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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 3–HYDROXYIMINO–5–METHYL–2–HEXANONE(HIMH) AND ITS DIOXIME DERIVATIVE

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Abstract: A new oxime, 3–hydroxyimino–5–methyl–2–hexanone (HIMH) has been synthesized by the reaction of 1–pentyl nitrite with 5–methyl–2–hexanone under acidic conditions. The subsequent treatment of HIMH with $NH_2OH{\cdot}HCl$ gives 5–methyl–2,3–hexanedione dioxime (H_2MHDDO). The structures of these compounds have been confirmed by physicochemical and spectral data. A preliminary screening of these compounds for biological activity against several microorganisms has indicated that they are selective growth inhibitors of *m–tuberculosis*, in particular.

Keywords: 1–pentyl nitrite, 5–methyl–2–hexanone, hydroxylamine hydrochloride, antimicrobial activity.

The title ligand (HIMH) contains a reactive grouping $-\overset{\overset{O}{\|}}{C}-\overset{\overset{NOH}{\|}}{C}-$, which determines the characteristic reactions of isonitrosoketones (1). Tautomeric isonitroso compounds (oximes) are potentially ambident ligands capable of forming metal complexes with different types of structures / bonding (2). These compounds find several applications as sensitive and selective reagents in the detection and determination of various metal ions. In addition, many of these compounds possess a wide spectrum of biological activity (3). The present paper deals with the preparation and characterization of the title ligand, *viz.* 3–hydroxyimino–5–methyl–2–hexanone (HIMH), and its derivative, 5–methyl–2,3–hexanedione dioxime (H_2MHDDO). Various physicochemical techniques such as: elemental analysis, NMR and IR, have been employed to assign the structures of the two ligands. Their biological activity has been tested to find minimum inhibitory concentrations against various microorganisms.

