FACILE SYNTHESIS AND BIOLOGICAL ACTIVITY OF SULFONATE ESTER-CONTAINING IMIDAZOLYLPYRIDINE, IMIDAZO(4,5-*b*)PYRIDINE AND IMIDAZO(5',1' : 2,3)IMIDAZO(4,5-*b*)PYRIDINE DERIVATIVES

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Different ring systems containing imidazole and/or pyridine moieties and accomodating sulfonate ester moiety in their structure were prepared via ring opening of 2-oxazolin-5-one derivatives under various reaction conditions. The assigned structures for the prepared compounds were established through elemental analysis, spectral data and if possible by alternative synthetic routes. The antimicrobial activity of the synthesized compounds was also investigated.

The discovery that imidazoline[1,2] and pyridine[3] derivatives possess a high degree of contraceptive, abortifacient, as well as antimicrobial[4] activities prompted the synthesis of a large number of additional substituted derivatives of these two moieties. Recently, 2-oxazolin-5-one derivatives (azlactones) were used as intermediates for syntheses of different imidazole analogues[5-7]. The fundamental of literature revealed sufficient scope for further studies on the synthesis of bicyclic and fused cyclic ring systems containing imidazole and/or pyridine moieties via ring opening of 2-oxazolin-5-one moiety under various conditions. Thus, as a continuation of our interest in chemistry of azlactone derivatives[8], the purpose of this paper is to enlighten the synthesis of such heterocycles – especially those accomodating highly antimicrobial[9] arenesulfonate ester moiety – with the hope to extend and/or improve their therapeutic activity. The regular introduction of methyl groups into the benzenesulfonate ester moiety was reported[10] to affect strongly their pharmacological properties.

The required 4-(4-arylsulfonyloxyphenylmethylene)-2-phenyl-2-oxazolin-5-one (*IIa* to *IIc*) were prepared by means of the reaction of 4-hydroxybenzaldehyde arenesulfonate esters (*Ia–Ic*) with hippuric acid and acetic anhydride in the presence of freshly fused sodium acetate according to Erlenmeyer synthesis[11].

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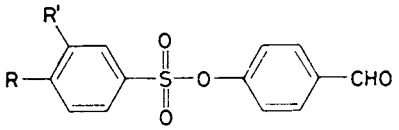
The IR spectra for these compounds were characterized by the presence of absorption bands at 1 770, 1 340 and 1 220 cm^{-1} due to lactone and sulfonate ester moieties, respectively.



I a, R = H ; R' = H
I b, R = CH_3 ; R' = H
I c, R = CH_3 ; R' = CH_3

Treatment of 4-arylmethylene-2-phenyl-2-oxazolin-5-one (*IIa*–*IIc*) with 1·1 equivalents of 2,3-diaminopyridine in ethanol containing a catalytic amount of freshly fused sodium acetate at the reflux temperature gave a single product in 65–74% yield.

On the basis of their spectroscopic and elemental analysis (experimental part), the structure 3-(4-arylsulfonyloxyphenyl-2-benzoylamino)-N-(3-aminopyrid-2-yl)propenamide (*IIIa*–*IIIc*) was assigned to the products (Scheme 1). The assumption that the reaction has involved the amino group at the position 2 and not that at the position 3 of the pyridine moiety is based on the work of Gurg[12]. This is also consistent with the relative basicity of the two amino groups. Thus, the isomeric structure *IV* for the obtained products was rejected.

