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

SYNTHESIS AND BIOLOGICAL ACTIVITY OF CERTAIN O-PYRIMIDINYLKETOXIMES

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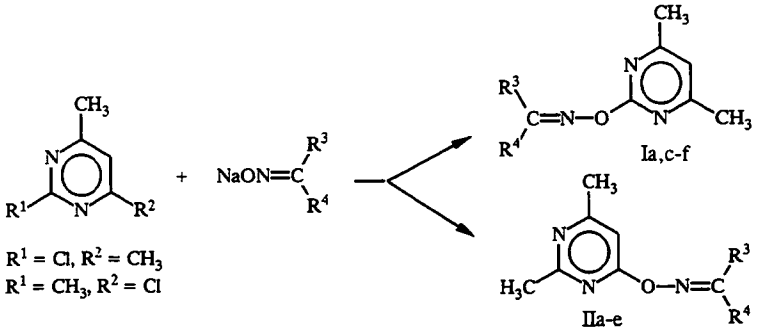
By the interaction of substituted chloropyrimidines with the sodium salts of oximes of aliphatic and alicyclic ketoximes, series of O-(4,6-dimethyl-2-pyrimidinyl)- and O-(2,4-dimethyl-6-pyrimidyl)ketoximes have been obtained. Through reactions of 2-methyl-4,6-dichloropyrimidine with salts of ketoximes, the corresponding monosubstituted and disubstituted products have been synthesized. The biological activities of the synthesized substances have been investigated.

We had reported previously on the synthesis and conversions of certain substituted pyrimidinyloximes of methyl aryl ketones [1]. Continuing our investigation of this series of compounds, we have now obtained new derivatives of 2-pyrimidinyl- and 6-pyrimidinylketoximes of the aliphatic series, and have studied their biological activity.

By reactions of 2-chloro-4,6-dimethyl- and 2,4-dimethyl-6-chloropyrimidines with the sodium salts of oximes of aliphatic and alicyclic ketones in DMF, we obtained (Scheme 1) the corresponding O-(4,6-dimethyl-2-pyrimidinyl)ketoximes (Ia,c-f) and O-(2,4-dimethyl-6-pyrimidinyl)ketoximes (IIa-e).

Scheme 1



I, II) R^3 = CH_3, a) R^4 = C_2H_5; b) R^4 = C_3H_7; c) R^4 = C_4H_9; d) R^4 = *i*-C_4H_9; e) R^4 = C_6H_{13}; If) R^3–R^4 = $(CH_2)_4$

By the interaction of 2-methyl-4,6-dichloropyrimidine with the sodium salts of the oximes of acetone and methyl ethyl ketone, we obtained with high yields either monosubstituted products, namely O-(2-methyl-4-chloro-6-pyrimidinyl)ketoximes (III) (Scheme 2) (at room temperature with a 1:1 reactant ratio), or the bis-adduct, in this case when the dichloropyrimidine was heated with a threefold excess of the salt of acetone oxime.

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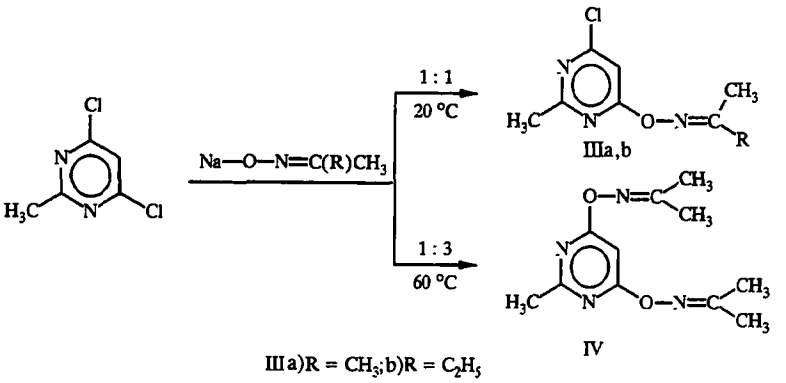
0009-3122/97/3307-0831$18.00

