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PYRAZOLINES AND ISOXAZOLINES (I). SYNTHESIS AND ANTIMICROBIAL ACTIVITIES OF P-(1-ACYL-3-METHYL-5-ARYL-4 PYRAZOLINOYL / P-(3-METHYL-5-ARYL-4-ISOXAZOLINOYL) ARSANILIC ACID

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Abstract

Reaction of readily available arsanilic acid (I) with ethylacetoacetate afforded 4-(acetoacetamido) arsanilic acid (II), which was then condensed with aryl aldehydes. The resulting product on reaction with hydrazine hydrate and hydroxyl amine hydrochloride yielded Pyrazolines (IV) and Isoxazolines (V), respectively. The antimicrobial activity of compounds against a number of microorganisms was evaluated. Some of these compounds showed significant antimicrobial activity.

Introduction

Modern work on arsenicals drugs can be said to have started in 1905 when Thomas [1] demonstrated that atoxyl can cure experimental trypanosomiasis. Arsanilic acid derivatives [2-4], Pyrazolines and Isoxazolines [3-15] are associated with a broad spectrum of biological activities. Hence it was thought, arsanilic acid if coupled to Pyrazoline or Isoxazoline, another pharmacophores, the resulting compound might have considerable biological potency. We report here on the synthesis and antimicrobial activity of some Pyrazoline (IV) and Isoxazoline (V) derivatives.

Results and Discussion

In continuation of our work [16] on synthesis and antimicrobial activity of Pyrazolines and Isoxazolines the present investigation was undertaken.

Reaction of 4-(acetoacetamido) arsanilic acid (II) with aryl aldehydes afforded 3-(p-Arsonoanilido)-4-aryl-but-3en-2 one (III). This,on reaction with hydrazine hydrate and hydroxyl amine hydrochloride afforded the desired compounds Pyrazolines (IV) and Isoxazolines (V) respectively (Scheme 1). The ^1H NMR spectra of Pyrazolines and Isoxazolines were in agreement with the suggested structures.

The antimicrobial activity of the compounds synthesized was determined using the cup-plate method [17] at a concentration of 50 μgm against Gram positive bacteria as *B. mageterium* and *B. subtilis*, Gram negative bacteria as *E. coli* and *Ps. flourescens* and fungi as *A. niger*.

It has been concluded from the antimicrobial screening data that most of the compounds were moderately active against different strains of bacteria and fungi (12-25 mm Zone of inhibition). However, comparatively significant activity was observed in the case of Pyrazolines bearing (along with Zone of inhibition in mm) R=4-methylphenyl (14-18), 2-methoxyphenyl (14-19), cinnamyl (14-21) and in the

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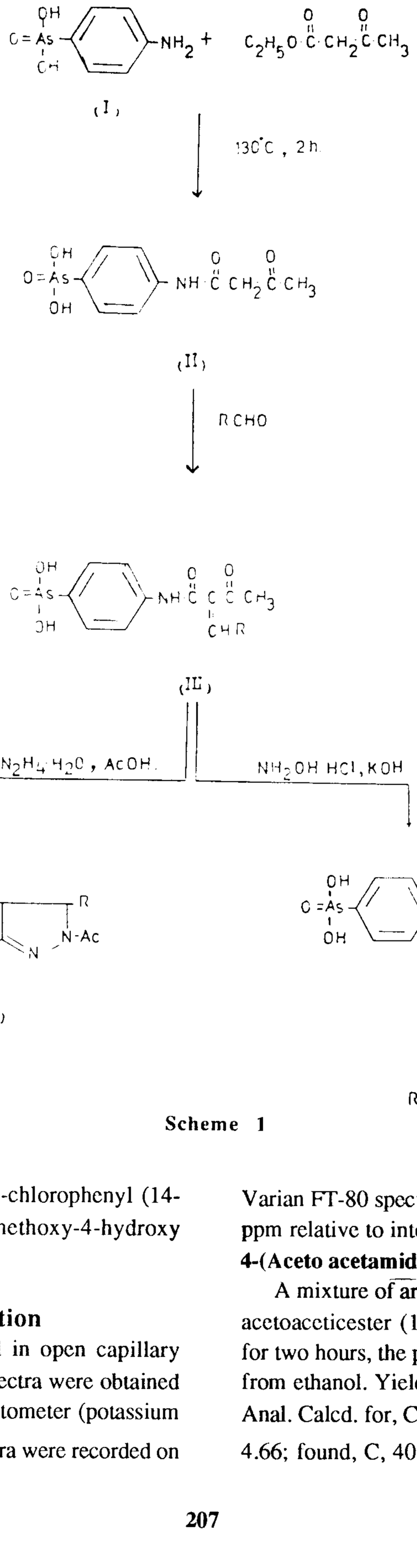