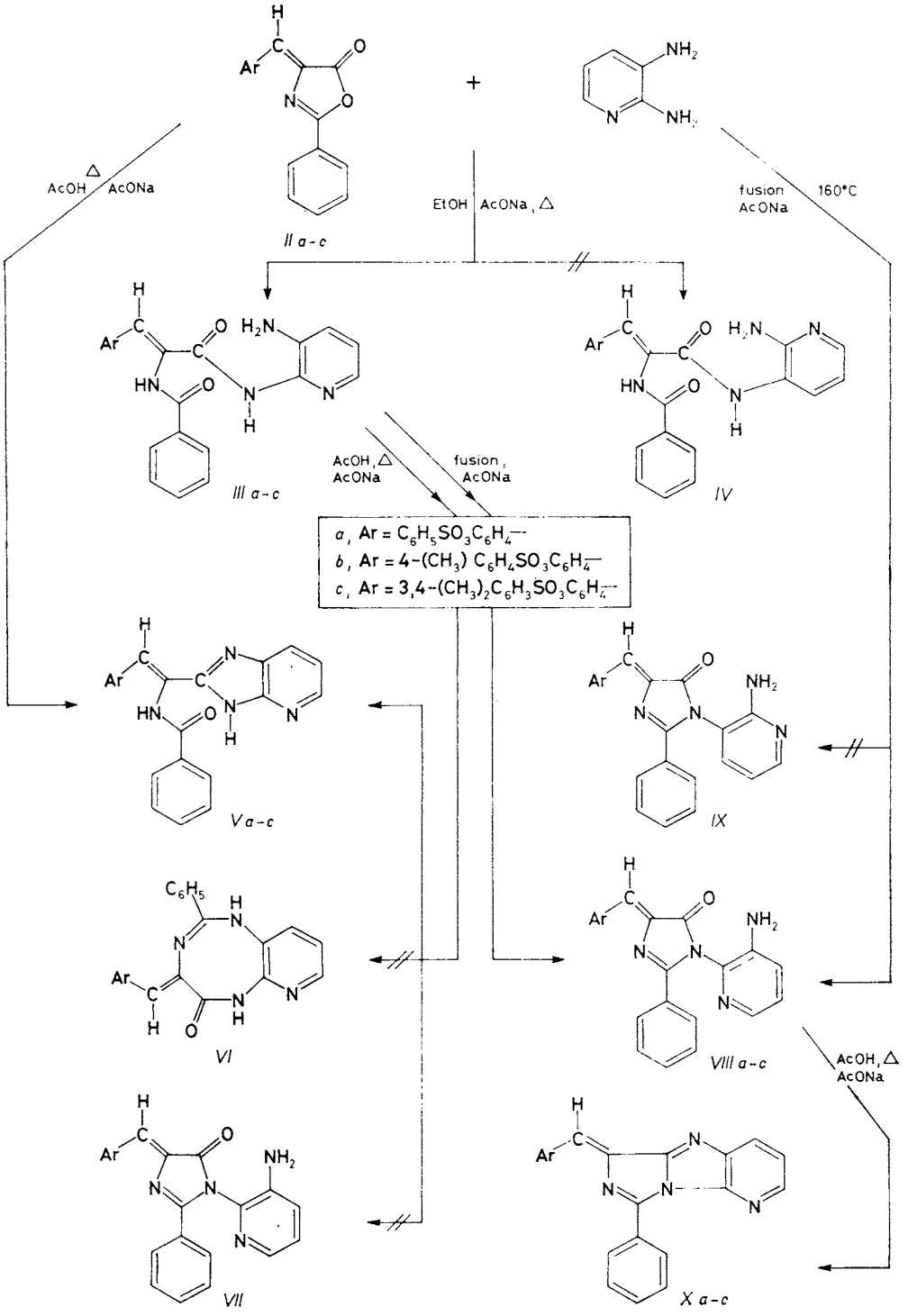
IR spectrum of *IIIb* as a representative example for this series revealed the absence of absorption bands at 1 800–1 700 cm^{-1} due to lactone moiety.

On the other hand, carrying out the above reaction using acetic acid instead of ethanol afforded 2-[2-[(4-arylsulfonyloxyphenyl)-1-benzoylamino]ethen-1-yl]-3*H*-imidazo(4,5-*b*)pyridine (*Va*–*Vc*), Scheme 1, in good yield. This reaction may involve ring opening of a lactone moiety at C-5 to give compounds *IIIa*–*IIIc* which, in turn, cyclize in the presence of acetic acid giving rise to *Va*–*Vc*.