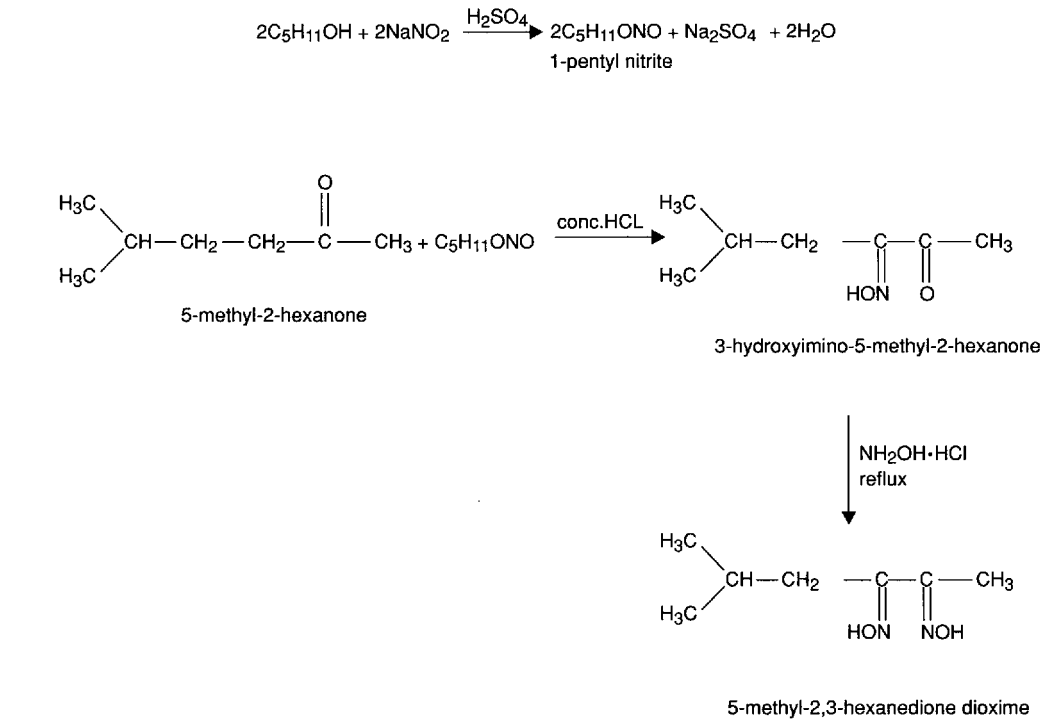
EXPERIMENTAL

The reactions were carried out with analytical reagent grade chemicals. The ketone (5–methyl–2–hexanone) and 1–pentanol were purchased from m/s Fluka Chemicals. The C. P. grade chemicals, whenever used, were purified by standard methods. The organic solvents were redistilled before use. A Hoover melting point apparatus was used with open capillary tubes for the determination of melting points, which were uncorrected. IR spectra were recorded on a Perkin–Elmer 1600 series FTIR spectrophotometer in KBr pellets. ^1H NMR spectra were recorded on a Bruker AMX–500 spectrometer in $CDCl_3$. The chemical shifts were reported in δ units relative to tetramethylsilane (TMS) used as an internal standard. The minimum inhibitory concentrations (MIC) of HIMH and H_2MHDDO were ascertained by using various biological strains, according to the method described elsewhere (4).

The monooxime HIMH was synthesized by reported methods (5) and recrystallized prior to the synthesis of its derivative, H_2MHDDO. The latter was prepared by the standard method (6), using an appropriate ratio of $NH_2OH{\cdot}HCl$ with pure HIMH.

General method of synthesis

The freshly prepared 1–pentyl nitrite (7) was added dropwise to 5–methyl–2–hexanone in an ice–water bath, in the presence of a trace amount of conc. hydrochloric acid. After complete addition, 33% aq. NaOH solution was added dropwise, the unreacted 1–pentyl nitrite was extracted with diethyl ether, and ice cold aqueous layer was acidified to pH=4 to obtain a reddish – brown oily compound, 3–hydroxyimino–5–methyl–2–hexanone (HIMH). It was recrystallized from diethyl ether. A mixture of the purified HIMH and hydroxylamine hydrochloride, in 1:1 molar proportion was refluxed for 1 h. Hot reaction mixture was poured into crushed ice. Colourless shiny crystals of 5–methyl–2,3–hexanedione dioxime (H_2MHDDO) were separated



Scheme 1.

Table 1. Physical characteristics and analytical data of compounds

Compound	Colour	Yield (%)	Mol. formula	M.P. (°C)	Elemental analysis (%) found / calc.			
					C	H	N	O
HIMH	Reddish brown	71	$C_7H_{13}NO_2$	<27	58.60 58.20	9.07 9.01	9.70 9.20	22.63 22.59
H_2MHDDO	Colourless	89	$C_7H_{14}N_2O_2$	76	53.16 53.12	8.86 8.81	17.72 17.78	20.26 20.21

Table 2. Spectral data of compounds

Compound	IR (KBr) cm^{-1}				^{1}H NMR $CDCl_3$/TMS (δ ppm)
	ν_{NOH}	$\nu_{C=O}$	$\nu_{C=N}$	ν_{N-O}	
HIMH	3312	1688	1461	1370	0.878–0.891 (d–2xCH_3), 2.360 (s–CH_3), 1.948–2.016 (m–CH), 2.458–2.473 (d–CH_2), 7.55 (s =NOH)
H_2MHDDO	3222	–	1450	1369.5	0.856–0.879 (d–2xCH_3), 1.972 (s–CH_3), 1.99–2.06 (m–CH), 2.52–2.53 (d–CH_2), 4.84 (s =NOH)

Table 3. Biological activity – MIC (μg/ml) of compounds

Compound	Antibacterial activity		Antifungal activity			Antitubercular activity
	1	2	3	4	5	6
HIMH	100	100	50	200	200	200
H_2MHDDO	100	100	50	200	200	200

1. *S. typhi*; 2. *S. aureus*; 3. *C. albican*; 4. *A. niger*; 5. *S. cerevisiae*; 6. *m-tuberculosis*

by filtration, and recrystallized from twice redistilled ethyl alcohol.

The physical characteristics of HIMH and H_2MHDDO is shown in Table 1.

RESULTS AND DISCUSSION

IR and ^{1}H–NMR spectra

Assignments of most important bands (peaks) are summarized in Table 2.

Antimicrobial activity

The two compounds were screened against different strains of Gram positive and Gram negative bacteria such as *S. aureus, S. typhi, C. albican, A. niger, S. cerevisiae,* by using the cup– plate method described elsewhere (4). The solvent used was DMF, and the sample concentration was 200–50 μg. The results show good / moderate activities against the said species. For antituberculosis, the two compounds were screened against *m–tuberculosis.*

CONCLUSIONS

From the physicochemical investigations, the chemical structures of HIMH and H_2MHDDO have been proposed as shown in the Scheme. Both the compounds revealed good / moderate activities against several microorganisms (Table 3).

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