SYNTHESIS OF SUBSTITUTED METHYL ARYL KETONE PYRIMIDINYLOXIMES AND THEIR REACTIONS WITH NUCLEOPHILES

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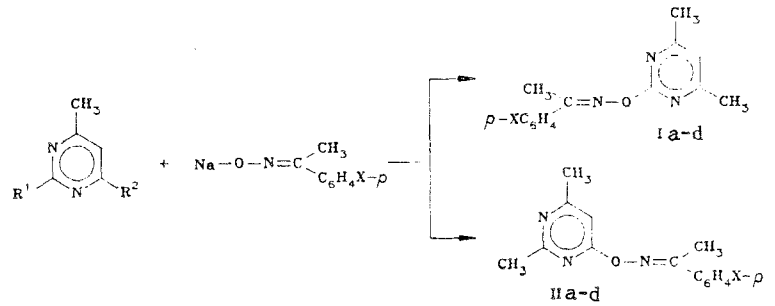
Chloropyrimidines react readily with the sodium salts of alkyl aryl ketoximes to give acetophenone O-(2,4-dimethylpyrimidin-6-yl)- and O-(4,6-dimethylpyrimidin-2-yl)oximes, the oximino-groups in which readily undergo nucleophilic substitution.

Nucleophilic substitution in pyrimidines has been extensively investigated [1, 2], especially in respect of replacement of chlorine [3, 4]. There are, however, no literature reports of the reactions of halopyrimidines with ketoximes to give O-substituted pyrimidinyloximes, although the compounds with the alternative bonding through nitrogen, hydroxyaminopyrimidines, are readily accessible [5].

The reaction between 2-chloro-4,6-dimethyl- and 2,4-dimethyl-6-chloropyrimidines and the sodium salts of acetophenone oxime and its substituted derivatives in small excess in DMF has given high yields of the acetophenone O-(4,6-dimethylpyrimidin-2-yl)- (Ia-d) and O-(2,4-dimethylpyrimidin-6-yl)oximes (IIa-d).



A R^1=Cl, R^2=CH_3; B R^1=CH_3, R^2=Cl; I, II a X=H; b X=Cl; c X=Br; d X=OC_2H_5

When the reaction was carried out in nonpolar solvents (benzene or toluene), low yields were obtained, and in DMSO the reaction was accompanied by side reactions which resulted in difficulties in the isolation of the oximes, and reduced yields.

TABLE 1. Peak Intensities for Characteristic Ions in the Mass Spectra of (I) and (II) (% Σ_{39})

Ions	Compound							
	a		b		c		d	
	I	II	I	II	I	II	I	II
W_M	6,9	5,9	7,7	3,4	7,8	4,9	8,6	5,4
Φ_1	39,3	34,6	48,7	34,2	40,8	32,9	28,0*	22,2**
Φ_2	21,6	19,2	15,2	12,1	12,4	15,3	1,6	1,0
Φ_3	0,8	1,0	1,1	0,2	1,3	1,9	0,5	0,4

*Also the ion [$\Phi_1 - C_2H_4$] (6.2%).
**Also the ion [$\Phi_1 - C_2H_4$] (8.0%).