In order to confirm this mechanism, each of the compounds *IIIa*–*IIIc* was allowed to boil with acetic acid in the presence of a catalytic amount of fused sodium acetate. A remarkable change was observed and the resulting products were identified as imidazo(4,5-*b*)pyridine derivatives *Va*–*Vc*. No depression was observed in m.p. after admixing with an authentic sample of *Va*–*Vc* prepared directly from *IIa*–*IIc*. The possibility of formation of pyrido(2,3-*b*)triazocine *VI* or 2-imidazolin-5-one derivative *VII* was excluded due to the spectral data of the products.

IR spectrum of compound *Va* showed a strong absorption band at 1 560 cm^{-1}, amide band of secondary non-cyclic amides[13]. No absorption bands were observed in the 1 750–1 700 cm^{-1} region for CO of the imidazoline moiety.

When 4-arylmethylene-2-phenyl-2-oxazolin-5-one (*IIa*–*IIc*) were allowed to react with 2,3-diaminopyridine in the absence of solvents by means of fusion with a cata-


AcOH, △ AcONa
EtOH AcONa, △
fusion AcONa 160°C
II a-c
III a-c
IV
AcOH, △ AcONa
fusion, AcONa
a, Ar = C6H5SO3C6H4—
b, Ar = 4-(CH3) C6H4SO3C6H4—
c, Ar = 3,4-(CH3)2C6H3SO3C6H4—
Va-c
IX
VI
VIII a-c
AcOH, △ AcONa
VII
X a-c

SCHEME 1

lytic amount of freshly fused sodium acetate, 3-amino-2-[4-(4-arylsulfonyloxyphenylmethylene)-5-oxo-2-phenylimidazolin-1-yl]pyridines (*VIIIa–VIIIc*) were produced.

The exclusion of the isomeric structure *IX* formation is similarly based on the relative reactivity of the two amino groups[12]. Again, the interaction of 2,3-diaminopyridine with 2-oxazolin-5-one derivatives *IIa–IIc* in the absence of solvents involves ring opening at C-5 of the lactone moiety, followed by cyclization to the corresponding imidazolinone derivatives *VIII*.

In order to confirm this mechanism, compound *IIIa* was fused with a catalytic amount of freshly fused sodium acetate in the absence of solvents. The product was found to be identical to that obtained from the previous experiment (no depression in m.p. was observed after admixing with a sample of *VIIIa* that was prepared through fusion of *IIa* with 2,3-diaminopyridine).

Cyclization of compounds *IIIa–IIIc* to *VIIIa–VIIIc* is accompanied by a loss of absorption bands in IR spectrum, due to secondary amide moiety.

Boiling *VIIIa–VIIIc* with acetic acid in the presence of a catalytic amount of freshly fused sodium acetate yielded 6-(4-arylsulfonyloxyphenylmethylene)-8-phenyl-6*H*-imidazo(5′,1′ : 2,3)-imidazo(4,5-*b*)pyridine (*Xa–Xc*). Its IR spectrum revealed the absence of absorption bands due to imidazolinone moiety.

Further support for the complete cyclization of compounds *VIIIa–VIIIc* to imidazo(5′,1′ : 2,3)imidazo(4,5-*b*)pyridine derivatives *Xa–Xc* was established from ^{1}H NMR spectra and on the basis of the absence of two protons, due to amino group, in comparison with the ^{1}H NMR spectrum of a representative example for this series, *VIIIc*.

New compounds prepared in this manner are expected to possess contraceptive, as well as abortifacient activities, and, for the time being, are under investigation for their antiimplantation activity in adult female rats. Complete details of the pharmacological findings, together with LD_{50} values for these products will be reported separately.

The prepared compounds were also tested in vitro for their antimicrobial activities: the microorganisms and the minimum inhibitory concentrations (MIC) in $\mu g\ ml^{-1}$ are given, unless they exceed $100\ \mu g\ ml^{-1}$: *Staphylococcus albus*, *IIb* 50, *IIc* 50, *Va* 25, *Xc* 100; *Staphylococcus aureus*; *IIIc* 12·5, *Vb* 50, *VIIIb* 25, *Xa* 100; *Escherichia coli*, *IIb* 75, *IIc* 50, *Vc* 25, *VIIIb* 50, *VIIIc* 12·5; *Diplococcal Neisseria catarhalis*, *IIb* 12·5, *IIIa* 25, *Vc* 50, *VIIIb* 100, *Xb* 25; *Saccharomyces cerevisiae*, *IIa* 25, *Vb* 50, *Vc* 12·5, *Xa* 75.

