Chemistry of Heterocyclic Compounds, Vol. 33, No. 7, 1997

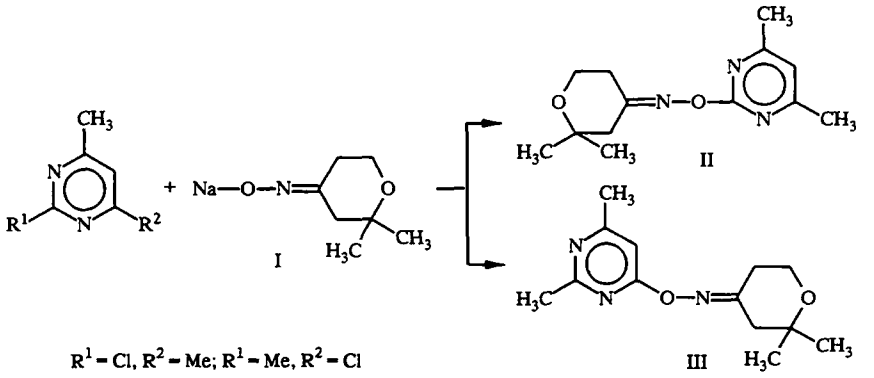
SYNTHESIS AND STRUCTURE OF CERTAIN O-PYRIMIDINYL-OXIMES OF 2,2-DIMETHYLTETRAHYDRO-4-PYRANONE

G. G. Danagulyan, A. A. Karapetyan, M. G. Zalinyan, N. G. Balasanyan, A. A. Safaryan, and N. Sh. Mailyan

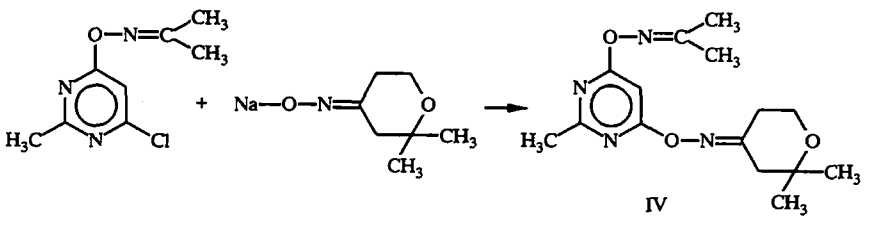
By reactions of substituted chloropyrimidines with the sodium salt of 2,2-dimethyltetrahydro-4-pyranone oxime, pyrimidinyloximes of 2,2-dimethyltetrahydro-4-pyranone have been obtained. On the basis of x-ray diffraction studies of the O-(2,4-dimethyl-6-pyrimidinyl)oxime of 2,2-dimethyltetrahydro-4-pyranone, it has been shown that the oxygen atoms of the oxime group and the carbon in position 2 of the pyran ring are in the anti *position relative to the double bond of the oxime.*

It has been established that certain mono- and dichloropyrimidines, when they interact with salts of substituted acetophenone oximes and aliphatic ketone oximes, form the corresponding O-pyrimidinylketoximes [1-3].

In the work reported here, we demonstrated that in the reactions of 2-chloro-4,6-dimethyl- and 2,4-dimethyl-6-chloropyrimidines with the sodium salt of 2,2-dimethyltetrahydro-4-pyranone (I), in dioxane, the O-(4,6-dimethyl-2-pyrimidinyl)oxime (II) and O-(2,4-dimethyl-6-pyrimidinyl)oxime (III) of 2,2-dimethyltetrahydro-4-pyranone are formed with high yields.



By interaction of the O-(2-methyl-4-chloro-6-pyrimidinyl)oxime of acetone, in DMF, with the salt of the same oxime I, the bis-adduct is obtained in a 90% yield, with a combined set of oxime groups, i.e., the O-(2-methyl-4-isopropylideneiminoxy-6-pyrimidinyl)oxime of 2,2-dimethyltetrahydro-4-pyranone (IV).



Erevan Institute of the National Economy, Erevan 375025. Molecular Structure Research Center, National Academy of Sciences of the Republic of Armenia, Erevan 375014. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 957-961, July, 1997. Original article submitted January 13, 1997.

