exo-3-Chloro-*endo*-6-cyano-2-norbornanone O-(Methylcarbamoyl)oxime. A New Type of Methylcarbamate with Acaricidal Activity

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5-Norbornene-*endo*-2-carbonitrile nitrosochloride dimer can be rearranged to a mixture of chlorocyanonorbornanone oximes which, when allowed to react with methyl isocyanate, gives as the major product, *exo*-3-chloro-*endo*-6-cyano-2-norbornanone O-(methylcarbamoyl)oxime. The structure was determined by n.m.r. studies. The compound is a new type of methylcarbamate possessing acaricidal properties.

A synthetic exploration of cyclic and bicyclic ketoxime methylcarbamates conducted in these laboratories resulted in the discovery of a series of compounds possessing insecticidal and acaricidal properties.[1] Among the compounds investigated, the chlorocyanonorbornanone oximes obtained from the rearrangement of 5-orbornene-*endo*-2-carbonitrile nitrosochloride dimer gave a mixture of methylcarbamates (Chart I) possess-

CHART I
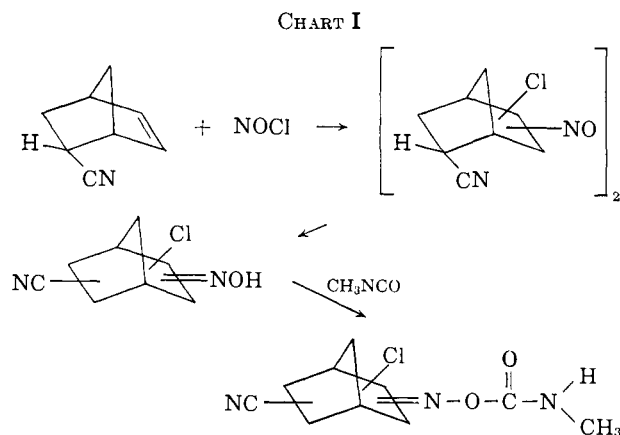
ing significant activity against the two-spotted mite (*Tetranychus telarius* L.). This mixture of isomeric chlorocyanonorbornanone O-(methylcarbamoyl)oximes has been subjected to extensive evaluation during recent years as an acaricide.[2] Efforts to isolate a pure isomer from this complex mixture have been unsuccessful. However, a synthetic innovation in the reaction sequence was recently uncovered which resulted in a good yield of a single isomer of chlorocyanonorbornanone O-(methylcarbamoyl)oxime. The important feature in this reaction scheme involved an improved synthesis of 5-norbornene-*endo*-2-carbonitrile nitrosochloride dimer. When 5-norbornene-*endo*-2-carbonitrile was allowed to react with nitrosyl chloride generated *in situ* from sodium nitrite, hydrochloric acid, and isopropyl alcohol, a nitrosochloride dimer resulted which melted with decomposition at a substantially higher point than the dimer obtained by conventional means, *i.e.*, reaction with nitrosyl chloride in an inert solvent. Apparently a higher degree of selectivity was accom-

plished in the ionic addition of NOCl to the unsymmetrical olefin in the isopropyl alcohol–HCl medium. The resulting nitrosochloride dimer was rearranged in 92% yield to a crystalline mixture of chlorocyanonorbornanone oximes (I) (Chart II). The reaction was