EXPERIMENTAL

Melting points of the analytical samples were determined in a Fisher–Johns apparatus and are not corrected. The IR spectra (KBr) were recorded on a Pye–Unicam SP 2000 spectrophoto-

meter. ^{1}H NMR spectra ($CDCl_3$) were recorded on Varian EM 360 spectrometer 60 MHz, and are given in δ (ppm) relative to TMS as an internal standard. The purity of the prepared compounds was checked by means of thin layer chromatography.

Arenesulfonate esters *Ia—Ic*

These compounds were prepared adopting the method reported in literature[14].

4-*Hydroxybenzaldehyde benzenesulfonate ester* (Ia), m.p. 84°C, 72% yield, ref.[15] — m.p. 84—85°C. For $C_{13}H_{10}O_4S$ (262·3) calculated: 59·53% C, 3·84% H, 12·22% S; found: 59·84% C, 3·79% H, 12·53% S. IR spectrum: 2 930—2 910 cm^{-1} (C–H stretching vibrations for aromatics and CH_3), 2 805, 2 735 cm^{-1} (C–H stretching vibrations for CHO group), 1 705 cm^{-1} (CO of aldehydic group) and 1 335, 1 225 cm^{-1} (sulfonate ester moiety).

4-*Hydroxybenzaldehyde* 4-*methylbenzenesulfonate ester* (Ib), m.p. 73°C, ref.[14] — m.p. 72 to 73°C.

4-*Hydroxybenzaldehyde* 3,4-*dimethylbenzenesulfonate ester* (Ic), obtained as white crystals from ethanol with m.p. 169°C, yield 80%. For $C_{15}H_{14}O_4S$ (290·3) calculated: 62·05% C, 4·86% H, 11·04% S; found: 61·89% C, 4·91% H, 11·31% S. IR spectrum: 2 930—2 900 cm^{-1} (aromatic and CH_3 stretching vibrations), 2 730 cm^{-1} (C–H stretching vibrations of CHO), 1 705 cm^{-1} (CO of aldehydic group) and 1 335, 1 225 cm^{-1} (sulfonate ester moiety).

4-(4-Arylsulfonyloxyphenylmethylene)-2-phenyloxazolin-5-one (*IIa—IIc*)

A mixture of 4-hydroxybenzaldehyde arenesulfonate esters *Ia—Ic* (0·0022 mol in each case), hippuric acid (0·002 mol), freshly fused sodium acetate (0·5 g) and acetic anhydride (30 ml) was refluxed on a steam bath for 2 hours, cooled, diluted with ethanol (30 ml) and left overnight. The crystalline solid that separated was filtered and recrystallized from ethanol (Table I). IR spectrum of *IIc*: 2 950—2 910 cm^{-1} (C–H stretching vibrations of aromatic and CH_3 group), 1 770 cm^{-1} (lactone moiety), 1 625 cm^{-1} (C=N) and 1 340, 1 220 cm^{-1} (sulfonate ester moiety). ^{1}H NMR spectrum of *IIb*: 7·9—6·8 m, 14 H (aromatic and ylidene protons) and 2·2 s, 3 H (CH_3 group).

