Synthesis and in Vitro Anticholinesterase Activity of a Series of Oxime *N*-Methylcarbamates. Structure–Activity Relationships†

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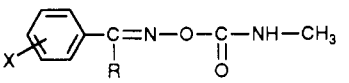
A series of 33 oxime *N*-methylcarbamates $R_1R_2C{=}NOCONHCH_3$ [R_1 and R_2 = H, alkyl, cycloalkyl, haloalkyl, substituted aryl, or groups like $(CH_3)_2C{=}CH$, CF_3COCH_2] was synthesized and tested for potential anticholinesterase activity. Some of those compounds such as the α,α,α-trifluoroacetophenoxime derivatives were studied for their in vitro and in vivo activity; other structures are novel ones. The configuration of those compounds was assigned by spectroscopic methods (NMR, IR, UV). The measure of the residual activity of the acetylcholinesterase (bovine erythrocyte) after the inhibition by those molecules allowed the determination of the dissociation constant K_d and the bimolecular carbamoylation rate constant k_i. To take isomerism into account, the group R_2 is always cis to the carbamic moiety. The structure–activity relationship studies were performed with the usual structural parameters and included commercial compounds such as aldicarb, methomyl, and oxamyl. The correlation equation obtained is $\log k_i = 0.465\Sigma\sigma^* + 0.474\sigma^*_{R2} + 0.407\Sigma\pi + 2.247$ ($n = 35$, $r = 0.862$, $s = 0.74$), where the electronic effect of the groups R_1 and R_2 is depicted by the Taft inductive constant σ^* and the lipophilic contribution by the Hansch parameter π. Specific correlations exhibit the prevailing participation of the group R_2 in the formation of the enzyme–inhibitor complex and in the interactions of the inhibitor with the trimethyl site.

INTRODUCTION

A large number of inhibition studies of acetylcholinesterase (AChE, EC 3.1.1.7) by *N*-methylcarbamates have been performed to rationalize the synthesis of that family of insecticides or to provide basic information about the active site of the acetylcholinesterase. The phenyl *N*-methylcarbamates were widely investigated for the relationship between the physicochemical parameters of the phenyl substituents and the inhibition parameters like the I_{50} values (the molar concentration causing 50% inhibition of enzyme) or the kinetic constants like the dissociation constant K_d, the carbamoylation constant k_2, or the rate of inhibition k_i (Fujita et al., 1977; Kamoshita et al., 1979a,b; Goldblum et al., 1981). In the case of the oxime *N*-methylcarbamates, those relations were done on a small number of molecules as they were related to chemical modifications (Frindinger et al., 1971; Kurtz and Durden, 1987).

Since the phenolic moiety was replaced by an oximic one (Weiden et al., 1965), often a thioaliphatic or a thioalicyclic oxime, the *N*-methylcarbamates of oxime were diversified. The presence of a sulfur atom in this part of the molecule led to the development of that family of compounds (Durden and Weiden, 1969, 1974; Frindinger et al., 1971; Magee and Limpel, 1977; Kurtz et al., 1987), and attempts to have other substitutions on the iminic bond such as a phenyl group did not end in a commercial product (Fukuto et al., 1969; Jones et al., 1972; Rosenfeld and Kilsheimer, 1974). Seeing that the in vitro anticholinesterase activity of the latter compounds has the same range of activity as the sulfur-containing ones, our interest was turned toward the synthesis of a series of benzaldoxime *N*-methylcarbamates substituted on the phenyl ring and α-substituted on the iminic bond



for the study of their inhibition of the acetylcholinesterase from bovine erythrocyte.

The inhibition tests on acetylcholinesterase from different sources such as bovine erythrocyte, brain of insects, or electrical eel organ are a good estimation of the potential insecticidal activity of the *N*-methylcarbamates (Kolbezen et al., 1954; Metcalf et al., 1962; Metcalf and Fukuto, 1967; Iverson and Main, 1969). As they are structural analogues of acetylcholine, the synaptic neuromediator involved in the neurotransmission of the central nervous system of the insect, those compounds lead to the accumulation of the neurotransmitter and perturb the transmission of the nervous influx (Colhoun, 1963).

Previous work gave information on the effects of the structure on the anticholinesterase activity (Fukuto et al., 1969; Jones et al., 1972; Rosenfeld and Kilsheimer, 1974). For a defined R group, electron attracting or donating, the anticholinesterase activity can be modulated by the substituent borne by the phenyl ring. The greatest activity was observed for the series described by Rosenfeld and Kilsheimer (1974) for which R was a trifluoromethyl group. Since the activity could be correlated to a conjugation effect of the iminic bond or to the presence of a specific group on the iminic carbon, a vinylic structure replaced the phenyl group and the trifluoromethyl group was introduced in other parts of the molecule. To harmonize the previous results, the rate constants of the inhibition of the acetylcholinesterase were reexamined and we tried to have a large variability for these parameters by a wide choice of substituents with the aim to develop structure–activity relationships, which have not been undertaken for those compounds as they were for phenyl *N*-methylcarbamates. Since the configuration about the oxime

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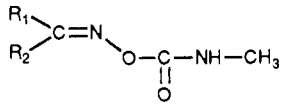
linkage is important, the structure



depicts the configuration where the R_2 group is always cis to the *N*-methylcarbamoyl group.

MATERIALS AND METHODS

The synthesized *N*-methylcarbamates were prepared by the reaction of methyl isocyanate with the corresponding oxime in an anhydrous medium (diethyl ether or benzene) at room temperature and with triethylamine or dibutyltin diacetate used as catalyst. The oximes were obtained by the action of hydroxylamine hydrochloride on commercial ketones or on ketones prepared by several different methods depending on the structure.

