue	$C_{11}H_{16}OS_2$	S, 28.08	S, 27.2
8	2-CH(SC$_3$H$_{7(n)}$)$_2$	46–7 (methanol at −78°)			$C_{15}H_{23}NO_2S_2$	N, 4.47 S, 20.46	N, 4.58 S, 20.47	Oily residue	$C_{13}H_{20}OS_2$	S, 25.01	S, 24.1
9	2-CH(SC$_3$H$_{7(i)}$)$_2$	77–8 (hexane)			$C_{15}H_{23}NO_2S_2$	N, 4.47 S, 20.46	N, 4.51 S, 20.38	Oily residue	$C_{13}H_{20}OS_2$	S, 25.01	S, 24.19
10		114–5 (toluene, isopropyl alcohol)	131	6400	$C_{11}H_{13}NO_4$	C, 59.18 H, 5.87 N, 6.28	C, 59.20 H, 5.92 N, 6.13	100/0.02 mm. (69–70, cyclohexane)	$C_9H_{10}O_3$	C, 65.05 H, 6.07	C, 64.92 H, 6.16
11		79 (methanol–water)			$C_{11}H_{13}NO_4$	C, 59.18 H, 5.87 N, 6.28	C, 59.28 H, 5.93 N, 6.35	113–5/0.05 mm.	$C_9H_{10}O_3$	C, 65.05 H, 6.07	C, 65.0 H, 6.2
12		40–60	2810	12000	$C_{12}H_{15}NO_4$	C, 60.75 H, 6.37 N, 5.90	C, 60.63 H, 6.39 N, 6.09	114/1.5 mm. crystallizes	$C_{10}H_{12}O_3$	C, 66.65 H, 6.71	C, 66.7 H, 6.6

13		76–9 (methanol-water or benzene-hexane)			$C_{13}H_{17}NO_4$	C, 62.14 H, 6.82 N, 5.57	C, 62.23 H, 6.83 N, 5.73	87–90/0.2 mm. (65–7, cyclohexane)	$C_{11}H_{14}O_3$	C, 68.02 H, 7.27	C, 68.2 H, 7.3
14a	 *dl-trans*	81–3 (ethyl acetate–hexane)	1050	4800	$C_{13}H_{17}NO_4$	C, 62.14 H, 6.82 N, 5.57	C, 61.96 H, 6.72 N, 5.75	78/0.03 mm. crystallizes	$C_{11}H_{14}O_3$	C, 68.02 H, 7.27	C, 68.1 H, 7.3
14b	*cis-syn*	123–5 (ethyl acetate–hexane)	230	1300	$C_{13}H_{17}NO_4$	C, 62.14 H, 6.82 N, 5.57	C, 62.28 H, 6.95 N, 5.65				
14c	*cis-anti*	Residue	330	1900	$C_{13}H_{17}NO_4$	C, 62.14 H, 6.82 N, 5.57	C, 61.43 H, 6.75 N, 6.02				
15		105–7 (toluene, carbon tetrachloride)	1060	800	$C_{14}H_{19}NO_4$	C, 63.38 H, 7.22 N, 5.28	C, 63.44 H, 7.09 N, 5.50	80–4/0.04 mm. (92–100)	$C_{12}H_{16}O_3$	C, 69.21 H, 7.74	C, 69.5 H, 7.8
16		133 (benzene)			$C_{15}H_{21}NO_4$	N, 5.01	N, 5.20	(132, acetonitrile)	$C_{13}H_{18}O_3$	C, 70.24 H, 8.16	C, 70.6 H, 8.5
17		Oily residue			$C_{13}H_{15}NO_4$	C, 62.64 H, 6.07 N, 5.62	C, 63.6 H, 6.4 N, 5.4	82/0.08 mm.	$C_{11}H_{12}O_3$	C, 68.73 H, 6.29	C, 68.7 H, 6.3
18		45–60			$C_{12}H_{14}ClNO_4$	Cl, 13.05 N, 5.16	Cl, 12.9 N, 5.1	111–4/0.25 mm.	$C_{10}H_{11}ClO_3$	Cl, 16.52	Cl, 16.5
19		Oily residue			$C_{13}H_{17}NO_5$	C, 58.42 H, 6.41 N, 5.24	C, 57.99 H, 6.29 N, 5.40	107/0.09 mm.	$C_{11}H_{14}O_4$	C, 62.84 H, 6.71 O, 30.44	C, 63.1 H, 6.9 O, 30.7
20		110 (alcohol, carbon tetrachloride)	284	800	$C_{11}H_{13}NO_3S$	N, 5.85 S, 13.40	N, 5.96 S, 13.66	(72–4, toluene)	$C_9H_{10}O_2S$	C, 59.32 H, 5.53	C, 59.3 H, 5.6
21		139 (methanol, benzene)	71	<50	$C_{11}H_{13}NO_2S_2$	N, 5.49 S, 25.11	N, 5.45 S, 25.29	142/0.07 mm. (48–50)	$C_9H_{10}OS_2$	C, 54.51 H, 5.08 S, 32.34	C, 54.3 H, 5.1 S, 32.4
22		98 (methanol)			$C_{11}H_{13}NO_2S_2$	N, 5.49 S, 25.11	N, 5.38 S, 25.01	Oily residue	$C_9H_{10}OS_2$	S, 32.34	S, 32.2
23		95–102	535	90	$C_{12}H_{15}NO_2S_2$	N, 5.20 S, 23.81	N, 5.32 S, 23.57	150/0.5 mm.	$C_{10}H_{12}OS_2$	C, 56.57 H, 5.70 S, 30.20	C, 56.7 H, 5.8 S, 29.9

(*continued*)

Table I. (*continued*)

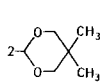
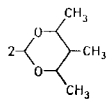
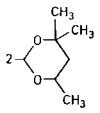
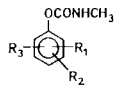
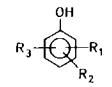
No.	R	M.p., ° C. (solvent used for crystallization)	Solubility (25° C.), p.p.m. Hexane	Water	Molecular formula	Analysis Calcd., %	Found, %	B.p., ° C. (m.p.)	Molecular formula	Analysis Calcd., %	Found, %
24		127–30 (isopropyl alcohol)			$C_{11}H_{13}NO_3S_2$	N, 5.16 O, 17.69 S, 23.63	N, 4.9 O, 17.6 S, 23.61				
25		129 (benzene, ethyl acetate)	139	6800	$C_{12}H_{15}NO_4$	C, 60.75 H, 6.37 N, 5.90	C, 60.86 H, 6.34 N, 5.96	100/0.02 mm. (55–8)	$C_{10}H_{12}O_3$	C, 66.65 H, 6.71	C, 66.3 H, 6.9
26		116 (ethyl acetate)			$C_{12}H_{15}NO_4$	C, 60.75 H, 6.37 N, 5.90	C, 60.57 H, 6.37 N, 5.94	(109–10, benzene)	$C_{10}H_{12}O_3$	C, 66.65 H, 6.71	C, 66.7 H, 6.7
27		151–4 (isopropyl alcohol)			$C_{12}H_{15}NO_4$	C, 60.75 H, 6.37 N, 5.90	C, 60.84 H, 6.33 N, 6.1	150/0.25 mm. (115–7, benzene)	$C_{10}H_{12}O_3$	C, 66.65 H, 6.71	C, 66.9 H, 6.6
28		146–8 (acetonitrile)			$C_{13}H_{17}NO_4$	C, 62.14 H, 6.82 N, 5.57	C, 62.08 H, 6.77 N, 5.6	90/0.06 mm.	$C_{11}H_{14}O_3$	C, 68.02 H, 7.27	C, 68.4 H, 7.2
29		128–9 (carbon tetrachloride)	343	550	$C_{14}H_{19}NO_4$	C, 63.38 H, 7.22 N, 5.28	C, 63.59 H, 7.11 N, 5.3	90/0.06 mm. crystallizes	$C_{12}H_{16}O_3$	C, 69.21 H, 7.74	C, 68.8 H, 7.7
30		121–32 (ether)			$C_{15}H_{21}NO_4$	C, 64.49 H, 7.58 N, 5.01	C, 64.73 H, 7.58 N, 5.00	90/0.005 mm.	$C_{13}H_{18}O_3$	C, 70.24 H, 8.16	C, 70.4 H, 8.2
31		147–8			$C_{15}H_{21}NO_4$	C, 64.49 H, 7.58 N, 5.01	C, 64.38 H, 7.50 N, 5.13	103/0.2 mm.	$C_{13}H_{18}O_3$	C, 70.24 H, 8.16	C, 70.6 H, 7.8
32		100–1 (toluene, carbon tetrachloride)	498	1650	$C_{13}H_{15}NO_4$	C, 62.64 G, 6.07 N, 5.62	C, 62.61 H, 6.01 N, 5.90	87/0.03 mm. (52–5)	$C_{11}H_{12}O_3$	C, 68.73 H, 6.29	C, 68.5 H, 6.7
33		151–3 (methanol)			$C_{12}H_{15}NO_2S_2$	N, 5.20 S, 23.81	N, 5.18 S, 23.7	(131–3, toluene)	$C_{10}H_{12}OS_2$	S, 30.20	S, 30.2
34		137–8 (methanol)			$C_{12}H_{15}NO_2S_2$	N, 5.20 S, 23.81	N, 5.18 S, 23.58	(127–9, toluene-cyclohexane)	$C_{10}H_{12}OS_2$	C, 56.57 H, 5.70 S, 30.20	C, 56.49 H 5.85 S, 30.4
35		94–5 and 101 (cyclohexane, methanol-water)	4360	40	$C_{14}H_{19}NO_2$	C, 72.07 H 8.21 N, 6.00	C, 72.38 H, 8.25 N, 6.21				