 0009-3122/97/3307-0838$18.00

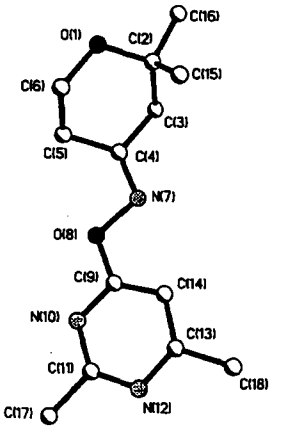
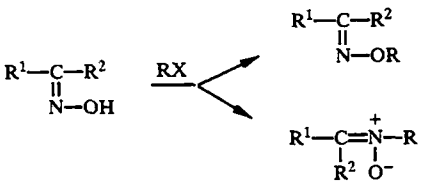


Fig. 1. Structure of molecule of compound III, with numbering of atoms.

The oxime III can also be obtained in DMF. For compound II, however, we were unable to accomplish the synthesis in this solvent; during the course of the reaction, we observed an increase of temperature, indicative of the occurrence of a condensation process; but in the stage of isolation of the compound and removal of the DMF under vacuum, tar was formed.

In the PMR spectra of all of the synthesized compounds, signals are observed from protons of the pyrimidine and tetrahydropyran rings, confirming that condensation has been accomplished. The spectra of compounds II and III are quite similar, with the only difference that the signals of the methyl groups of the pyrimidine ring in compound II coincide, whereas in compound III they have different chemical shifts. Let us note that the signal of the 5-H proton in the symmetric model II is displaced upfield by 0.4 ppm. Although the PMR spectra of all of the synthesized substances were close to what was expected, the spectra by themselves do not provide sufficient evidence for any positive statement that pyrimidinyloximes have been formed. Actually, O-substitution with nucleophilic attack of the oxygen atom appears to be the most probable; however, we cannot completely eliminate the possibility of the alternative process of N-hetarylization with attack of the nitrogen atom of the oxime and the formation of nitrones. It is known that the alkylation of oximes by alkyl halides and other alkylating agents may go either in the direction of obtaining the O-derivative or the direction of nitrone formation [4-6]; either process may predominate, depending on the nature and structure of the reactants and also on the reaction conditions.



The direction of condensation is determined by the geometric isomerism of the oxime [7, 8]. Thus, the *anti* isomers of benzaldoximes (arbitrarily assigned with respect to the methine hydrogen atom and the hydroxyl group) will give nitrones, whereas the *syn* isomers usually give the O-derivatives; this is apparently related to the steric accessibility of the nitrogen atom for electrophilic attack in the first case, and the accessibility of oxygen in the second case.

In order to elucidate the structure of compound III, we performed a structural analysis by x-ray diffraction, demonstrating that this is an oxime (Fig. 1); i.e., the addition is accomplished through the oxygen atom. In this molecule, the tetrahydropyran ring has a distorted chair conformation; deviations of atoms $O_{(1)}$ and $C_{(4)}$ from the mean square plane of the other ring atoms are −0.616 and 0.570 Å, respectively. The oxime group fragment, including the atoms $C_{(3)}$, $C_{(4)}$, $C_{(5)}$, $N_{(7)}$, $O_{(8)}$, is practically planar; the $N_{(7)}$ has the greatest individual deviation from the mean square plane of these atoms, 0.05 Å. The pyrimidine fragment is planar; the maximum individual deviation for any of the nine atoms included in the calculation of the mean square plane is no greater than 0.014 Å. The dihedral angles between the planes of the central fragment $C_{(4)}$, $N_{(7)}$, $O_{(8)}$, $C_{(9)}$, and the planes of the tetrahydropyran and pyrimidine ring were found to be 41.6° and 159.7°, respectively. The value of the torsion angle $C_{(3)}C_{(4)}-N_{(7)}O_{(8)}$ is −175.7°, indicating that the $O_{(8)}$ atom of the oxime group and the $C_{(2)}$ atom of the tetrahydropyran ring are in the *anti* position relative to the double bond $C_{(4)}=N_{(7)}$. The individual values of the bond

