PYRIMIDINES

XXXIV.* SYNTHESIS AND SOME PROPERTIES OF PYRIMIDINE-2-ALDOXIMES

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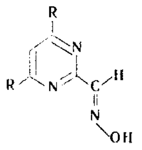
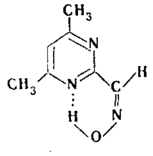
Pyrimidine-2-aldoxime and 4,6-dimethylpyrimidine-2-aldoxime were obtained by oximation of the corresponding aldehydes. On the basis of spectral data, it was shown that the oximes have the syn configuration. syn-4,6-Dimethylpyrimidine-2-aldoxime is converted to the corresponding anti isomer by photochemical isomerization. 1-Methyl-2-oximidomethylpyrimidinium iodide was obtained by the action of methyl iodide on pyrimidine-2-aldoxime.

In a continuation of our studies of 2-formylpyrimidines and their derivatives, we undertook the synthesis of some pyrimidine-2-aldoximes and their quaternary salts. It is known [2] that the quaternary salts of pyridinealdoximes, for example, 1-methyl-oximidomethylpyridinium iodide, are extremely effective reactivators of cholinesterase that has been inhibited by phosphorylation. 1-Methyl-4-oximidomethylpyrimidinium iodide [3] has proved to be a rather good reactivator of phosphorylated acetylcholinesterase in vitro. We obtained pyrimidine-2-aldoxime (I) and 4,6-dimethylpyrimidine-2-aldoxime (II) by the reaction of the appropriate aldehydes with hydroxylamine in aqueous solution at pH 7-8. Spectra data were used to determine the configurations of the oximes obtained. It is known [4] that the band of an unbonded hydroxyl group is present at 3580 cm^{-1} in the IR spectrum of syn-pyridine-2-aldoxime in carbon tetrachloride; this band is absent in the spectrum of the anti isomer, but there is a broad band at 2800 cm^{-1} due to an intramolecular hydrogen bond. The band of a free OH group at 3600 cm^{-1} is present in the IR spectrum of oxime I.† The IR spectrum of oxime II also contains an intense narrow band of an unbonded hydroxyl group at 3600 cm^{-1}, and, in addition, there is a narrow band at 3300 cm^{-1}, which is probably due to a strong intermolecular hydrogen bond, since the band disappears completely only in very dilute solutions ($4 \cdot 10^{-5}$ M).

On the basis of the IR spectra, the syn configuration might thus have been preliminarily assigned to compounds I and II:



I, II



III

I R = H; II R = CH_3

The definitive proof of the configurations of the oximes was obtained after isomer III was generated by a known method [5] by UV irradiation of the more accessible II. Compounds II and III differ markedly in physical properties: III has considerably higher chromatographic mobility and is quite soluble in nonpolar solvents (this made it possible to separate it from II); the melting point of III is 120° lower than that of II.

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* See [1] for the preceding communication.

† Because of the low solubility of I in carbon tetrachloride, all of the absorption bands were of very low intensity, even at a layer thickness of 15 cm.

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TABLE 1. Chemical Shifts of the Protons of the $-CH=N-$ and $=N-OH$ Groups in Dimethyl Sulfoxide

Group	Pyrimidine-2-aldoxime (I)	syn-4,6-Dimethylpyrimidine-2-aldoxime (II)	anti-4,6-Dimethylpyrimidine-2-aldoxime (III)
$-CH=N-$ δ, ppm	8,07	7,97	7,73
$=N-OH$ δ, ppm	11,90	11,70	15,07

These differences in properties are apparently due to the presence of an intramoleculear hydrogen bond in oxime III. The band of a free hydroxyl group at 3600 cm^{-1} is absent in the IR spectrum of III.

The 2800-3000-cm^{-1} region, in which one might have expected the appearance of the band of an intramolecular hydrogen bond, is covered by the absorption bands of CH_3 and CH groups in the spectrum of this compound.

It is known [6, 7] that the signal of the proton of the $-CH=N-$ group in the PMR spectra is shifted to strong field on passing from the syn-aldoxime to the anti-aldoxime, while the signal of the proton of the $=N-OH$ group is shifted to weak field. A comparison of the chemical shifts of the indicated protons (see Table 1) confirms the syn configuration of oxime II and the anti configuration of oxime III. At the same time, the closeness of the chemical shifts of I and II is evidence in favor of the syn configuration of oxime I.