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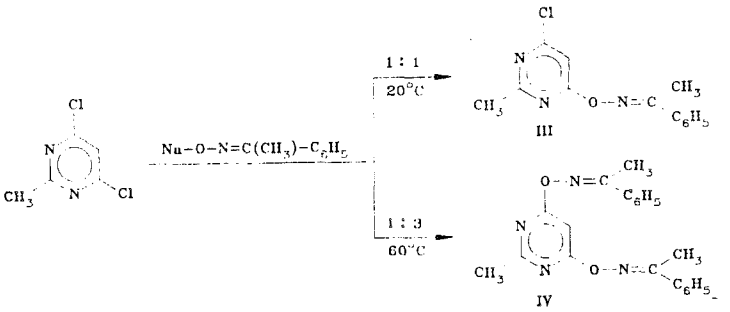
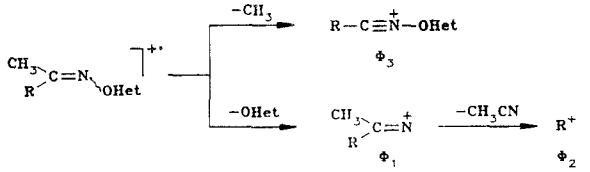
Reaction of the sodium salt of acetophenone oxime with 2-methyl-4,6-dichloropyrimidine gave, depending on the reaction conditions and the ratio of reactants, either the mono- or the disubstituted derivative. For example, at room temperature with equimolar amounts of the reactants, approximately 45% of the monosubstituted compound (III) was obtained, whereas on heating 2-methyl-4,6-dichloropyrimidine with a threefold excess of the sodium salt of acetophenone oxime 76% of the disubstituted compound (IV) was obtained.



Comparison of the stabilities of the molecular ions in the mass spectra of the compounds obtained shows (Table 1) that the W_M values for compounds (I) containing the 4,6-dimethylpyrimidin-2-yl residue are somewhat greater than those for the corresponding 6-isomers (II). The most characteristic mode of fragmentation of M^+ in both groups of compounds is by cleavage of the N–O bond with retention of the charge predominantly in the imine residue (ion Φ_1), followed by elimination of a molecule of acetonitrile to give the aromatic fragment Φ_2. Loss of a methyl group by the molecular ion (ion Φ_3) occurs to a small extent (1-2%), and the likelihood of the elimination of the radical R is even less (0.1-0.4%). The proportion of $HetO^+$ ions in the total ion current is also small (<0.9%).

The ions Φ_1-Φ_3, together with M^+, usually comprise more than 50% of the total ions, indicating the high selectivity of fragmentation of these compounds under electron impact. It is important to bear in mind that the mass spectra give no indication of rearrangements occurring during breakdown, such as have been observed in the spectra of other oximes [6, 7].



The symmetry of the hetaryl residues in (Ia-d) is evident from their PMR spectra (Table 2), in which the signals for the protons of the methyl groups in the 4- and 6-positions coincide, while those of the same protons in the spectra of (IIa-d) show differing chemical shifts. In addition, in the PMR spectra of the isomers (II), the signal for the 5-H proton [in comparison with (I)], as would be expected, is shifted to lower field by 0.3-0.4 ppm.

We have previously reported [8] the replacement of an oxime group by ethoxy in the reaction of pentan-2-one O-(2,4-dimethylpyrimidin-6-yl)oxime with sodium ethoxide. We have made a further study of this reaction by examining the reactions of some other nucleophiles with the ketone O-pyrimidinyloximes obtained here.

It was found that reaction of (Ib) with ethanolic sodium ethoxide also resulted in the formation of the ethoxy-compound, 2-ethoxy-4,6-dimethylpyrimidine, and the sodium salt of p-chloroacetophenone oxime was isolated. Similar removal of the oxime group was seen on heating (Ib) with aqueous-alcoholic potassium hydroxide. It should, however, be noted that in this instance replacement occurs with greater difficulty than with sodium ethoxide, and irrespective of the concentration of caustic alkali and the duration of heating, the reaction mixture contained unreacted starting material. This is apparently due to the greater nucleophilicity of the ethoxy-group as compared with hydroxy.

In order to assess the reactivity of the iminooxy-group toward a neutral nucleophile, we examined the reaction of (Ib) and (IIb) with hydrazine hydrate. The reaction of this nucleophile with pyrimidine is known to be not always straightforward. In addition to direct substitution of the groups, ring opening may occur and, in this case, the second amino-group

