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# Topographical Geometric Factors Governing the Biological Activities of Methomyl Derivatives on Mitochondrial Binding Receptors

## II. Synthesis

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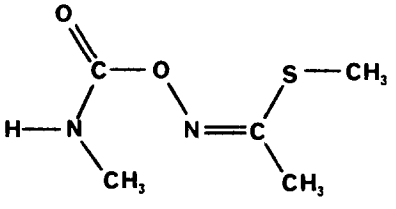
Methomyl derivatives for use as molecular probes were synthesized. Their spectroscopic properties, in particular $^{1}H$ and $^{13}C$ NMR and analytical data, are described. 

## INTRODUCTION

The insecticide methomyl, or *S*-methyl-*N*-[(methylcarbamoyl)oxy]thioacetimidate, mimics the action of the phytopathogenic fungus *Helminthosporium maydis*, but with a lower activity. Purified methomyl has a specific toxicity toward isolated mitochondria and sprouting corn seeds bearing Texas male sterile cytoplasm (T) but is inactive against mitochondria with normal male fertile cytoplasm (N). Using methomyl derivatives as molecular probes, the topographic study of T and N binding receptors showed that two biological activities related to topography and geometric isomerism could be distinguished in the T and N mitochondrial receptor sites (*1*). The synthesis of a family of carbamates related to the parent compound methomyl is described in this report.



Methomyl (Z isomer) **1**

## RESULTS AND DISCUSSION

The general synthetic method involved the condensation of an oxime with an appropriate isocyanate in the presence of triethylamine. The condensation of *S*-



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methyl thioacetoxyhydroximate with phosgene or trichloromethyl chloroformate and butylamine, for example, failed completely (*2*).

*Preparation of Isocyanates*

Methods with a practical value for synthesizing isocyanates are the Curtius, Lössen, and Hofmann reactions, respectively, involving the thermal transformation of acylazides $RCON_3$, the base-catalyzed rearrangement of RCONHOR′, and appropriate oxidations of amides $RCONH_2$. Acid chlorides and isocyanates not commercially available were synthesized as follows (*3*):

$$RCOOH + ClSi(CH_3)_2C(CH_3)_3 \rightarrow RCOOSi(CH_3)_2C(CH_3)_3 + ClCOCOCl/DMF$$

$$RCOCl + N_3Si(CH_3)_3 \rightarrow RCON_3 \xrightarrow{\Delta} RNCO$$

Lachrimatory isocyanates were utilized as crude products.

*Preparation of Oximes*

*S*-methyl thioacetoxyhydroximate is commercially available. Other oximes were obtained from ketones and hydroxylamine by the usual methods (*4*) or by the action of hydroxylamine on imido esters or thioesters in water in the presence of appropriate bases ($NaHCO_3$, $Na_2CO_3$, or NaOH):

$$CH_3COCH_2CH_3 + NH_2OH \rightarrow CH_3(CH_2CH_3)C{=}NOH$$

$$HN{=}C(CH_3)OR_1 \text{ or } SR_1 + NH_2OH \rightarrow HON{=}C(CH_3)OR_1 \text{ or } SR_1$$

The first case is illustrated by the mixture of oximes related to methyl ethylketone, as described in detail by Levy and Nelson (*5*).

The imido ester and imido thioester precursors of carbamates **2**, **3**, and **4** were obtained by the following procedure in the presence of gaseous hydrochloric acid (*6*):

$$CH_3C{\equiv}N + R_1OH \text{ or } R_1SH \rightarrow HCl,HN{=}C(CH_3)OR_1 \text{ or } SR_1$$

Imido thioester precursors of carbamates **2** and **3** were very hygroscopic. They generated oximes in the presence of hydroxylamine with a low yield, regardless of the solvent, bases, and conditions chosen.

Oximes isolated as liquid or crystallized samples were generally utilized as crude products with some exceptions as indicated.

*Preparation of Carbamates*

Methomyl was extracted from a commercial lannate solution and purified by chromatography and crystallization; mp = 78.5–79.5°C (*7*). It was identical to a sample synthesized by condensing *S*-methyl thioacetoxyhydroximate with methylisocyanate, a procedure described elsewhere (*8, 9*), and to a crystallized sample provided by Dupont de Nemours (France).

The condensation of the oxime with isocyanate is uncomplicated in the presence of triethylamine, with a yield greater than 85%:

$$R_2(R_1)C{=}NOH + R_3NCO \rightarrow R_2(R_1)C{=}NOCONHR_3$$

The condensation of *S*-methyl thioacetoxyhydroximate with dimethylcarbamyl chloride is best accomplished with pyridine and catalytic quantities of dimethylpyridine (DAP):

$$CH_3S(CH_3)C{=}NOH + ClCON(CH_3)_2 \rightarrow CH_3S(CH_3)C{=}NOCON(CH_3)_2$$

The sulfoxide was obtained from methomyl by oxidation with peracetic acid (*8*):

$$CH_3S(CH_3)C{=}NOCONHCH_3 + [O] \rightarrow CH_3\overset{\overset{O}{\uparrow}}{S}(CH_3)C{=}NOCONHCH_3$$

The carbamates most representative of recent studies (*1, 7, 10, 11*) are listed in Table 1.

