SYNTHESES OF SOME 1-ARYL-3-(5-NITRO-2-FURYL)-2-PROPEN-1-ONES AS POTENTIAL ANTI-BACTERIAL AGENTS

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ABSTRACT

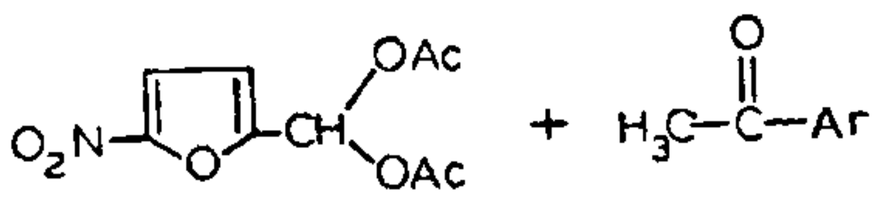
A number of 1-aryl-3-(5-nitro-2-furyl)-2-propen-1-ones were prepared as possible anti-bacterial compounds. Their structures were confirmed on the basis of elemental analysis, IR and NMR spectral data and by conversion of some of them into the respective acetates. These propenones were also subjected to antibacterial screening against both gram-positive and gram-negative bacteria. The results of the screening indicate highest activity for the propenone carrying *p*-hydroxy function in the aryl moeity.

INTRODUCTION

During our recent studies[1] on the synthesis and antibacterial activities of some 1-(5-nitro-2-furyl)-3-aryl-2-propen-1-ones, it was revealed that such propenones carrying hydroxy, halo and methyl substituents in the aryl moeity showed significant activity against *Aerobacter aerogenes* and *Escherichia coli*. This prompted us to synthesize 1-aryl-3-(5-nitro-2-furyl)-2-propen-1-ones with the aryl moeity carrying either hydroxy and alkoxy or halogeno functions. A survey of the literature revealed that very little work[2–5] is reported on the synthesis and biological activities of such compounds.

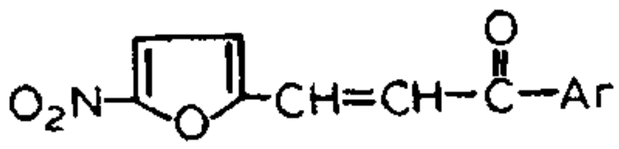
MATERIALS AND METHODS

5-Nitro-2-furfuraldehyde diacetate (I), obtained by the nitration of 2-furfuraldehyde[6], was allowed to condense in acidic media with substituted *o*-hydroxyacetophenones (II), carrying chloro, bromo, methoxy, ethoxy, methyl and benzyloxy functions and *p*-hydroxyacetophenone, (scheme 1). All *o*-hydroxyacetophenones employed in the condensation were prepared from the corresponding phenols employing either Fries[7,8] or Niencki reaction[9]. Partially *o*-alkylated acetophenones were prepared from the corresponding dihydroxyacetophenones employing diethyl or dimethylsulphate[10]. These alkoxy hydroxyacetophenones were further brominated to introduce the bromo function[11]. 2-Hydroxy-4-benzyloxyacetophenone is obtained by benzylation of resacetophenone[12]. Some of the newly



(I) (II)

Glacial HOAc
+
Conc. H_2SO_4



(III)

synthesized nitrofurylpropenones were characterized by conversion into their acetate derivatives employing standard methods. The melting points of the new compounds were determined by capillary method and are uncorrected. The IR spectra were obtained on a Perkin-Elmer infrared spectrophotometer in KBr pellet form. NMR spectra of some selected compounds were recorded on a 90 MHz NMR spectrometer using DMSO-d_6 as solvent and tetramethylsilane as an internal standard.

