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STEREOCHEMISTRY AND ANTIMICROBIAL EVALUATION OF OXIME CONTAINING COMPOUNDS AND THEIR INDICATOR PROPERTY

KAMINI J. DONDE[a], KANCHAN A. BARVE, SAMBHAJI S. RAUT and VISHWANATH R. PATIL[*]

Department of Chemistry, University of Mumbai, Santacruz (E), MUMBAI - 400 098 (M.S.) INDIA
[a]Department of Chemistry, Ramnarain Ruia College, Matunga (E), MUMBAI – 400 019 (M.S.) INDIA

ABSTRACT

The oxime containing compounds 3-hydroxyimino-5-metyl-hexan-2-one-2,4-dinitrophenyl hydrazine and bis(3-hydroxyimino-5-methyl-2-hexanone) dithiooxamide have been synthesized from the reaction of 3-hydroxyimino-5-methyl-2-hexanone and 2,4-dinitrophenyl hydrazine and dithiooxamide. The products have been characterized on the basis of elemental analysis, FTIR and ^{1}H NMR spectral data. Stereospecific formation of only one anti-isomer is shown from the stereochemistry of the said compounds. The compound shows indicator property in acid- base titrations. The synthesized compounds have been screened for antimicrobial evaluation against various biological strains such as *S. aureus*, *S. typhi*, *C. albicans*, *A. niger*, *S. cerevisiae* and *m-tuberculosis*. The result shows that the compounds exhibit moderate activity against the selected strains.

Key words: Oximes, Spectral data, Biological strains.

INTRODUCTION

Enormous amount of research on the synthesis and biological screening of nitrogen and sulphur containing compounds have been reported. Though many of these compounds showed promising pharmacological testing[1-6] and have played an important role in the medicinal chemistry, some of them have received considerable attention as sensitive indicators in acid-base titration[7-8]. Several nitrophenol isomers were also recommended as indicators by various investigators[9-12]. The metal complex of such compounds also finds wide applications in medicinal chemistry[13]. With transition metals, they forms stable coloured complexes[14,15]. Ethanedithioamide (rubeanic acid or dithiooxamide) also finds a

[*]Author for correspondence; E-mail: nitudonde@yahoo.co.in; vishwanathrpatil03@gmail.com

wide spectrum of applications in industry, in drugs for regulating the equilibrium of metals in human beings and as antidotes in cases of poisoning with heavy metals[16] and mainly as a chelating agent in calorimetric analysis[17]. Hydrazine containing compounds are associated with broad spectrum of biological activities[13,18,19] and are used in treatment of moderate to severe hypertension[20]. Substituted hydrazones have also been used in treatment of schizophrenia, leprosy, mental disorders and other illnesses[21]. These reports led us to carry out the synthesis of similar compounds and to evaluate their biological and indicator properties.

EXPERIMENTAL

The compounds 3-hydroxyimino-5-methyl-hexane-2-one-2,4-dinitrophenyl hydrazine **(1)** and bis(3-hydroxyimino-5-methyl-2-hexanone) dithiooxamide **(2)** were synthesized by using 3-hydroxyimino-5-methyl-2-hexanone[22]. The reactions were carried out with analytical grade chemicals. Melting points were uncorrected and determined by Hoover melting point apparatus. Infrared spectra of solid compounds were recorded in KBr pellets on Perkin-Elmer 1600 series FTIR spectrophotometer. PMR spectra were recorded in δ units relative to tetramethylsilane used as an internal standard.

Synthesis of 3-hydroxyimino-5-methyl-hexane-2-one-2,4-dinitrophenyl hydrazine (1)

The alcoholic solutions of 3-hydroxyimino-5-methyl-2-hexanone (0.1 mmol, 20 mL) and 2,4-dinitrophenylhydrazine (0.1 mmol, 20 mL) were mixed slowly with constant stirring. The shiny yellow needles of **(1)** were separated out, which were filtered, dried and recrystallized from pure ethanol.

Yield: 80%, m.p.: 129°C, FTIR (KBr) in cm^{-1}: 3125b (NOH), 3282s ($N\text{-}H_{assym.}$), 3222s $N\text{-}H_{sym.}$, 960s (N-O), 1520s ($NO_{2assym.}$), 1345s ($NO_{2symm.}$), 1625s (C=N), 845m and 735m (substituted benzene ring). ^1H NMR ($CDCl_3$) δ ppm: 0.892-0.980 (d, 2 x CH_3), 2.107 (s, CH_3), 2.126-2.193 (m, CH), 2.532-2.610 (d, CH_2), 7.519 (NH), 10.664 (NOH), 6.993-7.262 (substituted benzene ring)., Mol. Wt.: 323, (Anal. Calcd % for $C_{13}H_{17}N_5O_5$: C 48.29, H 5.26, N 21.67, O 24.79. Found %: C 48.20, H 5.23, N 21.73, O 24.87.)

Synthesis of bis(3-hydroxyimino-5-methyl-2-hexanone) dithiooxamide (2)

The mixture of alcoholic solution of 3-hydroxyimino-5-methyl-2-hexanone (0.2 mmol, 20 mL) and 1 : 1 alcoholic solution of dithiooxamide (0.1 mmol, 20 mL) was refluxed for nine hours. The mixture was allowed to stand for over night. Pale yellow

crystals of **(2)** were separated out, which were filtered, dried and recrystallized from pure ethanol.

