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SYNTHESIS AND ANTIMICROBIAL ACTIVITIES OF 1, 2-DI (6-METHYLQUINOLYL-2) 1, 2-ETHANEDION

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ABSTRACT

The 1,2-di(6-methylquinolyl-2)-1,2-ethanedion is obtained when 1,2-di(6-methylquinolyl-2)-1,2-ethenediol was oxidized using air as an oxidizing agent whereas the starting material itself was synthesized when 6-methyl quinoline-2-carboxaldehyde was subjected to condensation reaction in the presence of potassium cyanide. The biological screening of the resulting substituted 1,2-diketone revealed its significant antimicrobial activities.

INTRODUCTION

1,2-diketones are best known for their stability and high melting points. Their formation as intermediates especially in the metabolic reactions as well as their numerous industrial applications have made them significantly important in organic chemistry (Verter, 1970). They also act as pesticides, stabilizers and inhibitors in photography and are used as dyes in the textile industry (Kirk-Othmer, 1980).

The nitrogen containing conjugated heterocyclic compounds have always been under research for their biological activities being considerably used pharmaceutically as antiulcer, antimalarial, tubercluocidal and sedatives, besides as dyes in the textile industry (Fuson and Snyder, 1942). The 1,2-diketones when substituted appropriately with nitrogen containing heterocyclic rings could be well expected for enhanced biological activities and this led us not only to synthesize such compounds but also to determine their biological activities.

EXPERIMENTAL

Melting points were measured in open capillaries with an Electrothermal IA 9100 digital melting point apparatus. All infrared spectra were recorded on a Phillips PU9714 spectrophotometer using infrared grade potassium bromide. Nuclear magnetic resonance ^{1}H & ^{13}C) spectra were determined on "Varian 200MHz Gemini", "Bruker AC-200MHz FT-NMR" and "Bruker AM-500MHz FT-NMR spectrometers in deuteriochloroform and are reported in parts per million downfield from tetramethyl silane (TMS) as the internal standard (δ scale) Mass spectra were obtained with E1 MAT 312, Varian MAT 111, Varian MAT 112 and Hewlett Packard GC/MS 5890 spectrometer for the purpose of column chromatography silica gel 60 (70-230 mesh) from E. Merck AG was used. Eastman Kodak chromogram 13181 silica gel sheets with fluorescent indicator was used for thin layer chromatography (tlc).

The required heterocyclic carboxaldehyde was prepared according to the literature procedure by the reaction of SeO_2 with 2,6-dimethyl quinoline (Kaplan, 1941). The obtained heterocyclic carboxaldehyde was found to have properties similar to that given in the literature. SeO_2 for the reaction was freshly prepared just before use by the method given by Harry Kaplan (Blatt, 1966).

The antimicrobial activity of 1,2-Di(6-methylquinolyl-2)-1,2 ethanedione was determined by measuring diameter of the zones (mm) showing inhibition and growth inhibition was calculated with reference to the control. The results were compared with the control.

The ir, nmr, ms and analytical data along with the purification procedures are given as follows.

Procedure and Analytical Data:

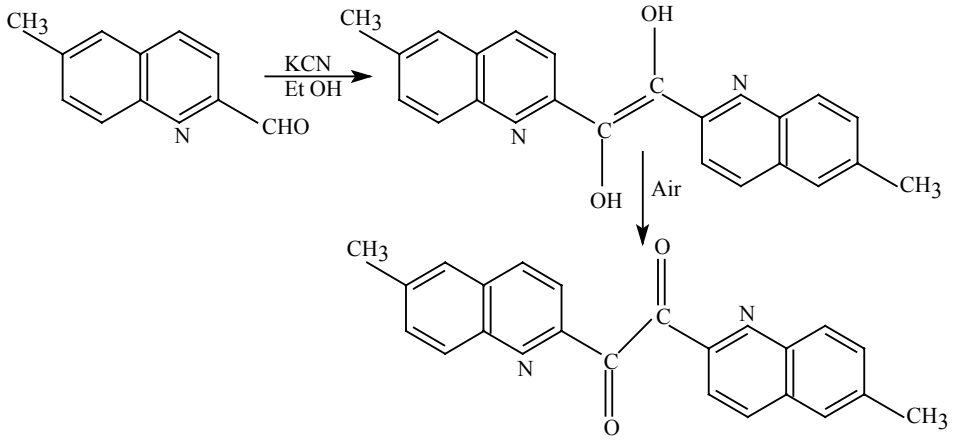
1, 2-Di(6-methylquinolyl-2)-1, 2-ethenediol (1a)

