Redox troponization as a novel method for the synthesis of stereoisomeric Eschenmoser's oximes and related non-benzenoid aromatic systems

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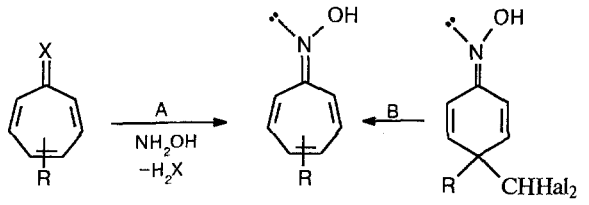
A novel method for the synthesis of the oxime of 4-methyl-2,4,6-cycloheptatrien-1-one (Eschenmoser's oxime) is proposed. The method involves redox enlargement of the ring of 4-dibromomethyl-4-methyl-2,5-cyclohexadien-1-one oxime through the action of $Ni(PPh_3)_4$ in DMF (in the presence of Zn). The product is formed as a mixture of *syn*- and *anti*-forms readily interconverting in solutions. A similar reaction of 4-methyl-4-trichloromethyl-2,5-cyclohexadien-1-one oxime afforded the dimer of a *gem*-α-centered semiquinoid carbene (1,2-bis-(1-methyl-4-oxyimino-2,5-cyclohexadienyl)-1,2-dichloroethylene), together with *syn*- and *anti*-isomers of 4-chloro-5-methyl-2,4,6-cycloheptatrien-1-one oxime, which are readily separable but also quickly interconverting in solutions. For the latter compounds, the complete ^1H NMR assignment of the stereoisomeric structures has been carried out.

Key words: non-benzenoid aromatic compounds, tropones, troponoximes, Pd^0 complexes in organic synthesis.

At present, two main synthetic strategies for the preparation of 2,4,6-cycloheptatrienone oximes (troponoximes **1**; Scheme 1) are known. One of these (path *A*) involves oximation of seven-membered cyclic ketones (**2**) or thioketones (**3**). The other strategy (path *B*) involves enlargement of the ring in a semiquinoid six-membered precursor that already contains an oxime group.

Scheme 1



2: X = O
3: X = S

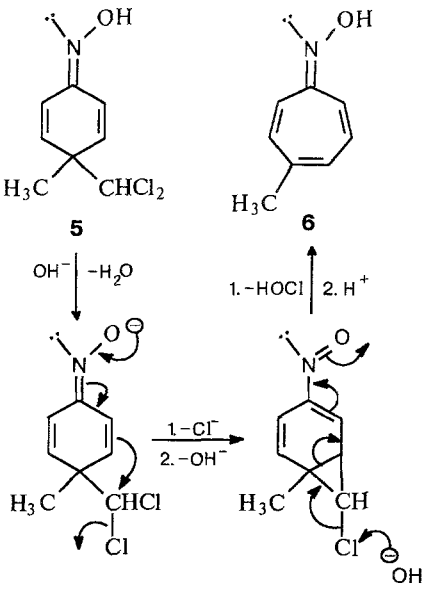
1 **4**

The use of the first approach is complicated by the facts that the starting tropones are difficult to obtain and their interaction with NH_2OH is ambiguous and may be accompanied by rearrangement of the *cine*-substitution type.[1] To prevent this, special expedients, such as the use of acids[1] or even replacement of the carbonyl group by the thiocarbonyl group (compound **3**),[3] should be used.

The second approach is based on the rearrangement of 4-dichloromethyl substituted 2,5-cyclohexadien-1-one oxime (**5**) into 4-methyltroponoxime (Eschenmoser's oxime (**6**)) discovered in 1958 by A. Eschenmoser (Scheme 2).[4]

It is believed that the first step of this reaction involves ionization of the OH group of the oxime fragment followed by transfer of the negative charge along

Scheme 2



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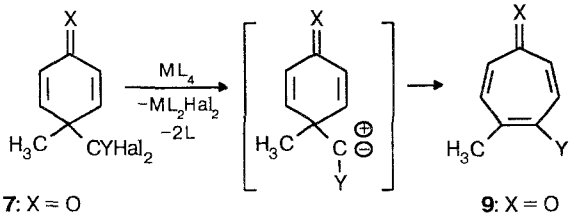
the n,π,π-conjugation system towards the α-position of the geminal unit of the molecule. Recently we discovered a fundamentally different type of troponoid enlargement of 2,5-cyclohexadienylidene derivatives containing C=O (**7**) and C=C (**8**) *exo*-bonds, which occurs under the action of *tetrakis*-triphenylphosphine complexes of Ni, Pd, and Pt to give product **9** (Scheme 3).