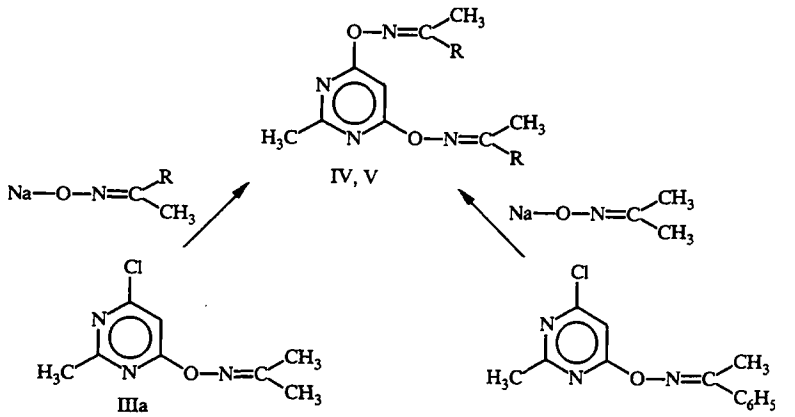
Scheme 2



IIIa)R = CH_3;b)R = C_2H_5

The disubstituted product can also be obtained by direct interaction of the chloropyrimidinylketoximes III with the sodium salt of the ketone oxime; depending on which ketoxime is used, this makes it possible to obtain a disubstituted product with identical oxime groups or a bis-adduct with a combined set of oxime groups (Scheme 3).

Scheme 3



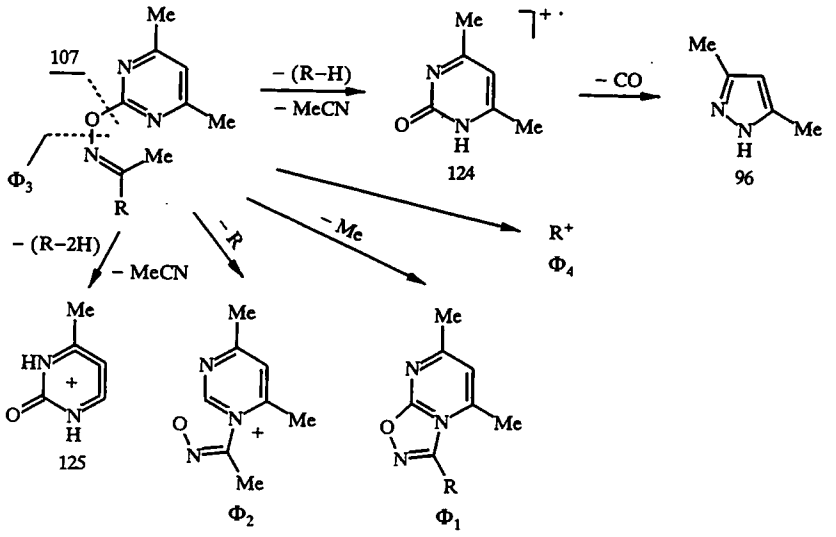
R = CH_3, C_6H_5

The PMR spectra of all of the synthesized compounds contain signals of protons of the pyrimidine ring and the oxime group, thus confirming the formation of condensation products. The symmetry of the pyrimidine residue in the compounds I is manifested in the PMR spectra by coincidence of the signals of the methyl groups in positions 4 and 6, whereas the protons of the hetaryl methyl groups in the compounds II differ in chemical shift. In the spectra of compounds IIIa and V, which contain a fragment of the oxime group of acetone, the signals of the alkyl groups are manifested separately as two singlets. The same sort of picture is observed in the spectrum of the dioxime IV, where two methyl-group singlets are noted, the integral of each of which corresponds to six protons.