Synthesis of Ketones and Oximes. For derivatives **1a–17a** and for derivative **19a**, the ketones were synthesized by the reaction of trifluoroacetic acid or pentafluoropropionic acid with the corresponding Grignard intermediate (Rosenfeld et al., 1973; Rosenfeld and Kilsheimer, 1974). The oximes were obtained by the action of hydroxylamine hydrochloride at 65 °C in a methanol–water mixture (v/v) containing sodium acetate (Lustig, 1961). Usually only one isomer was obtained except for the *o*-methoxy substitution (derivatives **16a** and **17a**).

For the compound **18a**, the ketone was synthesized by following the method of Nes and Burger (1950) and the oxime was obtained after the method of Jones (1948).

In the case of derivatives having a cyclopropyl group (derivatives **20a–25a**), the noncommercial ketones were prepared by the Friedel–Crafts reaction (Close, 1957). The corresponding oxime prepared in an ethanol–pyridine medium is a mixture of the two isomers separable by repeated recrystallization (derivatives **24a** and **25a**).

The compound **29a** was obtained from the corresponding ketone synthesized according to the method of Collet (1897). The oximes **28a** and **29a** prepared according to the method of Korten and Scholl (1901) are both in the cis form (the hydroxyl group is cis to the chloromethyl group).

According to Reid and Calvin (1950), the oximation of trifluoroacetyl ketones led to a trifluoroacetyl monoxime (**30a** and **31a**).

The oximation of the 4-methyl-3-penten-2-one described by Wiemann and Dubois (1961) led to the two isomers **32a** and **33a**, which could be separated by flash chromatography (Still et al., 1978).

The oximes obtained as oils were purified by distillation under reduced pressure. The crystalline ones were recrystallized from a suitable solvent mixture. Isomeric purity of the obtained oxime was checked by thin-layer chromatography. All of the corresponding carbamates were crystalline products; their recrystallization afforded a single isomer in good yields (Table II).

Spectroscopic Determinations. ^1H NMR spectra were recorded on a 80-MHz Bruker spectrometer using deuteriated DMSO as solvent for the oximes and deuteriated acetone for the final carbamates. A ^{13}C NMR study was undertaken in deuteriated DMSO on a 200-MHz Bruker spectrometer for the compounds **30a** and **31a** to confirm the oximation site. The infrared spectra of the *N*-methylcarbamates in KBr pellets were obtained on a Perkin-Elmer 683 spectrophotometer. The UV spectra of the oximes and carbamates were carried out in ethanol on a Cary 210 spectrophotometer.

Elemental Analyses. The elemental analyses of the carbamates were done by the analytical service of the Centre National de la Recherche Scientifique.

Standard Compounds. The following pesticides were purchased from Dr. Ehrenstorfer GmbH: aldicarb or 2-methyl-2-(methylthio)propionaldehyde *O*-(methylcarbamoyl)oxime, *E*-isomer [R_1 = $C(CH_3)_2SCH_3$, R_2 = H]; methomyl or *S*-methyl *N*-[(methylcarbamoyl)oxy]thioacetimidate, *Z*-isomer [R_1 = CH_3, R_2 = SCH_3]; oxamyl or *S*-methyl *N'*,*N'*-dimethyl-*N*-[(methylcarbamoyl)oxy]-1-thiooxamimidate, *Z*-isomer [R_1 = $CON(CH_3)_2$, R_2 = SCH_3] (products of 99.9% purity).

Acetylcholinesterase Inhibition. The acetylcholinesterase purchased from Sigma Chemical Co. is a purified bovine erythrocyte XII-S esterase having an activity of 0.44 unit/mg of solid for the first lot and 0.5 unit/mg for the second one. The acetylcholine hydrochloride used as substrate came from the same supplier. The solutions of inhibitors were prepared in ethanol just before use, and the final concentration of ethanol in the enzymatic medium did not exceed 2%. The enzyme (7.5 units/mL) and the substrate (0.01 M) were dissolved in a 10 mM phosphate buffer, pH 7.6, containing 0.1 M NaCl. The residual enzyme activity was determined by the pH-stat method previously used (Vilarem et al., 1989). The reaction rate is followed by an automatic titration device Radiometer pHM 64 coupled with a TTT 60 titrator and an ABU 13 autoburette delivering a carbonate-free solution of sodium hydroxide (1.85×10^{-2} N). The incubation time with the inhibitors was 3 min, and the reaction temperature was held at 25 ± 0.2 °C.

Taft Parameter σ^* Determined Values. Some values of the Taft inductive constant σ^* could not be found in the literature and were calculated on the basis of the following structure–reactivity relationships: $\sigma^*_{CH_2R} = 0.36\ \sigma^*_R$ for the CF_3CO-CH_2 group (Perrin, 1980) and $\sigma^*_{CR_1R_2R_3} = \sum_i \sigma^*_{CH_2R_i}$ for the CH_3S-$(CH_3)_2$ group (Leffler and Grunwald, 1963). The $\sigma^*_{C_2F_5}$ value was determined from a ^1H NMR study on the variation of the chemical shift of the hydroxyl proton vs the electronic effect on the iminic bond for a series of α-substituted benzaldoximes, for which the following relation was found:

$$\Delta(\delta_{OH}) = 0.88 \sum_{i=1,2} \sigma^*_{R_i} - 1.14$$

Structure–Activity Relationships. The structure–activity relationships were calculated with a Hewlett-Packard HP 9845B computer and its statistical library HP 98820A.

RESULTS AND DISCUSSION

Structure of the Oximes. The physicochemical and spectroscopic characteristics of the synthesized oximes are collected in Table I: melting or boiling point, ^1H NMR chemical shift of the proton of the hydroxyl group, and UV properties of those molecules. Since the groups R_1 and R_2 are different, the proton of the hydroxyl group resonates in a wide field range: between 8.2 and 13.4 ppm. The variations of the chemical shift observed between two isomers are small and differ from one R group to another: $\Delta\delta_{OH}$ = 0.10 when R is CF_3 (compounds **16a** and **17a**), $\Delta\delta_{OH}$ = 0.48 when R is a cyclopropyl (compounds **24a** and **25a**) and $\Delta\delta_{OH}$ = 0.29 for R = $(CH_3)_2C{=}CH$ (compounds **32a** and **33a**).