The syntheses of carbamates **3**, **4**, **16**, **17**, **18**, and **19** yield a mixture of geometric isomers which were identified. The double carbamate **20** was also isolated as a complex mixture which was not elucidated. Mixtures of carbamates **3**, **4**, and **20** gave the major constituent directly by crystallization. Other mixtures of **16**, **17**, **18**, and **19**, purified by column chromatography, were not separated since attempts to separate the two components were unsuccessful (*7*).

*Structures*

The crystalline structure of methomyl for insecticide use has been determined by X rays (*8, 11, 12*) and presented the Z configuration. The carbamate obtained by acid hydrolysis of methomyl had the E configuration and its crystalline structure was also determined by X ray diffraction (*11*). The geometric isomers E and Z were also obtained by reacting methyl isocyanate with the corresponding anti and syn oximes, the syn being obtained from the anti by uv irradiation (*9*). Labeled geometric isomers E and Z were also synthesized from the corresponding oximes and methyl isocyanate (*8, 13*), so the configuration of the two methomyls is unequivocal.

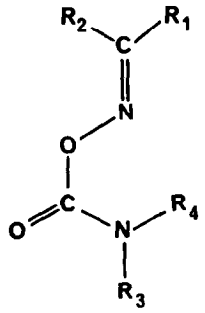
The Z configuration is attributed to carbamates **5–14** and **22** obtained by the action of various isocyanates and of dimethylcarbamyl chloride on *S*-methyl thioacetoxyhydroximate; mp = 95–97°C. This corresponds to the anti oxime, since the formation of the carbamate involves only the oxime hydrogen. Chemical spectroscopic data, in particular carbon and $^1H$ NMR and specific biological activities, are all consistent. Their Z configuration was also attributed to the sulfoxide **21**, since it corresponds to Z methomyl by an addition reaction. Carbamate **21** was inactive.

The synthesis of carbamate **3** furnished a mixture of geometric isomers. The Z configuration was attributed to the predominant component after examining $^1H$ and $^{13}C$ NMR data in comparison to those of the geometric isomers of methomyl. This attribute confirms those of the various *S*-alkylthiohydroximates (*9, 12, 14*) and of their derivatives, in particular carbamates.

The synthesis of carbamate **4** furnished a mixture in which the geometric E isomer was predominant, a situation identical to the synthesis of oximes obtained

TABLE 1

Methomyl Analogs



**1–21** $R_3 = H$
**22** $R_3 = CH_3$

| | $R_1$ | $R_2$ | $R_4$ |
|---|---|---|---|
| **1** | $CH_3$ | $SCH_3$ | $CH_3$ |
| **2** | $SCH_3$ | $SCH_3$ | $CH_3$ |
| **3** | $CH_3$ | $S(CH_2)_3CH_3$ | $CH_3$ |
| **4** | $CH_3$ | $OCH_2CH_3$ | $CH_3$ |
| **5** | $CH_3$ | $SCH_3$ | $C_2H_5$ |
| **6** | $CH_3$ | $SCH_3$ | $(CH_2)_2CH_3$ |
| **7** | $CH_3$ | $SCH_3$ | $CH(CH_3)_2$ |
| **8** | $CH_3$ | $SCH_3$ | $(CH_2)_3CH_3$ |
| **9** | $CH_3$ | $SCH_3$ | $(CH_2)_8CH_3$ |
| **10** | $CH_3$ | $SCH_3$ | $(CH_2)_{12}CH_3$ |
| **11** | $CH_3$ | $SCH_3$ | $(CH_2)_{14}CH_3$ |
| **12** | $CH_3$ | $SCH_3$ | $(CH_2)_{16}CH_3$ |
| **13** | $CH_3$ | $SCH_3$ | $(CH_2)_{20}CH_3$ |
| **14** | $CH_3$ | $SCH_3$ | $(CH_2)_7CH{=}CH(CH_2)_7CH_3$ |
| **15** | $C_2H_5$ | $C_2H_5$ | $CH_3$ |
| **16** | $CH_3$ | $C_2H_5$ | $CH_3$ |
| **17** | $CH_3$ | $(CH_2)_2CH_3$ | $CH_3$ |
| **18** | $CH_3$ | $CH_2CH(CH_3)_2$ | $CH_3$ |
| **19** | $CH_3$ | $CH(CH_3)COOC_2H_5$ | $CH_3$ |
| **20** | $CH_3$ | $(CH_2)_2C(=NOCONHCH_3)CH_3$ | $CH_3$ |
| **21** | $CH_3$ | $CH_3S \rightarrow O$ | $CH_3$ |
| **22** | $CH_3$ | $SCH_3$ | $CH_3$ |

from ethyl acetimidate, where the syn oxime predominates since the anti oxime is easily converted to the syn (*15, 16*). The crystalline structure of certain oximes, determined by X ray diffraction, confirmed this attribute (*15, 17*).