Table II. Physical and Analytical Data of *N*-Methylcarbamates and Phenols



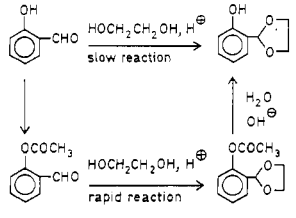


No.	R_1	R_2	R_3	M.p., ° C. (solvent used for crystallization)	Molecular formula	Analysis Calcd., %	Analysis Found, %	B.p., ° C. (m.p.)	Molecular formula	Analysis Calcd., %	Analysis Found, %
36		4-CH_3	H	104–6 (carbon tetrachloride	$C_{12}H_{15}NO_4$	N, 5.90	N, 6.2	95/0.009 mm. (48–54)	$C_{10}H_{12}O_3$	C, 66.65 H, 6.71	C, 66.6 H, 7.0
37		H	5-CH_3	96–9 (toluene)	$C_{12}H_{15}NO_4$	N, 5.90	N, 6.2	98/0.02 mm. (59–66)	$C_{10}H_{12}O_3$	C, 66.65 H, 6.71	C, 65.7 H, 6.5
38		H	6-CH_3	93–5 (carbon tetrachloride)	$C_{12}H_{15}NO_4$	N, 5.90	N, 5.9	76/0.01 mm.	$C_{10}H_{12}O_3$	C, 66.65 H, 6.71	C, 67.1 H, 6.9
39		4-Cl	5-CH_3	136–9 (alcohol)	$C_{12}H_{14}ClNO_4$	N, 5.16	N, 5.3	(91–3, methanol-water)	$C_{10}H_{11}ClO_3$	Cl, 16.52	Cl, 16.9
40		4-Cl	H	158–61 (methanol)	$C_{11}H_{12}ClNO_2S_2$	Cl, 12.23 N, 4.83 S, 22.13	Cl, 12.15 N, 4.70 S, 22.4	(62–3, cyclohexane)	$C_9H_9ClOS_2$	Cl, 15.23 S, 27.55	Cl, 15.3 S, 27.48
41		4-CH_3	6-CH_3	161-2 (methanol)	$C_{13}H_{17}NO_2S_2$	N, 4.94 S, 22.63	N, 5.1 S, 22.63	(107–8, cyclohexane)	$C_{11}H_{14}OS_2$	C, 58.37 H, 6.23	C, 58.5 H, 6.3
42	3-CH_3		5-CH_3	152–5 (alcohol)	$C_{13}H_{17}NO_2S_2$	N, 4.94 S, 22.63	N, 4.7 S, 23.0	144/0.2 mm.	$C_{11}H_{14}OS_2$	S, 28.33	S, 28.6

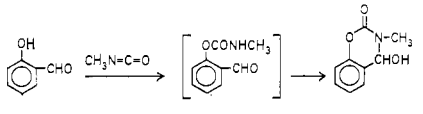
ether) by reacting methanol with epichlorohydrin (Ulbrich *et al.*, 1964).

Syntheses. In contrast to benzaldehyde, the reaction of hydroxybenzaldehydes with aliphatic hydroxy compounds to the corresponding acetals often proceeds with difficulty. Monohydric alcohols do not react in the presence of acidic catalysts under azeotropic distillation conditions—e.g., with benzene as the solvent. Ethylene glycol reacts slowly and the reaction does not go to completion. This phenomenon had previously been reported by Pauly and Buttlar (1911), (compare also Crowell *et al.*, 1963) and can be explained by the fact that strong electron-donating phenolic hydroxyl groups suppress typical carbonyl reactions. On the other hand, the formation of 5- and 6-membered rings occurs preferentially, particularly with secondary glycols which form relatively stable carbonium ions. For example, 2,3-butanediol reacts readily with salicylaldehyde. Therefore, all cyclic acetals listed in Tables I and II may be prepared by directly reacting hydroxybenzaldehydes with glycols.

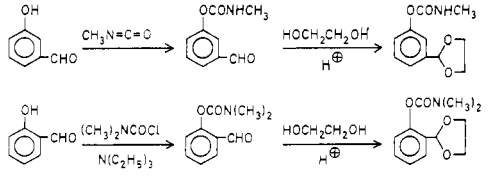
Modification of the hydroxyl group—e.g., by acetylation—should suppress the electronic effect, thus promoting acetalization. In fact, salicylaldehyde acetate prepared by the method of Neuberger (1948) readily reacts with ethylene glycol under the above conditions to yield the dioxolanyl compound. 2-(1,3-Dioxolan-2-yl)phenol may be obtained in high yield by alkaline hydrolysis of this acetate.



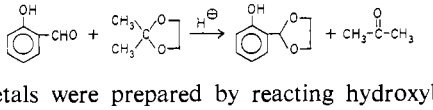
This reaction sequence suggests that the new carbamates may best be prepared by first transforming the hydroxybenzaldehydes to the corresponding carbamic acid esters and then, in the second step, to the acetals. This is unfortunately impossible with the biologically most interesting class, the *N*-methylcarbamates derived from salicylaldehyde. Salicylaldehyde *N*-methylcarbamate undergoes a cyclization process forming immediately 3,4-dihydro-4-hydroxy-3-methyl-2*H*-1,3-benzoxazin-2-one (Strube and Mackellar, 1964).



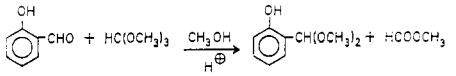
However, this method of synthesis is suitable for the preparation of *N*-methylcarbamates derived from 3-hydroxybenzaldehyde and for all *N*,*N*-dimethylcarbamates.



Another possibility for preparing cyclic acetals of ethylene glycol is the exchange dioxolanation.

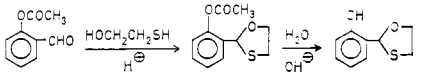


Dialkylacetals were prepared by reacting hydroxybenzaldehydes with corresponding orthoformic acid trialkylesters.



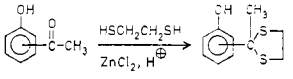
The reaction of hydroxybenzaldehydes with mercaptans to mercaptals, and with dithiols to 1,3-dithiolanes (5-membered, cyclic) or to 1,3-dithianes (6-membered, cyclic) proceeds in the presence of acidic catalysts exothermically with high yields. Contrary to the cyclic compounds, open-chain mercaptals cannot be distilled. These compounds were not purified further before being transformed to the carbamates.