TABLE 1. Bond Lengths δ (Å) in Compound III

Bond	δ, Å	Bond	δ, Å
O(1)—C(2)	1,442(2)	O(8)—C(9)	1,360(2)
C(2)—C(15)	1,518(2)	C(9)—C(14)	1,382(2)
C(2)—C(16)	1,517(2)	C(13)—C(14)	1,379(2)
C(2)—C(3)	1,536(2)	C(13)—C(18)	1,493(2)
C(3)—C(4)	1,496(2)	N(10)—C(9)	1,324(2)
C(4)—C(5)	1,490(2)	N(10)—C(11)	1,341(2)
C(5)—C(6)	1,518(2)	C(11)—C(17)	1,496(2)
O(1)—C(6)	1,418(2)	N(12)—C(11)	1,330(2)
N(7)—C(4)	1,280(2)	N(12)—C(13)	1,344(2)
O(8)—N(7)	1,4550(14)		

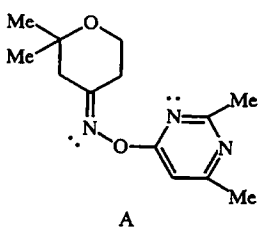
TABLE 2. Bond Angles ω (deg) in Compound III

Angle	ω(σ)	Angle	ω(σ)
C(6)—O(1)—C(2)	114,7(1)	C(9)—O(8)—N(7)	112,1(1)
O(1)—C(2)—C(3)	109,5(1)	O(8)—C(9)—C(14)	124,9(1)
O(1)—C(2)—C(15)	111,6(1)	N(10)—C(9)—O(8)	111,7(1)
O(1)—C(2)—C(16)	104,7(1)	C(9)—N(10)—C(11)	115,6(1)
C(15)—C(2)—C(16)	110,9(2)	N(10)—C(9)—C(14)	123,4(1)
C(15)—C(2)—C(3)	110,5(1)	N(10)—C(11)—C(17)	116,7(2)
C(16)—C(2)—C(3)	109,5(1)	N(12)—C(11)—N(10)	126,2(1)
C(4)—C(3)—C(2)	111,5(1)	C(13)—C(14)—C(9)	116,5(1)
C(5)—C(4)—C(3)	115,2(1)	C(14)—C(13)—C(18)	121,8(1)
C(4)—C(5)—C(6)	108,8(1)	N(12)—C(13)—C(14)	121,6(1)
O(1)—C(6)—C(5)	112,2(1)	N(12)—C(11)—C(17)	117,1(2)
N(7)—C(4)—C(3)	116,2(1)	N(12)—C(13)—C(18)	116,6(1)
N(7)—C(4)—C(5)	128,5(1)	C(11)—N(12)—C(13)	116,7(1)
C(4)—N(7)—O(8)	109,5(1)		

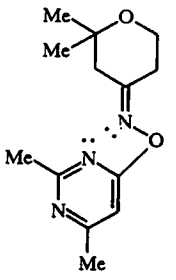
lengths and angles (Tables 1 and 2) are in good agreement with the corresponding standard values [9], so that no special comments are required.

Thus, on the basis of the x-ray diffraction data, we can state unambiguously that the products from these reactions are indeed pyrimidinyloximes of 2,2-dimethyltetrahydro-4-pyranone.

By means of molecular mechanics with the MMI&P2 method (QCPE 358), we calculated the possible conformations of compound III and analyzed all of the conformation models that are formed, depending on the rotation around the N−O and O−C bonds (pyrimidine). These calculations indicated that the energy minimum corresponds to an *anti* isomer, in particular conformer A, the structure of which coincides completely with that of the model described above. For this structure, the stress due to nonvalence interactions is at a minimum. At the same time, the most highly stressed for an *anti* isomer is structure B, which is 40 kcal/mole less favorable than the conformer with structure A.



A



B

Analogous calculations for the isomeric compound II show that in this case the *syn* form is more favorable; it proves to be approximately 80 kcal/mole more favorable energetically than the *anti* form. In view of the coincidence of results of x-ray structure analysis and calculation methods for compound III, and also the results of the calculations for compound II, we can conclude tentatively that compound II is a *syn* isomer.

EXPERIMENTAL

The PMR spectra were taken on a Varian T-60 instrument in CCl_4 and $CDCl_3$, internal standard TMS. The TLC was performed with Silufol UV-254 plates, development by iodine vapor and Erlich reagent.