As indicated by analysis of the mass spectra of some of the pyrimidinylketoximes that we have synthesized (Table 1), the principal directions of decomposition of their molecular ions (Scheme 4) involve cleavage of the N–O bond with retention of the charge on the imine fragment — the ions Φ_1 and Φ_2. The high stability of these ions is probably explained by the possibility of their stabilization through electrophilic cyclization on the neighboring nitrogen atom of the heterocycle. Characteristic for the mass spectra of compounds I and II is the presence of ions 107* and an increased intensity of the peaks of the ions 124 and 125, formed by transfer, in the molecular ion, of one or two hydrogen atoms from the alkyl radical R to the nitrogen atom (or atoms) of the pyrimidine ring.

*Here and subsequently, the ion peaks are denoted by values of m/z.

Scheme 4



The total fraction of the indicated ions $\Phi_1-\Phi_4$ (approximately 30% of all of the ions) is considerably smaller than for pyrimidinyloximes of aromatic ketones; this indicates a lower selectivity of their decomposition under the influence of electron impact. In the mass spectra of all of the O-hetaryloximes, the same as in the aliphatic-aromatic oximes [1], there are no ions indicating any possibility of rearrangement in the process of decomposition, which had been observed previously in the spectra of other oximes [2, 3].

Thus, analysis of the character of fragmentation of compounds I and II provides unambiguous proof of their O-hetaryloxime structure.

In a study of the biological activity of the synthesized compounds, it was established that substances Ia,g and IIa,c affect the resistance of the blood vessels of the brain. Thus, compound Ia, with intracarotid injection into cats at a dose of 1 μg/kg, lowers the resistance of the brain vessels from 130 to 110 mm Hg (by 15.4%) with a length of action 10 min; in a dose of 2 μg/kg, it lowers the resistance by 35 mm Hg (from 135 to 100, a reduction of 26%), with a 15-min action. The introduction of compound Id (5 μg/kg) lowers the resistance of the brain blood vessels from 110 to 70 mm Hg (36.4%), without any significant shifts in the systemic pressure. Compound IIc in a dose of 2 μg/kg lowers the resistance of the brain blood vessels from 105 to 60 mm Hg (43%) with a 30-min action; however, larger doses of the preparation are toxic, resulting in paralysis of the respiratory center. The strongest and most extended effect on the tonus of the brain blood vessels and on the arterial pressure is that of compound IIa. At a dose of 2 μg/kg, the blood vessel resistance is lowered from 120 to 70 mm Hg, or 41.7%, the effect lasting for 45 min. When the dose is increased to 1 mg/kg, the resistance of the vessels is lowered from 140 to 80 mm Hg (42.9%), with a brief reduction of the arterial pressure from 130 to 70 mm Hg, followed by a very rapid recovery of the arterial pressure in 2-3 min; the perfusion pressure remains at the lower level for another 45 min.

Compounds Ic and IId manifest high toxicity in all of the doses that were investigated.

Compound Id exhibits antiviral activity against influenza virus; IIc has a moderate effect on variolovaccine virus; IIIb manifests activity against Venezuelan equine encephalomyelitis (MPK 100 μg/ml).

EXPERIMENTAL

PMR spectra were registered on a Varian T-60 instrument in CCl_4 and $CDCl_3$, internal standard TMS. Mass spectra were taken in an LKB-2091 instrument with an ionization energy of 70 eV, direct introduction of the substance into the ion source, and automatic computerized data processing. Thin-layer chromatography was performed with Silufol UV-254 plates and a 3:1 mixture of benzene and acetone as the eluent, development by iodine vapor and Erlich reagent.