The conversion of salicylaldehyde with 2-mercaptoethanol met with difficulties; probably an open-chain mercaptal was formed. Salicylaldehyde acetate reacted smoothly with the stoichiometric amount of 2-mercaptoethanol to yield the expected oxathiolane which, after alkaline hydrolysis, gave the free phenol.



The mono *S*-oxide (**24**) was obtained by oxidation of 2-(1,3-dithiolan-2-yl)phenyl *N*-methylcarbamate (**21**) with peracetic acid. Treatment of 2-(1,3-oxathiolan-2-yl)phenyl *N*-methylcarbamate (**20**) with two molar equivalents of peracetic acid at maximum 45° C. yielded a crystalline product free from sulfur. During the reaction the sulfone probably is formed, which seems to be very unstable.

For comparison, Table III also lists carbamates derived from 2- and 3-hydroxyacetophenone. Reaction of these hydroxyacetophenones with 1,2-ethanedithiol was performed in the presence of zinc chloride.



The preparation of *N*-methyl- and *N*,*N*-dimethylcarbamates, starting with phenols and methyl isocyanate or dimethylcarbamoyl chloride, is well known and does not need further explanation.

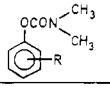
Tables I to III contain a selection of the numerous carbamates prepared together with their physical and analytical data. Their structure was proved by elemental analysis and by determination of their NMR and IR spectra.

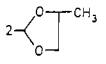
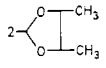
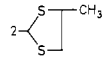
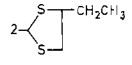
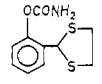
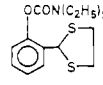
Typical peaks of the NMR spectra occur as follows: δ ($CDCl_3$) 2.1 (singlets, SCH_3), 2.6–4.2 (SCH, SCH_2), 3.2–3.3 (singlets, OCH_3), 3.5–4.7 (OCH, OCH_2), 2.7–2.9 (doublets, J = 5 Hz, $NHCH_3$), 5.0 – 5.4 (5.9) (broad, $NHCH_3$), 4.8 – 6.3 (singlets, benzyl H), 6.8 – 7.9 (multiplets, aromatic H). The following IR spectra bands have been observed (μ, CH_2Cl_2): 2.86 – 2.88, (m), ν N-H; 6.58 – 6.60, (m), δ N-H; 5.71 – 5.73, (s), ν C=O; 8.19 – 8.27, (s); 8.41 – 8.53, (m-s), and also a series of bands in the region 8.6 – 9.5, (w-m), ν C-O-C, (esters, acetals). Characteristic shifts of the ν N-H bands from 2.86 – 2.88 to 2.97 occurred in the spectra of the solid compounds. Almost the same absorption ranges were found by Chen and Benson (1966) for numerous other carbamates.

Stereochemistry. Many of the substances listed in Table I and III are mixtures of stereoisomers, which is usually evident from their melting point intervals.

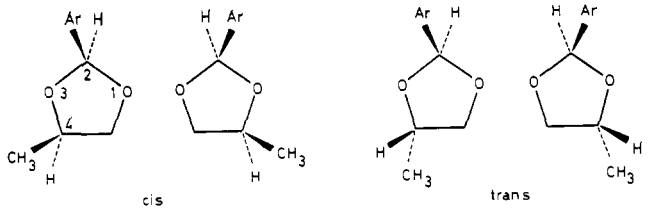
Dioxolanes, monosubstituted in position 4, may exist in cis and trans forms, and each of them may form a pair of enantiomers. 2-(4-Methyl-1,3-dioxolan-2-yl)phenyl *N*-methylcarbamate (**12**), which was prepared from commercial *dl*-1,2-propanediol contains the following stereoisomers.

Table III. Physical, Analytical, and Biological Data of *N,N*-Dimethylcarbamates



No.	R	B.p., °C. (m.p.)	Molecular formula	Analysis Calcd., %	Analysis Found, %	pI_{50} (M) AChE	pI_{50} (M) ChE	*Aphis fabae*[a]	LD_{50}, oral (mg./kg.) rat
43		(58–60, carbon tetrachloride–cyclohexane)	$C_{12}H_{15}NO_4$	C, 60.75 H, 6.37 N, 5.90	C, 60.93 H, 6.42 N, 6.1	5.57	5.96	+++	
44		135/0.001 mm.	$C_{13}H_{17}NO_4$	C, 62.14 H, 6.82 N, 5.57	C, 62.3 H, 6.5 N, 5.3	5.14	5.77	+	
45		120/0.02 mm.	$C_{14}H_{19}NO_4$	C, 63.38 H, 7.22 N, 5.28	C, 63.4 H, 7.1 N, 5.4	5.40	6.00	++	
46		128–30/0.25 mm.	$C_{12}H_{15}NO_3S$	N, 5.53	N, 6.0	5.96	6.48	+++	
47		150/0.001 mm.	$C_{12}H_{15}NO_2S_2$	C, 53.50 H, 5.61 N, 5.20 O, 11.88 S, 23.81	C, 53.65 H, 5.59 N, 5.2 O, 12.0 S, 24.0	6.52	6.72	++++	16
48		170/0.07 mm.	$C_{13}H_{17}NO_2S_2$	C, 55.09 H, 6.05 N, 4.94	C, 55.1 H, 6.1 N, 5.0	5.74	6.15	++++	140
49		174/0.2 mm.	$C_{14}H_{19}NO_2S_2$	N, 4.71	N, 4.9	5.70	6.48	0	
50		180/0.01 mm.	$C_{13}H_{17}NO_2S_2$	C, 55.09 H, 6.05 N, 4.94	C, 55.1 H, 6.4 N, 4.9	6.05	6.28	0	
51	 4-Cl	200/0.2 mm.	$C_{12}H_{14}ClNO_2S_2$	Cl, 11.67 N, 4.61	Cl, 11.7 N, 4.6		5.80	+++	
52		153/0.1 mm.	$C_{13}H_{17}NO_2S_2$	N, 4.94	N, 5.1	4.64	4.92	+	
53		180/0.12 mm.	$C_{13}H_{17}NO_2S_2$	C, 55.09 H, 6.05 N, 4.94	C, 55.2 H, 6.3 N, 5.3	5.05	5.46	0	
54		(139–42, methanol at −10°)	$C_{10}H_{11}NO_2S_2$	S, 26.57	S, 26.8	<4	<4	0	
55		162–5/0.05 mm.	$C_{14}H_{19}NO_2S_2$	N, 4.71	N, 5.5	<4	4.46	0	

[a] Rating system:
0 = less than 50% activity at 800 p.p.m.
+, ++, +++ = intermediate activities.
++++ = 100% activity at 100 p.p.m.



cis trans

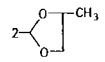
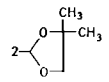
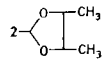
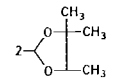
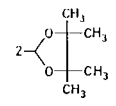
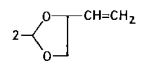
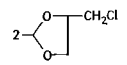
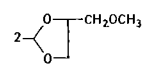
Ar = 2-$C_6H_4OCONHCH_3$

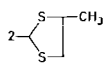
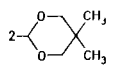
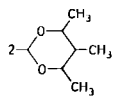
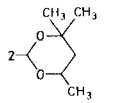
The NMR spectrum of compound **12** shows two peaks for benzyl protons at δ = 6.03 and 6.19. The unsubstituted carbamate **10**, in which the benzyl proton is necessarily in cis-position to two of the protons in positions 4 and 5, shows only one singlet at δ = 6.03. Based upon analogy the singlet at a higher field may therefore be attributed to the cis-isomer (Baggett *et al.*, 1965). The integration of the two peaks gave a cis-trans ratio of 55 to 45. This ratio was found in numerous preparations. However, this is no proof that the stereoisomers --both of course racemic—did really reach equilibrium during the acetalization reaction.

For compounds **18** (chloromethyl as substituent) and **19** (methoxymethyl as substituent) the cis-trans ratio was 3 to 2 and 4 to 1, respectively.