The quaternary salt of oxime I was obtained by heating a solution of the oxime in absolute dimethylformamide with methyl iodide at 70°. Oxime II could not be quaternized under similar conditions. The use of more severe conditions – heating II with methyl iodide in a sealed tube at 100°C – gave a black viscous product, upon treatment of which with water the presence of HI was detected. It has been shown [8] that 6-methylpyridine-2-aldoxime also does not form the normal quaternization product on reaction with methyl iodide but gives the hydriodide of the methyl ether of 6-methylpyridine-2-aldoxime. This hindrance to quaternization can apparently be explained primarily by steric factors.

1-Methyl-2-oximidopyrimidinium iodide (IV), which is completely stable in the solid state, proved to be labile in solutions, particularly on heating. A colorless aqueous solution of IV becomes intensely black on brief standing.

EXPERIMENTAL

The IR spectra of solutions of the compounds in carbon tetrachloride were recorded with a UR-10 spectrophotometer. The PMR spectra of 5% solutions of the oximes in dimethyl sulfoxide (DMSO) were recorded with a Varian A 56/60 spectrometer with an operating frequency of 60 MHz; the chemical shifts were reckoned from the C^{13} satellite of DMSO (221 Hz from tetramethylsilane). The thin-layer chromatography was carried out on Silufol UV-254 plates, and the spots were detected in UV light.

syn-Pyrimidine-2-aldoxime (I). A 0.38-g sample of hydroxylamine hydrochloride was added to a solution of 0.59 g (5 mmole) of 2-formylpyrimidine [9] in 2 ml of water, and the solution was neutralized to pH 7-8 with sodium bicarbonate and allowed to stand for 12-15 h. The precipitate was removed by filtration, washed with a small amount of water, and dried in a desiccator over phosphorus pentoxide to give 0.42 g (70%) of I with mp 237-240° (from chloroform–ethanol) and R_f 0.66 [acetone–ethyl acetate (1 : 1)]. Found: C 48.6; H 4.0; N 34.1%. $C_5H_5N_3O$. Calculated: C 48.8; H 4.1; N 34.1%.

syn-4,6-Dimethylpyrimidine-2-aldoxime (II). A 0.4-g sample of hydroxylamine hydrochloride was added to a solution of 0.54 g (4 mmole) of 2-formyl-4,6-dimethylpyrimidine [9] in the minimum amount of water, and the mixture was neutralized to pH 8 with solid sodium bicarbonate and allowed to stand for 24 h. It was then extracted with chloroform, and the extract was dried with magnesium sulfate. The solvent was removed by vacuum distillation to give 0.49 g (82%) of II with mp 196-198° (from benzene–chloroform) and R_f 0.54 (acetone). Found: C 55.7; H 6.2; N 27.8%. $C_7H_9N_3O$. Calculated: C 55.6; H 5.9; N 27.8%.

anti-4,6-Dimethylpyrimidine-2-aldoxime (III). A solution of 0.2 g of II in 20 ml of acetone was placed in a quartz test tube and irradiated with a BUF-718 mercury lamp at 5° for 20 h. The solution was then evaporated to dryness, and the residue, which contained a mixture of oximes II and III, was shaken several times with petroleum ether (40-60°). The combined extracts were filtered, and the filtrate was evaporated to give 0.035 g (17%) of III with mp 75-78° and R_f 0.91 (acetone). Found: N 28.3%. $C_7H_9N_3O$. Calculated: N 27.8%.

1-Methyl-2-oximidomethylpyrimidinium Iodide (IV). A mixture of 0.34 g (3 mmole) of I, 12 ml of methyl iodide, and 7 ml of anhydrous dimethylformamide was refluxed for 2 h (the bath temperature was 75°). The resulting yellow precipitate was removed by filtration and washed with dry acetone to give 0.49 g (70%) of IV with mp 207-208° (reprecipitated from aqueous solution by the addition of isopropyl alcohol). Found: N 15.7%. $C_6H_8IN_3O$. Calculated: N 15.8%.

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