CHART II
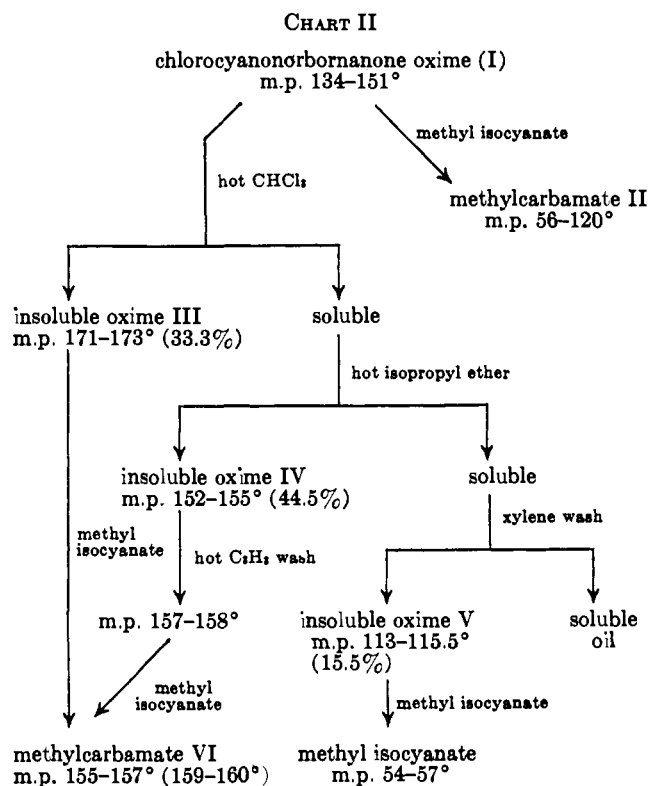
facilitated by treatment of the rearrangement solvent, dioxane, with a catalytic amount of a primary amine (0.03%). The heat-sensitive oxime mixture (I) was isolated by evaporation of the dioxane *in vacuo*, using a xylene chaser to remove the last traces of dioxane. When allowed to react with methyl isocyanate, the oximes (I) afforded a mixture of isomeric O-(methylcarbamoyl)oximes (II). However, the oximes (I) can be separated into several components as shown in Chart II. When extracted with hot chloroform an insoluble oxime (III) was obtained which represented 33.3% of the mixture (I). This oxime was also insoluble in benzene and ethyl ether.

(1) J. R. Kilsheimer and D. T. Manning, French Patent 1,343,654 (1963).
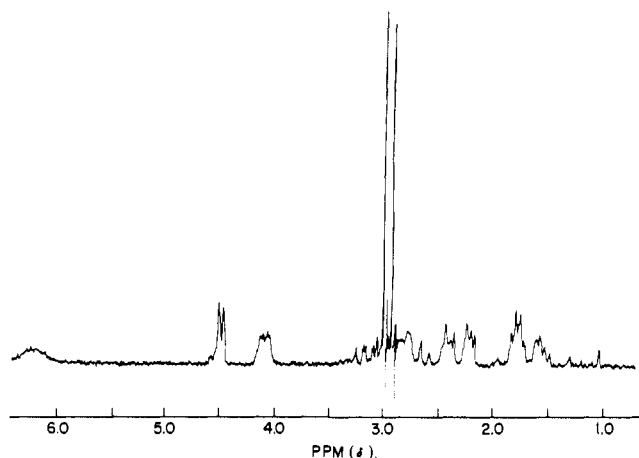(2) Coded U. C. 20047; U. S. Department of Agriculture, Entry No. 25962.

Figure 1.—N.m.r. spectrum of *exo*-3-chloro-*endo*-6-cyano-2-norbornanone O-(methylcarbamoyl)oxime in deuteriochloroform.

A second chlorocyanonorbornanone oxime (IV) was isolated by evaporating the chloroform extract and thoroughly extracting the residue with hot isopropyl ether. The isopropyl ether–insoluble oxime (IV) represented 44.5% of the original mixture of oximes (I). The chlorocyanonorbornanone oxime (IV) was further purified, with negligible loss, by extraction with hot benzene or by recrystallization from ethanol. The infrared spectra of III and IV were almost identical and the n.m.r. spectra were equally indistinguishable. Apparently III is a thermally sensitive isomer of IV, having similar infrared and n.m.r. spectra. Upon recrystallization of III or heating in dioxane solution, the melting point was depressed. Indeed, prolonged heating of IV in dioxane solution results in a melting point depression. The two chlorocyanonorbornanone oximes (III and IV), which when combined account for 77.8% of I, give an almost quantitative yield of the same methylcarbamate VI. It is probable that oximes III and IV are *syn* and *anti* isomers which under the conditions of reaction with methyl isocyanate result in the same methylcarbamate.