Scheme 1

case of Isoxazoline derivatives, R=2-chlorophenyl (14-18), 4-methoxyphenyl (13-25), 3-methoxy-4-hydroxy phenyl (13-18).

Experimental Section

Melting points were determined in open capillary tubes and are uncorrected. The IR spectra were obtained using a Shimadzu 435-IR spectrophotometer (potassium bromide disks). The ^1H NMR spectra were recorded on Varian FT-80 spectrometer and chemical shifts (δ) are in ppm relative to internal TMS.

4-(Aceto acetamido) arsanilic acid (II)

A mixture of arsanilic acid (2.49 gm, 0.01 M) and acetoacceticester (1.3 ml, 0.01 m) was heated at 130°C for two hours, the product was isolated and recrystallised from ethanol. Yield 1.83 gm (63%), M.P. 121°C.

Anal. Calcd. for, $C_{10}H_{12}O_5NAs$; C, 40.08; H, 4.01; N, 4.66; found, C, 40.01; H, 3.99; N, 4.60%.

IR (KBr): 3320 (-NH str.): 1690 (-C=O str.): 1660 (-C-N str.): 1590 (-NH bend.); 1100 (∅–As); 870, 770 ($-AsO_3$) Cm^{-1}.

3-(p-Arsonoanilido) -4-aryl-but-3-en-2-one (III)

A mixture of II (2.89 gm, 0.01 mole) and benzaldehyde (1.06 ml, 0.01 mole) was fused for 2.5 hours and the resulting mass was cooled and triturated with pet. ether (60-80). The product was thus isolated and recrystallised from ethanol. Yield 2.33 gm (60%), M.P. 145°C.

Anal. calcd. for, $C_{17}H_{16}O_5$ NAs; C, 52.49; H, 4.14; N, 3.59, found C, 51.86; H, 4.09; N, 3.55%.

IR (KBr) : 3310 (N-H str.); 1685 (-C=0 str.); 1655 (C-N str.): 1090 (∅-As): 810, 760 (AsO_3 str.) Cm^{-1};

^1H NMR (DMSO - d_6) : 2.5 (s, 3H, $-CH_3$); 6.6-7.4 (complex, 9H, Ar-H): 5.5 (s,1H,=C<u>H</u>-): 9.2 (s, 1H, -NH); 12.2 (s, 2H, -OH) ppm.

