# Synthesis, Biological Activities, and Properties of the syn and anti *exo*-3-Chloro-*endo*-6-cyano-2-norbornanone *O*-(Methylcarbamoyl)oximes. Absolute Structure of Tranid Miticide

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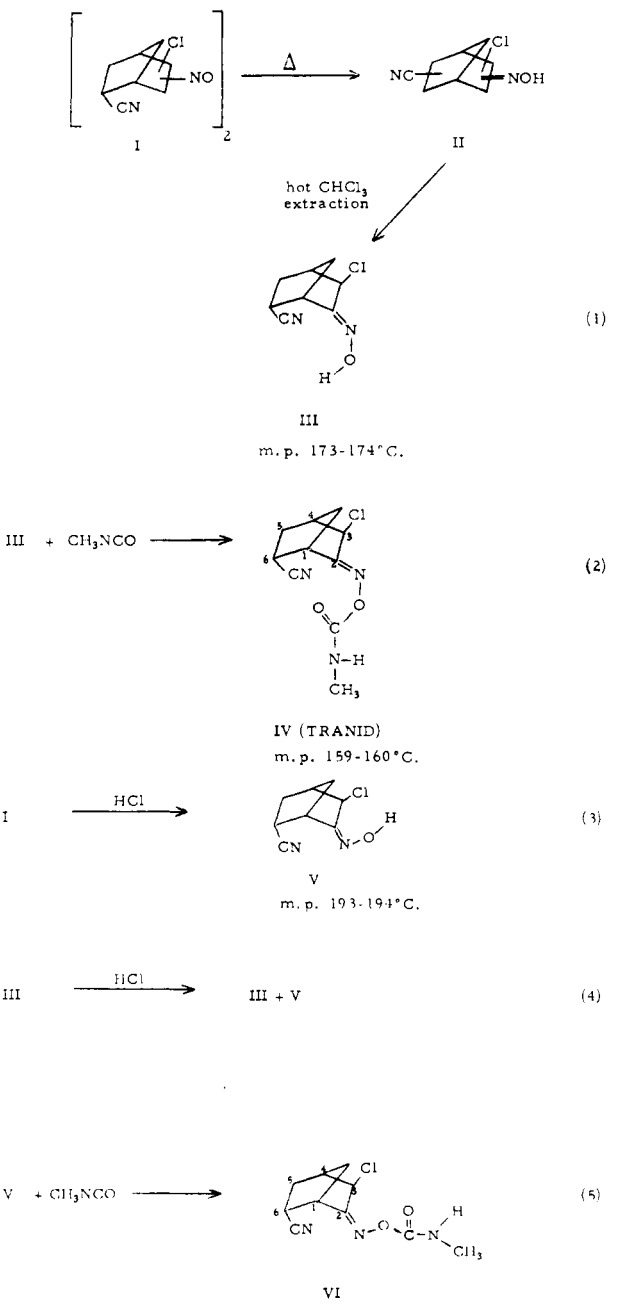
The syn and anti isomers of *exo*-3-chloro-*endo*-6-cyano-2-norbornanone oxime have been synthesized and identified by nuclear magnetic resonance spectroscopy. Reaction of the syn oxime with methyl isocyanate affords Tranid, establishing the absolute structure of this miticide. The anti oxime forms an isomeric methylcarbamate. The properties and biological activities of the two *O*-(methylcarbamoyl)-oximes are compared.

The 5-norbornene-*endo*-2-carbonitrile nitrosochloride dimer (I), upon thermal rearrangement, forms an isomeric mixture of oximes (II) from which a pure chloroform-insoluble oxime (III) can be obtained (Equation 1). Reaction of this oxime (III) with methyl isocyanate (Equation 2) affords a methyl carbamate (IV) which has been identified as *exo*-3-chloro-*endo*-6-cyano-2-norbornanone *O*-(methylcarbamoyl)oxime (U. C. 20047A; Tranid) (Payne *et al.*, 1965; Weiden *et al.*, 1965). Rearrangement of I in a steady current of hydrogen chloride has resulted in the isolation of a pure oxime, V, which is isomeric with III (Equation 3). When a smaller amount of hydrogen chloride was used, and added all at once, the isolated product was a mixture of isomeric oximes, III and V. Heating a dioxane solution of pure oxime III in the presence of hydrogen chloride caused a partial isomerization to oxime V (Equation 4). Reaction of V with methyl isocyanate resulted in the formation of an *O*-(methylcarbamoyl)oxime (VI), which was isomeric with IV (Tranid) (Equation 5). These observations are explained by a syn-anti relationship for oximes III and V. Nuclear magnetic resonance spectroscopy indicates that this is the case, oxime III being the syn isomer and oxime V the anti isomer. In this paper the isomer having the oximino oxygen cis to the bridgehead carbon, 1-C, is designated syn. Therefore, the absolute structure of Tranid is *exo*-3-chloro-*endo*-6-cyano-2-norbornanone syn-*O*-(methylcarbamoyl)oxime and VI has the anti configuration. These assignments also were confirmed by the NMR spectra of the *O*-(methylcarbamoyl) oximes.