The isopropyl ether soluble fraction was evaporated to dryness and the residue was washed with xylene. Recrystallization of the resulting solid from benzene yielded chlorocyanonorbornanone oxime(s) (V) which represented 15.5% of I. The benzene-soluble fraction, which accounted for the remaining 6.7% of the original mixture I was a viscous oil that could not be purified.

The chlorocyanonorbornanone oxime (V) was converted to a methylcarbamate (VII). This O-(methylcarbamoyl)oxime (VII) unlike VI, was very soluble in common nonpolar organic solvents like benzene and ether and was extremely difficult to purify. Nevertheless, the compound was obtained in sufficient purity to allow an accurate bioassay.

Using pure VI as a reference standard it has been demonstrated by n.m.r. analysis that the methylcarbamate II, obtained from the mixture of oximes I, contained about 80% of this isomer VI. The remainder appeared to be the methylcarbamate (VII) obtained from chlorocyanonorbornanone oxime (V).

The three chlorocyanonorbornanone oximes III, IV, and V represent 93.3% of the original chlorocyanonorbornanone oxime (I). The presence of three major

physically different components in I has been confirmed by thin layer chromatography. A 8:2 benzene–ethyl acetate mixture eluted three distinguishable spots when I was placed on silica gel. Brom cresol green was used to develop the spots which were yellow on a blue field.

Excluding the added complexity of *syn* and *anti* aliphatic hydroxyimino groups, and assuming the cyano group retained its *endo* configuration during the synthetic sequence, one would expect II to be composed of at least three chlorocyanonorbornanone O-(methylcarbamoyl)oximes. These are shown below.
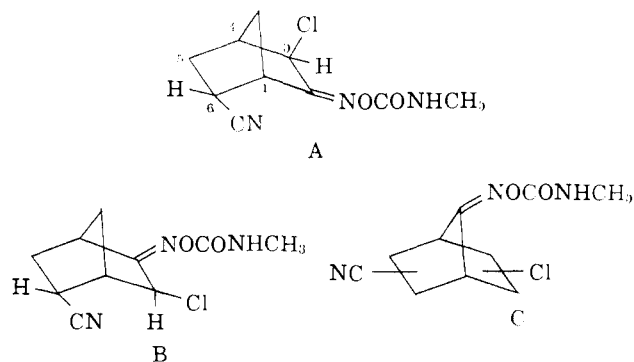
Isomers A and B would result from the initial addition of NOCl to the unsymmetrical double bond of 5-norbornene-*endo*-2-carbonitrile. Isomers having the hydroxyimino function on the methylene bridge as shown in C could result from skeletal rearrangement during the reaction of nitrosyl chloride with 5-norbornene-*endo*-2-carbonitrile *via* a "nonclassical" carbonium intermediate. The structure of the major isomer VI was determined by n.m.r. studies and found to be *exo*-3-chloro-*endo*-6-cyano-2-norbornanone O-(methylcarbamoyl)oxime[3] (A) as elucidated herein.

Nuclear Magnetic Resonance Studies on Methylcarbamate VI. Position and Configuration of the Chlorine Atom.

That the chlorine is *exo* is indicated by the established *cis,exo* mode of addition of nitrosyl chloride to the norbornene system.[4-6] More conclusively, the hydrogen at C-3 appears as a doublet at 4.47 p.p.m. in the n.m.r. spectrum (Figure 1). Miller observed a doublet at 4.4 p.p.m. (CDCl₃) for the analogous proton in 3-chloronorcamphor oxime.[7] The lines of the doublet are separated by 2.3 c.p.s. which is characteristic for the *endo* configuration of the proton.[8] Therefore, the chlorine at C-3 must be *exo*. When the hydrogen is *exo*, the dihedral angle with the vicinal bridgehead hydrogen is such that the spin–spin coupling constant is 4–5 c.p.s.[6,8,9] Since the pattern consists of a simple doublet the other vicinal carbon has no hydrogen atoms. This then places the chlorine adjacent to the hydroxyimino function.

Position and Configuration of the Cyano Group.