10.0mmoles of the 6-methyl quinoline-2-carboxaldehyde were dissolved in 6mL 50% aqueous ethanol in 100ml round bottom flask. To it was added a solution of 2.0 mmoles of potassium cyanide in a very little water. The colour of the solution at once changed to a dark brown along with the precipitation of a solid, this was stirred for two minutes and then heated on water bath using water condenser for half an hour. The reaction mixture was cooled, the resulting precipitates were filtered, washed with water, a little methanol and diethyl ether; yield: 3.01g (88%). Further recrystallization from pyridine gave the analytical sample "**1a**" mp 267-268ºC.

ir (potassium bromide): 3580-3080, 3040-2980, 2890, 1580, 1490, 1460, 1430, 1360, 1220, 1180, 1110, 865 and 825 cm^{-1}.
^{1}H nmr (deuteriochloroform): δ 2.55 (s, 2 x CH_3, 6H), 7.53-8.27 (m, aromatic, 10H).
^{13}C nmr (deuteriochloroform): δ 22.25 (methyl), 118.58 (alkene, C=C) 126.79 – 157.49 (heteroaromatic C=C & C=N),
uv (chloroform): λ_{max} 255.4, 294.8, 438.3 nm.
ms: m/z (relative intensity) 343 (M^{+1}) 342 (M^{+}),
Anal calcd for $C_{22}H_{18}N_2O_2$: C; 77.17, H; 5.30, N; 8.18 Found C; 77.35, H; 5.34, N; 8.35.

1, 2-Di (6-methylquinolyl 1-2), 1, 2-ethanedione (1b)
10.0 mmoles of the 1, 2-D1 (6-methylquinol 1-2) 1, 2-ethenediol were dissolved in dioxane and heated in an electrical bath and then air was passed through the solution till the dark brown colour changed to light yellow. After cooling water was added till precipitation. The obtained product (69%) was crystallized with dioxane, m.p. 276-8ºC.

ir (potassium bromide): 3080-2980, 1665, 1610, 1575, 1480, 1455, 1430, 1365, 1200, 1105, 860, 615, 700 cm^{-1}.



^{1}H nmr (deuteriochloroform: δ2.52 (s, 2x CH_3, 6H), 7.43-8.26 (m, aromatic, 10H).
uv (chloroform) λ_{max}, 260.4, 314.3 nm,

ms: m*ƒz* (relative intensity 341 (M^{+1}), 340 (M^+), 312, 274, 269, 170, 142, 127, 115.
Anal calcd for $C_{22}H_{16}N_2O_2$, C; 77.63, 11; 4.74, N; 8.23 found C; 77.62, H; 4.86, N; 7.97.

Anti Microbial Activity:

Bactericidal as well as anti fungal activities of 1,2-di (6-methylquinolyl-2) 1,2-ethanedione was investigated according to the standard procedures. The *antibacterial activity* was determined by agar well diffusion protocol whereas the *fungicidal properties* of the compound were determined against various pathogenic fungi using agar tube dilution method measuring diameter of zones (mm) showing inhibition and growth inhibition was calculated with reference to positive control.