The characteristics of oxime **1a** are in agreement with those given by Guillot-Edelheit et al. (1978) for the *Z*-isomer. For the other compounds (compounds **2a–17a**) the configuration cannot be determined by the chemical shift of the proton of the hydroxyl group since the variation of $\Delta\delta_{OH}$ due to the substitution of the phenyl group ($\Delta\delta_{OH}$ = 0.44) was larger than that due to the isomer configuration ($\Delta\delta_{OH}$ = 0.1).

In the series where R is a cyclopropyl group, the configuration can be assigned, since for the isomer **24a** the proton of the hydroxyl group resonates at lower fields (δ_{OH} = 10.88) than for the other isomer **25a** in agreement with a phenyl group trans to the hydroxyl group (Karabatsos and Taller, 1968). Then again, the $H_{1\alpha}$ proton of the cyclopropyl group resonates at 2.13 ppm for molecule **24a**, while it is found at 1.65 ppm for molecule **25a** in agreement with a cyclopropyl group cis to the hydroxyl group. In molecule **24a**, the $H_{1\alpha}$ proton is more deshielded since this proton is close to lone electron pairs of the hydroxyl group (Karabatsos and Taller, 1968; Berlin and Rengaraju, 1971). Since the derivatives **20a–23a** exhibit the same signal at 2.13 ppm corresponding to this $H_{1\alpha}$ proton, the *E*-configuration was attributed to the series of compounds **20a–**

Table I. Physicochemical and Spectral Characteristics of Oximes R_1R_2C=NOH

			mp, °C, or bp, °C/mmHg			UV (Et OH)	
compd	R_1	R_2	obsd	lit.	^{1}H NMR δ_{OH}	λ, nm	ε
1a	C_6H_5	CF_3	84	84[a]	13.37	235/235[a]	8320/8000[a]
2a	4-FC_6H_4	CF_3	oil[b]		12.83	236	5080
3a	CF_3	4-ClC_6H_4	oil[b]		13.00	242	9760
4a	4-$CH_3C_6H_4$	CF_3	62		12.60	242.5	9536
5a	4-$CH_3OC_6H_4$	CF_3	105		12.60	259.5	10608
6a	CF_3	4-$C_2H_5OC_6H_4$	70		12.56	261	11936
7a	CF_3	4-$C_6H_5OC_6H_4$	105–8		12.75	257	14000
8a	CF_3	4-$CF_3C_6H_4$	oil[b]		12.81	232	6000
9a	3-FC_6H_4	CF_3	91/1.5 mmHg		12.92	233	6456
10a	3-ClC_6H_4	CF_3	130/1 mmHg		12.95	235	6080
11a	3-$CH_3C_6H_4$	CF_3	oil[b]		12.64	236	5732
12a	CF_3	3-$CH_3OC_6H_4$	120/0.5 mmHg		12.70	238	4264
13a	2-FC_6H_4	CF_3	oil[b]		12.88		
14a	2-ClC_6H_4	CF_3	79/5 mmHg		12.89	265	560
15a	2-$CH_3C_6H_4$	CF_3	oil[b]		12.97	224	4560
16a	2-$CH_3OC_6H_4$	CF_3	75		12.75	280 240.5	3440 4080
17a	CF_3	2-$CH_3OC_6H_4$	98		12.85	280 240	3392 4576
18a	CF_3	$C_6H_5CH_2$	40–1	40–2[c]	12.56	252	290
19a	C_2F_5	C_6H_5	75–7		13.05	232.5	7168
20a	C_6H_5	cyclopropyl	91–3	90–2[d]	10.97	234	6280
21a	4-ClC_6H_4	cyclopropyl	101		11.13	248	6528
22a	4-$CH_3OC_6H_4$	cyclopropyl	134–5		10.86	249.5	10368
23a	4-$C_2H_5OC_6H_4$	cyclopropyl	127–9		10.79	256	6768
24a	4-$CH_3C_6H_4$	cyclopropyl	68–73		10.88	241.5	7472
25a	cyclopropyl	4-$CH_3C_6H_4$	101–3		10.40	234	8752
26a	C_6H_5	H	34		11.42	252	17600
27a	C_6H_5	CH_3	57–8	58.5[a]	11.26	244	13120
28a	C_6H_5	CH_2Cl	87	88–9[e]	12.02	250.5	12592
29a	4-ClC_6H_4	CH_2Cl	100–4		12.15	257	15392
30a	CH_2COCF_3	C_6H_5	144	143–4[f]	8.61	252	14440
31a	CH_2COCF_3	CH_3	87	86–7[f]	8.21	285	8
32a	$(CH_3)_2C$=CH	CH_3	oil[b]		10.58	232	9068
33a	CH_3	$(CH_3)_2C$=CH	49	50–1[g]	10.29		

[a] Guillot-Edelheit et al. (1978). [b] Pure after extraction, was not distilled. [c] Nes and Burger (1950). [d] Marshall and Perkin (1891). [e] Korten and Scholl (1901). [f] Reid and Calvin (1950). [g] Belly et al. (1972).

24a, the compound **25a** being the only *Z*-isomer. The UV spectrum of the compound **25a** presents an absorption maximum at 234 nm as the isomer **24a** has it maximum at 241 nm. The assigned configuration agree with the UV characteristics mentioned by Karabatsos and Hsi (1967) for a series of benzaldoximes.

