

411. Spectroscopic Studies of Quaternary Aldoximes and Ketoximes.

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2,2'-Pyridil monoxime has the β -configuration and forms intramolecular N·OH···O·C bonds. Structures are tentatively assigned to the isomeric 2,2'-pyridil dioximes on the basis of their N-O stretching frequencies. The intensity of the C=N absorption is very variable in heterocyclic aldoximes and is particularly affected by quaternization which in general raises this frequency. Changes in frequency and intensity of this absorption are related to the reactivating properties of pyridine-2- and -4-aldehyde oxime derivatives for di-O-ethylphosphorylacetocholinesterase.

2,2-PYRIDIL MONOXIME (I) in the solid state has bonded O-H stretching frequencies at 3200 and 2800 cm^{-1} and a carbonyl stretching frequency at 1700 cm^{-1} . These frequencies remain unchanged in dilute chloroform solution, indicating that bonding is intramolecular. Similar data are obtained for β -benzil monoxime in which the C=O mode occurs at the same frequency (1675 cm^{-1}) in both solid and solution spectra. In the α -isomer this vibration shifts from 1645 cm^{-1} for the solid to 1670 cm^{-1} for solutions. Hence the monoxime of 2,2'-pyridil has the β -configuration. Earlier work has shown correlation between O-H stretching frequencies and the α - and β -forms of substituted benzaldoximes.¹ These have bands at 3250 and 3115 cm^{-1} , respectively, in the solid state. Isomeric 2,2'-pyridil dioximes do not clearly differ in the 3 μ region (Table 1), but do in the N-O

TABLE 1. Frequencies (cm^{-1}) of isomeric 2,2'-pyridil and benzil oximes in potassium bromide discs.

2,2'-Pyridil α -dioxime	3550	3250	3100	2900	1630	1590	1480	1435	1225	1095	1005			
2,2'-Pyridil β -dioxime		3200	3050	2900	1630	1590	1480	1440	1235	1095	1005—	970	945	
											1095			
2,2'-Pyridil β -monoxime		3200		2800	1700	1630	1580	1470	1435	1225	1090	1000—	965	935
												1094		
Benzil α -dioxime	3400		3050				1490	1440	1220	1095	990		
Benzil β -dioxime	3450		3050		1600		1500	1440	1225	1075	985	960	940

stretching mode. Assignments² for this band have ranged from 800 to 1075 cm^{-1} (800—850, 900, 1020, and 975—1075). For benzil α -dioxime a single strong peak occurs in the N-O stretching region at 990 cm^{-1} , whereas the β -dioxime shows more complex absorption with maxima at 940, 960, and 985 cm^{-1} . As 2,2'-pyridil dioxime (m. p. 237°) has a single strong band at 1005 cm^{-1} and its isomer (m. p. 247°) has maxima at 970, 985, and 995—1005 cm^{-1} , they are tentatively assigned the α - and the β -configuration respectively.

Two series of stereoisomers may be obtained for the quaternary pyridinium oxime derivatives.³ Only those belonging to the more stable group are listed in Table 2. Attempts to assign configuration to the two series by chemical methods failed,³ because quaternization need not occur with retention of configuration—quaternary ions may

¹ Palm and Werbin, *Canad. J. Chem.*, 1953, **31**, 1004.

² Haszeldine and Jandes, *J.*, 1954, 691; Tarte, *Bull. Soc. chim. belges*, 1953, **62**, 401; Giguère and Liu, *Canad. J. Chem.*, 1952, **30**, 948; Goubeau and Fromme, *Z. anorg. Chem.*, 1949, **258**, 18; O'Sullivan and Sadler, *J. Org. Chem.*, 1957, **22**, 283; Hadži, *J.*, 1956, 2725.

³ Ginsberg and Wilson, *J. Amer. Chem. Soc.*, 1957, **79**, 481.

catalyse the isomerisation of oximes.⁴ It is impossible to assign configurations to the oximes on the basis of their O-H stretching frequencies,¹ for these are complex owing to the formation of intermolecular bonds. Only tertiary aldehydes give oximes sufficiently soluble in non-polar solvents to provide records in the $3\ \mu$ region, and it has been suggested⁵ that the presence of a non-bonded O-H absorption in pyridine-2-aldehyde oxime in carbon tetrachloride solution indicates the α -form (II) for the compound, as the β -form should show an intramolecular O-H...N bond. Further structural information is afforded by

TABLE 2. *Frequencies (cm.⁻¹) of oximes of tertiary and quaternary aldehydes in potassium bromide discs.*