Scheme 3



7: X = O
8: X = CR_2 L = PPh_3
Y = H, Cl M = Ni, Pd, Pt
Hal = Cl, Br

In this reaction, the primary attack occurs directly at the 4-polyhalomethyl substituent, rather than at the unsaturated *exo*-C=X group, since the acting reagents in this case are zero-valent platinum metals having substantial affinities for halogen atoms (redox troponization, see Ref. 5 for a review).

In the present work, in order to elaborate a new version of the semiquinoid strategy of the synthesis of troponoximes (Scheme 1, path *B*), we studied the possibility of the occurrence of redox troponization of polyhalomethyl-substituted derivatives of type **5**, containing an *exo*-oxime group.

Results and Discussion

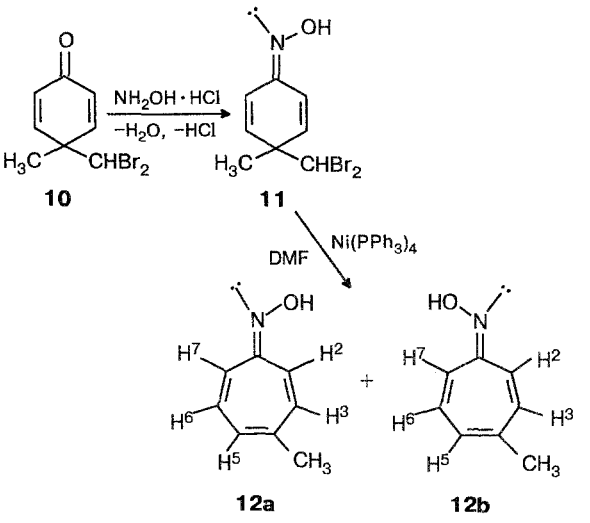
As the starting compound we chose the previously unknown 4-dibromomethyl-4-methyl-2,5-cyclohexadien-1-one oxime (**11**) prepared by the condensation of $NH_2OH \cdot HCl$ with 4-dibromomethyl-4-methyl-2,5-cyclohexadien-1-one (**10**). The latter was, in turn, obtained from *para*-cresol and the $CHBr_3/NaOH/C_{16}H_{33}NMe_3^+Br^-$ system by a PTC method (phase-transfer catalysis),[6] which had been adapted[7] to sterically hindered 2,5-disubstituted cyclohexadienones.

The reaction of compound **11** with $Ni(PPh_3)_4$ prepared *in situ* was carried out in DMF (Scheme 4) at 10 °C (at a 1:1 ratio between the reactants). Product **12** was isolated by thin-layer chromatography, and its structure was determined on the basis of spectroscopic data.

The mass spectrum of compound **12** exhibits a molecular ion peak at m/z = 135, whose fragmentation is typical of compounds of the tropone series.

The ^1H NMR spectrum of product **12** was interpreted on the basis of the data on chemical shifts and

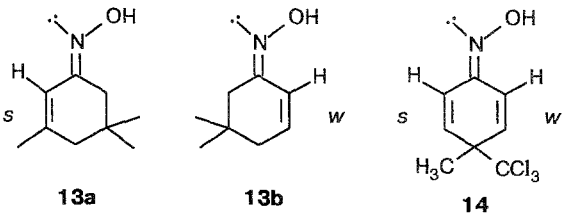
Scheme 4



spin coupling constants obtained by us previously[8] for substituted tropones and also using selective decoupling experiments.