The synthesis of carbamates **16–19** also furnished a mixture in which the E isomer predominate, a situation identical to the synthesis of oximes obtained, e.g., from methylethylketone (*5*). Here again, data from $^1H$ and $^{13}C$ NMR of

carbamates **16–19**, from the methylethylketone oximes, and from the nonspecific biological activities were all consistent.

The synthesis of the double carbamate **20** also furnished a mixture. After crystallization a derivative was obtained whose NMR data were consistent with the E configuration of each carbamate function. This compound was also inactive.

The examination of NMR data showed diagnostically useful features, depending on whether or not the heteroatom X was present (X=S or O).

In particular, the $^{13}C$ NMR of the carbons of the $R_1$ methyls of the Z carbamates systematically resonated downfield from the E carbamates (Table 2). The same was true for the $R_2$ $\beta$ carbons bound to the heteroatom of carbamates **1**, **3**, and **4**. The opposite was observed for the $\alpha'$ carbons of carbamates **16–19**, lacking a

TABLE 2

$^{13}C$ Chemical Shifts of Methomyl Analogs as Solutions in $CDCl_3$ + 1% TMS (ppm)

| No. | $R_1$ | $R_2$ | $R_4$ | $sp^2$ carbons[a] |
|---|---|---|---|---|
| **1** (Z) | 18.9 | 13.4 | 27.6 | 155.5 160.7 |
| (E) | 18.2 | 13.4 | 27.7 | 156.4 160.7 |
| **2** | | 13.8 and 15.2 | 27.8 | 155.5 162.3 |
| **3** (Z) | 19.1 | 13.3, 21.6, 30.0, 31.6 | 27.4 | 155.4 160.0 |
| (E) | 18.3 | 13.7, 22.0, 29.9, 30.1 | 27.65 | 156.1 162.5 |
| **4**[b] (Z) | 15.3 | 15.0, 65.85 | 27.6 | 156.35 158.1 |
| (E) | 14.2 | 14.8, 63.3 | 27.6 | 156.4 166.5 |
| **5** | 18.95 | 13.4 | 15.0, 36.1 | 154.7 160.5 |
| **6** | 19.0 | 13.6 | 11.2, 23.0, 42.9 | 154.8 160.5 |
| **7** | 19.0 | 13.5 | 22.9, 43.4 | 153.9 160.5 |
| **8** | 19.0 | 13.5 | 13.8, 20.0, 31.9, 41.0 | 154.8 160.5 |
| **9** | 19.0 | 13.5 | 14.2, 22.7, 26.8, 29.5, 29.8, 31.9, 41.2 | 154.8 160.5 |
| **10–11** | 19.0 | 13.5 | 14.2, 22.7, 26.8, 29.5 | 154.8 160.4 |
| **12–13** | | | 29.8, 31.9, 41.2 | |
| **14** | 19.0 | 13.5 | 14.1, 22.7, 26.8, 27.3, 29.2, 29.4, 29.8, 32.0 | 154.8 160.4 |
| **15** | | 10.4, 22.5, 27.2 | 27.5 | 156.7 168.7 |
| **16**[c] | 16.7 (Z) | 9.60, 23.1 (Z) | 27.0 | 156.0 164.7 (Z) |
| | 14.6 (E) | 10.04, 28.6 (E) | 27.0 | 156.0 164.0 (E) |
| **17**[c] | 20.0 (Z) | 13.6, 14.0, 19.2, 19.4, 32.2 (Z) | 27.5 | 156.5 164.0 (Z) |
| | 15.25 (E) | 37.7 (E) | | 156.5 163.5 (E) |
| **18**[c] | 20.6 (Z) | 22.35, 25.7, 26.0, 39.1 (Z) | 27.5 | 156.4 163.3 (Z) |
| | 15.45 (E) | 44.7 (E) | | 156.4 163.0 (E) |
| **19**[c] | 17.2 (Z) | 13.4, 13.6, 14.1, 39.8 (Z) | 27.6 | 155.9 161.6 |
| | 14.3 (E) | 45.8 (E), 61.4 | | 171.4, ester |
| **20**[d] | 15.4 | 15.4, 27.65, 32.1, 156.6, 162.2 | 27.65 | 156.6 162.2 |
| **21** | 11.2 | 37.6 | 27.5 | 153.6 169.2 |
| **22** | 18.7 | 13.3 | 36.3 = $R_4$ + $R_3$ | 154.3 161.1 |

[a] The first number corresponds to the carbonyl chemical shifts.

[b] Chemical shifts measured at the same concentration: 5 mg/0.40 ml.

[c] Attributions made from mixtures of E + Z.