For the compounds **30a** and **31a**, previously synthesized by Reid and Calvin (1950), the oximation occurs on the carbonyl group in the α-position to the R group (methyl or phenyl) and not on the carbonyl in the α-position to the trifluoromethyl group. The ^{1}H NMR study shows that the protons of the hydroxyl group resonate at higher field (8.61 and 8.21 ppm) when they had to resonate at about 12 ppm if the oxime was obtained in the α-position to the trifluoromethyl group. The oximation site is also confirmed by a ^{13}C NMR study. The signal of the carbonyl α to the trifluoromethyl group is a quartet at 103 ppm, corresponding to the shielding of the trifluoromethyl group and the nuclear spin coupling of the ^{13}C atom with the fluorine atoms. For compound **31a**, the carbon of the methyl group is shielded (12.2 ppm) and that of the methylene is deshielded (δ_{CH_2} = 42.1), implying that the trans configuration can be assigned for the CF_3COCH_2 group according to the method of Hawkes et al. (1974). This group has the same position in compound **30a**, since the signal of the carbon of the methylene group is located at the same field (δ_{CH_2} = 45.6).

Belly et al. (1972) assigned the *Z*-configuration to their crystalline compound (compound **33a** in our study), which is in agreement with the observed chemical shift of the proton borne by the hydroxyl group (δ_{OH} = 10.29) as the other isomer, the liquid one, has a proton resonating at lower fields (δ_{OH} = 10.58). The study of the chemical shift for the proton on the vinyl part confirms this assignment since the values obtained (δ_H = 5.62 for compound **32a** and δ_H = 6.00 for compound **33a**) correspond to the configurations trans–trans and trans–cis determined by Buczkowski and Plenkiewicz (1970) for those oximes, their trans–cis derivative being the *Z*-isomer.

Structure of the Carbamates. The melting points, elemental analyses, UV and IR spectrophotometric characteristics, and the configurations of the *N*-methylcarbamates are reported in Table II. The expected structures of the synthesized products are corroborated by the results of the elemental analyses and the physicochemical data. When the configuration of the oxime is *E*, this configuration is not changed by the carbamoylation when anhydrous ether and triethylamine are used for the reaction (Kurtz et al., 1987), but if the configuration is different for the starting oxime, a mixture of the isomers is obtained, one of them being predominant. For the differentiation of the isomers, the IR spectroscopy gave the most determinative data.

For the compounds **24b** and **25b**, the *E*-isomer is characterized by two bands, one at 3255 cm^{-1} corresponding to a bonded stretching vibration of the NH bond as the other one at 1545 cm^{-1} corresponds to the bending of the NH (amide II band). The *Z*-isomers have the same bands at 3380 and 1500 cm^{-1}, respectively. These frequencies retained for the vibrations of the NH bond are in agreement with the results of Bellamy (1954) and those of Katritzky and Jones (1960). The same bands (3255 and 1545 cm^{-1}) are found again for compounds **20b–23b**,

Table II. Physicochemical and Spectral Characteristics of Oxime *N*-Methylcarbamates $R_1R_2C{=}NOC(=O)NHCH_3$

					elemental analyses									
		mp, °C			calcd			found			IR (KBr)		UV (EtOH)	
compd	isomer	obsd	lit.	yield,[c] %	C	H	N	C	H	N	NH	NHCO	λ, nm[d]	ε
1b	*Z*	101	96–8[a]	75	48.79	3.68	11.38	49.18	3.65	11.31	3295	1545	240.5	7240
2b	*Z*	106	80–2.5[a]	60	45.47	3.05	10.60	46.11	3.20	10.84	3285	1550	245	6976
3b	*E*	104	74–6[a]	86	42.80	2.87	9.98	43.46	2.87	10.20	3360	1500	248.5	9960
4b	*Z*	86	97–9[a]	76	50.77	4.26	10.77	50.76	4.26	10.67	3320	1540	254.5	8640
5b	*Z*	85–8	85–7[a]	75	47.83	4.01	10.14	47.84	4.05	10.43	3300	1550	272.5	10320
6b	*E*	95		81	49.66	4.51	9.65	49.69	4.53	9.72	3330	1510	280	10880
7b	*E*	56–8		86	56.81	3.87	8.28	56.92	4.08	8.64	3330	1505	269.5	12928
8b	*E*	96–9		68	42.05	2.57	8.92	42.42	2.73	9.34	3340	1510	229	7600
9b	*Z*	105–6	102–4[a]	79	45.47	3.05	10.60	45.63	2.94	10.52	3290	1540	237	6536
10b	*Z*	102–4		87	42.80	2.87	9.98	43.09	2.88	10.28	3310	1540	237	6440
11b	*Z*	71–3	66–9[a]	81	50.77	4.26	10.77	51.46	4.28	10.64	3290	1540	244	6080
12b	*E*	85–6	81–3[a]	86	47.83	4.01	10.14	48.59	3.96	10.02	3355	1510	245[sh]	4600
13b	*Z*	86–8	76–81[a]	45	45.47	3.05	10.60	44.93	2.96	10.85	3280	1545	237[sh]	4920
14b	*Z*	70	oil[a]	84	42.80	2.87	9.98	42.82	2.99	10.06	3285	1540	231[sh]	4800
15b	*Z*	102	oil[a]	90	50.77	4.26	10.77	51.02	4.33	10.74	3310	1540	223[sh]	4560
16b	*Z*	58–9		90	47.83	4.01	10.14	48.00	4.29	10.80	3330	1530	282	3152
17b	*E*	82–3	85–7[a]	83	47.83	4.01	10.14	47.91	4.22	10.74	3370	1505	289.5	2800
18b	*E*	35		89	50.77	4.26	10.77	50.93	4.33	10.68	3350	1510	258	410
19b	*E*	69–70		83	44.61	3.06	9.46	44.85	3.16	9.44	3370	1500	241	6080
20b	*E*	68		76	66.04	6.47	12.83	66.11	6.43	12.94	3255	1545	220[sh]	8590
21b	*E*	153		92	57.03	5.19	11.09	57.31	5.24	11.02	3255	1540	230	9760
22b	*E*	97–9		89	62.89	6.50	11.28	62.70	6.61	11.45	3260	1545	260	12200
23b	*E*	98		84	64.10	6.92	10.68	64.00	7.10	10.62	3260	1540	260.5	16200
24b	*E*	115–20		74	67.22	6.94	12.06	66.57	6.96	12.10	3255	1545	231.5	9664
25b	*Z*	135–7		77	67.22	6.94	12.06	67.22	6.96	11.98	3380	1500	232	9152
26b	*E*	98	94–6[b]	75	60.66	5.66	15.72	60.52	5.70	15.78	3375	1520	255.5	19880
27b	*E*	97	93–7[b]	77	62.49	6.29	14.57	62.21	6.45	14.81	3350	1495	245	14512
28b	*Z*	120		95	52.99	4.89	12.36	53.43	5.24	12.04	3350	1500	256	12080
29b	*Z*	138		72	46.00	3.86	10.73	46.05	4.19	10.78	3370	1500	262.5	15728
30b	*Z*	109		92	50.01	3.85	9.72	50.06	4.06	10.01	3350	1550	250	14424
31b	*E*	118		45	37.18	4.01	12.39	37.40	4.02	12.37	3375	1530	294	4.5
32b	*E*	45–6		80	56.45	8.29	16.46	56.69	8.43	16.46	3370	1505	239	11080
33b	*Z*	oil		95	56.45	8.29	16.46	56.34	8.32	16.51			235	9440