Oxime of 2,2-Dimethyltetrahydro-4-pyranone (I). To a mixture of 64 g (0.5 mole) of 2,2-dimethyltetrahydro-4-pyranone and 35 g (0.5 mole) of hydroxylamine hydrochloride in 25 ml of ethanol and 25 ml of water, a hot solution of 28 g (0.026 mole) of Na_2CO_3 in 60 ml of water was added dropwise; then the mixture was refluxed while stirring for 4-5 h. The next day, the mixture was extracted with ether, and the solution was dried with calcium chloride. The ether was driven off, and the residue was vacuum-distilled, obtaining 58.6 g (82%) of compound I, bp 104-105°C/5 mm Hg, n_D^{20} 1.4880. Found, %: C 58.91; H 9.18; N 9.65. $C_7H_{13}NO_2$. Calculated, %: C 58.74; H 9.09; N 9.79.

O-(4,6-Dimethyl-2-pyrimidinyl)oxime of 2,2-Dimethyltetrahydro-4-pyranone (II). To 0.1 mole of the sodium salt of 2,2-dimethyltetrahydro-4-pyranone oxime, obtained at 70-75°C by slow addition of a solution of 15.7 g (0.11 mole) of the oxime I in 60 ml of absolute dioxane to 2.3 g (0.1 mole) of a sodium suspension in 100 ml of dioxane, with subsequent heating to complete dissolution of the sodium, there was added at 75°C a solution of 7.1 g (0.05 mole) of 2-chloro-4,6-dimethylpyrimidine in 40 ml of dioxane. The temperature of the mixture was raised to 80-82°C, and NaCl precipitated out. The reaction mixture was left for 5 h. The precipitate was filtered off, the solvent was removed under vacuum, 20 ml of water was added to the residue, and this mixture was extracted with chloroform. The chloroform extract was dried with magnesium sulfate. The solvent was driven off, ether was added to the residue, and the crystals that were formed were filtered off, obtaining 7.5 g (60%) of compound II, mp 135°C (from acetone), R_f 0.44 (benzene–acetone, 4:1). Found, %: C 62.89; H 7.91; N 16.55. $C_{13}H_{19}N_3O_2$. Calculated, %: C 62.63; H 7.68; N 16.86. PMR spectrum, ppm (CCl_4): 1.40 (3H, s, 2′-CH_3); 1.42 (3H, s, 2′-CH_3); 2.48 (2H, s, 3′-H); 2.50 (6H, s, 4- and 6-CH_3); 2.8 (2H, m, 5′-H); 3.95 (2H, dt, 6′-H); 6.70 md (1H, s, 5-H).

O-(2,4-Dimethyl-6-pyrimidinyl)oxime of 2,2-Dimethyltetrahydro-4-pyranone (III). A. Analogously, by reaction of 0.05 mole of the sodium salt of the oxime I and 3.55 g (0.025 mole) of 2,4-dimethyl-6-chloropyrimidine in 100 ml of absolute dioxane at 70-75°C, obtained 4.4 g (71%) of compound III.

B. To 0.011 mole of the sodium salt of the oxime I, obtained in 50 ml of absolute ether by the interaction of 0.25 g (0.011 mole) of a sodium suspension and 2.9 g (0.02 mole) of the oxime I, after driving off the ether, 25 ml of DMF was added; then, after dissolution of the salt, a solution of 1.43 g (0.01 mole) of 2,4-dimethyl-6-chloropyrimidine in 10 ml of DMF was added. The mixture was heated and then was left for 5 h. Then the solvent and the excess oxime I were distilled off by heating on a water bath, under vacuum; 100 ml of hexane was added to the residue, and the precipitated material was filtered off. The filtrate was evaporated down, 5 ml of petroleum ether was added to the residue, and the precipitated crystals were filtered off, obtaining 2.0 g (80%) of compound III, mp 108°C, R_f 0.45 (benzene–acetone, 4:1). Found, %: C 62.41; H 7.71; N 16.75. $C_{13}H_{19}N_3O_2$. Calculated, %: C 62.63; H 7.68; N 16.86. PMR spectrum, ppm ($CDCl_3$): 1.33 [6H, s, 2′-$(CH_3)_2$]; 2.47 (2H, s, 3′-CH_2); 2.55 (3H, s, 2-CH_3); 2.67 (3H, s, 4-CH_3); 2.85 (2H, t, $J_{5',6'}$ = 7 Hz, 5′-CH_2); 3.9 (2H, t, $J_{6',5'}$ = 7 Hz, 6′-CH_2O); 7.01 md (1H, s, 5-H).