[d] In deuterated pyridine.

heteroatom. The $sp^2$ carbons C=N bound to the nitrogen of the Z isomers resonated upfield from the E isomers (carbamates **1**, **3**, and **4**). The opposite was observed for carbamates **16–19**. It is important to note the systematic downfield variation of these carbons in the course of the transformation of oximes into carbamates. All the variations observed follow exactly those shown in the case of the oximes corresponding to carbamates **3**, **4** (*15*), and **16** (*5*). In order to eradicate any ambiguity concerning the identification of these $^{13}C$ NMR data, several selective decouplings were carried out:

| Carbamate | $^1H$ irradiation (ppm) | Examination of $^{13}C$ (ppm) |
|---|---|---|
| **1** (Z) | 2.20 (s) | 18.9 (q) → (s) |
| **3** (Z) | 0.94 (t) | 13.3 (q) → (s) |
| **3** (E) | 0.95 (t) | 13.7 (q) → (s) |
| **4** (E) | 1.30 (s) | 14.8 (q) → (s) |
| **21** (Z) | 2.30 (s) | 11.2 (q) → (s) |

In $^1H$ NMR (Table 3), the hydrogens of $R_1$ methyl groups of the Z isomers exhibited chemical shifts downfield form the E isomers when the heteroatom was sulfur (*9*). For all the other carbamate couples, the rule was inverted. Methylene hydrogens, whether they be $\alpha'$ or bound to the heteroatom of Z isomers, were shifted downfield from the E isomers (carbamates **3**, **4**, **16**, and **17**). This situation is identical to that described for oximes (*15*) and the syn and anti amidoximes (*18*).

The rule of melting points concerning the syn and anti oximes (*19*) is not a criterion of differentiation for related carbamates, since there are too many exceptions (*15*). Only carbamate **4** obeys the rule. On the other hand, the chromatographic behavior of the geometric isomers of carbamates **1**, **3**, and **4** on silica gel leads to an easy distinction: the E isomer always has the highest $R_f$, in agreement with prior observations (*9*, *11*).

## EXPERIMENTAL

### *Methods*

Melting points were determined on a Reichert microscope hot plate and are uncorrected. Infrared (ir) spectra were recorded on a Perkin–Elmer 399 spectrophotometer. Proton NMR spectra were recorded at either 60 MHz on a Varian T-60 spectrometer or 200 MHz on a Bruker spectrometer. Carbon NMR were recorded on either a Varian CFT-20 spectrometer or a Bruker spectrometer. NMR samples were prepared in $CDCl_3$ containing 1% tetramethylsilane (TMS). Chemical shifts are reported as units downfield from TMS. The microanalysis of crystallized samples was performed at the Central Microanalysis Laboratory, CNRS, Gif-sur-Yvette, France. Mass spectra were recorded on a ZAB.2F.VG micromass spectrometer.

TABLE 3

$^1$H NMR Data of Methomyl Analogs as Solutions in $CDCl_3$ + 1% TMS (ppm)

| No. | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| **1** (Z) | 2.20 (s) | 2.37 (s) | 6.00 (br) | 2.85 (d, $J$ = 4,8 Hz) |
| (E) | 2.16 (s) | 2.39 (s) | 6.10 (br) | 2.89 (d, $J$ = 4.8 Hz) |
| **2** | | 2.47, 2.50 (2 s) | 6.0 (br) | 2.91 (d, $J$ = 4.9 Hz) |
| **3** (Z) | 2.25 (s) | 0.94 (t, $J$ = 7.5 Hz), 1.46 and 1.63 (m), 2.91 (br, t, $J$ = 8.0 Hz) | 6.12 (br) | 2.91 (d, $J$ = 5.0 Hz) |
| (E) | 2.17 (s) | 0.95 (t, $J$ = 7.2 Hz), 1.44 and 1.66 (m), 2.05 (t, $J$ = 7.5 Hz) | 6.20 (br) | 2.92 (d, $J$ = 4.86 Hz) |
| **4**[a] (Z) | 2.01 (s) | 1.34 (t, $J$ = 7.05 Hz), 4.14 (q) | 6.10 (br) | 2.84 (d, $J$ = 4.86 Hz) |
| (E) | 2.06 (s) | 1.30 (t, $J$ = 7.1 Hz), 4.06 (q) | 6.10 (br) | 2.87 (d, $J$ = 4.86 Hz) |
| **5** | 2.21 (s) | 2.37 (s) | 5.87 (br) | 1.37 (t, $J$ = 7.0 Hz), 3.30 (d, q) |
| **6** | 2.20 (s) | 2.37 (s) | 6.0 (br) | 0.93 (t, $J$ = 6.5 Hz), 1.52 (d, q), 3.20 (q, $J$ = 6.0 Hz) |
| **7** | 2.22 (s) | 2.40 (s) | 5.73 (br) | 1.21 (d, $J$ = 6.5 Hz), 3.91 (m) |
| **8** | 2.25 (s) | 2.42 (s) | 5.97 (br) | 0.92 (br, t), 1.47 (br), 3.28 (q, $J$ = 6.0 Hz) |
| **9** | 2.20 (s) | 2.35 (s) | 5.87 (br) | 0.88 (br, t), 1.27 (br), 3.13 (q, $J$ = 6.0 Hz) |
| **10–13** | 2.22 (s) | 2.38 (s) | 5.87 (br) | 0.85 (br, t), 1.25 (br), 3.18 (q, $J$ = 6.0 Hz) |
| **14** | 2.22 (s) | 2.37 (s) | 5.93 (br) | 0.87 (br, t), 1.30 (br), 3.23 (q, $J$ = 6.0 Hz), 5.27 (t, $J$ = 5.0 Hz) |
| **15** | 1.12, 1.15 (2t), 2.42, 2.45 (2 q, $J$ = 7.5 Hz) | | 6.43 (br) | 2.92 (d, $J$ = 4.8 Hz) |
| **16**[b] (Z) | 1.96 (s) | 1.10 (t, $J$ = 7.35 Hz), 2.48 (q) | 6.35 (br) | 2.90 (d, $J$ = 4.54 Hz) |
| (E) | 2.01 (s) | 1.14 (t, $J$ = 7.35 Hz), 2.34 (q) | 6.35 (br) | 2.91 (d, $J$ = 4.54 Hz) |
| **17**[b] | 1.93 (s) (Z) | 0.93 (t, $J$ = 7.0 Hz), 1.57 (m) | 6.47 (br) | 2.86 (d, $J$ = 4.8 Hz) |
| | 1.97 (s) (E) | 2.20 (m) (E), 2.38 (m) (Z) | | |
| **18**[b] | 1.90 (s) (Z) | 0.92 (t, $J$ = 6.0 Hz), 2.11 (d) | 6.25 (br) | 2.85 (d, $J$ = 4.8 Hz) |
| | 1.95 (s) (E) | 2.30 (m) | | |
| **19**[b] | 2.00 (s) (Z) | 1.25 (t, $J$ = 7.0 Hz), 1.38 (d, $J$ = 7.0 Hz) | 6.37 (br) | 2.87 (d, $J$ = 4.5 Hz) |
| | 2.02 (s) (E) | 3.45 (q), 4.50 (q) | | |
| **20**[c] | 1.80 (s) | 2.37 (br) | 5.0 (br) | 2.92 (d, $J$ = 4.7 Hz) |
| **21** | 2.30 (s) | 2.85 (s) | 6.30 (br) | 2.89 (d, $J$ = 4.8 Hz) |
| **22** | 2.20 (s) | 2.35 (s) | 2.95 (s) | 2.95 (s) |