O-(4,6-Dimethyl-2-pyrimidinyl)ketoximes and O-(2,4-Dimethyl-6-pyrimidinyl)ketoximes (Ia,c-f, IIa-e) (General Procedure). To 2.5 g (0.11 mole) of a sodium suspension in 300 ml of absolute ether, a solution of 0.12 mole of the appro-

TABLE 1. Intensities of Characteristic Ions Peaks in Mass Spectra of Compounds $R-C(CH_3)=N-O-Het$

Compound	R	W_M	Φ_1	Φ_2	Φ_3
Ia	C_2H_5	1,6	0,8	15,4	11,5
Ic	C_4H_9	5,1	—	8,6	11,8
Id	i-C_4H_9	1,8	0,6	6,8	6,9
If	$(R + CH_3)-(CH_2)_4$	4,2	10,1*	10,1	3,7
IId	i-C_4H_9	2,4	1,1	13,8	9,0

Compound	m/z_{124}	m/z_{125}	m/z_{107}	m/z_{96}	$R^+(\Phi_4)$	m/z_{42}
Ia	0,4	—	0,9	3,9	—	32,5
Ic	4,2	—	0,7	3,1	5,0	23,6
Id	3,4	10,2	0,8	3,3	12,2	14,4
If	1,8	3,3	1,2	10,0	8,8*2	1,1
IId	3,8	4,1	1,4	2,1	16,2	—

*$\Sigma(M - C_nH_{2n})$, n = 2 ... 3.
*2ΣC_nH2_{n-1}, n = 2, 3.

priate oxime in 100 ml of absolute ether was added dropwise over the course of 30 min. The mixture was stirred until the metallic sodium had completely disappeared (10-12 h), after which the ether was driven off, and 50 ml of DMF was added to the residue. After stirring for 15 min, if the sodium salt had completely dissolved, the oxime was decanted from the residue of unreacted sodium; then, a solution of 14.3 g (0.1 mole) of the appropriate chloropyrimidine in 30 ml of DMF was added; in order to avoid tar formation, the temperature was not allowed to rise above 35°C. The mixture was stirred for 2-3 h at room temperature and then left overnight. The DMF was removed by vacuum distillation to dryness at a temperature of 45-50°C, after which the residue was cooled, 20 ml of water was added, the mixture was extracted with chloroform (2 × 100 ml), and the extract was dried with magnesium sulfate. After driving off the chloroform, the residue was vacuum-distilled (Table 2).

O-(2-Methyl-4-chloro-6-pyrimidinyl)oximes of Acetone and Methyl Ethyl Ketone (IIIa,b). In the same manner as just described, from 0.69 g (0.03 mole) of a sodium suspension in 50 ml of absolute ether and 0.03 mole of the oxime of acetone (2.2 g) or methyl ethyl ketone (2.6 g), the sodium salt of the oxime was obtained; to this mixture, without driving off the ether, a solution of 4.9 g (0.03 mole) of 2-methyl-4,6-dichloropyrimidine in 40 ml of DMF was added with cooling (10-12°C), after which the mixture was stirred at room temperature for an additional 15-18 h. After removing the solvents under reduced pressure, 50 ml of water was added to the residue, and this solution was extracted with chloroform. The extract was dried with magnesium sulfate. The solvent was driven off, and the residue was sublimed at 85-100°C (6 mm Hg) (compound IIIa) or was distilled in an inert gas atmosphere (compound IIIb) (Table 2).

2-Methyl-4,6-(diisopropylideneiminoxy)pyrimidine (IV). A. To the sodium salt of the oxime of acetone, obtained from 1.38 g (0.06 mole) of metallic sodium and 4.4 g (0.06 mole) of acetone oxime, prepared by the general method described above, a solution of 3.26 g (0.02 mole) of 2-methyl-4,6-dichloropyrimidine in 20 ml of DMF was added. The mixture was heated for 5-6 h at 50-60°C, after which the solvent was removed under reduced pressure; then 100 ml of chloroform was added to the residue, the solution was filtered, and the extract was dried with magnesium sulfate. The chloroform was driven off, and the residue was vacuum-distilled (Table 2).

B. The sodium salt of acetone oxime was prepared by the interaction of 3.65 g (0.05 mole) of acetone oxime with 1.035 g (0.045 mole) of a sodium suspension in 80 ml of absolute ether; after removing the ether, 25 ml of DMF was added, and then a solution of 4 g (0.02 mole) of the oxime IIIa in 25 ml of DMF. A temperature increase was observed. The mixture was left overnight, the solvent was driven off, 30 ml of water was added, and the residue was filtered off. Dried in air. Recrystallized from water. Yield 3.9 g (83%).