RESULTS AND DISCUSSION

The physical constants, yield data, analytical and spectral data of the new compounds are reported in table 1. All the chalcone analogues exhibited halochromic effects with concentrated sulphuric acid. They also showed IR absorption bands in the region of 1630-1640 cm^{-1} characteristic of the intramolecularly hydrogen-bonded α,β-unsaturated carbonyl functions of the propenones. The hydroxy

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Table 1 *Characterization data of 1-aryl-3-(5-nitro-2-furyl)-2-propen-1-ones and their derivatives*

Compound No.	Ar	Yield (%) m p (°C)	Colour and crystal form	Halochromism with conc. H_2SO_4	Analysis, Found (calcd)%			IR (cm^{-1})		
					C	H	N	γC=O	γO–H	γNO_2 asym. sym.
IIIa	2-hydroxy-4-methoxyphenyl	96 237[a]	Orange yellow crystal	Dark red	58 00 (58.13)	4.03 (3 80)	4.77 (4 84)	1630	3120	1545 1360
IIIb	2-hydroxy-4-ethoxyphenyl	67 184-6[b]	Yellow micro needles	Pink	60 01 (59.41)	4 04 (4 29)	4.54 (4 62)	1640	3140	1530 1360
IIIc	2-hydroxy-5-methoxyphenyl	54 124[a]	Violet micro needles	Dark red	58.05 (58.13)	3 60 (3 80)	4 98 (4 83)	1645	3130	1550 1380
IIId	2-hydroxy-5-ethoxyphenyl	40 154–5[a]	Violet red micro needles	Dark red	59 13 (59.40)	4 43 (4 29)	4 58 (4 62)	1640	3120	1565 1350
IIIe	2-hydroxy-4-methyl-5-chlorophenyl	91 173[c]	Rose red micro needles	Red	54.50 (54 63)	3 40 (3 25)	4 38 (4 55)	1635	3100	1555 1350
IIIf	2-hydroxy-4-methoxy-5-bromophenyl	59 169–71[c]	Golden yellow crystals	Light red	45 60 (45 65)	2 59 (2 71)	4 01 (3 80)	1630	3090	1560 1365
IIIg	2-hydroxy-4-ethoxy-5-bromophenyl	81 182–5[c]	greenish micro needles	Blood red	47.45 (47.12)	3 02 (3 14)	3 48 (3 66)	1640	3120	1540 1380
IIIh	2-hydroxy-4-benzyloxyphenyl	60 194[a]	Light yellow needles	Dark red	66.25 (65.75)	3 93 (4 10)	3.72 (3 83)	1640	3110	1550 1375
IIIi	4-hydroxyphenyl	81 186–9[c]	Brown micro needles	Rose red	60 05 (60 23)	3 52 (3 47)	5 26 (5 40)	1650	3140	1570 1340
IIIj	2-acetoxy-4 methoxyphenyl	60 166[c]	Brown red micro needles	Dark red	58 42 (58.00)	3 81 (3 92)	4 10 (4 22)	1650 1730 (ester)		1550 1360
IIIk	2-acetoxy-4-methoxy-5-bromophenyl	59 163–5[c]	White flakes	Orange red	46 56 (46 82)	3 04 (2 92)	3.65 (3 41)	1650 1735 (ester)		1560 1355
IIIl	4-acetoxyphenyl	66 159–61[c]	Light yellow micro needles	Rose red	59.51 (59 80)	3.32 (3 65)	4 68 (4 65)	1655 1740 (ester)		1570 1350

Solvent of crystallization: a) Dimethylformamide; b) Glacial acetic acid; c) Ethanol.

stretching frequency was observed as a sharp and weak band in the region of 3090-3140 cm^{-1}. In compound (IIIi) where no intramolecular hydrogen bonding is possible, the carbonyl stretching frequency was seen at 1650 cm^{-1}. Two more absorption bands were observed in the region of 1530-1570 cm^{-1} and 1350-1380 cm^{-1} characteristic of the asymmetric and symmetric stretching frequencies of the nitro group. When the propenones were acetylated the hydroxy stretching frequency disappeared and an additional ester carbonyl stretching frequency[13] was observed around 1730-1740 cm^{-1}.

The NMR spectrum of propenone (IIIe) was fully consistent with the assigned structure. A downfield siglet at δ, 11.93 was observed which is characteristic of intramolecularly hydrogen bonded hydroxy proton[14]. The signal due to the aromatic methyl proton was found as a singlet at δ, 2.33 with an integration for three protons. The signal due to the aromatic 6-H was also observed as a singlet at δ, 7.53. The peaks due to nitrofuryl protons, α and β protons of the propenone moeity and the aromatic 3-H, were found to overlap with one another and a complex pattern of signals integrating for five protons appeared around δ, 6.66 – 7.36.