Antibacterial Activity:

Name of Bacteria	Clinical implications	Zone of inhibition (mm)	Reference drug/ Zone of inhibition (mm)
Escherichia coli ETEC	Infections of wounds and urinary tract, inflammations of peritoneum and GIT, dysentry, septicemia, neonatal meningitis.	6	Amoxicillin $(H_2O)_3$ / 9 Ampicillin $(H_2O)_3$ / 11
Salmonella typhi	Typhoid fever, salmonella food poisoning, localized infections etc.	6	Amoxicillin $(H_2O)_3$ / 9.5 Ampicillin $(H_2O)_3$ / 11
Shigella boydii	Inflammation of GIT, bacterial dysentry	6	Amoxicillin $(H_2O)_3$ / 11 Ampicillin $(H_2O)_3$ / 11
Streptococcus pyogenes	Acute rheumatic fever, scarlet fever, sore throat, septic wound etc.	6	Amoxicillin $(H_2O)_3$ / 9.5 Ampicillin $(H_2O)_3$ / 8

Antifungal Activity:

Name of Fungi	Sample	Control	(mm) inhibition %	Std drugs	MIC µg/ml
Human pathogens					
Aspergillus niger	30	56	46.4	Miconazole Ketoconazole	100 100
Pseudallescheria boydii	50	80	37.5	Miconazole Ketoconazole	100 100
Trichophyton schoenleinii	45	80	43.7	Miconazole Ketoconazole	100 100
Animal pathogens					
Microsporum canis	30	60	50	Miconazole Ketoconazole	100 100
Trycophyton simii	62	70	11.42	Miconazole Ketoconazole	100 100
Plant pathogens					
Fusarium solanai var lycopersici (tomato)	25	50	50	Benlate	100
Fusarium oxysporum var lycopersici (tomato)	30	56	46.4	Benlate	100

RESULTS AND DISCUSSIONS

The Condensation of aromatic and heterocyclic aldehydes in the presence of potassium cyanide normally results in the formation of corresponding benzoins, but in the case of the condensation of 6-methylquinoline-2-carboxaldehyde, relevant enediol was obtained instead of benzoin, thus proving the stability of the enediol over its benzoin tautomer. The structures of the enediol was proved on the basis of its spectroscopic data which also revealed the preference of the formation of trans-enediol over it's cis-form, because of the higher structural stability of the former. The two factors responsible for the stability of the enediol over its benzoin tautomer are 1) the maximum degree of conjugation and 2) chelation provided by the presence of the oxygen atom of the hydroxyl group in the enediols. Furthermore the stability of trans-structure over cis-one is supported by the fact that the effective chelation if at all possible in the cis-enediols will be extremely difficult since the cis-enediols are not uniplanar. The presence of the trans-structure is also proved by the ir spectral data which shows no absorption band for C=C stretching vibrations between 1660-1600 cm^{-1}, i.e. characteristic for symmetrically substituted C=C bonds (Dean J.A., 1987). The enediol was oxidized using air as oxidising agent to the respective 1, 2-Di (6-methylquinolyl-2)-1, 2 ethanedione. The presence of C=O bond in Het-COCO-Het skeleton is characterized by the presence of strong band between 1700-1660 cm^{-1} in the ir spectrum. In the aliphatic 1, 2-diketo compounds the band is observed between 1730-1710 cm^{-1} whereas in the aromatic 1, 2-diketo compounds it is in between 1760-1730 cm^{-1} (Pavia, Lampman and Kria,

1979). The fall of the vibration band towards low energy in 1, 2-Di (6-methylquinolyl-2)-1, 2-ethanedione is certainly due to the presence of hetaryl groups facilitating conjugation in the compound the fact has also been revealed by Pavia and Bellamy (Dean, 1987 and Bellemy 1960).

Bactericidal Activity of 1, 2-Di (6-methylquinolyl-2)-1, 2-ethanedione:

The anti-bacterial activity of 1,2-Di(6-methylquinolyl-2)-1,2-ethanedione was determined by measuring diameter of the zones (mm) showing inhibition and growth inhibition was calculated with reference to the control. The results were compared with the control.

The bactericidal studies of the compound revealed its significant activity against bacteria. The detailed tests showed its moderate activity against *Escherichia coli, Shigella boydii*, *Salmonella typhi* and S*treptococcus pyogenes*. The anti-fungal activities were also determined and the compound was found active against many human pathogens e.g., *Aspergillus niger, Trichophyton schoenleinii* etc., animal pathogens e.g., *Microsporum caniis* and plant pathogens e.g., *Fusarium solanai var lycopersici* (tomato) and *Fusarium oxysporum var lycopersici* (tomato).

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