The bonds of the sulfur atoms in sulfoxides are in a tetrahedral configuration, one position being occupied by a free electron pair. Sulfoxide **24** has therefore the same isomeric

Table IV. Biological Activities of *N*-Methylcarbamates Derived from Acetals and Mercaptals of Hydroxybenzaldehydes

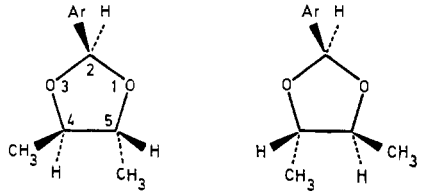
No.	R	pI_{50} (M) AChE[a]	pI_{50} (M) ChE[b]	*M.d.* Contact[c]	*M.d.* Bait[c]	*S.g.*[d]	*E.v.*[e]	*O.g.*[f]	*A.f.*[g]	*P.a.*[h]	*R.b.*[i]	LD_{50}, oral (mg./kg.) rat
1	2-$CH(OCH_3)_2$	5.27	4.35	++++	+++	+++	+++	++	+++	+++	++	160
2	3-$CH(OCH_3)_2$	4.70	<4	++	0	+++	+++	+	++	++	++	
3	2-$CH(OC_2H_5)_2$	4.60	4.46	+	+	0	+	0	0	+++	++	
4	2-$CH(SCH_3)_2$	6.30	5.24	++	++	++	+	++	+++	+++	++++	
5	3-$CH(SCH_3)_2$	5.92	5.01	+	0	+	+	0	+++	+++	++++	
6	4-$CH(SCH_3)_2$	<4	<4	0	0	0	0	0	0	0	0	
7	2-$CH(SC_2H_5)_2$	4.46	5.52	+	+	0	0	0	0	+	0	
8	2-$CH(SC_3H_{7(n)})_2$	<4	6.30	+	0	0	0	0	0	+	0	
9	2-$CH(SC_3H_{7(i)})_2$	<4	5.89	0	0	0	0	0	+		0	
10		5.19	5.05	++++	+++	+++	+++	++++	++++	++++	++++	120
11		4.57	4.17	++	++	++	++++	+	+	++	++	
12		5.0	5.28	++++	++++	+++	+++	+++	++++	++++	++++	110
13		5.13	5.62	++++	+++	++++	+++	+++	+++	+++	++	110
14a		5.62	5.89	+++	+++	+++	+	++	+++	++++	++++	60
	dl-trans											
14b	*cis-syn*	4.98	5.67	++	++	0	+++	++	+	+++	++++	300
14c	*cis-anti*	5.37	5.85	+++	+++	+++	+	+++	++++	++++	++++	90
15		4.72	6.12	++	+++	++	++	+	+	+++	++++	
16		4.74	6.14	0	+	0	+	0	+	++	++	
17		4.92	5.50	++	+++	++	0	++	+	++	++++	
18		4.74	5.43	++	+++	0	+++	+	++	+++	++	
19		4.60	5.17	+++	+++	++	+++	++	0	++	++	

20		5.96	.68	++	++++	+	++++	+	++++	+++	++	56
21		6.57	5.89	++	+++	0	+	+++	++++	++	++++	80
22		5.62	5.00	0	0	0	+	0	0	+	++++	
23		5.55	5.12	++	+++	0	++	++	+	++	++++	
24		5.34	4.70	0	++	0	+	0	++++	++	0	
25		5.72	6.07	+++	+++	0	+++	+	++++	++++	+++	142
26		<4.0	~4.0	0	0	0	0	0	0	+	0	
27		<4.0	<4.0	0	0	0	0	0	0	0	0	
28		5.47	5.85	0	++	0	++	+	0	+++	++	
29		4.68	5.80	0	+	0	0	0	0	0	+++	
30		4.0	5.30	0	+	0	0	0	0	0	+	
31		4.30	5.12	0	0	0	0	0	0	0	0	
32		4.96	5.19	+	++	0	+++	+	+++	+++	++	35
33		6.35	6.19	0	0	0	+++	++	0	0	++++	
34		4.80	4.14	0	0	0	0	0	0	0	++++	
35		5.22	4.96	0	+	0	+++	0	0	0	++++	

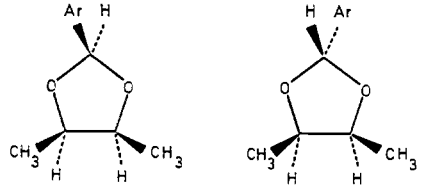
[a] AChE: bovine erythrocyte cholinesterase. [b] ChE: human plasma cholinesterase. [c] *Musca domestica*. [d] *Sitophilus granarius*. [e] *Epilachna varivestis*. [f] *Orgyia gonostigma*. [g] *Aphis fabae*. [h] *Periplaneta americana*. [i] *Rhipicephalus bursa*. Rating system: 0 = no or only slight activity at the highest concentration tested. +, ++, +++ = intermediate activities. ++++ = 100% activity at the lowest concentration tested (more than 40% activity in the contact test with housefly).

possibilities as position 4 monosubstituted dioxolanes. It was not investigated whether the compound melting at 127–30°C., which was obtained by peracetic acid oxidation of dithiolane **21,** is uniform or consists of a mixture of stereoisomers. However, two strong bands in the IR spectrum near 9.5 microns suggest the presence of two stereoisomeric sulfoxides.

Compound **13** with two methyl groups in position 4 of the dioxolane ring consists of a pair of enantiomeric forms. If positions 4 and 5 are each occupied by one methyl group, the following stereoisomers are possible.



trans
one enantiomeric pair (dl-form)



cis-syn cis-anti

It is evident that the cis-syn and the cis-anti forms have a plane of symmetry and cannot be split into antipodes. A mixture of these isomeric *N*-methylcarbamates **14b** and **14c** was formed in the ratio 2 to 1 when *meso*-2,3-butanediol was used as a starting material. Separation was accomplished by crystallization. The main compound was assigned the cis-syn configuration on the basis of NMR studies (Gagnaire and Robert, 1965). Racemic 2,3-butanediol as a starting material gave the pure *dl*-form **14a.**

BIOLOGICAL PROPERTIES

Anticholinesterase Activity. The intrinsic toxicities of the compounds were determined by measuring the inhibition of human serum cholinesterase (ChE) and bovine erythrocyte cholinesterase (AChE).

The pI_{50} (M) values of *N*-methylcarbamates are given together with the insecticidal test results in Table IV. The compounds are listed according to the chemistry of the anionic interactants; open-chain, 5-, 6-, and higher membered cyclic compounds, acetals, mercaptals, position isomers, homologues, and substituted compounds.

Open-Chain and Cyclic Compounds. Comparison of the anti-ChE activities of the lowest unsubstituted members of the above chemical classes shows, among the acetals of the ortho series, a rising activity in the following sequence: open-chain compound **1,** dioxolane **10,** 6-membered cyclic compound **25.** With the 7-membered compound, **32,** the activity decreases. Contrary to these findings, the values for the enzyme AChE, which is biochemically similar to insect cholinesterase, are high and relatively constant. Thus for this enzyme the aliphatic and the cyclic 5- and 6-membered ace al groups are excellent anionic interactants in spite of their differing rigidity or mobility. The mercaptals **4, 21,** and **33** behave in a similar manner.

Among these acetals and mercaptals the highest anti-AChE activity is shown by 2-(1,3-dioxan-2-yl)phenyl *N*-methylcarbamate (**25**) and 2-(1,3-dithiolan-2-yl)pheny *N*-methylcarbamate (**21**), respectively.

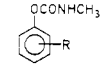
Table V. Differences in pI_{50} Values between the Isomeric Ortho- and Meta-Compounds

i.e., pI_{50} (ortho) − pI_{50} (meta)

R	—CH $(OCH_3)_2$	—CH $(SCH_3)_2$				
AChE	0.57	0.38	0.62	0.95	>1.7	1.55
ChE	>0.35	0.23	0.88	0.89	2	2.05

Table VI. Comparison between the Anticholinesterase Activities of Mercaptals and Acetals

i.e., pI_{50} (X = S) − pI_{50} (X = 0)



R	2-CH $(XCH_3)_2$				
AChE	1.03	0.77	1.38	0.63	1.05
ChE	0.89	0.63	0.84	0.12	0.83

The AChE pI_{50} values of the meta series decrease in the following sequence: from open-chain compounds **2, 5** to 5-membered cyclic **11, 22,** and to 6-membered cyclic **26, 34.** Dreiding stereomodels demonstrate that the equatorially bound chair form of 6-membered rings in the meta position is very unfavorably orientated with regard to the carbamic ester group.