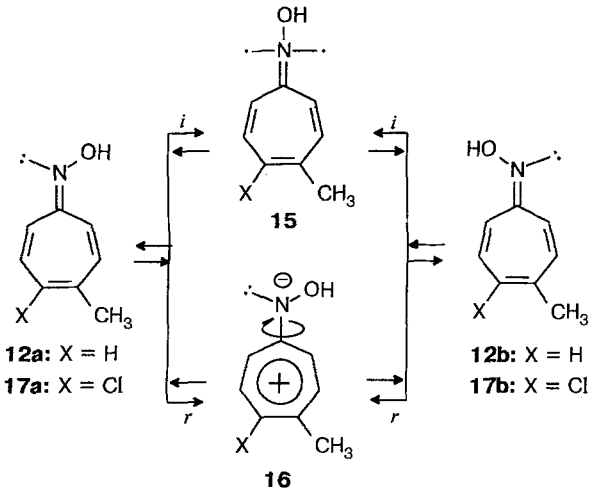
In the ^1H NMR spectrum of product **12**, one can clearly distinguish two groups of signals, which correspond to the *syn*- (**12a**) and *anti*-forms (**12b**) in a 2:1 ratio. The signal of the H(2) proton of the *syn*-form is the furthest downfield in the spectrum (6.92 ppm), since this proton is located next to the electron-withdrawing hydroxyl group, and, moreover, it is located in a non-alternate position with respect to methyl and, therefore, experiences no donating effect of the latter. It is interesting to note in this connection that the results that we have obtained for oximes of the non-benzenoid aromatic series are in complete agreement with the data obtained by Underwood *et al.*,[9] who showed using a variety of examples that the protons located in the *trans*-position with respect to the OH group (*i.e.*, situated in the neighborhood of the lone electron pair of nitrogen) in stereoisomeric unsaturated ketoximes of other types (Scheme 5) are the most shielded (**13a**), whereas the protons *trans*-arranged with respect to the lone electron pair (*i.e.*, in the vicinity of the OH group) are exhibited further downfield (**13 b**).

Scheme 5



s is high field, *w* is low field

Scheme 6



i is inversion, *r* is rotation

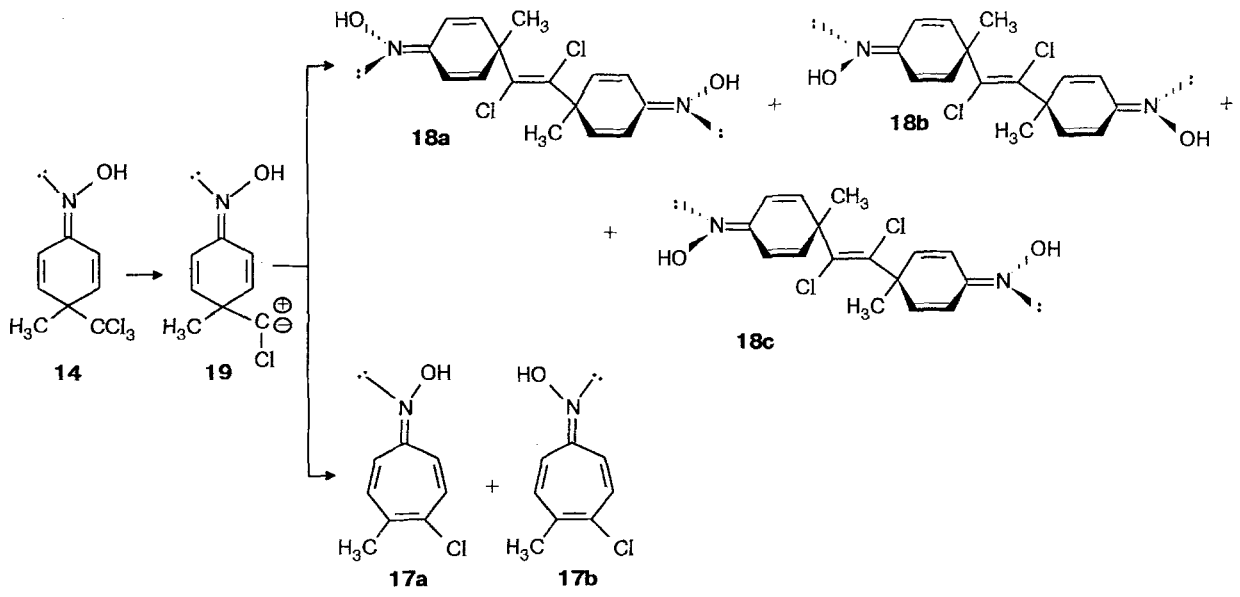
The signal of the H(7) proton is broadened due to long-distance spin coupling with the methyl-group protons (in this case, the calculation gives J = 0.7 Hz for protons).[8] Broadening of the signals of the H(5) proton in the *anti*- and *syn*-forms results from spin coupling with H(3) and the methyl-group protons (the calculation for the analogous tropone yields J = 1.3 Hz).[8] Our attempts to carry out preparative-scale separation of isomers **12a** and **12b** were unsuccessful. This may be due to spontaneous interconversion of the oximes in solution not only through the usual planar inversion (Scheme 6, **15**), but also *via* the possible rotation involving intermediate aromatization and the formation of dipolar intermediate **16**.