*Note.* (s) = singlet, (br) = broad.
[a] Chemical shifts measured at the same concentration: 5 mg/0.40 ml.
[b] Attributions made from mixtures of E + Z.
[c] In deuterated pyridine.

Analytical thin-layer chromatography (TLC) was routinely used to monitor reactions. Plates precoated with E. Merck silica gel $60F_{254}$ 0.25 mm thick were used. Developed plates were visualized under short-wavelength uv light. Carbamates **15–20** and **4** were not fluorescent and were detected after exposure to iodine vapors. Medium pressure chromatographies were done on columns packed with E. Merck silica gel 60H with a Jobin-Yvon instrument.

Methylene chloride was distilled from $K_2CO_3$, followed by distillation from $P_2O_5$. Benzene and ethyl ether were distilled from sodium/benzophenone. Dimethylformamide was distilled from calcium hydride under reduced pressure. Triethylamine was distilled and maintained from KOH pellets. Acetonitrile was distilled from $K_2CO_3$. Methylisocyanate and oxalyl chloride were distilled prior to use.

*Materials*

*Precursors of* **2**. Methyl thiocyanate ($10^{-1}$ mol, 7.3 g), i.e., 6.83 ml, and 100 ml of anhydrous ethyl ether were placed in a round flask equipped with a dry ice trap. In an atmosphere of $N_2$ at the temperature of an ice-salt bath, methyl mercaptan (0.203 mol, 10 g) was added and condensed and gaseous HCl was then added until saturation. The expected hydrochloride rapidly appeared and deposited. After 2 days at 0°C, it was filtered through a Büchner funnel, washed with cold anhydrous ether, and dried under vacuum. 15.4 g (98%) was isolated. $(CH_3S)_2C{=}NH,HCl$ (0.46 mol, 7.32 g) was dissolved in 25 ml of tetrahydrofuran and 5 ml of water in the presence of $NH_2OH,HCl$ ($6.25 \times 10^{-2}$ mol, 4.34 g), and NaOH (0.109 mol, 4.36 g) dissolved in 55 ml of water was then added dropwise with vigorous magnetic stirring. The aqueous solution was extracted the next day with four 75-ml aliquots of ethyl ether. The ether solution was dried over $K_2CO_3$ and the solvent was removed *in vacuo*. 1.80 g (28%) of a crystalline residue was isolated and recrystallized in a mixture of hexane and ethyl ether; mp = 76–76.5°C. $^1H$ and $^{13}C$ NMR indicated a single product characterized by mass spectrometry: $M^+ = 137$. $^1H$ NMR: 2.425 and 2.45 (2 s), $CH_3S \times 2$, 9.75 (br) NOH; $^{13}C$ NMR: 13.4, 15.1, 154.9.