[a] Rosenfeld and Kilsheimer (1974). [b] Fukuto et al. (1969). [c] Yield after purification. [d] sh, shoulder.

confirming the *E*-configuration assigned previously by the ^1H NMR study of the oximes.

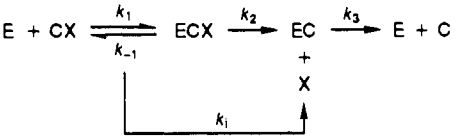
In the series of the *N*-methylcarbamates of substituted trifluoroacetophenoxime, the configuration can be determined by examining the shift in these NH bands. The compound **1b**, synthesized from the oxime **1a** which has the trifluoromethyl group in the cis position, exhibits a band at 3295 cm^{-1} and another one at 1545 cm^{-1}. Then, the trans isomers can be characterized by the increase of the frequency of the first band at 3370 cm^{-1} and the decrease of the frequency of the second band at 1500 cm^{-1}. So, the *E*-configuration was assigned to the compounds **3b**, **6b**, **7b**, **8b**, **12b**, and **17b**. In the same manner, the compounds **18b** (benzyl, CF_3) and **19b** (phenyl, C_2F_5) had an *E*-configuration.

The spectral characteristics of the *N*-methylcarbamate of acetophenoxime **27b** (3350 and 1495 cm^{-1}) allow the assignment of the configuration for its α-chloro analogues **28b** and **29b**. Both will have the chloromethyl group in the cis position to the methylcarbamoyloxy part and the *Z*-configuration can be retained.

Structure–Activity Relationships. The competitive inhibition of the acetylcholinesterase follows the scheme proposed by Hastings et al. (1970), where the different kinetic parameters of this inhibition are apparent (Scheme I).

The equilibrium dissociation constant K_d, the carbamoylation rate constant k_2, and the bimolecular carbamoylation rate constant k_i were determined for all 33 synthesized molecules and for 3 commercial products (aldicarb, methomyl, and oxamyl) by following the residual activity of the enzyme incubated during 3 min with each inhibitor and after the addition of its substrate (acetylcholine) by the pH-stat method used by Nishioka et al. (1976). Table III reports the different values observed for the inhibition parameters which cover a wide range of activity, about 5 logarithmic units for the dissociation constant K_d [from 3.1×10^{-3} M (**26b**) to 2.6×10^{-8} M (**13b**)] or for the bimolecular carbamoylation rate constant k_i [from 1.38×10^2 M^{-1} min^{-1} (**26b**) to 1.78×10^7 M^{-1} min^{-1} (**13b**)] and gives the structural parameters used in the structure–activity correlations.

Scheme I. AChE Inhibition[a]



[a] E, acetylcholinesterase; CX, carbamate; ECX, reversible complex; EC, carbamoylated enzyme; K_d, k_1/k_{-1} equilibrium dissociation constant; k_2, carbamoylation rate constant; k_i, bimolecular carbamoylation rate constant.

For the series studied herein, all of the compounds gave a competitive inhibition, and the anticholinesterase activity expressed by log $(1/K_d)$ and by log k_i ($k_i = k_2/K_d$) was investigated with the different structural parameters usually used. The electronic effect due to the R_1 and R_2 groups (R_1 being always trans to the carbamic moiety of the molecule) is analyzed with the Taft inductive constant σ^* of each group or with the global effect of the two groups expressed by their sum $\sum\sigma^*$. The partial electronic effect due to the ring substitution was expressed by the usual Hammett parameter σ or by the parameter of Swain and Lupton, $\mathcal{F}$. The steric effect is estimated by the van der Waals volume V_w of the oximic moiety of the molecule, calculated after Moriguchi et al. (1976, 1977), or by its