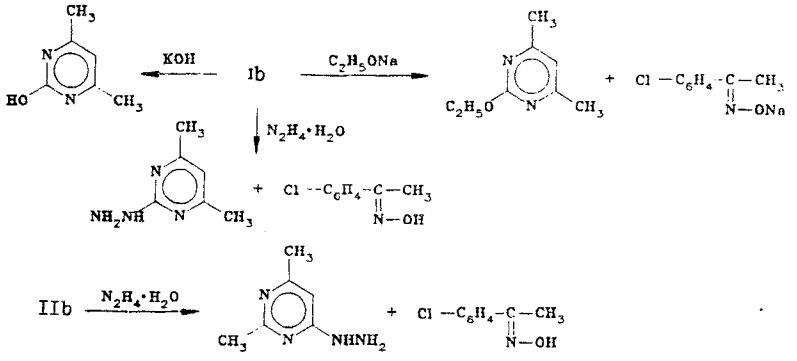
TABLE 2. Properties of Compounds (I-IV)

Compound	Empirical formula	mp, °C	R_f*	PMR spectrum (CCl_4), δ, ppm	Yield, %
Ia	$C_{14}H_{15}N_3O$	115...116	0,47	2,33 (6H, s, 4-and 6-CH_3); 2,42 (3H, s, CH_3—C=N); 6,53 (1H, s, 5-H); 7,2...7,8 (5H, m, C_6H_5)	80
Ib	$C_{14}H_{14}ClN_3O$	87...88	0,42	2.30 (6H, s, 4- and 6-CH_3); 2,34 (3H, s, CH_3—C=N); 6,61 (1H, s, 5-H); 7,4...7,7 (4H, s, C_6H_4)	85
Ic	$C_{14}H_{14}BrN_3O$	105	0,42	2,27 (6H, s, 4- and 6-CH_3); 2,30 (3H, s, CH_3—C=N); 6,50 (1H, s, 5-H); 7,43 (4H, q C_6H_4)	85
Id	$C_{16}H_{19}N_3O_2$	91...92	0,38	1,28 (3H, t, CH_3—CH_2, J=6,5 Hz); 2,28 (6H, s, 4- and 6-CH_3); 2,35 (3H, s, CH_3—C=N); 3,89 (2H, q, CH_2—CH_3, J=6,5 Hz); 6,5 (1H, s, 5-H); 6,67 and 7,6 (4H, q, C_6H_4, J=8,5 Hz)	72
IIa	$C_{14}H_{15}N_3O$	84...86	0,45	2,42 (3H, s, 2-CH_3); 2,45 (3H, s, 4-CH_3); 2,51 (3H, s, CH_3—C=N); 6,90 (1H, s, 5-H); 7,3...7,7 (5H, m, C_6H_5)	82
IIc	$C_{14}H_{14}ClN_3O$	94,5	0,44	2,42 (3H, s, 2-CH_3); 2,50 (3H, s, 4-CH_3); 2,56 (3H, s, CH_3—C=N); 6,93 (1H, s, 5-H); 7,4...7,8 (4H, q, C_6H_4)	81
IId	$C_{14}H_{14}BrN_3O$	93...94	0,44	2,4 (3H, s, 2-CH_3); 2,44 (3H, s, 4-CH_3); 2,54 (3H, s, CH_3—C=N); 6,95 (1H, s, 5-H); 7,6 (4H, s, C_6H_4)	80
IId	$C_{16}H_{19}N_3O_2$	71...72	0,44	1,30 (3H, t, CH_3—CH_2, J=6,5 Hz); 2,32 (3H, s, 2-CH_3); 2,35 (3H, s, 4-CH_3); 2,44 (3H, s, CH_3—C=N); 3,92 (2H, q, CH_2—CH_3, J=6,5 Hz); 6,72 (1H, s, 5-H); 6,84 and 7,73 (4H, q C_6H_4, J=8 Hz)	75
III**	$C_{13}H_{12}ClN_3O$	94...95	0,76	2,58 (3H, s, CH_3—C=N); 2,72 (3H, s, 2-CH_3); 7,38 (1H, s, 5-H); 7,5...7,95 (5H, m, C_6H_5)	44
IV**	$C_{21}H_{20}N_4O_2$	177...180	0,63	2,58 (6H, s, CH_3—C=N); 2,71 (3H, s, 2-CH_3); 7,37 (1H, , 5-H); 7,5...7,95 (10H, m, C_6H_5)	76

*In the system benzene—acetone, 3:1.
**The PMR spectra of (III) and (IV) were obtained in $CDCl_3$.

of the reagent is frequently capable of participating in a second nucleophilic attack to give, depending on the ring substituents, a variety of products, including total degradation of the ring to give pyrazoles or triazoles [9-11]. Furthermore, in some cases the hydrazinolysis products of pyrimidines have been found to include β-diketone bishydrazones [12].