3-(4-Arylsulfonyloxyphenyl)-2-benzoylamino-N-(3-aminopyrid-2-yl)propenamide (*IIIa—IIIc*)

A mixture of oxazolinone *IIa—IIc* (0·005 mol in each case) and 2,3-diaminopyridine (0·0055 mol) in ethanol (30 ml) was refluxed for 3 hours. The reaction mixture was cooled, and the precipitated solid was collected and recrystallized from ethyl alcohol to give the product (Table I). For compound *IIIb*, IR spectrum: 3 490, 3 450 cm^{-1} (sym. and asym. stretching of amino group), 3 330 cm^{-1} (NH of amide moiety), 2 950— 2 910 cm^{-1} (C–H stretching vibrations of aromatic and CH_3 groups), 1 645, 1 560 cm^{-1} (secondary amide moieties), 1 630 cm^{-1} (C=N) and 1 340, 1 220 cm^{-1} (sulfonate ester group). ^{1}H NMR spectrum: 8·6—7·3 m, 16 H (aromatic and pyridine moiety), 6·8 s, 1 H (–CH=C–), 5·9 broad, 2 H (protons of the two secondary amide moieties, exchanged with D_2O), 4·6 broad, 2 H (NH_2 group, exchanged with D_2O) and 2·2 s, 3 H (CH_3).

2-[2-[(4-Arylsulfonyloxyphenyl)-1-benzoylamino]ethen-1-yl]-3*H*-imidazo(4,5-*b*)pyridine (*Va— Vc*)

A mixture of oxazolinone derivative *IIa—IIc* (0·005 mol in each case) and 2,3-diaminopyridine (0·0055 mol) in acetic acid (30 ml) containing freshly fused sodium acetate (0·3 g) was refluxed

for 4 hours. The reaction mixture was cooled and the precipitate was collected by filtration and recrystallized from acetic acid to give the required products, Table I. For compound *Va*, IR spectrum: 3 330 cm^{-1} (NH, imidazolyl and benzoylamino), 1 645 cm^{-1} (amide band for CONH moiety), 1 620 cm^{-1} (C=N), 1 560 cm^{-1} (amide band of secondary noncylic amides) and 1 340, 1 220 cm^{-1} (sulfonate ester moiety.)

Boiling of *IIIa—IIIc* (0·005 mol in each case), in acetic acid (30 ml) and in the presence of a catalytic amount of sodium acetate (0·3 g) for 4 hours afforded the same products of imidazo-(4,5-*b*)- pyridine derivatives *Va— Vc*, as established by mixed melting points.

3-Amino-2-[4-(4-arylsulfonyloxyphenylmethylene)-5-oxo-2-
-phenylimidazolin-1-yl]pyridine (*VIIIa— VIIIc*)

Equimolar quantities (0·005 mol) of 2,3-diaminopyridine and each of the oxazolone derivatives *IIa— IIc* were mixed and fused with freshly prepared sodium acetate (0·3 g), at 160°C for 3 hours. The reaction mixture was cooled and washed several times with light petroleum ether and re-

TABLE I

Characterization data for compounds *II*, *III* and *V*

Compound	M.p., °C (yield, %)	Formula (M.w.)	Calculated/Found			
			% C	% H	% N	% S
IIa	140	$C_{22}H_{15}NO_5S$	65·17	3·73	3·46	7·91
	(74)	(405·4)	65·35	3·56	3·58	7·66
IIb	175	$C_{23}H_{17}NO_5S$	65·86	4·09	3·34	7·64
	(70)	(419·4)	65·47	4·24	3·73	7·81
IIc	180	$C_{24}H_{19}NO_5S$	66·50	4·42	3·23	7·40
	(65)	(433·5)	66·62	4·46	3·10	7·58
IIIa	130	$C_{27}H_{22}N_4O_5S$	63·02	4·31	10·89	6·23
	(60)	(514·5)	63·36	4·16	10·57	6·44
IIIb	146	$C_{28}H_{24}N_4O_5S$	63·62	4·58	10·60	6·09
	(66)	(528·6)	63·85	4·78	10·88	6·37
IIIc	170	$C_{29}H_{26}N_4O_5S$	64·19	4·83	10·33	5·91
	(61)	(542·6)	64·34	4·96	10·51	5·66
Va	110	$C_{27}H_{20}N_4O_4S$	65·31	4·06	11·28	6·46
	(76)[a]	(496·5)	65·10	4·32	11·63	6·88
Vb	150	$C_{28}H_{22}N_4O_4S$	65·87	4·34	10·97	6·28
	(71)[a]	(510·6)	65·99	4·29	10·59	6·07
Vc	173	$C_{29}H_{24}N_4O_4S$	66·40	4·61	10·68	6·11
	(80)[a]	(524·6)	66·21	4·68	10·44	6·36