Table III. Kinetic Constants for Bovine Erythrocyte AChE: Inhibition and Structural Parameters of Oxime N-Methylcarbamates

compd	K_d, M	k_2, min^{-1}	k_i, M^{-1} min^{-1}	$\sigma^*_{R_1}$	$\sigma^*_{R_2}$	$\Sigma\sigma^*$	π_{R_1}	π_{R_2}	$\Sigma\pi$
1b	5.02×10^{-7}	1.15	2.28×10^{6}	0.60	2.85	3.45	1.96	0.88	2.84
2b	1.29×10^{-5}	2.43	1.89×10^{5}	0.62	2.85	3.47	2.10	0.88	2.98
3b	6.53×10^{-7}	0.69	1.06×10^{6}	2.85	0.75	3.60	0.88	2.67	3.55
4b	7.90×10^{-7}	0.93	1.18×10^{6}	0.46	2.85	3.31	2.52	0.88	3.40
5b	5.04×10^{-7}	0.76	1.50×10^{6}	0.36	2.85	3.21	1.94	0.88	2.82
6b	2.50×10^{-5}	3.08	1.23×10^{5}	2.85	0.31	3.16	0.88	2.34	3.22
7b	5.66×10^{-6}	0.93	1.65×10^{5}	2.85	0.35	3.20	0.88	4.04	4.92
8b	8.38×10^{-7}	0.90	1.07×10^{6}	2.85	0.96	3.81	0.88	2.84	3.72
9b	7.28×10^{-7}	0.67	9.20×10^{5}	0.82	2.85	3.67	2.10	0.88	2.98
10b	8.99×10^{-7}	0.78	8.64×10^{5}	0.85	2.85	3.70	2.67	0.88	3.55
11b	5.48×10^{-7}	1.33	2.42×10^{6}	0.48	2.85	3.33	2.52	0.88	3.40
12b	1.38×10^{-6}	1.16	8.40×10^{5}	2.85	0.66	3.51	0.88	1.94	2.82
13b	2.59×10^{-8}	0.46	1.78×10^{7}	0.06	2.85	2.91	2.10	0.88	2.98
14b	6.76×10^{-8}	0.61	8.99×10^{6}	0.13	2.85	2.98	2.67	0.88	3.55
15b	4.69×10^{-8}	0.60	1.29×10^{7}	−0.03	2.85	2.82	2.52	0.88	3.40
16b	2.20×10^{-7}	1.98	9.02×10^{6}	0.00	2.85	2.85	1.94	0.88	2.82
17b	4.02×10^{-7}	0.79	1.98×10^{6}	2.85	0.00	2.85	0.88	1.94	2.82
18b	9.67×10^{-7}	1.33	1.38×10^{5}	2.85	0.22	3.07	0.88	2.01	2.89
19b	6.05×10^{-6}	1.47	2.43×10^{5}	2.56	0.60	3.16	1.68	1.96	3.64
20b	8.07×10^{-5}	1.32	1.64×10^{4}	0.60	−0.15	0.45	1.96	1.14	3.10
21b	3.49×10^{-5}	0.66	1.89×10^{4}	0.75	−0.15	0.60	2.67	1.14	3.81
22b	5.22×10^{-4}	0.78	1.49×10^{3}	0.36	−0.15	0.21	1.94	1.14	3.08
23b	8.44×10^{-5}	0.56	6.60×10^{3}	0.31	−0.15	0.16	2.34	1.14	3.48
24b	6.03×10^{-5}	0.54	8.96×10^{3}	0.46	−0.15	0.31	2.52	1.14	3.66
25b	7.03×10^{-5}	1.02	1.46×10^{4}	−0.15	0.46	0.31	1.14	2.52	3.66
26b	3.13×10^{-3}	0.43	1.38×10^{2}	0.60	0.49	1.09	1.96	0.00	1.96
27b	3.39×10^{-3}	0.53	1.56×10^{2}	0.60	0.00	0.60	1.96	0.56	2.52
28b	2.22×10^{-4}	1.15	5.17×10^{3}	0.60	1.05	1.65	1.96	0.17	2.13
29b	1.77×10^{-5}	1.17	6.59×10^{4}	0.75	1.05	1.80	2.67	0.17	2.84
30b	4.95×10^{-4}	1.16	2.35×10^{3}	1.33	0.60	1.93	0.58	1.96	2.54
31b	4.37×10^{-4}	0.52	1.17×10^{3}	1.33	0.00	1.33	0.58	0.56	1.14
32b	3.46×10^{-4}	0.87	2.51×10^{3}	0.19	0.00	0.19	1.74	0.56	2.30
33b	1.03×10^{-4}	1.43	1.38×10^{4}	0.00	0.19	0.19	0.56	1.74	2.30
methomyl	1.74×10^{-5}	1.06	6.10×10^{4}	0.00	1.47	1.47	0.56	0.61	1.17
oxamyl	6.73×10^{-6}	1.02	1.52×10^{5}		1.47		−0.83	0.61	−0.22
aldicarb	1.40×10^{-4}	1.66	1.19×10^{4}	0.33	0.49	0.82	1.71	0.00	1.71

square value V_W^2. The Taft steric parameter E_S was used for analyzing the steric effect due to the ring substitution. The role of the lipophilicity for the substances was taken into account either separately by the Hansch parameter π for each group R_1 or R_2 or in bulk by the sum of the contribution of each group borne by the oximic carbon ($\sum\pi = \pi_{R_1} + \pi_{R_2}$) as the only source of structural variations is the oximic moiety. In the same way, the effects due to the polarizability of the molecule were estimated by the molar refractivity constant MR or its square value $(MR)^2$ for the oximic part. The values employed for the different parameters (σ^*, σ, $\mathcal{F}$, E_s, π, MR) are those reported by Hansch and Leo (1979) or were estimated as mentioned before.

Enzyme inhibition data for the 33 compounds and 2 commercial products (aldicarb and methomyl) were regressed stepwise against the physicochemical parameters previously discussed to obtain an equation of the general expression

$$\log (BR) = \rho^* \sum \sigma^* + \rho^*_{R_2} \sigma^*_{R_2} + a \sum \pi + \text{const}$$

where the biological response is an enzymatic parameter (K_d or k_i) and where ρ^* is the susceptibility constant for the general inductive effect through the iminic bond, $\rho^*_{R_2}$ is the susceptibility constant for the specific inductive effect due to the group R_2, and a is the coefficient of lipophilicity. The values of these susceptibility constants and the correlation coefficients are given in Table IV.