No.		3400	3200	3100	1640m	1480	1405	1295	1025	900
1	HON·HC·[CH ₂] ₂ ·NMe ₃ Cl	3500		3050	1630m	1480	1420	1295	1060—	915
2	2-2'-Oxoethylpyridinium oxime chloride								1040	
3	NN'-Dimethyl- <i>p</i> -2'-oxoethyl-anilinium oxime chloride	3450	3150	3050	2850 1625w	1590	1490— 1480	1410	1295	1030 985
4	<i>p</i> -Dimethylaminobenzaloxime	3300	3150		2950 1610	1530		1300		960
5	<i>p</i> -Dimethylaminobenzaloxime methochloride		3250	3050	1605vw		1480	1405	1280	970
6	Pyridine-2-aldehyde oxime		3250		2800 1620w	1595 1560	1510	1430	1320	980
7	Pyridine-2-aldehyde oxime methiodide			3050	2950 1620m	1570	1500	1420	1300	1000
8	Pyridine-2-aldehyde oxime isopropyl iodide		3200		1630m	1600	1570	1500	1450	1300 995
9	Pyridine-3-aldehyde oxime		3150		2800 1620w	1570	1510	1410	1305	990
10	Pyridine-4-aldehyde oxime		3150		2900 1640w	1600	1500	1420	1305	990
11	Pyridine-4-aldehyde oxime butyl iodide		3150		2750 1640m	1610	1590	1490	1425	1295 990
12	Pyridine-4-aldehyde oxime 3'-bromopropylbromide	3450		3050	2850 1640	1610	1480		1298— 1290	1005
13	Pyridine-4-aldehyde oxime 5'-bromopentylbromide	3450		3050	2900 1650	1610	1480		1298— 1290	1010
14	NN'-Trimethylene-bis-(4-hydroxyiminomethylpyridinium bromide)	3450	3150	3050	2900 1645	1610	1480		1295	1015
15	NN'-Tetramethylene-bis-(4-hydroxyiminomethylpyridinium bromide)	3500	3150	3050	2900 1640	1610	1485		1295	1000
16	4,4'-Dimethyl-2,2'-bipyridyl				2900	1590	1540	1450		
17	4,4'-Dimethyl-2,2'-bipyridyl dimethiodide				2950 1620	1575		1450		

Bands quoted are strong unless otherwise marked.

the O-H deformation mode. This has been examined for several groups of compounds⁶ and identified between 1020 and 1420 cm.⁻¹. In particular, it has been demonstrated at 1300 and 1350 cm.⁻¹, respectively, in the Nujol spectra of the α - and the β -forms of substituted benzaloximes.⁷ The strong band at 1300 cm.⁻¹ for *p*-dimethylaminobenzaloxime is lowered to 1280 cm.⁻¹ on quaternization. A similar shift (1320 to 1300 cm.⁻¹)

⁴ Sidgwick, "The Organic Chemistry of Nitrogen," Clarendon Press, Oxford, 1942, p. 192.

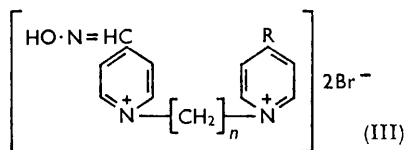
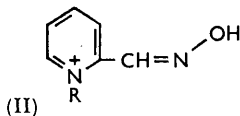
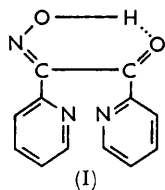
⁵ Hanania and Irvine, *Nature*, 1959, **183**, 40.

⁶ Barchewitz, *Compt. rend.*, 1953, **237**, 237; Hadži and Sheppard, *Proc. Roy. Soc.*, 1953, *A*, **216**, 247; Quinan and Wiberley, *J. Chem. Phys.*, 1953, **21**, 1896.

⁷ Palm and Werbin, *Canad. J. Chem.*, 1954, **32**, 858.

occurs in the spectra of the tertiary and the quaternary form of pyridine-2-aldehyde oxime, and a slightly smaller one for the 4-isomer. All the quaternary derivatives of these two oximes examined show this strong absorption near 1300 cm^{-1} , which suggests the α -configuration.

The C=N stretching frequency in spectra of aliphatic ketoximes⁸ is fairly well defined at $1650\text{--}1675\text{ cm}^{-1}$, but aromatic ketoximes have been little studied. Acetophenone



oxime shows feeble absorption at 1630 cm^{-1} and the dioximes⁹ of cyclohexane-1,2-dione and cycloheptane-1,2-dione have two weak bands at 1506 and 1524 cm^{-1} . The C=N band was not found in the spectra of benzoin α -oxime, which casts doubt on the structure of this compound.¹⁰ It is also absent from that of benzil α -dioxime, but is present as a weak-to-medium band at 1630 cm^{-1} for benzil β -dioxime and the oximes of 2,2'-pyridyl (Table 1).