O-(2-Methyl-4-isopropylideneiminoxy-6-pyrimidinyl)oxime of 2,2-Dimethyltetrahydro-4-pyranone (IV). To 0.011 mole of the sodium salt of the oxime I, obtained in absolute ether from 0.25 g (0.11 mole) of a sodium suspension and 2.9 g (0.02 mole) of the oxime I, after driving off the ether, there was added a solution of 2 g (0.01 mole) of the O-(2-methyl-4-chloro-6-pyrimidinyl)oxime of acetone [3] in 50 ml of DMF, after which the mixture was heated for 6 h at 75°C. After removing the solvent under vacuum, 35 ml of water was added to the residue, after which the precipitate was filtered off and washed with 15 ml of a 5% $NaHCO_3$ solution and then with 5 ml of water. The residue was air-dried, obtaining 2.8 g (90%) of compound IV, mp 172-174 °C, R_f 0.41 (benzene–acetone, 4:1). Found, %: C 58.41; H 7.11; N 18.05. $C_{15}H_{22}N_4O_2$. Calculated, %: C 58.81; H 7.24; N 18.29. PMR spectrum, ppm ($CDCl_3$): 1.35 [6H, s, 2′-$(CH_3)_2$]; 2.10 (2H, d, 3-CH_2); 2.45 C3H, s, 2-CH_3); 2.55 [6H, s, $(CH_3)_2$]; 2.8 (2H, t, 5′-H); 3.95 (2H, t, 6′-H); 6.25 md (1H, s, 5-H).

X-Ray Structure Study of Compound III. The elementary cell constants and the intensities of 2676 independent reflections were measured in an Enraf-Nonius CAD-4 four-circle automatic diffractometer (λMoKα, $\omega/2\theta$ scanning, graphite monochromator, θ_{max} = 26°). The crystals are triclinic: a = 8.046(2), b = 8.439(2), c = 10.802(2) Å, α = 80.31(3), β = 82.15(3), γ = 71.82(3)°, V = 684.1(3) Å^3, M = 249.3, d_{calc} = 1.21 g/cm^3, Z = 2, space group P-1.

The structure was deciphered by the direct method with LMS refinement in the anisotropic approximation for the nonhydrogen atoms. All of the H atoms were identified in a difference synthesis of electron density and were incorporated into a refinement in the isotropic approximation. The structural calculations were performed on an IBM 486 computer, using SHELXTL-93 programs. The final values of the divergence factors was R = 0.041 on the basis of 2532 reflections with I > 2σ(I). A general view of the molecule, with numbering of the atoms, is shown in Fig. 1. The coordinates of the atoms and the values of the equivalent isotropic temperature parameters will be furnished by the authors upon request.

This work was performed within the framework of a scientific theme (No. 96-559) subsidized from sources of the State Centralized Financing of the Republic of Armenia, and also with financial support from the International Science Fund (Grant MVT 000).

REFERENCES

1. G. G. Danagulyan, N. G. Balasanyan, P. B. Terent'ev, and M. G. Zalinyan, Khim. Geterotsikl. Soedin., No. 12, 1644 (1989).
2. G. G. Danagulyan, N. G. Balasanyan, and M. G. Zalinyan, Khim. Geterotsikl. Soedin., No. 4, 563 (1988).
3. G. G. Danagulyan, N. G. Balasanyan, M. G. Zalinyan, A. V. Topchyan, and P. B. Terent'ev, Khim. Geterotsikl. Soedin., No. 7, 950 (1997).
4. L. I. Smith, Chem. Rev., **23**, 222 (1938).
5. J. Hamer and A. Maculuso, Chem. Rev., **64**, 474 (1964).
6. J. March, Organic Chemistry [Russian translation], Mir, Moscow (1987), Vol. 2, p. 139.
7. O. L. Brady, F. B. Dunn, and R. F. Coldstein, J. Chem. Soc., 2386 (1926).
8. E. Buchler, J. Org. Chem., **32**, 261 (1967).
9. F. H. Allen, O. Kennard, and D. G. Watson, J. Chem. Soc., Perkin Trans. II, No. 1, S1 (1987).