No correlation could be obtained with the carbamoylation constant k_2, showing that the anticholinesterase activity depends mostly on the ability of the inhibitor to be fixed on the enzyme. For the phenyl N-methylcarbamates, Hetnarski and O'Brien (1975) observed the same

Table IV. Correlation of Kinetic Constants Log $(1/K_d)$ or Log k_i vs Structural Parameters $\Sigma\sigma^*$, $\sigma^*_{R_2}$, and $\Sigma\pi$

kinetic constant	$\Sigma\sigma^*$	$\sigma^*_{R_2}$	$\Sigma\pi$	const	n	r	s	F	eq
log $1/K_d$	0.796			3.311	35	0.765	0.90	46.54	1
log k_i	0.829			3.215	35	0.788	0.87	53.97	2
log $1/K_d$	0.523	0.449		3.383	35	0.822	0.81	33.23	3
log k_i	0.571	0.424		3.283	35	0.836	0.79	37.18	4
log $1/K_d$	0.408	0.503	0.442	2.259	35	0.853	0.75	27.51	5
log k_i	0.465	0.474	0.407	2.247	35	0.862	0.74	29.75	6

dependence on the dissociation constant K_d. The carbamoylation constant k_2 is strongly sensitive to changes in affinity and a close fit of the inhibitor in the receptor site improves the effectiveness of the carbamoylation step. This step can be taken into account by the bimolecular constant k_i. The slight increase of the correlation coefficient r for the regressions with log k_i is in agreement with Hetnarski and O'Brien's proposal.

Though the sum of the electronic contribution of the groups R_1 and R_2 on the iminic carbon ($\sum\sigma^*$) is the first parameter retained, no correlation includes $\sigma^*_{R_1}$ and $\sigma^*_{R_2}$ independently. If one of the groups has a high σ^* value, i.e., the case of electron-attracting groups, its weight in the parameter $\sum\sigma^*$ is increased. The other group will just modulate the electronic influence. Since the electronic parameter $\sum\sigma^*$ is prevalent, the groups R_1 and R_2 are directly and jointly in interaction with the carbamoylation reaction site through the iminic bond. If the observed value ($\rho^* = 0.83$, eq 2) is lower than the values observed by Jarv et al. (1976) for a series of β-substituted alkyl acetates ($\rho^* = 2.8$) or by Fujita et al. (1977) for a series of phenyl N-methylcarbamates ($\rho^0 = 2.2$) in their structure–activity correlations on the AChE inhibition, this value is

close to that which can be calculated (ρ^* calculated = 0.88) when the attenuation ratio τ of the electronic effect through the iminic bond is taken in account (τ = 0.4; Mrlina and Calmon, 1980). Equation 4 shows that the group R_2 has a specific electronic contribution due to its particular position (cis to the carbamic moiety) which is structurally comparable to the meta position for the substituted phenyl *N*-methylcarbamates. Then again, the observed value $\rho^*_{R_2}$ is close to that estimated from the ρ_m determined by Nishioka et al. (1977) (ρ_m = 0.83; $\rho^*_{R_2}$ estimated to be 0.33 if τ = 0.4). Our results confirm that there is an analogy between the oxime *N*-methylcarbamates and the phenyl *N*-methylcarbamates where the oxime *N*-methylcarbamates fulfill the structural criteria retained by Metcalf and Fukuto (1965) for a good binding to the acetylcholinesterase. Likewise, the lipophilicity of those molecules is directly correlated by the sum of the Hansch parameter of the groups R_1 and R_2 (eqs 5 and 6). The value of the coefficient of lipophilicity is inferior to those observed by Jarv et al. (a = 1.64) or by Nishioka et al. (a = 1.40) but is close to that observed by the latter authors for the para-substituted phenyl *N*-methylcarbamates (a = 0.23). The desolvation due to the oxime *N*-methylcarbamates is then less effective as one of their phenyl analogues.

A study of the specific contribution of the group R_2 was undertaken by using parameters related to that group only since it appears independently in eqs 3–6 and since the constant of dissociation K_d between two isomers (**16b, 17b**; **24b, 25b**; **32b, 33b**) is varying in a small range (1–5.5) as noticed by Corkins et al. (1980). For 36 compounds, oxamyl included, the relations are

$$\log (1/K_d) = 0.949\sigma^*_{R_2} + 0.639\pi_{R_2} + 3.134 \quad (7)$$

$n = 36$ $r = 0.831$ $s = 0.78$ $F_{2,33} = 36.9$

$$\log k_i = 0.969\sigma^*_{R_2} + 0.688\pi_{R_2} + 3.026 \quad (8)$$

$n = 36$ $r = 0.844$ $s = 0.76$ $F_{2,33} = 40.92$

Those equations are similar and express that the group R_2 is determinant for the binding of the oxime *N*-methylcarbamates on the active site and for the anticholinesterase activity. The value of the specific susceptibility constant $\rho^*_{R_2}$ close to unity indicates that there is a strong electronic interaction between the R_2 group and the "anionic" subsite as in the case of the phenyl *N*-methylcarbamates. The coefficient of lipophilicity has a greater value than in eqs 5 and 6 (Table IV), and its value is close to that observed for the series of *N*-methylcarbamates of meta-substituted phenyl (a = 0.87; Hansch and Deutsch, 1966). The introduction of other substituent parameters like the steric one or the polarizability did not improve these correlations. Then the different specific interactions known for the structural analogues of acetylcholine or for the phenyl *N*-methylcarbamates cannot be taken in consideration for that series. In their description of the trimethyl site of the acetylcholinesterase, Hasan et al. (1980) mentioned that the low dielectric constant of this part of the active site gives a high sensitivity of the enzyme toward the electron-attracting groups and that the hydrophobic interactions allow the exclusion of the molecules of water from the inner part of the site. Equations 7 and 8 are in agreement with those proposals and corroborate the prevalent participation of the group cis to the carbamic moiety in the enzyme inhibitor association.