The *endo* configuration has been assigned to the cyano group since pure 5-norbornene-*endo*-2-carbonitrile was used as a starting material. Epimerization of the

(3) Coded U. C. 20047A.
(4) J. Meinwald, Y. C. Meinwald, and T. N. Baker, *J. Am. Chem. Soc.*, **85**, 2513 (1963).
(5) T. N. Baker, "The Addition of Nitrosyl Chloride to Norbornadiene and Norbornene," University Microfilms, Inc., Ann Arbor, Mich., 1964.
(6) J. Meinwald, Y. C. Meinwald, and T. N. Baker, *J. Am. Chem. Soc.*, **86**, 1073 (1964).
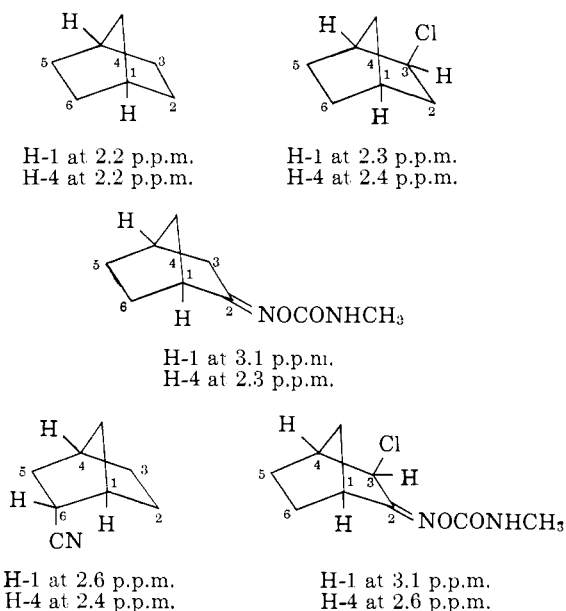(7) J. B. Miller, *J. Org. Chem.*, **26**, 4905 (1961).
(8) F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961).
(9) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

cyano group can be induced with strong bases,[10,11] but no such reagent was employed in the reaction sequence to VI. Further confirmation of the geometry is obtained from the n.m.r. spectrum. The resonance position of the hydrogen on the carbon bearing the cyano group was about 3.1 p.p.m. in $CDCl_3$ and was observed to be a complex multiplet consisting of five major lines (Figure 1). This resonance multiplet was more completely resolved in pyridine solution and was centered at 3.24 p.p.m. (Figure 2). The high degree of splitting is the result of spin–spin coupling to the *exo* and *endo* hydrogens of the vicinal methylene along with a fairly large coupling of about 4 to 5 c.p.s. to the adjacent bridgehead hydrogen. This pattern places the cyano in the *endo* position. If the cyano group had been *exo*, the multiplet would have been simpler due to zero coupling of the *endo* proton to the adjacent bridgehead hydrogen, resulting in a maximum of four lines.[8,12,13]

The position of the cyano group at C-6 can also be ascertained from the n.m.r. spectrum. The proton at C-1 gives a signal at 4.06 p.p.m. This strong paramagnetic shift is a result of the inductive and anisotropic effects of the hydroxyimino group combined with the similar but lesser influence of the adjacent cyano group. The proton at C-4 gives a response at 2.7 p.p.m. This is the proper position for the signal of a bridgehead proton adjacent to a chlorine and to a methylene group.[7]

In order to verify these assignments which prove the position of the cyano group the n.m.r. spectra of the following model compounds were studied.

H-1 at 2.2 p.p.m.
H-4 at 2.2 p.p.m.

H-1 at 2.3 p.p.m.
H-4 at 2.4 p.p.m.

H-1 at 3.1 p.p.m.
H-4 at 2.3 p.p.m.

H-1 at 2.6 p.p.m.
H-4 at 2.4 p.p.m.

H-1 at 3.1 p.p.m.
H-4 at 2.6 p.p.m.