O-(2-Methyl-4-isopropylideneiminoxy-6-pyrimidinyl)oxime of Acetophenone (V). A. To the sodium salt of acetophenone oxime, obtained from 0.46 g (0.02 mole) of metallic sodium and 2.7 g (0.02 mole) of acetophenone oxime, a

TABLE 2. Characteristics of Compounds I-V

Compound	Empirical formula	Found, % / Calculated, %			bp, °C/mm Hg (or mp, °C)	n_D^{20}	d_4^{20}	R_f	PMR spectrum, δ, ppm	Yield, %
		C	H	N						
1	2	3	4	5	6	7	8	9	10	11
Ia	$C_{10}H_{15}N_3O$	62,37 / 62,15	8,05 / 7,82	21,50 / 21,74	118...119/4	1,5190	1,0415	0,35	1,24 (3H, t, $\underline{CH_3}CH_2$); 2,1 (3H, s, CH_3–C=N); 2,31 (6H, s, 4- and 6-CH_3); 2,35 (2H, q, CH_2–CH_3); 6,6 (1H, s, 5-H)	82
Ic	$C_{12}H_{19}N_3O$	64,91 / 65,13	8,48 / 8,65	19,14 / 18,99	122...124/2	1,5120	1,0185	0,40	0,71...1,64 (9H, m, C_4H_9); 2,0 (3H, s, CH_3C=N); 2,38 (6H, s, 4- and 6-CH_3); 6,69 (1H, s, 5-H)	80
Id	$C_{12}H_{19}N_3O$	65,40 / 65,13	8,89 / 8,65	19,21 / 18,99	115...116/1	1,5140	1,0228	0,42	1,15...1,7 (7H, m, $CH(CH_3)_2$); 1,8 (3H, s, CH_3–C=N); 1,85 (2H, d, CH_2–$CH(CH_3)_2$); 2,35 (6H, s, 4- and 6-CH_3); 6,72 (1H, s, 5-H)	79
Ie	$C_{14}H_{23}N_3O$	67,68 / 67,44	9,55 / 9,30	16,66 / 16,85	145...147/2	—	—	0,45	1,05...1,85 (13H, s, C_6H_{13}); 1,8 (3H, s, CH_3–C=N); 2,30 (6H, s, 4- and 6-CH_3); 6,65 (1H, s, 5-H)	80
If	$C_{11}H_{15}N_3O$	64,51 / 64,37	7,49 / 7,37	20,64 / 20,47	— (71...73)	—	—	0,43	1,4...1,6 (4H, m, 3'-CH_2 and 4'-CH_2); 1,8...2,0 (4H, t, 2'-CH_2 and 5'-CH_2); 2,3 (6H, s, 4- and 6-CH_3); 6,4 (1H, s, 5-H)	44
IIa	$C_{10}H_{15}N_3O$	62,40 / 62,15	7,97 / 7,82	21,51 / 21,74	120/4	1,5130	1,0384	0,5	1,15 (3H, t, $\underline{CH_3}CH_2$); 2,0 (3H, s, CH_3–C=N); 2,3 (2H, q, $\underline{CH_2}CH_3$); 2,32 (3H, s, 2-CH_3); 2,4 (3H, s, 4-CH_3); 6,77 (1H, s, 5-H)	82
IIb	$C_{11}H_{17}N_3O$	63,89 / 63,74	8,50 / 8,27	20,04 / 20,27	98/2	1,5080	1,0375	0,55	1,2...1,8 (5H, m, $\underline{CH_3CH_2}CH_2$); 2,0 (3H, s, CH_3–C=N); 2,28 (2H, q, $\underline{CH_2}CH_2CH_3$); 2,36 (6H, s, 2- and 4-CH_3); 6,82 (1H, s, 5-H)	80
IIc	$C_{12}H_{19}N_3O$	64,87 / 65,13	8,74 / 8,65	19,75 / 18,99	134...135/4	1,5035	0,9613	0,56	1,15...1,75 (9H, m, C_4H_9); 1,9 (3H, s, CH_3–C=N); 2,38 (3H, s, 2-CH_3); 2,40 (3H, s, 4-CH_3); 6,85 (1H, s, 5-H)	83