For the series of the *N*-methylcarbamates of substituted α,α,α-trifluoroacetophenoximes, eqs 9–11 obtained with another set of substituent parameters (Table V) reveal the complementary requirements for the groups R_1 and R_2 in view of a good anticholinesterase activity.

Table V. Supplemental Structural Parameters for the *O*-(Methylcarbamoyl)-α,α,α-trifluoroacetophenoximes

	compd					
	3b	**6b**	**7b**	**8b**	**12b**	**17b**
V^a	1.452	1.676	2.062	1.579	1.522	1.522
$MR_{R_2}{}^b$	3.036	3.639	5.253	2.935	3.174	3.174

[a] van der Waals' volume of the oximic moiety $R_1R_2C{=}N$ (10^2 Å^3). [b] Molar refractivity of substituted phenyl group represented by a tenth of the usually reported value (Hansch and Leo, 1979).

$$Z\text{-isomers: } \log k_i = -1.605\sigma^*_{R_1} + 7.038 \quad (9)$$

$n = 11$ $r = 0.843$ $s = 0.34$ $F_{1,9} = 22.16$

$$E\text{-isomers: } \log k_i = -1.635V_W + 8.438 \quad (10)$$

$n = 6$ $r = 0.740$ $s = 0.37$

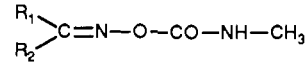
$$E\text{-isomers: } \log k_i = -0.405MR_{R_2} + 7.195 \quad (11)$$

$n = 6$ $r = 0.730$ $s = 0.37$

While the inhibitory activity of the *Z*-isomers depends on the electronic effect, in contrast, the activity of the *E*-isomers depends on the volume of the oximic part and of the polarizability of the R_2 groups. The change in the sign of the electronic susceptibility constant for the specific effect due to the group R_1 ($\rho^*_{R_1}$) points out that the electron-attracting groups are less favorable for that position on the iminic bond. The electron-attracting CF_3 group increases the electron deficiency on the iminic bond and thus reduces the stability of the compound. Thus, the groups having a low or a negative σ^* will have a better anticholinesterase activity; that is the case of the ortho-substituted phenyl derivatives which were put forward by Rosenfeld and Kilsheimer (1974). For the series of the *E*-isomers, the phenyl group is cis to the carbamic moiety and then it will be entirely lodged in the trimethyl site. The larger the substituent, the less the enzyme–inhibitor association is favorable. Elsewhere, the interaction of R_2 (a substituted phenyl in that case) with the electric charge of the anionic subsite is sensitive to the polarizability of the phenyl ring: the groups of low polarizability like Cl or CF_3 enhance the anticholinesterase activity.

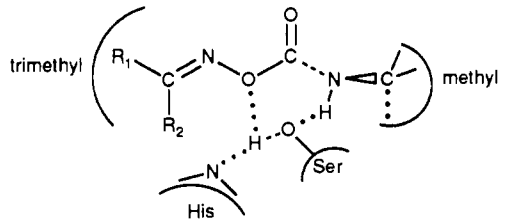
CONCLUSION

This study of the anticholinesterase activity for a series of 33 oxime *N*-methylcarbamates with the general formula



where R_1 and R_2 are groups such as H, alkyl, haloalkyl, or substituted aryls defines the characteristics of the R_1 and R_2 groups required for a good inhibition of acetylcholinesterase. Of the results of the correlation, the highest anticholinesterase activity is obtained when R_2 is an electron-withdrawing group of small dimension and with a low polarizability. To decrease a too high electronic deficiency on the iminic bond and to stabilize the carbamic derivative, the R_1 group had to be an electron-donating one. Since the first parameter taken into account is the Taft inductive effect, those two groups interact with the esteratic site of the acetylcholinesterase through the

Scheme II. Interaction of the Oxime *N*-Methylcarbamates and the Different Subsites of the Acetylcholinesterase



iminic bond. As it is the sum of their electronic contributions which prevails on the direct contribution of each group, neither R_1 nor R_2 can interact independently. The conjugated action of the two groups borne by the iminic carbon is also corroborated by the use of the sum of the Hansch parameters for evaluating the lipophilic interactions. The inclusion of commercial products in the correlations provides a good proof of the strength of those relationships.

As shown in Scheme II, the group R_2 is determinant for the formation of the enzyme–inhibitor complex (eqs 7 and 8) since it is responsible for the positioning of the inhibitor in the trimethyl site described by Hasan et al. (1980) and it has the required criteria propounded by those authors.

The participation of the group R_2 in the inhibition of the acetylcholinesterase is then comparable to that of the ortho or meta substituent in the phenyl *N*-methylcarbamates. This comparison is supported by the values obtained for the susceptibility constants $\rho^*_{R_2}$ and a_{R_2}. For the anticholinesterase activity the electronic and lipophilic characteristics of the group R_2, cis to the carbamic moiety, seem to prevail over the isomery, since small variations of the activity were observed for the three pairs of isomers studied herein. This limited effect of the isomeric nature of the oximic part for the carbamates of ketoximes was previously mentioned by Corkins et al. (1980). Other studies on the in vivo and in vitro activities of that series of oxime *N*-methylcarbamates are under investigation to evaluate the effects due to the nature of the substituents R_1 and R_2 and those due to the isomerism so that an understanding of the structural features responsible for a better inhibitory activity of oxime *N*-methylcarbamates may be gained.

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