As shown by the model compounds, the downfield shift of the bridgehead proton is most pronounced when there is an adjacent hydroxyimino function. Miller observed peaks at 3.53 and 2.96 p.p.m. ($CDCl_3$) for the bridgehead proton adjacent to the hydroxyimino group in 3-chloronorcamphor oxime.[7] The two

(10) P. S. Starcher and C. A. Noffsinger, Research Department, Chemicals Division, Union Carbide Corp., private communication.

(11) W. R. Boehme, E. Schipper, W. G. Scharpf, and J. Nichols, *J. Am. Chem. Soc.*, **80**, 5488 (1958).

(12) R. R. Fraser, *Can. J. Chem.*, **40**, 78 (1962).

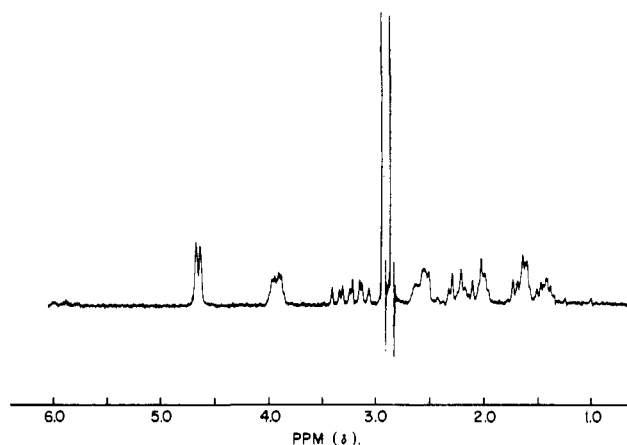(13) E. W. C. Wong and C. C. Lee, *ibid.*, **42**, 1245 (1964).

Figure 2.—N.m.r. spectrum of *exo*-3-chloro-*endo*-6-cyano-2-norbornanone O-(methylcarbamoyl)oxime in pyridine.

peaks were attributed to *syn* and *anti* forms. A paramagnetic effect is induced to a lesser extent by an adjacent chlorine or cyano group. Therefore the cyano group must be at C-6 relative to the hydroxyimino group at C-2 with both groups contributing to the strong downfield shift of the adjacent proton.

The lower melting isomer VII was an amorphous solid which could not be obtained in a sufficient state of purity to allow a conclusive determination of structure by n.m.r. analysis.

Biological Data.—Bioassay of the isomeric chlorocyanonorbornanone O-(methylcarbamoyl)oximes against the two-spotted mite (*Tetranychus telarius* L.) (Table I) indicates a high order of activity for *exo*-3-chloro-*endo*-6-cyano-2-norbornanone O-(methylcarbamoyl)oxime (VI), the major isomer produced by the synthetic route described herein. Isomer VII and the isomeric mixtures are less effective. Compound VI is a cholinesterase inhibitor with an $I_{50} = 2 \times 10^{-6}\ M$.[14] The acute oral LD_{50} to the female albino rat is 25 mg./kg. (1% in propylene glycol).[15]

TABLE I
ACARICIDAL ACTIVITY

Compd.	*Tetranychus telarius* L. LD_{50}, p.p.m.[a]
Crude chlorocyanonorbornanone O-(methylcarbamoyl)oximes[b]	36
Isomeric O-(methylcarbamoyl)oximes II	20
O-(Methylcarbamoyl)oxime VI[c]	12
O-(Methylcarbamoyl)oxime VII	32
1,1-Bis(*p*-chlorophenyl)-2,2,2-trichloroethanol[d]	12

[a] Aqueous dispersions applied to infested plants on a turntable; see H. L. Haynes, J. A. Lambrech, and H. H. Moorefield, *Contrib. Boyce Thompson Inst.*, **18**, 507 (1957). [b] U.C. 20047. [c] U.C. 20047A. [d] Kelthane®.

Experimental

Melting points are uncorrected and were determined on a Mel-Temp apparatus in open capillary tubes. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. The infrared spectra were determined in KBr pellets on

(14) Warburg manometric technique using housefly head brei; see H. H. Moorefield and E. R. Tefft. *Contrib. Boyce Thompson Inst.*, **19**, 295 (1958).