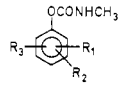
Position Isomers. A comparison of the corresponding ortho and meta isomers reveals that the latter are inferior. This is evident in Table V in which the differences of the pI_{50} values between the pairs of isomers are given.

The meta isomers are apparently not capable of forming optimal distances between esteratic and anionic interactants (Foldes *et al.*, 1958), and thus are less complementary with the enzyme (Metcalf and Fukuto, 1965). It is characteristic that the open-chain, and thus more flexible, anionic interactants show the lowest differences in inhibitory activity.

As expected, the para-isomers, **6** and **27,** are weak inhibitors. Further studies with the easily prepared homologues of compound **6** may confirm the results of Metcalf and Fukuto (1967), who found that an increase in the chain-length of para-substituted phenylcarbamates resulted in higher inhibitory action.

Acetals and Mercaptals. The isosteric mercaptals and acetals were compared by calculating the differences between their pI_{50} values. The values listed in Table VI indicate the thio-compounds are generally 10 times better inhibitors than the corresponding oxygen-compounds. This behavior may be due to an intimate interaction of the anionic site of the enzyme with the free *d*-orbital of the sulfur atom. However, dioxane **25** and dithiane **33** exhibit a distinct difference minimum. Furthermore, dioxane **25** shows a 50 times greater inhibitory action (ChE) than dimethylacetal **1,** whereas compound **33** is only nine times more potent than compound **4.** This implies that the structural requirements are less rigid with mercaptals than with acetals. Thus, in addition, steric factors are responsible for the differences between these two types of compounds.

Table VII. Biological Activities of *N*-Methylcarbamates Derived from Acetals and Mercaptals of Substituted Hydroxybenzaldehydes[a]



No.	R_1	R_2	R_3	*M.d.* Contact	*M.d.* Bait	*S.g.*	*E.v.*	*O.g.*	*A.f.*	*R.b.*
36		4-CH_3	H	+	++	+	++	++	++	
37		H	5-CH_3	++++	++++	0	0	0	0	
38		H	6-CH_3	0	+		0	0	0	0
39		4-Cl	5-CH_3	+	+++	0	0	+	0	0
40		4-Cl	H	0	0		+++	+++	0	
41		4-CH_3	6-CH_3	0	0		0	+	0	
42	3-CH_3		5-CH_3	0	+		++	++	0	++

[a] Rating system:

0 = no or only slight activity at the highest concentration used.
+, ++, +++ = intermediate activities.
++++ = 100% activity at the lowest concentration tested (more than 40% activity in the contact test with housefly).

The relationships between structure and anticholinesterase activity of these compounds follow closely the behavior of the alkoxy and alkylthio phenyl *N*-methylcarbamates (Metcalf and Fukuto, 1965).

SUBSTITUTED COMPOUNDS, HOMOLOGUES. In the following, comparisons will always refer to the appropriate unsubstituted carbamates **1, 4, 10,** and **25.** The highly substituted compound **16,** with four methyl groups on the dioxolane ring, which cannot form stereoisomers, shows reduced activity against AChE and a distinctly higher potency against ChE. The same behavior is also shown by the open-chain homologues **3,** and **7** to **9.** With compounds **12, 13, 15, 17, 18,** and **19,** at least one of the stereoisomeric forms probably follows the same pattern.

It is not likely that these substituents have a significant inductive effect on the carbamoylation step of enzyme inhibition. The higher activity of the *dl*-form **14a** against AChE demonstrates that with a small number of methyl groups in the proper geometrical arrangement a better fit to the active site of the enzyme is possible.

The higher choline esters—e.g., butyrylcholine—are better substrates for ChE than acetylcholine. ChE apparently has a specific structure which enables both the esteratic and the anionic site to interact with larger groups. The size of these groups has an upper limit. This is demonstrated for example by the behavior of the substituted dioxane **29.**

N,N-DIMETHYLCARBAMATES. Among the synthesized *N,N*-dimethylcarbamates, 2-(1,3-dithiolan-2-yl)phenyl *N,N*-dimethylcarbamate (**47**) has highest activity against both enzymes (Table III). Its anticholinesterase values, when compared with the *N*-monomethylcarbamate **21**, are equal for AChE and markedly higher for ChE. This is exceptional in that *N,N*-dimethylcarbamates have previously been found to be always poorer inhibitors than their *N*-monomethyl counterparts (Metcalf and Fukuto, 1965).

For reasons discussed in the previous section the activity of the *N,N*-dimethylcarbamates is always higher against ChE than against AChE.

Insecticidal Properties. The results of some selected tests performed on several insects and one tick species are listed in Tables IV and VII.

It is generally accepted that anticholinesterase activity is the basis for the mode of action of insecticidal carbamates. However, it is known that in addition to this mode of action, the following factors may play a role in evaluating the properties of an insecticide under practical conditions.

Stability in the environment (plants, animals, soil, water, etc.) to which the preparation is applied, especially against hydrolytic, oxidative, and photochemical effects.

Contact and penetration into the organism, translocation to the site of action.

Storage, metabolism, and excretion.

Synergists inhibit metabolic decomposition of the active substances—e.g., by hydroxylation and hydrolysis. A better correlation between anti-AChE activity and insecticidal action than that which is given in Tables III and IV might be expected from tests where these carbamates are combined with synergists. At present, there is no data available on this subject.

PROPERTIES OF 2-(1,3-DIOXOLAN-2-YL)PHENYL *N*-METHYLCARBAMATE (**10**). The acetal 2-(1,3-dioxolan-2-yl)phenyl *N*-methylcarbamate (**10**), (code no. C-8353) showed the broadest and strongest action in the laboratory and especially in field tests.

In plant protection trials it exhibited a high activity against such pests as *Aphididae*, *Psyllidae*, *Miridae*, *Coleoptera*, *Diptera*, and *Hymenoptera*. On the other hand, its activity against *Lepidoptera* and *Acarina* was rather low. However, contrary to carbaryl, spider mite populations were not stimulated.

The insecticidal compound acts as a contact and as a stomach poison and penetrates well through plant tissues. No phytotoxicity to plants has been observed when a normal dosage of the substance was applied. Because of the quick action, the substance is especially suitable against virus transferring vectors. In contrast to 2-chlorophenyl *N*-methylcarbamate, when compound **10** was applied to rice, it did not affect its flavor. Field tests with 2-(1,3-dioxolan-2-yl)-phenyl *N*-methylcarbamate and related compounds have been reported by Bachmann and Legge (1968).

Malathion- and diazinon-resistant cockroaches (Grayson, 1966) and various other pests are efficiently controlled by this compound; when walls and floors are treated with the compound, it retains its activity for approximately half a year.

Substituted Compounds, Homologues, and Position Isomers. Of practical interest are compounds **12** and **14a,** in which the dioxolane ring is substituted by one or two methyl groups. In the field tests they were less active than the corresponding unsubstituted compound **10.** They are nevertheless important because of their physical properties. A methyl group in the dioxolane ring (compound **12**) causes a considerable increase in solubility in organic solvents and makes possible the preparation of emulsifiable concentrates. The same is true for compound **13.** In field trials compound **14a,** with two methyl groups, gave excellent results in control of soil insects such as root maggots, white grubs, and wireworms.

The insecticidal properties within a homologues series compare well with the anti-AChE values (compare, e.g., **1** with **3** and **4** with **7** and **8**). Large substituents (**18, 19**) or a high degree of substitution (e.g., **16**) gave invariably poor insecticidal properties.

Some of the numerous compounds, which are substituted in the aromatic ring, are listed in Table VII. They show, in general, no advantages over the previously described compounds.

Of the acetals, the dioxanyl compound **25** shows the highest anti-AChE activity. However, as an insecticide it is less active than the dioxolanyl compound **10.** Neither the hydrolytic decomposition at pH 5 and 8, determined by measuring the reduction in the ChE inhibitory activity, nor the solubility data of the compound, gave differences by which this behavior could be explained.