The compounds (Ib) and (IIb) were found to react with hydrazine hydrate to give the nucleophilic substitution products only, none of the other possible degradation or recyclization products being detected.



The oxime group in O-pyrimidinyloxides therefore readily undergoes nucleophilic replacement.

EXPERIMENTAL

PMR spectra were obtained on a Varian T-60 in CCl_4, internal standard HMDS. Mass spectra were recorded on an LKB-2091 instrument (Sweden), ionization energy 70 eV, with direct intro-

duction of the sample into the ion source, and automatic data manipulation by computer. TLC was carried out on Silufol UV-254 plates, visualized with iodine vapor or Ehrlich's reagent. The elemental analysises for C, H, and N were in agreement with the calculated values.

Acetophenone O-(2,4-Dimethylpyrimidin-6-yl)- and O-(4,6-Dimethylpyrimidin-2-yl)oximes (Ia-d) and (IIa-d) (General Method). To 2.5 g (0.11 mole) of sodium dust in 300 ml of dry ether was added dropwise over 30 min a solution of 0.12 mole of the methyl aryl ketone oxime in 100 ml of dry ether. The mixture was stirred until all of the sodium had disappeared (5-6 h), the ether evaporated to dryness, and the residue treated with 40 ml of DMF. When the mixture had been stirred for 15 min and the sodium salt of the oxime had dissolved completely, a solution of 14.3 g (0.1 mole) of the chloropyrimidine in 30 ml of DMF was added at a temperature not exceeding 40°C, and the mixture stirred at 20°C for a further 4-5 h, the DMF removed under reduced pressure to dryness, cooled, and 20 ml of water added. The mixture was extracted with chloroform (2 × 100 ml), dried over magnesium sulfate, the chloroform removed, and the residue recrystallized from hexane–acetone (6:1) (Table 2).

Acetophenone O-(2-Methyl-4-chloropyrimidin-6-yl)oxime (III). As in the preceding example, from 0.46 g (0.2 mole) of metallic sodium and 2.7 g (0.02 mole) of acetophenone oxime there was obtained the sodium salt of the oxime, which was then treated with cooling (5-10°C) with a solution of 3.26 g (0.02 mole) of 2-methyl-4,6-dichloropyrimidine in 40 ml of DMF. The mixture was stirred for 15-20 h at 20°C, the solvent removed under reduced pressure, and the residue treated with 50 ml of water. The solid which separated was filtered off, and recrystallized from hexane. Yield 2.28 g (Table 2).

Acetophenone O-(2-Methylpyrimidin-4,6-yl)bisoxime (IV). To the sodium salt of acetophenone oxime, obtained from 1.38 g (0.06 mole) of metallic sodium and 8.1 g (0.06 mole) of acetophenone oxime, obtained by the general method, was added a solution of 3.26 g (0.02 mole) of 2-methyl-4,6-dichloropyrimidine in 20 ml of DMF. The mixture was heated for 2 h on the water bath, the solvent removed under reduced pressure, and the residue treated with 100 ml of water. The solid which separated was filtered off, washed with hexane, and recrystallized from a mixture of benzene and acetone (4:1). Yield 5.5 g (Table 2).