Table 1. Characterization Data of Compounds III, IV and V

Sr. No.	R	Compound (III)			Pyrazoline (IV)			Isoxazoline (V)		
		M.P. °C	Yield %	N % found (calcd.)	M.P. °C	Yield %	N % found (calcd.)	M.P. °C	Yield %	N % found (calcd.)
a	Phenyl	145	60	3.59 (3.55)	118	70	9.43 (9.40)	121	62	6.93 (6.93)
b	4 - Tolyl	138	58	3.47 (3.43)	122	65	9.14 (9.11)	128	64	6.77 (6.73)
c	2-Chlorophenyl	129	62	3.30 (3.28)	112	63	8.75 (8.70)	112	58	6.38 (6.34)
d	4 - Chlorophenyl	130	63	3.30 (3.28)	114	64	8.75 (8.69)	118	63	6.38 (6.36)
e	2,6 - Dichlorophenyl	134	58	3.05 (3.00)	118	69	8.17 (8.12)	108	59	5.92 (5.90)
f	3-Aminophenyl	140	59	6.93 (6.85)	98	62	12.22 (12.19)	132	52	10.02 (10.00)
g	4-Aminophenyl	139	60	6.93 (6.89)	100	68	12.22 (12.20)	134	69	10.02 (9.95)
h	2-Hydroxyphenyl	135	64	3.45 (3.42)	114	61	9.11 (9.09)	98	64	6.66 (6.62)
i	4-Hydroxyphenyl	137	64	3.45 (3.43)	116	61	9.11 (9.10)	110	68	6.66 (6.62)
j	2-Methoxyphenyl	133	62	3.34 (3.32)	126	64	8.84 (8.80)	135	62	6.45 (6.42)
k	4-Methoxyphenyl	135	60	3.34 (3.32)	124	66	8.84 (8.82)	138	61	6.45 (6.43)
l	3,4-Dimethoxyphenyl	141	60	3.11 (3.10)	119	67	8.31 (8.29)	148	54	6.03 (6.00)
m	3-Methoxy-4-Hydroxy-phenyl	143	61	3.21 (3.19)	123	64	8.55 (8.51)	170	64	6.22 (6.19)
n	3-Nitrophenyl	147	62	6.45 (6.42)	112	64	11.35 (11.31)	146	64	9.35 (9.31)
o	Cinnamyl	126	62	3.37 (3.32)	118	62	8.91 (8.82)	104	62	6.51 (6.48)
p	4-Dimethylamino-phenyl	140	63	6.48 (6.46)	102	64	11.47 (11.42)	98	63	9.39 (9.35)

Similarly, other aryl aldehydes were fused. All compounds gave satisfactory nitrogen analyses. The physical constants are recorded in Table 1.

N-Acetyl-3-methyl-4-(p-arsonoamido)-5-aryl-pyrazoline (IV)

A mixture of III (3.89 gm 0.01 mole), hydrazine hydrate (0.7 ml, 0.01 mole), gl. acetic acid (0.6 ml) and ethanol (2 ml) was refluxed for 8-10 hrs. The product was isolated and recrystallised from ethanol. Yield 3.00 gm (70%); M.P. 118°C.

Anal. calcd. for, $C_{19}H_{20}O_5N_3As$; C, 51.24; H, 4.52; N, 9.40; found, C, 51.20; H, 4.48; N, 9.43%.

IR (KBr) : 3330 (-NH str.); 1680 (-C=0 str.); 1640 (C-N str.); 1230 (C=N str.): 1090 (∅-As); 870, 770 ($-AsO_3$) Cm^{-1}.1_{NMR} : (DMSO - d_6) : 2.65 (s, 3H, $-CH_3$); 2.22 (s, 3H, -C-C$\underline{H}_3$); 7.6-8.2 (m, 9H, Ar-H); 7.2 (d, -1H, -N-C$\underline{H}$ -R); 6.91 (d, 1H, -C$\underline{H}$ -C-), 9.06 (s, 1H, -NH-); 13.2 (s, 2H, -OH) ppm.

Similarly, other pyrazolines were prepared. All compounds gave correct nitrogen analysis. Physical constants are recorded in Table 1.

3-Methyl-4-(p-arsonoanilido) -5-aryl-isoxazoline (V)

A mixture of II (3.89 gm, 0.01 m), hydroxylamine hydrochloride (0.8 gm, 0.01 m), potassium hydroxide (0.6 gm, 0.015 m) and ethanol (2 ml) was refluxed for 10 hours. The product was isolated and recrystallised from ethanol. Yield 2.50 gm (62%), M.P. 121°C.

Anal. calcd. for, $C_{17}H_{17}O_5N_2As$; C, 50.50; H, 4.23; N, 6.90%, found, C, 50.44; H, 4.20; N, 6.93%.

IR (KBr) : 3325 (N-H str.): 1695 (C=0 str.); 1645 (C-N str.); 1460 (-C-O str.); 1100 (∅ As); 870, 770 ($-AsO_3$) Cm^{-1}

^1H NMR: (DMSO -d_6); 2.5 (s, 3H, $-CH_3$); 7.0 (d, 1H, -O-C$\underline{H}$-R); 6.9 (d, 1H, -C$\underline{H}$-C-); 7.4-7.7 (m, 9H, Ar-H); 9.0 (s, 1H, -NH); 11.1 (s, 2H, -OH) ppm.

Similarly, other isoxazolines were prepared. All compounds gave satisfactory nitrogen analyses. The physical constants are recorded in Table 1.

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