The meta-isomers **2, 5, 11, 22, 26,** and **34,** except for some selective activity, are invariably less effective than the corresponding ortho-isomers. The para-isomers **6** and **27** show no activity. Even compound **42** with two methyl groups in the meta positions has only slight insecticidal activity.

Comparison of Acetals with Mercaptals. There is no correlation between anticholinesterase activity and insecticidal action when mercaptals are compared with acetals. Although the mercaptals are approximately 10 times more active against cholinesterase than their oxygen analogues, as contact insecticides they are invariably weaker. To explain this behavior two reasons are suggested.

A known way of metabolic conversion of sulfides is the oxidation to sulfoxides and sulfones. In this respect, the mercaptals have an intrinsic disadvantage as they may be attacked at two points by oxidation. The insect test results of the sulfoxide **24** show that the introduction of one oxygen atom causes a marked decrease in activity.

Solubility, absorption, and resorption processes play an important role during penetration through the cuticle and translocation of the insecticide to the site of action. O'Brien (1967) has reviewed the various theories, including those of Hansch and Fujita (1964), on this subject.

Table VIII. Activity against *Aedes aegypti* (L.) Females (% kill after 1-hour exposure to a residue in a Petri dish)

Phenyl *N*-methylcarbamates	Mg. Active Ingredient per Dish				LD_{50}, Oral[a] (Mg./Kg.)
	1	0.1	0.01	0.001	Rat
2-$CH(OCH_3)_2$	100	100	100	100	160
2-$OC_3H_{7(i)}$	100	100	100	40	95–104
3-$C_3H_{7(i)}$	100	100	100	100	16
Carbaryl	...	...	75	0	540
Other compounds					
DDT	45	25	0	0	87–420
Dimethoate	0	0	0	0	155–500
Malathion	100	100	92	32	885–2800

[a] Data for comparative compounds taken from Metcalf and Fukuto (1965) and Kenaga (1966).

Based on the solubility data in hexane and distribution coefficients between hexane-water of various carbamates and phosphates, Hadaway and Barlow (1966) tried to explain the poor correlation between anticholinesterase and contact activity against *Anopheles stephensi.*

Table I lists the solubilities of some carbamates in hexane and water. Striking are the high water solubilities of the acetal carbamates, whereas the solubilities of the mercaptals are considerably lower. 2-(1,3-Dithiolan-2-yl)phenyl *N*-methylcarbamate **21**, with the highest anti-AChE activity of the discussed *N*-methylcarbamates [pI_{50}(M) = 6.57], shows a low solubility in both hexane and water. This physical property may be partly responsible for the poor contact activity against *Musca domestica, Sitophilus granarius,* and *Periplaneta americana.*

The oxathiolane **20,** with respect to inhibitory action and solubility, behaves as an intermediate between the acetal **10** and mercaptal **21.** Contrary to expectations, laboratory and field trials showed that this preparation was inferior to dioxolane **10.** Metabolic oxidation of the sulfur atom is suggested as a limiting factor of the insecticidal activity of compound **20.**

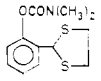
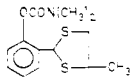
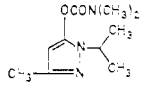
Comparison of Acetals and Mercaptals with Isosteric Carbon Compounds. Of particular interest is the comparison of acetals or mercaptals with the isosteric (cyclo) alkylphenyl *N*-methylcarbamates. Investigations here include, as an example, 2-cyclohexylphenyl *N*-methylcarbamate **(35),** which has been described by Kolbezen *et al.* (1954). The superior inhibitory action of both the dioxanyl compound **25,** and dithiane **33,** shows that these acetals and mercaptals possess a higher intrinsic potential than the isosteric carbon compounds. 2-Cyclohexylphenyl *N*-methylcarbamate shows the same anticholinesterase activity as the dioxolanyl compound **10,** but its activity against insects is considerably lower and equals approximately that of dithiane **33.** *A priori* one would expect the contrary because alkyl radicals should be less susceptible to metabolic attack than acetal and mercaptal groups. Solubility properties might partly explain this behavior.

Open-Chain Acetals and Mercaptals, and *N,N*-Dimethylcarbamates. Most of the open-chain compounds and *N,N*-dimethylcarbamates are of no particular interest. However, a few show a remarkable selective toxicity.

Salicylaldehyde dimethyl acetal *N*-methylcarbamate **(1),** with a low mammalian toxicity, is highly active against adult mosquitoes—e.g., *Aedes aegypti* (L.) and *Anopheles stephensi* Lister. The results of laboratory tests, in which the contact activity against *A. aegypti* was investigated and compared with some known compounds, are listed in Table VIII. This table also contains acute oral toxicities to the rat.

Table IX. Activity against *Aphids*

(% kill after 2-day exposure to a 25- and 12-p.p.m. spray-residue on host plants)

Structure of Carbamate	*Aphis fabae* Scopoli (bean aphid) P.P.M. 25	12	*Aphis pomi* De Geer (apple aphid) P.P.M. 25	12	*Acyrthosiphon pisi* Harris (pea aphid) P.P.M. 25	12	LD_{60}, Oral (MG./KG.) rat
	100	97	100	90	88	67	16
	97	85	96	91	72	50	140
	100	98	100	98	85	42	18[a] (mice)

[a] Ferguson and Alexander (1953).

Further trials will show whether compound **1** will be sufficiently stable under practical conditions.

The *N,N*-dimethylcarbamates **47** and **48** (Table III) are excellent systemic aphicides. This activity greatly depends on the structure of the anionic interactant. Also, alteration of the esteratic interactant (compounds **54, 55**) destroys the activity. Compound **47,** with the highest anticholinesterase activity, is also the best aphicide. But, in general, the correlation between aphicidal activity and inhibitory action in this series of carbamates is poor. The potency of compounds **47** and **48** was demonstrated in tests using low concentrations and several species of aphids (Table IX). Isolan served as a reference compound in these tests.

Conclusions on Structures and Activity Relationships. The relationship between structure and activity of insecticidal *N*-methylcarbamates derived from hydroxybenzaldehyde acetals and mercaptals may be summarized as follows: acetals are more active than isosteric mercaptals; ortho-isomers are more active than meta-isomers and para-isomers are practically inactive; within a homologous series (ortho compounds) the lowest member is the most active; and in the ortho series the five-membered cyclic compounds are the best.

EXPERIMENTAL

Physical, Analytical, and Enzymatic Determinations. The melting points were determined with a Leitz melting point microscope. Above 100° C., melting points of carbamates are influenced by the rate of heating.

The infrared absorption spectra of the compounds were recorded on a Perkin-Elmer Model 121 spectrometer. Sixty Mc NMR spectra were determined in D-chloroform with tetramethylsilane as internal standard using Varian A-60 or A-60 D spectrometers.

The water solubilities were determined using substances which had been finely ground in water at pH 7. The aqueous dispersions were diluted with water until a clear solution was obtained.

The anticholinesterase activities were measured by the automated method of Voss and Geissbühler (1967) and Voss (1968), using human serum cholinesterase (ChE) and bovine erythrocyte cholinesterase (AChE). Acetylthiocholine was used as a substrate. The thiocholine formed by enzymatic hydrolysis reduces 5,5-dithiobis-2-nitrobenzoic acid to the yellow anion of 5-thio-2-nitrobenzoic acid. The amount of the latter compound, which represents a measure of cholinesterase activity, was determined colorimetrically at 420 mμ (Ellman *et al.*, 1961).

Chemical Syntheses. The following describes some of the typical syntheses. The remaining substances listed in Tables I to III may be prepared in an analogous manner.

Salicylaldehyde Dimethyl Acetal. To a mixture of 244 grams of salicylaldehyde, 250 grams of orthoformic acid trimethyl ester, and 500 grams of methanol, was added 1 ml. of concentrated hydrochloric acid. The temperature rose immediately. The solution was kept for 1 hour at 55° C., and was then concentrated to a small volume under reduced pressure. The residue was fractionated at 77° C./0.06 mm., yielding 159 grams of salicylaldehyde dimethyl acetal. According to the IR spectrum, no salicylaldehyde could be detected in the product.