*Precursor of* **3**. $CH_3(CH_2)_3SC(CH_3){=}NH,HCl$ ($10^{-2}$ mol, 3.34 g), obtained using the method described above, starting with acetonitrile, butyl mercaptan, and gaseous HCl was dissolved in 25 ml of water with $NH_2OH,HCl$ ($5 \times 10^{-2}$ mol, 6.95 g). $Na_2CO_3$ ($6 \times 10^{-2}$ mol, 6.36 g) dissolved in 25 ml of water was added at ambient temperature with mixing. Two days later, the aqueous solution was extracted with methylene chloride ($4 \times 100$ ml). After drying over $K_2CO_3$ and removal of the solvent *in vacuo*, 0.664 g (23%) of a white crystalline product was isolated. It was a mixture of oximes characterized by mass spectrometry: $M^+ = 147$, and by $R_f$ values of 0.72 and 0.20 (ethyl ether and pentane, 1/1, as solvent), with $R_f = 0.20$ as the major compound. Low pressure chromatography yielded two constituents, 0.262 and 0.356 g. The first was a liquid. $^1$NMR: 0.92 (t) $CH_3$, 1.85 (m) $(CH_2)_2$, 2.07 (s) $CH_3C{=}$, 2.83 (t, $J = 7.0$ Hz) $CH_2S$; $^{13}C$ NMR: 16.4 $CH_3S$, 13.5 $CH_3$, 21.9 and 29.6, $CH_2CH_2$, 30.6, $CH_2S$, 156.0, C=N. The second was recrystallized from pentane; mp = 50–50.5°C. $^1H$ NMR: 0.92 (t) $CH_3$, 1.53 (m) $(CH_2)_2$, 2.145 (s) $CH_3C{=}$, 2.83 (t, $J = 7.0$ Hz) $CH_2S$; $^{13}C$ NMR; 18.9 $CH_3S$, 13.5 $CH_3$, 21.8 and 29.3 $CH_2CH_2$, 32.0 $CH_2S$, 153.9 C=N.

*Precursor of* **4**. Commercial $CH_3CH_2OC(CH_3){=}NH,HCl$ ($5 \times 10^{-2}$ mol, 6.18 g) was dissolved in 25 ml of tetrahydrofuran with $NH_2OH,HCl$ ($7.5 \times 10^{-2}$ mol, 5.21 g). $Na_2CO_3$ ($3.75 \times 10^{-2}$ mol, 3.87 g) dissolved in 50 ml of water was added at ambiant temperature with mixing. One day later, the aqueous solution was extracted with ethyl ether ($4 \times 100$ ml). After drying over $K_2CO_3$ and removal of the solvent, 2.94 g (57%) of a colorless oil was isolated, which crystallized on standing in the refrigerator. After recrystallization from pentane and drying under a nitrogen stream, the major constituent was characterized by: mp = 26–26.5°C. Reported for the E oxime 25–26°C (*20*). $^1H$ NMR: 1.275 (t, $J = 7.0$ Hz) $CH_3$, 2.0 (s) $CH_3C{=}$, 3.975 (q) $OCH_2$, 7.83 (br) NOH; $^{13}C$ NMR: 12.9 $CH_3C$, 14.2 $CH_3$, 62.2 $OCH_2$, 163.1 C=N. These spectroscopic data agree with those reported earlier

(*15, 21*). Mass spectrometry: $M^+ = 103$. The Z isomer was detected in the mother liquor. It was characterized by $^{13}C$ NMR: 15.2 $CH_3C$, 14.6 $CH_3$, 64.6 $OCH_2$, 155.0 C=N. It accounted for only 4–5%. Other procedures give 12.5% (*22*).

*Precursor of* **20**. Acetonylacetone ($2.50 \times 10^{-2}$ mol, 2.85 g) was dissolved in a mixture of water (20 ml) and methanol (45 ml) with $NH_2OH$,HCl ($6 \times 10^{-2}$ mol, 4.17 g). $Na_2CO_3$ ($3.125 \times 10^{-2}$ mol, 3.60 g) was added in several times at ambiant temperature with mixing. Two days later, the methanol was removed *in vacuo*. The crystalline residue was filtered through a Büchner funnel, washed with water, and dried under high vacuum over $P_2O_5$; it was insoluble in chloroform; mp = 137–141°C; 3.31 g (92%). TLC indicated only one spot (ethyl ether, ethyl acetate, 1/1) but $^{13}C$ NMR ($CDCl_3$ $CD_3OD$, 4/1) showed two products in a ratio of 29/71. δ minor isomer: 19.7 $CH_3$, 25.9 and 31.6 $CH_2CH_2$, 157.7 C=N. δ major isomer: 13.4 $CH_3$, 32.8 ($CH_2 \times 2$), 157.3 C=N. $^1H$ NMR. δ minor: 1.875 and 1.92 (2 $CH_3$), 2.40 ($CH_2 \times 2$). δ major: 1.89 ($CH_3 \times 2$), 2.40 ($CH_2 \times 2$).

*Synthesis of carbamates* **2**, **3**, *and* **4**. $(CH_3S)_2C$=NOH (2.79 mmol, 0.382 g) was dissolved in 4 ml of $(C_2H_5)_3N$ under nitrogen, at the temperature of an ice bath. Methyl isocyanate (0.30 ml) was dissolved in 2 ml of methylene chloride and added. Three hours later, TLC (ethyl ether as solvent) indicated the disappearance of the oxime. The carbamate was isolated after removal of solvent and reagents by vacuum distillation. The crude crystalline residue obtained (0.56 g, 100%) was dissolved in a mixture of ethyl ether and hexane, filtered through celite and recrystallized; mp = 55.5–56°C.