To confirm the general character of this reaction, we studied the interaction of $Ni(PPh_3)_4$ with 4-trichloromethyl-4-methyl-2,5-cyclohexadien-1-one oxime (**14**),[10] which contains a CCl_3 group in the geminal unit. This reaction was of additional interest, since one could hope that the resulting *syn*- and *anti*-troponoximes (**17**) would be stable and we would be able to separate them. The reaction of **14** with $Ni(PPh_3)_4$ was carried out under the same conditions as the reaction of compound **11**. Chromatographic separation of the resulting reaction mixture afforded two fractions (Scheme 7). The first of these contained 4-chloro-5-methyltroponoxime (**17**), and the second fraction contained the product of the reductive dimerization of oxime **14**, *viz.*, 1,2-bis(1-methyl-4-oximino-2,5-cyclohexadienyl)-1,2-dichloroethylene (**18**); the ratio between these products was 3 : 1. A similar dual reactivity of the reaction indicating the possible intermediacy of the substituted *para*-semiquinoid carbene **19** (in the singlet or triplet state) was observed previously for 4-trichloromethyl-4-methyl-2,5-cyclohexadien-1-one.[11]

The mass spectrum of dimer **18** exhibits a molecular ion peak and characteristic isotopic groups of peaks typical of molecules containing two chlorine atoms. The low-field region of the ^1H NMR spectrum of the product displays partially overlapping signals of two AB systems corresponding to the vinyl protons of the cyclohexadiene ring.* The mass spectrum of troponoxime **17** contains a molecular ion peak, whose subsequent frag-

* Under the conditions studied by us, no splitting of signals to indicate the presence of the mixture of stereoisomers presented in Scheme 6 as the racemic (**18a,b**) and *meso*-forms (**18c**) is observed in the ^1H NMR spectra of bis-oxime **18**. This seems to be due to the fact that the difference between the chemical shifts of these isomers is too small, since there are no specific factors in this reaction that would favor the predominant formation of either of the above-mentioned stereoisomers.

Scheme 7



mentation is typical of both oximes (the loss of the OH group) and troponoids (the loss of the CNOH group to give the radical cation of the corresponding arene). In the ^{1}H NMR spectrum of oxime **17** four AB systems occur, which indicates that the reaction yielded two stereoisomers. The assignment of signals to each of the isomers was carried out using spin-tickling.

The ratio between the isomers, **17a/17b** = 1:1, was determined by comparing the integral intensities of the two groups of signals. We were able to find chromatographic conditions for separating the **17a,b** mixture into individual isomers: using a hexane—ether (1:1) solvent system, two clearly distinguishable chromatographic zones with R_f 0.47 and 0.57 were detected on Silufol UV 254 plates. However, after these zones were eluted with ether, the ether was evaporated, and the residues were dissolved in $CDCl_3$, the ^{1}H NMR spectra of both solutions exhibited signals corresponding to equilibrium mixtures of stereoisomers (in a 1:1 ratio), which indicates quick interconversion of these isomers in solution.

Thus, it has been shown that the presence of the free hydroxyl in the oxime fragment does not prevent the reductive enlargement of the ring of *gem*-polyhalomethylated cyclohexadienone oximes. However, one cannot rule out the possibility of coordination bonding of some of the acting reagent ($Ni(PPh_3)_4$) to the oxime fragment under the reaction conditions, which can account for some decrease in the rate of the reaction of oximes and the total yield observed for these compounds compared with non-oximated cyclohexadienones, which we have studied previously.[5]

Experimental

NMR spectra were recorded on a Varian-VXR-400 instrument using TMS as the internal standard, and mass spectra were measured on an MS-1303 (at an ionizing voltage of 50 eV).