4,6-Dimethyl-2-ethoxypyrimidine. A mixture of 0.7 g (2.5 mmole) of the oxime (Ib) and ethanolic sodium ethoxide [obtained from 20 ml of ethanol and 0.12 g (5 mmole) of metallic sodium] was boiled for 3 h. When all the oxime had reacted (TLC), the ethanol was removed to dryness, the residue washed with 20 ml of hexane, and the hexane removed to give 0.29 g (75%) of 4,6-dimethyl-2-ethoxypyrimidine, identical by TLC and the PMR spectrum with an authentic sample.

The hexane-insoluble portion was dissolved in 2 ml of water, neutralized with dilute hydrochloric acid, and extracted with benzene. Removal of the solvent gave 0.24 g (56%) of p-chloroacetophenone oxime, mp 86-87°C, identical in its melting point and by TLC with an authentic sample.

4,6-Dimethyl-2-hydrazinopyrimidine. To a solution of 0.67 g (2.43 mmole) of the oxime (Ib) in 10 ml of ethanol was added 1 ml of 85% hydrazine hydrate solution, and the mixture boiled for 5-6 h. It was then evaporated to dryness under reduced pressure, the residue washed with hot hexane, and the residue treated with 5 ml of water and the solid filtered off to give 0.31 g (93%) of 4,6-dimethyl-2-hydrazinopyrimidine, mp 163-165°C (according to [13], mp 164°C). PMR spectrum ($CDCl_3$): 2.28 (6H, s, 4- and 6-CH_3); 3.78 (br. s, $NHNH_2$); 6.3 ppm (1H, s, 5-H).

Removal of the hexane gave 0.32 g (80%) of p-chloroacetophenone oxime, mp 87-88°C (identical in its melting point and by TLC with an authentic sample).

2,4-Dimethyl-6-hydrazinopyrimidine. As in the preceding preparation, from 0.45 g (1.6 mmole) of the oxime (IIb) and 1 ml of 85% hydrazine hydrate in 15 ml of ethanol there were obtained 0.21 g (76%) of p-chloroacetophenone oxime and 0.2 g (89%) of 2,4-dimethyl-6-hydrazinopyrimidine, mp of the latter 187-188°C (according to [13], mp 186-187°C). PMR spectrum (in CD_3OD): 2.23 (3H, s, 2-CH_3); 2.38 (3H, s, 4-CH_3); 6.38 ppm (1H, s, 5-H).

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SYNTHESIS AND LIQUID CRYSTAL PROPERTIES OF SUBSTITUTED 1,4-BIS(PYRIMIDIN-2-YL)BENZENES

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Some symmetrical and unsymmetrical alkyl-, alkoxy-, and acyloxy-1,4-bis(pyrimidin-2-yl)benzenes have been prepared, and their liquid-crystal properties examined. A distinguishing feature of these compounds is their ability to form only a nematic mesophase, the greatest range of liquid-crystal states and the lowest temperatures at which they appear being found in nonsymmetrical dialkoxy- and alkyl-alkoxy compounds.

The liquid-crystal properties of organic compounds are extremely sensitive to changes in the chemical structure of the molecule. There have been numerous publications in which changes in the aromatic ring system have been shown to not only reduce the lower limit of existence of the mesophase and increase thermal stability, and the criteria governing the type of mesophase established.

In this respect, the pyrimidine analogs of diphenyl and terphenyl systems are of considerable interest [1-3], and these have found practical application as components of liquid-crystal materials in various types of electrooptical equipment [4-6]. The pyrimidine analogs of diphenyl and terphenyl systems frequently enable the range of operating temperatures to be increased, the operating voltage to be reduced, and materials to be obtained having a lower viscosity-temperature relationship, which is of particular importance for equipment operating at temperatures below 0°C [7]. There have been recent reports of the synthesis and liquid-crystal properties of aryl derivatives of bipyrimidines of various types [8-11]. For example, some 1,4-bis(pyrimidin-2-yl)benzenes have been reported [11] to be liquid crystals of low viscosity with a wide range of mesophase, but only alkyl derivatives were considered, and only a single example was given, namely 5-pentyl-5'-propyl-1,4-bis(pyrimidin-2-yl)benzene, nematic liquid crystal in the temperature range 147-199°C.

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