(15) C. P. Carpenter, private communication.

a Baird-Atomic Model 4–55 and the n.m.r. spectra were run on a Varian 60 Mc. spectrometer in $CDCl_3$.[16]

5-Norbornene-*endo*-2-carbonitrile Nitrosochloride Dimer.—To a well-cooled solution of 120 ml. (1.44 moles) of concentrated HCl and 120 ml. of isopropyl alcohol was added 35.7 g. (0.3 mole) of 5-norbornene-*endo*-2-carbonitrile. The solution was stirred at −5° while 23 g. (0.333 mole) of sodium nitrite in 50 ml. of water was added dropwise over 20-min. period. The resulting slurry was stirred at −5° for an additional hour, diluted with an approximately equal volume of water, and filtered. The precipitate was transferred to a beaker and stirred with 250 ml. of water and again filtered. The process of washing was repeated twice and the precipitate finally was washed with a small amount of cold (−20°) methanol and allowed to dry *in vacuo*. The resulting nitrosochloride dimer was a white powder with a slight green-blue tinge. It weighed 52 g. (94% yield based on olefin charged) and melted at 170–173° dec. when heated at 10° per min. in a block preheated to 150°.

Anal. Calcd. for $C_8H_9ClN_2O$: C, 52.0; H, 4.9; N, 15.2. Found: C, 51.7; H, 5.1; N, 15.0.

Reaction of the same olefin in ether solution with NOCl resulted in a 94% yield of nitrosochloride dimer melting at 159–163°. In pentane solution a 95% yield of nitrosochloride dimer was obtained; m.p. 156–160°.

Chlorocyanonorbornanone Oxime (I).—To a 1-l. flask containing 540 ml. of dioxane and 150 mg. of benzylamine was added 60 g. of 5-norbornene-*endo*-2-carbonitrile nitrosochloride dimer. The slurry was stirred and heated rapidly to 98°. The solid dissolved in 25 min. to give a green solution. This solution was stirred at 98° for an additional 2.5 hr. during which the solution turned yellow. The dioxane was then stripped from the product rapidly under reduced pressure. A 45° water bath was employed to supply heat to the kettle. The last traces of dioxane were removed from the product by chasing with 500 ml. of xylene and collecting about 300 ml. of distillate. During this rapid distillation the kettle temperature was not allowed to exceed 35°. The xylene slurry was filtered and the solid was washed thoroughly with xylene. There was obtained 55 g. (92%) of oxime: m.p. 134–151°; infrared, NOH at 3.07, C≡N at 4.40, and N–O at 10.35 μ.[17]

Anal. Calcd. for $C_8H_9ClN_2O$: C, 52.0; H, 4.9; N, 15.2. Found: C, 51.9; H, 5.0; N, 15.1.

Separation of the Chlorocyanonorbornanone Oxime Isomers.—A 45-g. sample of the above-mentioned oxime (I) was stirred at 60° with 250 ml. of $CHCl_3$. The hot slurry was filtered and the insoluble white solid was washed thoroughly with hot chloroform. After drying the solid weighed 15 g. (33.3% of I) and melted at 171–173° dec. (III). This oxime was insoluble in benzene and ether but soluble in ethyl acetate and isopropyl alcohol and very slightly soluble in water.

Anal. Calcd. for $C_8H_9ClN_2O$: C, 52.0; H, 4.9; N, 15.2. Found: C, 51.8; H, 5.2; N, 15.0.

The chloroform extracts were combined and the solvent was evaporated at low temperature under reduced pressure. The solid was thoroughly agitated with boiling isopropyl ether and the hot slurry was filtered. After drying, the insoluble solid weighed 20 g. (44.5% of I) and melted at 152–155° (IV). The melting point was raised to 157–158° by thoroughly washing with hot benzene. The loss in weight was negligible. The same

(16) The authors wish to thank H. L. Joyce for obtaining the infrared spectra and C. B. Strow, Jr., for obtaining and interpreting the n.m.r. spectra.