[a] Compounds *Va— Vc*, prepared by different method were obtained nearly in the same yield.

crystallized from acetic acid to give the product, Table II. For compound *VIIIc*, IR spectrum: 3 490, 3 450 cm^{-1} (sym. and asym. stretching vibrations of NH_2 group), 2 950, 2 910 cm^{-1} (aromatic and CH_3 stretching vibrations), 1 710 cm^{-1} (CO of imidazolone moiety), 1 620 cm^{-1} (C=N) and 1 340, 1 220 cm^{-1} (sulfonate ester moiety). ^1H NMR spectrum: 8·6—7·2, m 15 H (aromatic and pyridine moiety), 6·8 s, 1 H (–CH=C–), 4·6 broad, 2 H (NH_2 group, exchanged with D_2O) and 2·2 s, 6 H (two methyl groups).

The fusion of 1 g of 3-(4-arylsulfonyloxyphenyl)-2-benzoylamino-N-(3-aminopyrid-2-yl)-propenamide (*IIIa—IIIc*) in the presence of freshly fused sodium acetate (0·1 g) for 3 hours at 160—180°C and processing as in the previous experiment yielded in the same products *VIIIa* to *VIIIc*.

6-(4-Arylsulfonyloxyphenylmethylene)-8-phenyl-6*H*-imidazo(5′,1′ : 2,3)imidazo(4,5-*b*)pyridine (*Xa—Xc*)

A mixture of each of the imidazolinone derivatives *VIIIa—VIIIc* (0·003 mol) in acetic acid (20 ml) and a catalytic amount of sodium acetate (0·1 g) was heated at reflux temperature for 3 hours. Cooling of the reaction mixture afforded crystalline products which were crystallized from acetic acid to give *Xa—Xc* (Table II). For compound *Xb*, IR spectrum: 2 950, 2 910 cm^{-1} (C–H stretching vibrations of aromatics and CH_3 group), 1 620 cm^{-1} (C=N) and 1 340, 1 220 cm^{-1} (sulfonate ester moiety). ^1H NMR spectrum: 8·6—7·3 m, 16 H (aromatic and pyridine moieties), 6·8 s, 1 H (–CH=C–) and 2·2 s, 3 H (CH_3).

TABLE II

Characterization data for compounds *VIII* and *X*

Compound	M.p., °C (yield, %)	Formula (M.w.)	Calculated/Found			
			% C	% H	% N	% S
VIIIa	105 (62)[a]	$C_{27}H_{20}N_4O_4S$ (496·5)	65·31 65·02	4·06 4·23	11·28 11·56	6·46 6·71
VIIIb	165 (70)[a]	$C_{28}H_{22}N_4O_4S$ (510·6)	65·87 65·49	4·34 4·11	10·97 10·79	6·28 6·55
VIIIc	175 (66)[a]	$C_{29}H_{24}N_4O_4S$ (524·6)	66·40 66·73	4·61 4·73	10·68 10·99	6·11 6·02
Xa	55 (81)	$C_{27}H_{18}N_4O_3S$ (478·5)	67·77 67·62	3·79 3·56	11·71 11·48	6·70 6·96
Xb	200 (75)	$C_{28}H_{20}N_4O_3S$ (492·5)	68·28 68·57	4·09 4·06	11·38 11·77	6·51 6·80
Xc	>300 (73)	$C_{29}H_{22}N_4O_3S$ (506·6)	68·76 68·51	4·38 4·48	11·06 11·23	6·33 6·12

[a] Compounds *VIIIa—VIIIc*, prepared by different method were obtained nearly in the same yield.

The bacteriostatic effects of the prepared compounds were determined using the agar diffusion sensitivity test. The microorganisms were pure cultures grown on a bactonutrient broth and bactonutrient agar[16]. The antifungal activity was tested using the turbidimetric method[17].

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