Thin layer chromatography was performed on Silufol UV-254 plates, and the spots were visualized by UV irradiation or by treatment by iodine vapor and then by water.

4-Dibromomethyl-4-methyl-2,5-cyclohexadiene-1-one oxime (11). Anhydrous ethanol (5 mL) and anhydrous pyridine (2.5 mL) were added to a mixture of 4-dibromomethyl-4-methyl-2,5-cyclohexadien-1-one[12] (0.5 g, 1.8 mmol) and hydroxylamine hydrochloride (0.49 g, 7.5 mmol). The reaction mixture was kept for 5 h at 85 °C, the solvent was evaporated, and the residue was treated with ether (10 mL). The ethereal solution was separated and washed with water (3×10 mL), and a part of the solvent was evaporated. The residual solution was treated with 10 mL of a 2 *N* solution of NaOH. The precipitate was separated, washed with benzene, suspended in 10 mL of water, and treated with 1 mL of 18 % HCl. The mixture was extracted with ether (15 mL), and the extract was concentrated. The resulting oxime was recrystallized from a hexane—benzene mixture (2:1) to give small crystals with a micaceous luster. Yield 0.37 g (70%), m. p. 122.5—123.5 °C. Found (%): C, 32.62; H, 2.81; N, 4.38. $C_8H_9Br_2NO$. Calculated (%): C, 32.57; H, 3.08; N, 4.75. ^{1}H NMR ($CDCl_3$), δ: 1.46 (s, 3 H); 6.07 (s, H); 6.52 and 6.77 (AB system, 2 H, J_{AB} = 12 Hz); 6.75 and 7.51 (AB system, 2 H, J_{AB} = 10 Hz); 8.08 (br s, H). MS, *m/z* (I_{rel}(%)): 293 $[M]^+$ (20), 214 $[M-Br]^+$ (49), 199 $[M-Br-CH_3]^+$ (26), 135 $[M-2Br]^+$ (40), 122 $[M-CHBr_2]^+$ (100).

4-Methyl-4-trichloromethyl-2.5-cyclohexadien-1-one oxime (14) was prepared from a mixture of 4-methyl-4-trichloromethyl-2,5-cyclohexadien-1-one (3 g, 13 mmol)[10] and hydroxylamine hydrochloride (3 g, 42 mmol) in anhydrous ethanol (30 mL) and anhydrous pyridine (15 mL) in a way similar to that described for compound **11**, as colorless crystals with a micaceous luster. Yield 3.0 g (94%), m.p. 126.5—127.5 °C, (lit.[10] m. p. 134 °C). Found (%): C, 39.74; H, 3.49; Cl, 45.10; N, 5.51. $C_8H_8Cl_3NO$. Calculated (%): C, 39.95; H, 3.35; Cl, 44.22; N, 5.83. ^{1}H NMR ($CDCl_3$), δ: 1.60 (s, 3 H); 6.43 (m, H); 6.61 (m, 2H); 7.20 (m, H); 10.80 (br s, H). MS, *m/z* (I_{rel}(%)): 239 $[M]^+$ (21), 204 $[M-Cl]^+$ (9), 189 $[M-Cl-CH_3]^+$ (19), 169 $[M-2Cl]^+$ (21), 122 $[M-CCl_3]^+$ (100).

Tetrakis-triphenylphosphinenickel. Anhydrous DMF (2 mL) was added with stirring under argon to a dry solid mixture of triphenylphosphine (0.132 g, 0.5 mmol), metallic zinc (0.131 g, 2 mmol), and $NiBr_2 \cdot 2PPh_3$ (0.185 g, 0.25 mmol). The color of the reaction mixture changed instantaneously from malachite to blood-red. The resulting solution of $Ni(PPh_3)_4$ was immediately used in reactions.