$CH_3(CH_2)_3SC(CH_3)$=NOH (0.109 mol, 1.60 g), a mixture of E and Z oximes treated with methyl isocyanate in the same conditions, furnished 2.10 g (94.6%) of a mixture of carbamates characterized by $R_f$ values of 0.46 and 0.62 (pure ethyl ether as solvent) with $R_f$ 0.46 as the major compound. After recrystallizing in pentane/ethyl ether, the major isomer was recovered as long wide crystals; mp = 72.5–73°C. Yield: 80%.

$CH_3(CH_2)_3SC(CH_3)$=NOH as pure E oxime (1.78 mmol, 0.262 g) was treated with methyl isocyanate as described above. A colorless oil was isolated (0.357 g) and chromatographed under low pressure: the starting material was recovered first (12 mg) followed by the pure E carbamate (0.262 g) as a colorless oil which turned yellow on standing. Dissolved in the mixture of pentane/ethyl ether, the E isomer crystallized on standing in the refrigerator at −20°C; mp = 32–32.5°C.

$C_2H_5OC(CH_3)$=NOH as crude material (0.011 mol, 1.143 g) was dissolved in 18 ml of methylene chloride and 2 ml of $(C_2H_5)_3N$ under nitrogen. Methyl isocyanate (1 ml) dissolved in 7 ml of $CH_2Cl_2$ was added at the temperature of an ice bath. One day later, the solution was washed with a cold 10% NaOH solution and water, dried over $MgSO_4$, and distilled under vacuum. 1.66 g (94%) of a crystalline residue was obtained. After two recrystallizations, the E isomer was the sole compound isolated; mp = 80.5–81°C; yield 70–75%, in the form of thin needles. The Z isomer was isolated from the mother liquor after chromatography on silica gel plates. Five milligrams was recrystallized from isopropyl ether and $CH_2Cl_2$; mp = 65–66°C, in the form of small cubes. Z and E carbamates were characterized respectively by $R_f$ values of 0.14 and 0.48 (ethyl ether, ethyl acetate, 7/3 as solvent).

*Synthesis of carbamates* **5–8**. The condensation between the *S*-methyl thioacetoxyhydroximate and commercial isocyanates was done in the presence of triethylamine in various dry solvents, such as methylene chloride benzene or chloroform, in a nitrogen atmosphere at the temperature of an ice bath, and left overnight. The resulting carbamates were isolated after washing and drying as described above. The crude carbamates were purified by recrystallization or by chromatography, followed by recrystallization in the indicated solvents (Table 4).

*Synthesis of carbamates* **9–14**. A typical procedure for carbamates obtained with isocyanates corresponding to saturated or unsaturated fatty acids is as follows.

Behenic acid $CH_3(CH_2)_{20}COOH$ (0.0153 mol, 5.22 g) was dissolved in 18 ml of anhydrous dimethylformamide (DMF) in the presence of imidazole (0.035 mol, 2.38 g). *tert*-Butyldimethylchlorosilane (0.017 mol, 2.55 g) was rapidly added with magnetic stirring under $N_2$. After 75 ml of pentane and 50 ml of ethyl ether were added the next day, the organic solution was washed with a solution of $NaHCO_3$, then with water, and was dried over $K_2CO_3$. 7.94 g of a white crystalline residue was obtained which was dissolved in 40 ml of methylene chloride and 10 drops of DMF under $N_2$. Freshly distilled oxalyl chloride (0.011 mol, 1.40 g) was added dropwise at the temperature of an ice bath. The silylic ester dissolved slowly. The flask was stored in a refrigerator overnight. The ir spectrum showed the unique presence of the acid chloride as 1805 $cm^{-1}$. After removal of $CH_2Cl_2$ and DMF under vacuum, the acid chloride was dissolved in 40 ml of benzene and 2 ml of