The structure of Tranid has previously been determined as *exo*-3-chloro-*endo*-6-cyano-2-norbornanone *O*-(methylcarbamolyl)oxime (Payne *et al.*, 1965). No information has been reported regarding the configuration of the oxime function. Recent efforts in these laboratories resulted in the isolation of both the syn and anti isomers of high purity and allowed a determination and assignment of an absolute structure to each of these compounds.

NMR spectroscopy was first utilized in the determination of syn and anti oxime isomers by Phillips (1958), who studied the NMR spectra of simple aliphatic aldoximes and observed that the —CH=N— resonance consisted of two




DETERMINATION OF THE SYN-ANTI RELATIONSHIPS FOR OXIMES III AND V AND FOR TRANID AND METHYLCARBAMATE VI.

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triplets separated by approximately 0.6 p.p.m. Phillips postulated that the two signals were due to syn and anti isomers and that the proximity of oxygen induced a paramagnetic nuclear reasonance shift in the syn isomer. Therefore, the signal at lower field for —CH=N— could be assigned to the syn isomer and at higher field to the anti form. This technique could then be used to determine quantitatively the syn/anti ratio in a mixture of oximes or for identification purposes when the two isomers were available in the pure state.

The validity of Phillip's postulate was confirmed by Lustig (1961), who investigated the NMR spectra of pure syn and pure anti-*p*-chlorobenzaldehyde oximes. He observed that the origin of the —CH=N— multiplet in the anti isomer lies at higher field, by about 0.7 p.p.m., than that of the syn oxime.

Further support for this method was supplied by Slomp and Wechter (1962), who studied the syn (VII) and anti (VIII) isophorone oximes. These researchers demonstrated the deshielding effect of the oxime oxygen atom on the nearby proton at 2-C for the syn isomer in this approximately coplanar system. Thus, the signal for the syn 2H was observed to be at lower field by about 0.65 p.p.m. than the anti 2H. Conversely, the 6-$CH_2$ signal appeared at lower field in the anti isomer and higher field in the syn isomer.