4-Methyl-2,4,6-cycloheptatrien-1-one oxime (4-methyltropone oxime) (12). A solution of 4-dibromomethyl-4-methyl-2,5-cyclohexadien-1-one oxime (0.120 g, 0.41 mmol) in anhydrous DMF (0.5 mL) was added dropwise over a period of 10 min to a solution of $Ni(PPh_3)_4$ (0.41 mmol) in DMF (7 mL) stirred in a flask filled with argon at 10 °C. The mixture was stirred for an additional 10 min without cooling and quenched with 10 mL of water. Ether (200 mL in 4 portions) was added, the ethereal solution was separated, and the solvent was evaporated. The resulting red-brown oil was chromatographed on a column with Silica gel L40/100 (l = 15 cm, d = 1.5 cm) using a benzene—ether mixture (3:2) as the eluent. The fraction with R_f = 0.48 was collected. It contained 4-methyltropone oxime **12**, which was obtained as a red-orange oil. The oil crystallized after thrice-repeated trituration with pentane. Yield 30 mg (54 %), m.p. 64—65 °C (lit.[4]: m.p. 63—65 °C). ^{1}H NMR ($CDCl_3$), δ for the *syn*-isomer: 2.60 (s, 3 H); 6.07 (br d, H(5), $^3J_{H(5)-H(6)}$ = 8 Hz); 6.10 (dd, H(6), $^3J_{H(6)-H(5)}$ = 8 Hz, $^3J_{H(6)-H(7)}$ = 12.4 Hz); 6.19 (dd, H(3), $^3J_{H(3)-H(2)}$ = 12.4 Hz, $^4J_{H(3)-H(5)}$ = 1.6 Hz); 6.29 (br d, H(7), $^3J_{H(7)-H(6)}$ = 12.4 Hz, $^4J_{H(7)-H(2)}$ = 2.8 Hz); 6.92 (dd, H(2), $^3J_{H(2)-H(3)}$ = 12.4 Hz, $^4J_{H(2)-H(7)}$ = 2.8 Hz); for the *anti*-isomer: 2.60 (s, H); 6.00 (br d, H(5), $^3J_{H(5)-H(6)}$ = 8 Hz); 6.08 (dd, H(3), $^3J_{H(3)-H(2)}$ = 12.4 Hz, $^4J_{H(3)-H(5)}$ = 1.8 Hz); 6.19 (dd, H(6), $^3J_{H(6)-H(5)}$ = 8 Hz, $^3J_{H(6)-H(7)}$ = 12.4 Hz); 6.34 (dd, H(2), $^3J_{H(2)-H(3)}$ = 12.4 Hz, $^4J_{H(2)-H(7)}$ = 2.8 Hz); 6.84 (dd, H(7), $^3J_{H(7)-H(6)}$ = 12.4 Hz, $^4J_{H(7)-H(2)}$ = 2.8 Hz). MS, *m/z* (I_{rel}(%)): 135 $[M]^+$ (100), 118 $[M-OH]^+$ (12), 103 $[M-OH-CH_3]^+$ (9), 92 $[M-CNOH]^+$ (76), 91 $[M-CNOH-H]^+$ (40), 77 $[M-CNOH-CH_3]^+$ (10).

4-Chloro-5-methyl-2,4,6-cycloheptatrien-1-one oxime (4-chloro-5-methyltropone oxime) (17). A solution of 4-trichloromethyl-4-methyl-2,5-cyclohexadien-1-one oxime (0.12 g, 0.5 mmol) in anhydrous DMF (0.5 mL) was added dropwise over a period of 10 min to a solution of $Ni(PPh_3)_4$ (0.5 mmol) in DMF (8 mL) stirred in a flask filled with argon

at 8 °C. The mixture was stirred for an additional 20 min without cooling and quenched with 5 mL of water. Ether (200 mL in 4 portions) was added, the ethereal solution was separated, and the solvent was evaporated. The resulting quickly crystallizing red-brown oil was chromatographed on a column with Silica gel L40/100 (l = 15 cm, d = 1.5 cm) using a benzene—ether mixture (3:2) as the eluent. Fractions with R_f = 0.57 and 0.38 were collected.