Aliphatic aldoximes have C=N bands between 1650 and 1670 cm^{-1} ; for aromatic compounds the range is $1614\text{--}1650\text{ cm}^{-1}$. Increased bond polarization which results from the formation of oxime dimers raises this frequency,¹¹ and quaternization of heterocyclic compounds produces a similar effect.¹² For most of the compounds listed in Table 2 both effects are possible, with the result that, in addition to frequency shifts, the relative intensities of the two C=N frequencies vary considerably. The C=N absorption occurs near 1595 cm^{-1} for pyridine derivatives and is raised to 1610 cm^{-1} on quaternization; in the case of 4,4'-dimethyl-2,2'-bipyridyl the increase is from 1590 to 1620 cm^{-1} . Pyridine-2-aldehyde oxime shows two C=N frequencies, at 1595 and 1620 cm^{-1} . The latter absorption, which results from the oxime group, is very weak, but is considerably increased in intensity on quaternization, and for the isopropyl iodide is also raised ten wave-numbers. Similar results are obtained for the tertiary and quaternary derivatives of pyridine-4-aldehyde oxime, the increase in intensity of the 1640 cm^{-1} band being even more marked. Quite different results are obtained with *p*-dimethylaminobenzaloxime in which strong C=N absorption at 1610 cm^{-1} almost disappears on quaternization, while the N-O stretching frequency at 960 cm^{-1} is raised to 970 cm^{-1} . The reactivating properties of the quaternary oximes for di-*O*-ethylphosphorylacetocholinesterase^{13,14} are not directly related to the strong N-O stretching frequency which occurs in the region $960\text{--}1050\text{ cm}^{-1}$, but they are paralleled by the increase in frequency and intensity of the C=N absorption which ranges from 1620 to 1650 cm^{-1} for the active compounds.

In the isomeric pyridinealdehyde oxime methiodides the order of activity¹⁴ is $2- > 4- > 3-$, as indicated by their spectra (ultraviolet spectra of the methochlorides are similar¹⁵). If pyridine-2-aldehyde oxime derivatives have the α -configuration the hydroxy-imino-group is suitably projected to effect reactivation of the phosphorylated esteratic site. The length of the alkyl chain has little effect on either the ultraviolet

⁸ Schechter and Conrad, *J. Amer. Chem. Soc.*, 1954, **76**, 2716; Cross and Rolfe, *Trans. Faraday Soc.*, 1951, **47**, 354; Brown, *J. Amer. Chem. Soc.*, 1955, **77**, 6341.

⁹ Voter, Banks, Fassel, and Kehres, *Analyt. Chem.*, 1951, **23**, 1730.

¹⁰ Duckaerts, *Bull. Soc. roy. Sci. Liège*, 1952, **83**, 614.

¹¹ Califano and Lüttke, *Z. phys. Chem.*, 1956, **6**, 83.

¹² Edwards and Singh, *Canad. J. Chem.*, 1954, **32**, 465; Witkop, *J. Amer. Chem. Soc.*, 1954, **76**, 5597.

¹³ Hobbiger, O'Sullivan, and Sadler, *Nature*, 1958, **182**, 1498; Hobbiger and Sadler, *ibid.*, p. 1672; Hobbiger and Sadler, *Brit. J. Pharmacol.*, 1959, **14**, 192.

¹⁴ Hobbiger, Pitman, and Sadler, *Biochem. J.*, 1960, **75**, 363.

¹⁵ Mason, *J.*, 1960, 22.

spectra or the reactivities in this group (Table 3), but in the polymethylenbispyridinium dioximes (III; R = CH₂N·OH) and the corresponding monoximes (III; R = H) bathochromic shifts occur in λ_1 , and the hydrolytic power of the oximes is increased as the length of the alkyl chain diminishes.

TABLE 3. *Ultraviolet absorption spectra (λ in m μ) and reactivating properties of mono- and bis-quaternary formylpyridinium oximes.*

	λ_1	ϵ	Hydrol. of Et ₄ P ₂ O ₇	Activity †
Pyridine-2-aldehyde oxime methiodide	330	18,700	1	1
" " ethiodide	335	18,490	1	0.54
" " propyloiodide	335	16,590	0.94	0.63
" " butyloiodide.....	335	16,500	1.1	0.87
Pyridine-4-aldehyde oxime methiodide	335	22,200	0.36	0.06
NN'-Trimethylene-1-(4-hydroxyiminomethylpyridium)-3- pyridinium dibromide.....	345	25,680	0.56	8.0
NN'-Tetramethylene homologue	337.5	24,530	0.53	6.7
NN'-Pentamethylene homologue	337.5	25,240	0.47	7.5
NN'-Ethylenebis-(4-hydroxyiminomethylpyridinium bromide)	352.5	44,460	1.5	17
NN'-Trimethylene homologue	347.5	44,000	1.1	22
NN'-Tetramethylene homologue	340	43,450	0.99	18
NN'-Pentamethylene homologue	340	43,400	0.91	16

† Potency as reactivator of diethylphosphorylacetocholesterase.

Experimental.—Compounds in chloroform and potassium bromide discs were examined with a Perkin-Elmer 21 double-beam recording spectrophotometer. Ultraviolet absorption curves were determined for 0.1N-NaOH solutions, with matched quartz cells in a Hilger-Uvispek spectrophotometer. Preparative details have already been given.^{13,14,16}

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¹⁶ Pitman and Sadler, *J.*, 1961, 759.