Salicylaldehyde Dimethyl Acetal *N*-Methylcarbamate (**1**). Salicylaldehyde dimethyl acetal (159 grams) and 0.3 gram of 1,4-diazabicyclo[2,2,2]octane were mixed with 400 ml. of toluene. Sixty grams of methyl isocyanate were added in small portions. During the addition, the temperature was kept at 30° to 35° C. by external cooling. The mixture was allowed to stand overnight at 30° C. It was then cooled to 5° C., and the product filtered off to yield 163 grams, m.p. 64–5° C. After recrystallization from benzene-hexane, the product melted at 67–8° C.

2-(1,3-Dioxolan-2-yl)phenol (Salicylaldehyde Ethylene Acetal). A mixture of 100 grams of salicylaldehyde, 116 grams of acetone ethylene ketal, and 50 mg. of *p*-toluene sulfonic acid was heated to boiling and the acetone formed was continuously distilled off using a column 30 cm. in length fitted with Raschig rings. The residue was dissolved in 500 ml. of ether, washed with sodium bicarbonate solution, dried, and concentrated to a small volume. The product was distilled under vacuum. The distillation yielded first mostly unchanged starting material, and then at 100° C./0.02 mm., 64 grams of 2-(1,3-dioxolan-2-yl)phenol, which crystallized immediately. An analytical sample was obtained by recrystallization from cyclohexane, m.p. 69–70° C.

2-(1,3-Dioxolan-2-yl)phenyl *N*-Methylcarbamate (**10**). This compound was prepared from 2-(1,3-dioxolan-2-yl)-phenol in a manner similar to compound **1.** The analytical sample was obtained by recrystallization from isopropyl alcohol and from toluene, m.p. 114–5° C.

IR (CH_2Cl_2) 2.86 (m), 5.71 (s), 6.19 (w), 6.58 (m), 6.72 (m),

6.87 (w), 7.15 (w), 7.42 (w), 8.21 (s), 8.41 (s), 8.91 (m), 9.12 (m), 9.31 (s), 9.64 (w), 9.74 (w), 10.35 (w), 10.60 (m), 10.75μ (w).

NMR ($CDCl_3$) δ 2.83 (d, 3, J = 5 Hz, NHCH_3), 3.9–4.2 (m, 4, OCH_2CH_2O), 5.0–5.3 (b, 1, NHCH$_3$), 6.03 (s, 1, ArCH), 7.0–7.4 (m, 3, ArH), 7.4–7.7 (m, 1, ArH).

Mass spectrum m/e 224, 193, 178, 166, 165, 149, 135, 121, 107, 104, 94, 77, 73, 65, 58, 51, 45, 39, 28.

3-Formyl-phenyl *N*-Methylcarbamate. This compound was prepared from 3-hydroxybenzaldehyde and methyl isocyanate, m.p. 50–3° C. Analysis. Calculated for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.1; H, 5.1; N, 8.0.

2-(cis-4,5-Dimethyl-1,3-dioxolan-2-yl)phenol. A mixture of 120 grams of salicylaldehyde, 93 grams of *meso*-2,3-butanediol, 1 gram of zinc chloride, 1 ml. of concd. phosphoric acid, and 300 ml. of benzene was boiled in a circulating still apparatus with water separator until the formation of water was complete. Subsequently the solution was filtered and the solvent was evaporated. The residue was distilled under vacuum at 90–4° C./0.04 mm. to yield 136 grams of a crystalline mixture of the syn and anti form of 2-(*cis*-4,5-dimethyl-1,3-dioxolan-2-yl) phenol.

2-(*cis*-4,5-Dimethyl-1,3-dioxolan-2-yl)phenyl *N*-Methylcarbamates (**14b**) and (**14c**). 2-(*cis-4,5*-Dimethyl-1,3-dioxolan-2-yl)phenol (97 grams) was reacted with methyl isocyanate (32 grams) in 600 ml. of hexane in the presence of 0.3 gram of 1,4-diazabicyclo[2,2,2]octane for 14 hours at 30° C. The precipitate was collected by filtration and was washed with hexane to afford 124 grams (99% yield) of a white solid, m.p. 82° to 111° C.

Seventy-four grams of this product were twice crystallized from a mixture of ethyl acetate (200 ml.) and hexane (250 ml.) to yield 30 grams of the pure cis-syn stereoisomer **14b,** m.p. 123–5° C.

NMR ($CDCl_3$) δ 1.1–1.4 (m, 6, CHCH_3), 2.85 (d, 3, J = 5 Hz, NHCH_3), 4.0–4.5 (m, 2, CHCH$_3$), 5.0–5.4 (b, 1, NHCH$_3$), 5.99 (s, 1, ArCH), 7.0–7.5 (m, 3, ArH), 7.5–7.8 (m, 1, ArH).

The mother liquor was cooled to −10° C., filtered, and concentrated. The residue was dissolved in a mixture of 100 ml. of cyclohexane and 50 ml. of toluene. After several days at room temperature, the precipitate was filtered and the filtrate was concentrated again. The residual oil (17 grams) slowly crystallized. NMR ($CDCl_3$) δ 6.30 and 5.99 (two s, integrals in the ratio 9 to 1, together 1 H, ArCH). The preparation contains approx. 90% of the cis-anti stereoisomer **14c.**

dl-2-(*trans*-4,5-Dimethyl-1,3-dioxolan-2-yl)phenyl *N*-Methylcarbamate (**14a**). This compound was synthesized by the procedure described for the mixture of stereoisomers **14b** and **14c** except that *dl*-2,3-butanediol was used as a starting material. Purification was effected by recrystallization from a mixture of ethyl acetate and hexane (1 to 3); m.p. 81–3° C.

NMR ($CDCl_3$) δ 1.1–1.5 (m, 6, CHCH_3), 2.78 (d, J = 5 Hz, 3, NHCH_3), 3.5–4.0 (m, 2, CHCH$_3$), 5.1–5.6 (b, 1, NHCH$_3$), 6.13 (s, 1, ArCH), 7.0–7.5 (m, 3, ArH), 7.5–7.8 (m, 1, ArH).

2-(1,3-Oxathiolan-2-yl)phenyl Acetate. A mixture of 283 grams of salicylaldehyde acetate (prepared by the method of Neuberger, 1948), 139 grams of 2-mercaptoethanol, 1 gram of zinc chloride, 1 ml. of 85% phosphoric acid, and 1 liter of benzene was boiled in a circulating still apparatus until 38 ml. of water had separated. The reaction mixture was then washed with 100 ml. of sodium bicarbonate solution, dried with anhydrous sodium sulfate, filtered, and the solvent evaporated *in vacuo*. The residue distilled at 125° C./0.15 mm. to yield 300 grams of the product.

2-(1,3-Oxathiolan-2-yl)phenol. Three hundred grams of 2-(1,3-oxathiolan-2-yl)phenyl acetate was added at 60° C. to a vigorously stirred solution of 132 grams of sodium hydroxide in 600 ml. of water. The temperature rose to 70° C. and the solution became clear. The solution was then cooled to 0° C., and 660 ml. of methylene chloride was added, followed by dropwise addition of 96 grams of concentrated sulfuric acid in 500 ml. of water. The pH of the solution was adjusted to 8, the organic layer was separated, and dried with anhydrous sodium sulfate. The solution was filtered and the solvent was evaporated. The yield of 2-(1,3-oxathiolan-2-yl)-phenol was 231 grams, m.p. 64–73° C. The product was pure enough for further reaction with methyl isocyanate. The analytical sample was obtained by recrystallization from toluene, m.p. 72–4° C.

2-(1,3-Dithiolan-2-yl)phenol. Salicylaldehyde (610 grams) was added dropwise to a vigorously stirred mixture of 470 grams of ethanedithiol, 150 grams of calcium chloride, and 8 ml. of concentrated hydrochloric acid in a nitrogen atmosphere. The reaction mixture was kept near 50° C. by external cooling. After the reaction had ceased, the mixture was stirred at 50° C. for 2 hours more, diluted with 2 liters of toluene and filtered. The solvent was evaporated under reduced pressure and the residue distilled at 142° C./0.07 mm. to yield 934 grams of 2-(1,3-dithiolan-2-yl)phenol, m.p. 48–50° C.