The fraction with R_f = 0.38 contained dimer **18**. Yield 18 mg (11 %). ^{1}H NMR ($CDCl_3$), δ: 1.48 (s, 3 H); 6.15 and 6.32 (AB system, 2 H, J_{AB} = 10); 6.32 and 7.93 (AB system, 2 H, J_{AB} = 10). MS, m/z (I_{rel}(%)): 338 $[M]^+$ (15), 321 $[M-OH]^+$ (20), 303 $[M-Cl]^+$ (13), 122 $[M-C_9H_8Cl_2NO]^+$ (78), 92 $[M-C_9H_8Cl_2NO-NO]^+$ (100).

From the fraction with R_f = 0.57, an oil containing a mixture of *cis*- and *trans*-isomers of 5-methyl-4-chlorotropone oxime was isolated. By reprecipitation with hexane from chloroform the oil was converted into red-orange crystals of compound **17**. Yield 29 mg (34%), m.p. 122—124 °C. ^{1}H NMR ($CDCl_3$) δ for the *syn*-isomer: 2.05 (s, 3 H); 6.06 (br d, H(6), $^3J_{H(6)-H(7)}$ = 12.8 Hz); 6.22 (br d, H(7), $^3J_{H(7)-H(6)}$ = 12.8 Hz); 6.32 (d, H(3), $^3J_{H(7)-H(2)}$ = 12.8 Hz); 6.73 (dd, H(2), $^3J_{H(2)-H(3)}$ = 12.8 Hz, $^4J_{H(2)-H(7)}$ = 1.2 Hz); for the *anti*-isomer: 2.05 (s, 3 H); 6.14 (d, H(6), $^3J_{H(6)-H(7)}$ = 12.8 Hz); 6.15 (br d, H(2), $^3J_{H(2)-H(3)}$ = 12.8 Hz); 6.24 (d, H(3), $^3J_{H(3)-H(2)}$ = 12.8 Hz); 6.77 (dd, H(7), $^3J_{H(7)-H(6)}$ = 12.8 Hz, $^4J_{H(7)-H(2)}$ = 1.6 Hz). MS, m/z (I_{rel}(%)): 169 $[M]^+$ (99), 152 $[M-OH]^+$ (16), 139 $[M-NO]^+$ (7), 126 $[M-CNOH]^+$ (93), 91 $[M-CNOH-Cl]^+$ (100).

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References

1. I. L. Buchanan and D. R. Lockhart, *J. Chem. Soc.*, 1959, 3586.
2. T. Nozoe, *Pure & Appl. Chem.*, 1982. **54**(5), 975.
3. T. Machiguchi, H. Otani, Y. Ishii, and T. Hasegawa, *Tetrahedron. Lett.*, 1987, **28**, 203.
4. J. Schreiber, M. Pesaro, W. Leimgruber, and A. Eschenmoser, *Helv. Chim. Acta.*, 1958. **41**(7), 2103.
5. V. A. Nikanorov, G. V. Gavrilova, S. V. Sergeev., V. I. Rozenberg, and O. A. Reutov, *Metalloorg. khim.*, 1989, **2**(1), 102 [*Organomet. Chem. USSR,* 1989, **2**(1) (Engl. Transl.)].
6. M. Makosza and N. Wawrzyniewich, *Tetr. Lett.*, 1969, (53), 4659.
7. M. Barbier, D. H. Barton, M. Devys, and R. S. Topgi, *Tetrahedron*, 1987, **43**(21), 5031.
8. V. I. Bakhmutov, M. V. Galakhov, V. A. Nikanorov, G. V. Gavrilova, V. I. Rozenberg, and O. A. Reutov, *Dokl. Akad. Nauk SSSR*, 1987, **295**(6), 1376 [*Dokl. Chem.*, 1987, **295**(6) (Engl. Transl.)].
9. G. R. Underwood and K. El Bayoumy, *J. Am. Chem. Soc.*, 1982. **104**, 3007.
10. T. Zincke, R. Suhl, *Ber.*, 1906, **39**, 4148.
11. G. V. Gavrilova, V. I. Bakhmutov, V. I. Rozenberg, V. A. Nikanorov, A. A. Gavrilov, and O. A. Reutov, *Metalloorg. khim.*, 1990, **4**(2), 299 [*Organomet. Chem USSR,*. 1990, **4**(1) (Engl. Transl.)]
12. M. Cobreros, F. Jato, E. Ravina, *Chim. Ther.*, 1973, **8**(4), 896.

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