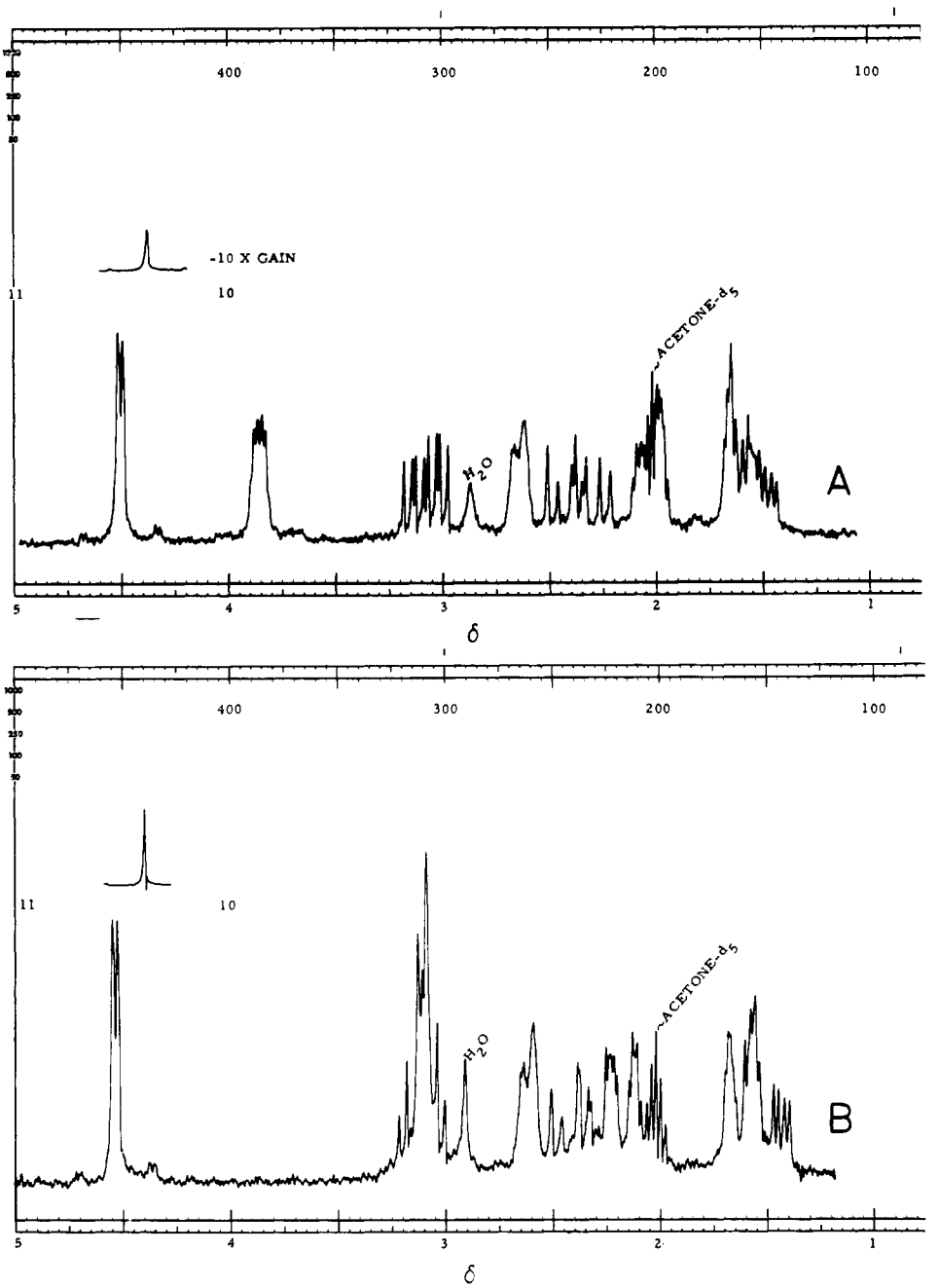
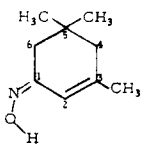


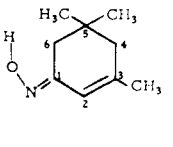

**Figure 1. NMR spectra**

*A. exo*-3-Chloro-*endo*-6-cyano-2-norbornanone syn-oxime (III)
*B. exo*-3-Chloro-*endo*-6-cyano-2-norbornanone anti-oxime (V) in $CD_3COCD_3$



Syn

VII



Anti

VIII

When this technique is employed with the *exo*-3-chloro-*endo*-6-cyano-2-norbornanone oximes, III and V, the proton at 1-C gives a signal at 3.85 p.p.m. for III (Figure 1*A*) and 3.1 p.p.m. for V (Figure 1*B*). Therefore, the oxime oxygen is deshielding 1H in III, showing it has the syn configuration, and V is the anti isomer. The infrared spectra of isomers III (Figure 2*A*) and V (Figure 2*B*) are clearly different and also serve as a basis for differentiating between the two oximes.

The same phenomenon is observed when the oximes, III and V, are converted to methylcarbamates. Oxime III gives Tranid (IV) which shows a signal for 1H at 4.03 p.p.m. (Figure 3*A*). Oxime V is converted to VI by the action of methyl isocyanate and the chemical shift for 1H in this compound is centered at 3.25 p.p.m. (Figure 3*B*). Thus, the chemical shift for 1H occurs at lower field in Tranid, which indicates it has the syn configuration. The infrared spectra of IV and VI are similar and are not as useful for differentiating the isomeric carbamates.