The propenones (IIIa-i) were screened for their *in vitro* anti-bacterial activity against four bacteria employing the disk-diffusion method[15]. Nitrofurazone[16], 5-nitro-2-furfuraldehydesemicarbazone, was used as a standard drug and the results of the antibacterial screening are given in table 2. Propenone (IIIi) with a *p*-hydroxy substituent in the aryl moeity possessed excellent activity against all the micro organisms tested. Propenone (IIIc and IIIe) also possessed significant activity. It is interesting to note that introduction of the bromo substituent in the aryl moeity and replacement of a methoxy group by an ethoxy group did not cause any appreciable change in the antibacterial activity.

Table 2 *Antibacterial activity of 1-aryl-3-(5-nitro-2-furyl)-2-propen-1-ones*

Compound No.	Minimum inhibitory concentration μg/disk[a]			
	Bs[b]	S.au[b]	A.aer[b]	Es[b]
IIIa	80	70	100	90
IIIb	40	70	150	70
IIIc	<5	10	5	50
IIId	90	80	20	5
IIIe	10	<5	20	<5
IIIf	40	40	70	20
IIIg	40	70	70	70
IIIh	70	100	100	100
IIIi	<5	<5	<5	<5
Nitrofurazone	<5	30	<5	5

[a] minimum inhibitory concentration is the lowest concentration of the compound that prevents visible growth after 24 hr of incubation.

[b] Bs: *Bacillus Subtilis;* S.au: *Staphylococcus aureus;* A. aer: *Aerobacter aerogenes;* Es: *escherichia coli.*

EXPERIMENTAL

General method for the preparation of 1-aryl-3-(5-nitro-2-furyl)-2-propen-1-ones (III):

A solution of 5-nitro-2-furfuraldehyde diacetate (2.43 g, 0.01 mol) and appropriate acetophenone (0.01 mol) in glacial acetic acid (20 ml) was treated with concentrated sulphuric acid (1-2 ml). The mixture was allowed to stand at room temperature with stirring for 24 hr. The precipitated crystals of propenones (III) were collected by filtration, washed with methanol and recrystallized from suitable solvents. Dilution of the mother liquor yielded a second crop of the propenones which were further purified by successive recrystallizations. The colour, yield, melting point and spectral data of the propenones, thus synthesized are listed in table 1.

General method for the conversion of the propenones (III) into their acetyl derivatives:

Propenones (III, 0.01 mol) were treated with an acetylating mixture (10 ml) prepared from acetic anhydride and anhydrous pyridine (1:4). The contents were heated under reflux on a boiling water bath for 2-3 hr. The mixture was cooled and diluted with ice-cold water. The precipitated acetate derivatives were collected by filtration and recrystallized from alcohol. The characterization data of such derivates are shown in table 1 along with those of propenones.

Evaluation of antibacterial activity by disk-diffusion method:

Antibacterial activity of the test compunds (IIIa-i) was determined against *Bacillus subtilis, Staphylococcus aureus, A. aerogenes* and *E. coli* by disk-diffusion method. The disks measuring 6.25 mm in diameter were punched from Whatman no.1 filter paper. Batches of 100 disks were dispensed to each screw-capped bottles and sterilized by dry heat at

140°C for 1 hr. The test compounds were prepared with different concentration using dimethyl formamide. One ml containing 100 times the amount of chemical required in each disk was added to each bottle containing 100 disks. The disks of each concentration were placed in triplicate on nutrient agar medium seeded with fresh bacterial cultures separately. The incubation was carried at 37°C for 24 hr. Nitrofurazone was used as a standard drug and solvent control was kept. Results are summarized in table 2.

ACKNOWLEDGEMENTS

The authors are thankful to Head, RSIC, CDRI, Lucknow and Head, RSIC, IIT, Madras for elemental analysis and NMR spectra respectively. One of us (BK) is grateful to Mangalore University for a research fellowship.

24 February 1986

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