Yield: 61%, m.p.: 191°C, FTIR (KBr) in cm^{-1}: 3129b (NOH), 3256s (N-$H_{assy.}$), 3220w (N-$H_{sym.}$), 954s (N-O), 1683s (N-C=S), 745m (C=S), 770m (N-N), 1541s (C=N). ^1H NMR ($CDCl_3$) δ ppm: 0.975-0.996 (d, 2 x CH_3), 2.069 (s, CH_3), 2.213-2.298 (m, CH), 2.654-2.739 (d, CH_2), 7.626 (NH), 10.283 (NOH), 2.451 (NH_2), Mol. Wt.: 370, (Anal. Calcd % for $C_{16}H_{26}N_4O_2S_2$: C 51.89, H 7.08, N 15.10, S 17.27, O 8.63. Found %: C 51.92, H 7.02, N 15.14, S 17.29, O 8.65.)

RESULTS AND DISCUSSION

The structures of the compounds synthesized (Figure 1) were elucidated on the basis of elemental analysis, FTIR and ^1H NMR spectral data. The carbonyl group in 3-hydroxyimino-5-methyl-2-hexanone possesses environmental dissymmetry. Hence, the geometrical isomers (anti- and amphi-forms) are expected, provided that no steric change at α-oximino group occurs and the syn-isomer would be possible in the event of such a change. The isomers could not be obtained, even after several variations in the process of preparation and crystallization. In practice, a good yield of only one isomer could be obtained in all the cases[23].

On the treatment of 3-hydroxyimino-5-methyl-2-hexanone with 2,4-dinitrophenylhydrazine and dithiooxamide, there was no replacement of α-oximino hydrogen. This shows that the hydroxyl group does not fall in the proximity of the carbonyl group and confirms that the products have anti-structure. This shows that the incoming group occupies less hindered syn-methyl position[24]. If this incoming group occupied anti-methyl position, the product in syn-form would have invariably yielded cyclised products[23, 24]. As no such products were formed, possibility of syn-form is discarded.

The literature study of oxime reveals that the products with amphi-structure are generally least stable[24]. Moreover, if at all, these are formed, amphi-product would have a cyclised structure. Since such compounds have not been obtained during preparation, amphi-structure was ruled out. The derivatives of oxime under the present study are found to be stable in anti-form and remain unchanged during purification process and on heating in an oven below their melting points.

Further, the compounds give wine red (sodium salt) coloration in alkaline medium, and it retains the original yellow colour in acidic medium. This sensitiveness of these compounds to the acidic and basic medium supports the use of these compounds as an acid-base indicator. It has been observed that the compounds exhibit indicator property in wide pH range. The results of acid-base titrations studied with both these reagents are summarized in Table 1.

Table 1: Indicator study of the compounds

Compd.	pH Transition interval	Colour		Solution in 96% ethanol (%)	Drops of the compound solution/10 mL of the titrant solution to be tested
		Acid	Alkali		
1	7.0-12.0	Yellow	Wine red	0.01	1-3
2	6.5-12.0	Yellow	Wine red	0.01	1-3

Acid- HCl, CH_3COOH, HNO_3, **Alkali-** NaOH, KOH, Na_2CO_3

Low concentrations of compounds were used to prepare the indicator solution, which gives sharp colour change at end point and shows satisfactory results as compared with other indicators such as phenolphthalein (pH 8.2-10), methyl orange (pH 3.1-4.4), alizarin yellow R (S) (pH 10-12.1) etc[25].

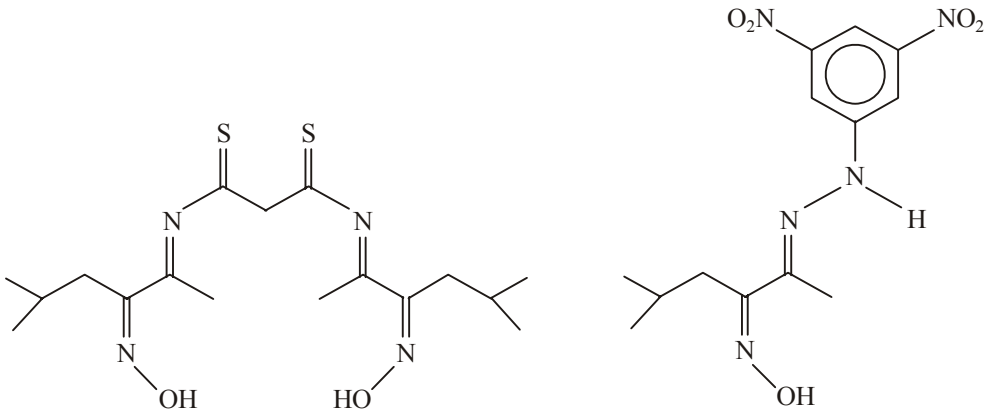
Compounds **(1)** and **(2)** have been tested for their antimicrobial evaluations against *S. typhi*, *S. aureus*, *C. albicans*, *A. niger*, *S. cerevisiae* and *m-tuberculosis* by cup-plate method [26] using DMF as solvent at 100-25 mg concentration and growth inhibition was calculated. The results showed that compound **(2)** was active and showed maximum activity. The dithiooxamide moiety is responsible for greater degree of inhibition (Table 2). The antibacterial, antifungal and antitubercular activities of compounds were compared with standard drugs such as penicillin, streptomycin and pyrozinamide, respectively. However, the activity of compounds was low in comparison to standard.

It is evident from the preliminary data that both the compounds are inhibitory at the screening concentration against a said strain and they were found to be selective growth inhibitors of m-tuberculosis in particular.

Table 2: Antimicrobial activities of compounds in µg/mL

Compound	Antibacterial activity		Antifungal activity			Antitubercular activity
	a	**b**	**c**	**d**	**e**	**f**
1	50	25	50	100	50	100
2	25	25	50	100	25	100

a. S. typhi; **b.** S. aureus; **c.** C. albicans; **d.** A. niger; **e.** S. cerevisiae; **f.** m-tuberculosis



(1) **(2)**

Fig. 1: Proposed structures of the compounds

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