## BIOLOGICAL EVALUATION

The insecticidal and miticidal data recorded in Table I were obtained by the methods described previously (Payne *et al.*, 1966). Slight differences in activity of the two isomeric methylcarbamates are apparent with the bean aphid, the two-spotted mite, and the housefly. The acute oral $LD_{50}$ to the female albino rat is 25 mg. per kg. for Tranid and 7 mg. per kg. for VI. Isomer VI is slightly more effective as a cholinesterase inhibitor, having an $I_{50}$

**Table I. Activity of Isomeric *exo*-3-Chloro-*endo*-6-cyano-2-norbornanone *O*-(Methylcarbamoyl)oximes, IV and VI**

| | $LD_{50}$, P.P.M. | | | | |
|---|---|---|---|---|---|
| | BA[a] | M[a] | AW[b] | BB[b] | HF[c] |
| IV (Tranid) | 54 | 14 | >500 | 100 | 90 |
| VI | 28 | 20 | >500 | 120 | 225 |

BA. Bean aphid (*Aphis fabae*)
M. Two-spotted spider mite (*Tetranychus urticae*)
AW. Southern armyworm (*Prodenia eridania*)
BB. Mexican bean beetle (*Epilachna varivestis*)
HF. Housefly (*Musca domestica*)

[a] Spray test. [b] Leaf feeding test. [c] Bait test.