TABLE 2 (continued)

Compound	Empirical formula	Found, % / Calculated, %			bp, °C/mm Hg (or mp, °C)	n_D^{20}	d_4^{20}	R_f	PMR spectrum, δ, ppm	Yield, %
		C	H	N						
1	2	3	4	5	6	7	8	9	10	11
IId	$C_{12}H_{19}N_3O$	64,84 / 65,13	8,41 / 8,65	18,78 / 18,99	127/5	1,5022	1,0025	0,55	1,13...1,80 (9H, m, C_4H_9); 1,80 (3H, s, CH_3–C=N); 2,40 (3H, s, 2-CH_3); 2,43 (3H, s, 4-CH_3); 6,85 (1H, s, 5-H)	85
IIe	$C_{14}H_{23}N_3O$	67,65 / 67,44	9,09 / 9,30	16,62 / 16,85	132/2	1,4990	0,9848	0,50	1,1...1,9 (13H, m, C_6H_{13}); 1,9 (3H, s, CH_3–C=N); 2,25 (3H, s, 2-CH_3); 2,3 (3H, s, 4-CH_3); 6,80 (1H, s, 5-H)	82
IIIa	$C_8H_{10}ClN_3O$	47,87 / 48,13	5,18 / 5,05	21,24 / 21,05	85...100/6 subl. (78...79)	—	—	0,75	1,95 (3H, s, CH_2); 2,07 (3H, s, CH_3); 2,5 (3H, s, 2-CH_3); 6,83 (1H, s, 5-H)	75
IIIb	$C_9H_{12}ClN_3O$	50,42 / 50,59	5,41 / 5,66	19,50 / 19,65	111...112/3 (30...35)	—	—	0,77	1,1 (3H, t, $\underline{CH_3}CH_2$); 2,0 (3H, s, CH_3C=N); 2,3 (2H, q, $\underline{CH_2}CH_3$); 2,45 (3H, s, 2-CH_3); 7,0 (1H, s, 5-H)	57
IV	$C_{11}H_{16}N_4O_2$	55,80 / 55,92	6,65 / 6,82	23,57 / 23,71	132...134/2 (103...105)	—	—	0,57	1,9 (6H, s, CH_3); 1,98 (6H, s, CH_3); 2,30 (3H, s, 2-CH_3); 6,66 (1H, s, 5-H)	65
V	$C_{16}H_{18}N_4O_2$	64,24 / 64,41	5,91 / 6,08	18,95 / 18,78	— (175...176)	—	—	0,67	1,95 (3H, s, $(CH_3)_2C$=N); 1,98 (3H, s, $(CH_3)_2C$=N); 2,32 (3H, s, CH_3–C=N); 2,40 (3H, s, 2-CH_3); 6,9 (1H, s, 5-H); 7,3...7,6 (5H, m, C_6H_5)	67

solution of 4 g (0.02 mole) of the oxime IIIa in 25 ml of DMF was added. The mixture was heated for 6 h at 50-60°C, after which the solvent was removed under reduced pressure; 50 ml of water was added, and the precipitate was filtered off, washed with hexane, and recrystallized from a 4/1 mixture of benzene and acetone.

B. Analogously, from 0.012 mole of the sodium salt of acetone oxime and 2.6 g (0.01 mole) of the O-(2-methyl-4-chloro-6-pyrimidinyl)oxime of acetophenone [1] in 20 ml of DMF, obtained 1.9 g (64%) of compound V (Table 2).

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

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