Salicylaldehyde *N,N*-Dimethylcarbamate. Dimethylcarbamoyl chloride (107 grams) was added in small portions at 0° C. to a mixture of 122 grams of salicylaldehyde, 101 grams of triethylamine, and 250 ml. of dry dioxane. The mixture was then refluxed for 14 hours. The triethylamine hydrochloride was removed by filtration and washed with 700 ml. of toluene. The combined filtrates were washed twice with 500 ml. of water, dried with anhydrous sodium sulfate, and the solvent evaporated under reduced pressure. The residue (167 grams) was distilled at 112° C./0.35 mm. to yield 136 grams of salicylaldehyde *N,N*-dimethylcarbamate.

2-(1,3-Dithiolan-2-yl)phenyl *N,N*-Dimethylcarbamate (**47**). This compound was prepared either from salicylaldehyde *N,N*-dimethylcarbamate and ethanedithiol following the method described for 2-(1,3-dithiolan-2-yl)phenol or by condensing the latter with dimethylcarbamoyl chloride in the presence of triethylamine, b.p. 150° C./0.001 mm., n_D^{25} 1.5992.

2-(1,3-Dithiolan-2-yl)phenyl *N*-Methylcarbamate *S*-Oxide (**24**). Forty-seven grams of 60% aqueous peracetic acid was added dropwise at 0–3° C. to 76.5 grams of 2-(1,3-dithiolan-2-yl)phenyl *N*-methylcarbamate suspended in 2 liters of ethyl acetate. The suspended starting material dissolved gradually and the product precipitated. The suspension was stirred for 12 hours at room temperature, and the precipitate filtered. The filtrate was washed with a sodium bicarbonate solution until acid free and dried with anhydrous sodium sulfate. Toluene was added and the mixture was concentrated. The residue was combined with the filtered material and recrystallized from isopropyl alcohol, m.p. 127–130° C.

3-(2-Methyl-1,3-dithiolan-2-yl)phenol. Fifty grams of 3-hydroxyacetophenone was added in small portions at 30° to 50° C. to a mixture of 40 grams of 1,2-ethanedithiol, 5 ml. of concentrated hydrochloric acid, and 15 grams of anhydrous zinc chloride. The mixture was stirred for 1 hour at room temperature and then diluted with 350 ml. of toluene. The organic layer was washed with bicarbonate solution at 0° C.

until acid free, dried with anhydrous sodium sulfate, and filtered. The solvent was evaporated, and the product was distilled at 155° C./0.1 mm. The yield was 51 grams, m.p. 46–50° C.

Formulation and Insect Treatments. Standard screening procedures were used for the evaluation of all compounds. The test animals were bred in the usual manner and no resistant types were used.

For the tests on *Musca domestica L.* (housefly), sugar baits containing 0.037 to 0.33% active ingredient were prepared. Contact activity tests were run in Petri dishes with 0.65 to 130 mg. of active material per sq. meter. *Sitophilus granarius* (L.) (granary weevil) was kept on filter paper containing 1.3 to 130 mg. of active ingredient per sq. meter. All the above tests were evaluated after 2 hours.

Epilachna varivestis Mulsant (Mexican bean beetle) in the fourth larval stage and *Orgyia gonostigma F.* in the third larval stage were kept for five days on *Phaseolus vulgaris* and *Malva sylvestris*, respectively, as host plants. These plants had been previously sprayed with 100- to 800-p.p.m. emulsions prepared from 20% wettable powders or 20% emulsifiable concentrates of the carbamates. *Aphis fabae Scopoli* (bean aphid) on *Vicia faba* was treated with the above emulsions and evaluated after two days.

Periplaneta americana L. (American cockroach) in the fourth and fifth larval stages was kept for 24 hours on filter paper which had been uniformly treated with a dust formulation of the compounds. The concentration range of active material was from 3 to 200 mg. per sq. meter.

Ticks of the species *Rhipicephalus bursa Canestrini and Fanzago* were dipped for 1 minute in aqueous dispersions containing 10 and 100 p.p.m. of active ingredient and were then kept for 14 days in contact with cotton wool which had absorbed the liquid.

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LITERATURE CITED

Bachmann, F., Legge, J. B., paper presented at Symposium on Pesticidal Carbamates, London, April 23, 1968; *J. Sci. Food Agr.* Suppl. **1968**, p. 39.
Baggett, N., Buck, K. W., Foster, A. B., Randall, M. H., Webber, J. M., *J. Chem. Soc.* **1965**, p. 3394.
Bergmann, E. D., Herman, D. F., *J. Appl. Chem. (London)* **3**, 42 (1953).
Berres, C. (to Farbenfabriken Bayer), U. S. Patent **2,903,483** (1959).
Chen, J.-Y. T., Benson, W. R., *J. Assoc. Offic. Anal. Chemists* **49**, 412 (1966).
Crowell, E. P., Powell, W. A., Varsel, Ch. J., *Anal. Chem.* **35**, 184 (1963).
Dakshinamurty, H., Santappa, M., *J. Org. Chem.* **27**, 1840 (1962).
Duff, J. C., *J. Chem. Soc.* **1941**, p. 549.
Ellman, G., Courtney, D., Andres, V., Featherstone, R. M., *Biochem. Pharmacol.* **7**, 88 (1961).
Ferguson, G. R., Alexander, C. C., J. AGR. FOOD CHEM. **1**, 888 (1953).
Foldes, F. F., Van Hees, G., Davis, D. L., Shanor, S. P., *J. Pharmacol. Exptl. Therap.* **122**, 457 (1958).
Gagnaire, D., Robert, J.-B., *Bull. Soc. Chim. France* **1965**, p. 3646.
Geissbühler, H., CIBA, Ltd., Basle, Switzerland, unpublished data, 1967.
Grayson, J. McD., *Pest Control* **34**, 12 (1966).
Groll, H. P. A., Hearne, G. (to Shell Development Co.), U. S. Patent **2,078,534** (1937).
Hadaway, A. B., Barlow, F., *Bull. Entomol. Res.* **56**, 569 (1966).
Hansch, C., Fujita, T., *J. Am. Chem. Soc.* **86**, 1616 (1964).
Kenaga, E. E., *Bull. Entomol. Soc. Am.* **12**, 161 (1966).
Kolbezen, M. J., Metcalf, R. L., Fukuto, T. R., J. AGR. FOOD CHEM. **2**, 864 (1954).
Liggett, L. M., Diehl, H., *Proc. Iowa Acad. Sci.* **52**, 191 (1945).
Metcalf, R. L., Fukuto, T. R., J. AGR. FOOD CHEM. **13**, 220 (1965).
Metcalf, R. L., Fukuto, T. R., J. AGR. FOOD CHEM. **15**, 1022 (1967).
Neuberger, A., *Biochem. J.* **43**, 599 (1948).
Nikles, E., Dittrich, V., Pintér, L. (to CIBA, Ltd.), Belgian Patent **670,630** (April 7, 1966).
O'Brien, R. D., "Insecticides, Action and Metabolism," pp. 22–31, Academic Press, New York and London, 1967.
Pauly, H., v. Buttlar, R., *Ann. Chem.* **343**, 230 (1911).
Roulston, W. J., Wharton, R. H., *Australian Vet. J.* **43**, 129 (1967).
Strube, R. E., Mackellar, F. A., *Rec. Trav. Chim.* **83**, 1191 (1964).
Ulbrich, V., Makes, J., Jurecek, M., *Collection Czech. Chem. Commun.* **29**, 1466 (1964).
Voss, G., Geissbühler, H., Mededelingen Rijksfaculteit Landbouwwetenschappen Gent **32**, 877 (1967).
Voss, G., *Residue Rev.* **23**, 71 (1968).
Weiden, H. J., Moorefield, H. H., *World Rev. Pest Control* **3**, 102 (1964).
Weil, E. D., Schlichting, H. L. (to Hooker Chemical Co.), U. S. Patent **3,349,115** (1967).
Wilson, Ch. E., Lucas, H. J., *J. Am. Chem. Soc.* **58**, 2396 (1936).
Whitmore, W. F., Krems, I. J., *J. Am. Chem. Soc.* **71**, 2427 (1949).

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