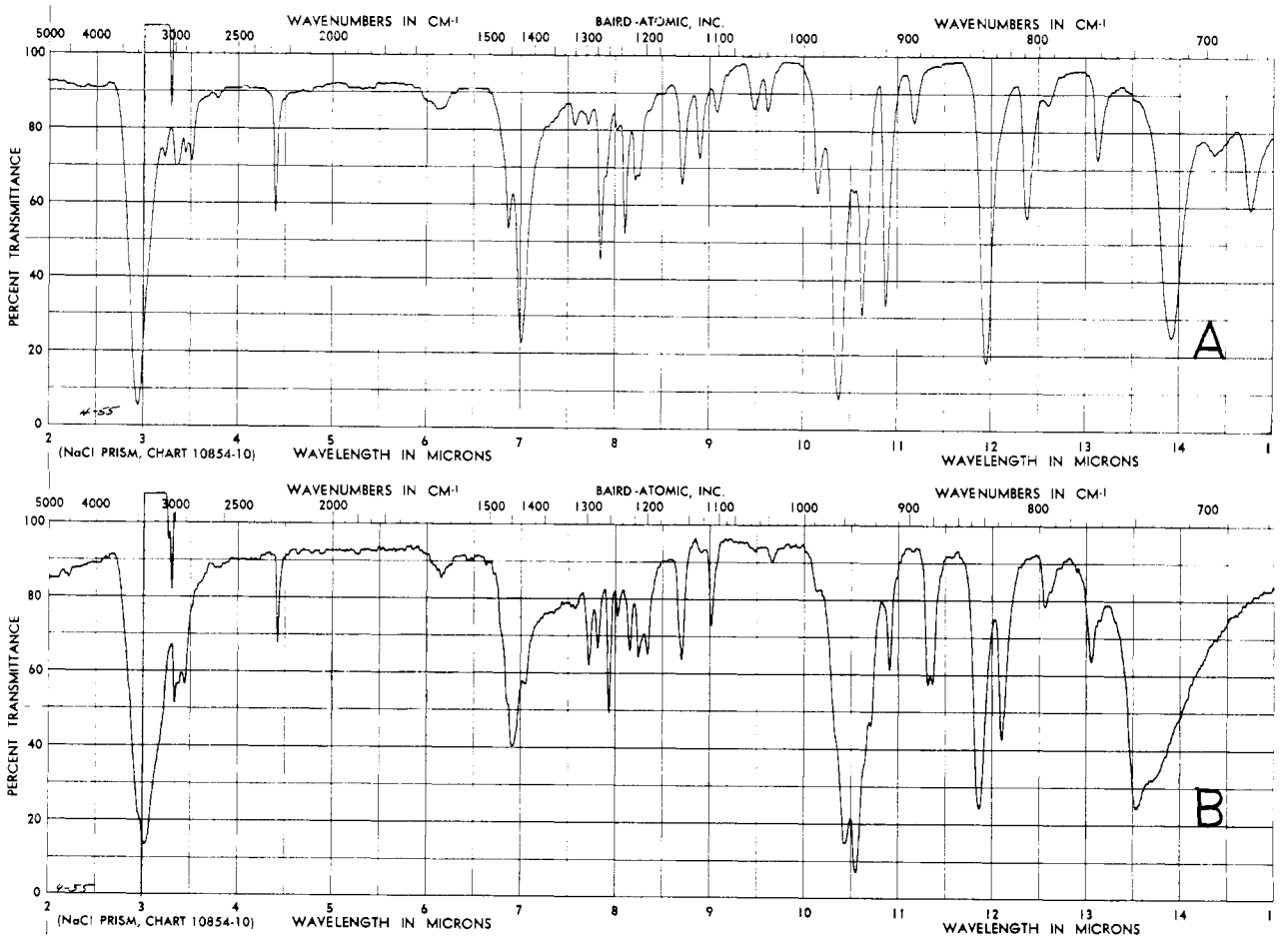



**Figure 2. Infrared spectra in KBr pellet**

*A. exo*-3-Chloro-*endo*-6-cyano-2-norbornanone syn-oxime (III)
*B. exo*-3-Chloro-*endo*-6-cyano-2-norbornanone anti-oxime (V)