TABLE 4

Analytical Data

| No. | Melting point (°C) | Solvent[a] | Formula | Calculated | | | Found | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | C(%) | H(%) | N(%) | C(%) | H(%) | N(%) |
| **2** | 55.5–56 | d | $C_5H_{10}N_2O_2S_2$ | 30.92 | 5.19 | 14.42 | 31.13 | 5.16 | 14.18 |
| **3** (Z) | 72.5–73.5 | b | $C_8H_{16}N_2O_2S$ | 47.04 | 7.89 | 13.71 | 47.06 | 7.72 | 13.57 |
| (E) | 32–32.5 | b | $C_8H_{16}N_2O_2S$ | 47.04 | 7.89 | 13.71 | 47.20 | 7.84 | 13.27 |
| **4** (Z) | 80.5–81 | a | $C_6H_{12}N_2O_3$ | 45.0 | 7.55 | 17.48 | 45.17 | 7.43 | 17.18 |
| **5** (Z) | 55–55.5 | a | $C_6H_{12}N_2O_2S$ | 40.89 | 6.86 | 15.89 | 40.94 | 6.72 | 15.87 |
| **6** (Z) | 44–44.5 | b | $C_7H_{14}N_2O_2S$ | 44.20 | 7.42 | 14.72 | 44.47 | 7.42 | 14.50 |
| **7** (Z) | 73.5–74 | b | $C_7H_{14}N_2O_2S$ | 44.20 | 7.42 | 14.72 | 44.52 | 7.51 | 14.76 |
| **8** (Z) | 42.5–43 | b | $C_8H_{16}N_2O_2S$ | 47.04 | 7.89 | 13.71 | 47.37 | 7.89 | 13.70 |
| **9** (Z) | 24.5–25 | a | $C_{13}H_{26}N_2O_2S$ | 56.90 | 9.55 | 10.20 | 56.89 | 9.56 | 10.09 |
| **10** (Z) | 48–49 | b | $C_{17}H_{34}N_2O_2S$ | 61.77 | 10.87 | 8.48 | 61.87 | 10.15 | 8.51 |
| **11** (Z) | 56–57 | b | $C_{19}H_{38}N_2O_2S$ | 63.64 | 10.77 | 7.81 | 63.73 | 10.80 | 7.75 |
| **12** (Z) | 63–63.5 | c | $C_{21}H_{42}N_2O_2S$ | 65.23 | 10.96 | 7.24 | 65.22 | 10.99 | 7.24 |
| **13** (Z) | 74–75 | c | $C_{25}H_{50}N_2O_2S$ | 67.82 | 11.38 | 6.33 | 67.79 | 11.04 | 6.61 |
| **20** | 186–188 | d | $C_{10}H_{18}N_4O_4$ | 46.50 | 7.02 | 21.70 | 46.69 | 6.98 | 22.09 |
| **21** (Z) | 73.5–74 | e | $C_5H_{10}N_2O_3S$ | 33.70 | 5.65 | 15.71 | 33.64 | 5.66 | 15.47 |
| **22** (Z) | 76–76.5 | a | $C_6H_{12}N_2O_2S$ | 40.89 | 6.86 | 15.89 | 41.24 | 6.81 | 15.85 |

[a] (a) Ethyl ether or isopropyl ether; (b) hexane/$CH_2Cl_2$ or ethyl ether; (c) acetone/$CH_2Cl_2$; (d) aqueous methanol; (e) ethyl acetate and isopropyl ether.

$(CH_3)_3SiN_3$ and was boiled for 2 h. After the benzene was evaporated under vacuum, the resulting white crystalline residue was dried under vacuum over $P_2O_5$. The ir spectrum of this residue showed the presence of strong absorption at 2270 $cm^{-1}$. It was redissolved in 25 ml of methylene chloride and 5 ml of $(C_2H_5)_3N$. *S*-methyl thioacetoxyhydroximate (0.148 mol, 1.55 g) dissolved in 5 ml of $CH_2Cl_2$ was added under $N_2$ at the temperature of an ice bath. After dilution with $CH_2Cl_2$ the next day, the organic solution was washed with cold 10% NaOH solution, then with water, and dried over $MgSO_4$, and $CH_2Cl_2$ was removed under vacuum. 6.20 g (92%) of a yellowish white crystallized product were obtained which was recrystallized first from acetone, and then from a mixture of inert isopropyl ether and methylene chloride; mp = 74–75°C.

*Synthesis of carbamates* **15–22**. The condensation of crude oximes corresponding to various ketones with an excess of methylisocyanate was done in methylene chloride at 0°C under nitrogen as described above. They were purified by column chromatography. E carbamate was the major compound of mixtures **16–19**, respectively, 75, 63, 85, and 96%. The double carbamate **20** was obtained from the oxime corresponding to $CH_3CO(CH_2)_2COCH_3$. It was isolated in pure form after several recrystallizations. It was insoluble in chloroform and methanol at ambient temperature, and was characterized by chemical ionization mass spectrometry: $(M + 1)^+ = 259$.

Carbamate **21** was obtained by the oxidation of Z methomyl by peracetic acid (*8*). After it was washed with a cold 10% $NaHCO_3$ solution, the organic solution was dried over $MgSO_4$ and the solvent was removed under vacuum. A viscous colorless oil was isolated (2.12 g, 30%) which crystallized slowly on standing in the refrigerator.

Carbamate **22** was obtained by the action of dimethylcarbamylchloride on *S*-methyl thioacetoxyhydroximate in pyridine and a catalytic amount of DAP (100 mg) at ambient temperature, under nitrogen for 2 days. It was isolated after removal of the pyridine under high vacuum, then as described above. Yield: 70%

Spectroscopic data, particularly $^{13}C$ chemical shifts and $^1H$ NMR chemical shifts are shown in Table 2 and 3. All infrared spectra, neat or as chloroform solutions, are characterized by strong absorptions at 3350–2290, 1725, 1645, 1510, 1240, and 1110 $cm^{-1}$. The solvents chosen for recrystallization and the analytical properties of the crystallized carbamates are shown in Table 4. The melting points of carbamates **14** and **15** were lower than +5°C.

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