(17) N. B. Colthup, L. H. Daly, and S. E. Wiberley, "Introduction to Infrared and Raman Spectroscopy," Academic Press Inc., New York, N. Y., 1964, p. 389.

melting point can be obtained by recrystallization from ethanol or xylene.

Anal. Calcd. for $C_8H_9ClN_2O$: C, 52.0; H, 4.9; N, 15.2. Found: C, 51.7; H, 5.2; N, 14.9.

The isopropyl ether filtrate was evaporated *in vacuo* at room temperature or lower. The solid residue was washed with xylene and dried to afford 9 g. (20% of I) of a solid, m.p. 112–131°. This solid was recrystallized several times from a small amount of benzene giving 7 g. (15.5% of I) of an oxime (V), m.p. 113–115.5°.

Anal. Calcd. for $C_8H_9ClN_2O$: C, 52.0; H, 4.9; N, 15.2. Found: C, 51.7; H, 5.1; N, 14.8.

Evaporation of the benzene gave an oil that could not be induced to crystallize.

Chlorocyanonorbornanone O-(Methylcarbamoyl)oximes. Methylcarbamate VI.—One part of oxime III, m.p. 170–173°, was allowed to react with four parts of methyl isocyanate at 40° for 4 hr. in a pressure bottle. The excess methyl isocyanate was stripped from the product under reduced pressure and the residue was recrystallized from isopropyl alcohol. The O-(methylcarbamoyl)oxime VI was obtained in 95% yield; m.p. 151–155°. A small sample was treated with Darco and recrystallized from ethanol and again from isopropyl alcohol. The resulting white needles, m.p. 159–160°, were used as an infrared reference standard; infrared, N–H at 3.02 and 6.63, C≡N at 4.48, C=O at 5.85, C–O at 7.95, and N–O at 10.45 μ.[17]

Anal. Calcd. for $C_{10}H_{12}ClN_3O_2$: C, 49.7; H, 5.0; N, 17.4. Found: C, 49.7; H, 4.9; N, 17.2.

Methylcarbamate VI.—One part of oxime IV, m.p. 157–159°, was dissolved in four parts of methyl isocyanate and allowed to react at 40° for 3 hr. in a pressure bottle. The excess methyl isocyanate was distilled rapidly *in vacuo* and the resulting residue was recrystallized from isopropyl alcohol. The methylcarbamate, m.p. 155–157°, was obtained in 95% yield. This compound did not depress the melting point of the pure O-(methylcarbamoyl)oxime obtained from oxime III. The infrared and n.m.r. spectra were the same and in a bioassay against five pests they were indistinguishable.

Methylcarbamate VII.—One part of oxime V, m.p. 113–115.5°, was dissolved in four parts of methyl isocyanate and allowed to react at 40° for 4 hr. Upon evaporation of the excess methyl isocyanate *in vacuo*, a white sticky solid was obtained. This solid (VII) was stirred with hexane, filtered, and dried; m.p. 54–57°. Attempts to further purify this product by recrystallization from a variety of solvents were unsuccessful; infrared, N–H at 2.92 and 6.63, C≡N at 4.41, C=O at 5.75, C–O at 8.05, and N–O at 10.5 μ.[17]

Anal. Calcd. for $C_{10}H_{12}ClN_3O_2$: C, 49.7; H, 5.0; N, 17.4. Found: C, 50.1; H, 5.3; N, 17.0.

Methylcarbamate II.—One part of oxime I was dissolved in four parts of methyl isocyanate and allowed to react at 40° for 4 hr. The excess methyl isocyanate was stripped from the reaction product under reduced pressure, and the product was held at room temperature under 3 mm. for 2 hr. The solid was stirred with cyclohexane, filtered, and washed with cyclohexane. After drying at 36° (2 mm.) for 16 hr. II melted at 56–120°, yield 98.5%. The compound was 98% pure by infrared analysis using VI (m.p. 159–160°) as a standard and measuring the optical density of the carbonyl absorption at 5.85 μ. N.m.r. studies indicate the product is approximately 80% O-(methylcarbamoyl)-oxime VI and 20% O-(methylcarbamoyl)oxime VII.