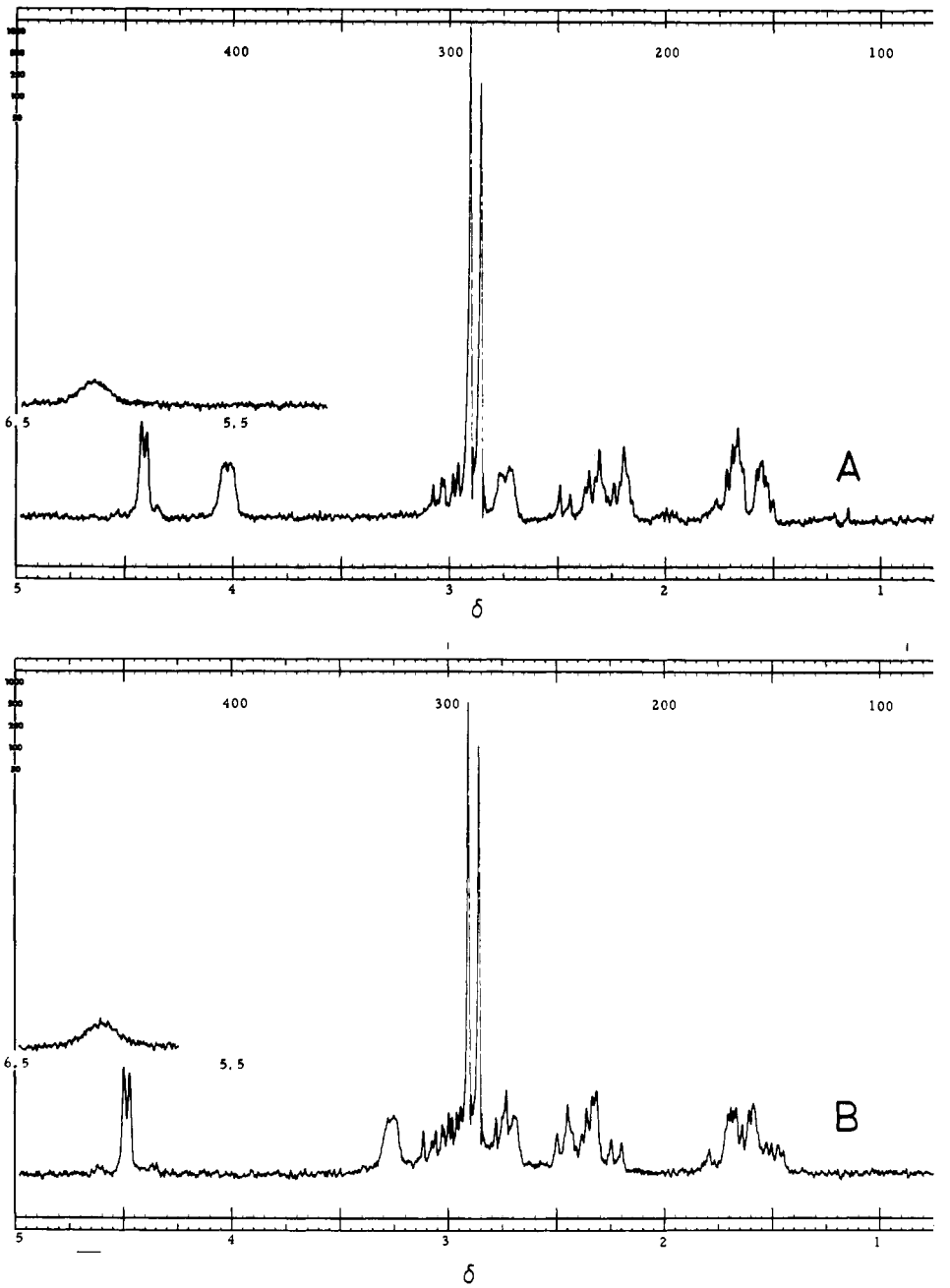



**Figure 3. NMR spectra**

*A. exo*-3-Chloro-*endo*-6-cyano-2-norbornanone syn-*O*-(methylcarbamoyl)oxime (Tranid; IV)
*B. exo*-3-Chloro-*endo*-6-cyano-2-norbornanone anti-*O*-(methylcarbamoyl)oxime (VI) in $CDCl_3$

$= 1 \times 10^{-6}$ compared with $2 \times 10^{-6}$ for Tranid, when determined by the Warburg manometric technique using housefly head brei according to Moorefield and Tefft (1958).

## EXPERIMENTAL

Melting points were obtained in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and by Union Carbide Research Associates, Brussels, Belgium. The infrared spectra were obtained on a Baird-Atomic Model 4-55 and the NMR spectra were run on a Varian 100-mc. spectrometer. The carbamates were scanned in $CDCl_3$ and the oximes in $CD_3COCD_3$ using TMS as an internal standard.

***exo*-3-Chloro-*endo*-6-cyano-2-norbornanone syn-Oxime (III).** The 5-Norbornene-*endo*-2-carbonitrile nitrosochloride dimer (I) was synthesized by the method of Payne *et al.* (1965). The nitrosochloride dimer was rearranged to a mixture of chlorocyanonorbornanone oximes and the chloroform-insoluble syn oxime separated as described previously; m.p. 171° to 173° C. (dec.). Repeated recrystallization from ethanol gave a product (III) which melted at 173° to 174° C. (dec.). A mixed-melting point determination with the anti isomer (V; m.p. 193° to 194° C.) melted at 152° to 158° C.

Anal. Calcd. for $C_8H_9Cl\ N_2O$: C, 52.0, H, 4.9, N, 15.2. Found: C, 51.9; H, 5.0; N, 15.1. (Infrared, see Figure 2*A*. NMR, see Figure 1*A*.)

*exo*-**3-Chloro-***endo*-**6-cyano-2-norbornanone anti-Oxime (V).** The 5-norbornene-*endo*-2-nitrosochloride dimer (100 grams) was slurried in 1,1,2-trichloroethane (600 ml.) and stirred at 104° to 108° C. for 2 hours while sparging with hydrogen chloride (0.25 mole per hour). The resulting dark brown solution was filtered and then stirred at 50° C. for 24 hours.

The solvent then was stripped from the product and the thick black residue extracted thoroughly with benzene and filtered. There was obtained 47 grams (47% yield) of crude *exo*-3-chloro-*endo*-6-cyano-2-norbornanone anti-oxime; m.p. 157° to 178° C. That this product was predominantly the anti isomer was supported by the presence of strong bands in the infrared spectrum at 11.35 and 12.1 microns, plus a strong band at 13.53 microns. The absence of absorption at 13.91 microns—a band characteristic for the syn isomer—also was noted. The oxime was purified by repeated recrystallization from isopropyl alcohol; m.p. 193° to 194° C.

Anal. Calcd. for $C_8H_8Cl\ N_2O$: C, 52.0; H, 4.9; N, 15.2. Found: C, 52.2; H, 5.0; N, 15.2. (Infrared, see Figure 2*B*. NMR, see Figure 1*B*.)

**Rearrangement of 5-Norbornene *endo*-2-Carbonitrile Nitrosochloride Dimer in Dioxane Containing Hydrogen Chloride.** The nitrosochloride dimer (I) was slurried in dioxane (720 grams) to which hydrogen chloride (5 grams) had been added. The reaction mixture was stirred at 98° to 100° C. for 5½ hours. The solid dissolved completely in about 4 hours to give a green solution which slowly turned yellow.

The solvent was stripped from the product under reduced pressure at a kettle temperature of 25° to 35° C. Xylene was used as a chaser to remove the last traces of dioxane and the solid was collected by filtration, washed with xylene, and allowed to air-dry. There were obtained 70 grams (88% yield) of isomeric oximes (II); m.p. 120° to 175° C.

A portion (65 grams) of the oxime mixture (II) was washed thoroughly with chloroform and the insoluble solid collected by filtration to give 48 grams (65% yield based on starting nitrosochloride dimer) of chloroform-insoluble oximes; m.p. 155° to 175° C. Analysis by NMR indicated the mixture was composed of 44% *exo*-3-chloro-*endo*-6-cyano-2-norbornanone syn-oxime and 56% of the anti oxime. Infrared analysis, using the absorbance of the 13.53- and 13.91-micron absorption bands, indicated that the mixture was composed of approximately 40% of the syn oxime and 60% of the anti isomer.

Anal. Calcd. for $C_8H_8Cl\ N_2O$: C, 52.0; H, 4.9; N, 15.2. Found: C, 52.2; H, 4.9; N, 15.0.

**Partial Isomerization of *exo*-3-Chloro-*endo*-6-cyano-2-norbornanone syn-Oxime to the anti Isomer.** The *exo*-3-*endo*-6-cyano-2-norbornanone syn-oxime (m.p. 171° to 173° C.) (5 grams) was dissolved in dioxane (50 grams) containing hydrogen chloride (2 grams). The solution was heated at 95° to 100° C. for 2 hours, during which time a copious evolution of HCl was observed. The solution was cooled, filtered, and the solvent evaporated in vacuo at 25° to 35° C. The resulting light purple solid was slurried in 50 ml. of benzene, filtered, and dried. There was recovered 4.6 grams of isomeric *exo*-3-chloro-*endo*-6-cyano-2-norbornanone oximes; m.p. 149° to 172° C. Infrared and NMR analyses indicated the mixture to be approximately a 50:50 mixture of syn and anti isomers.

*exo*-**3-Chloro-***endo*-**6-cyano-2-norbornanone syn-*O*-(Methylcarbamoyl)oxime (Tranid; IV).** This compound, m.p. 159° to 160° C., was synthesized from *exo*-3-chloro-*endo*-6-cyano-2-norbornanone syn-oxime (m.p. 170° to 173° C.), by reaction with methyl isocyanate as described previously (Payne *et al.*, 1965). (NMR, see Figure 3*A*.)

*exo*-**3-Chloro-***endo*-**6-cyano-2-norbornanone anti-*O*-(Methylcarbamoyl)oxime (VI).** The *exo*-3-chloro-*endo*-6-cyano-2-norbornanone anti-oxime (4.6 grams) was slurried in 25 ml. of methyl isocyanate and heated in a pressure bottle at 40° C. for 3 hours. The reaction mixture then was allowed to stand undisturbed for 5 days. The resulting solution was filtered and the solvent evaporated in vacuo to give a thick oil which foamed badly under vacuum. The residue was held at about 2 mm. overnight and the resulting sticky white solid induced to crystallize by agitation with isopropyl ether. Upon filtration of the isopropyl ether slurry 5 grams (80% yield) of a crystalline white solid was obtained, m.p. 113° to 114° C.

The carbamate was further purified by recrystallization from a mixture of isopropyl alcohol–isopropyl ether in a ratio of about 1 to 10. When the solution was allowed to cool slowly, a solid deposited which melted at 129° to 132° C. Repeated recrystallization from this solvent pair afforded a pure product melting at 133° to 134° C. to a colorless liquid.

A mixture of ethanol and heptane also was used to recrystallize the carbamate but was less satisfactory. The *exo*-3-chloro-*endo*-6-cyano-2-norbornanone anti-*O*-(methylcarbamoyl)oxime has a tendency to precipitate as a gum, which then solidifies unless allowed to cool slowly. The product obtained by rapid cooling of a warm solution of the anti carbamoyloxime melts over a range from 114° to 134° C.

A mixed melting point determination with Tranid (m.p. 157° to 159° C.) showed a strong depression, melting at 113° to 120° C.

Anal. Calcd. for $C_{10}C_{12}Cl\ N_3O_2$: C, 49.7; H, 5.0; N, 17.4; Cl, 14.7; O, 13.2. Found: C, 49.7; H, 5.0; N, 17.4; Cl, 15.1; O, 13.0. (NMR, see Figure 3*B*.)

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