SYNTHESIS OF SOME NEW N-SUBSTITUTED QUINOLIMIDES WITH ANTIBACTERIAL ACTIVITIES

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Received November 20, 1989
Accepted March 8, 1991

Quinolinic anhydride condensed with 4-aminoacetophenone gave quinolinimide *I*. Condensation of *I* with aromatic aldehydes afforded the corresponding chalcones *II*. Interaction of *II* with hydrazine hydrate in dry ethanol gave unstable pyrazolines, but when the reaction was carried out in the presence of glacial acetic acid[1], stable pyrazolines *III* were obtained. Phenylhydrazine reacted with *II* to give N-phenylpyrazolines *IV*. Compounds *II* were refluxed with ethanolic solution of hydroxylamine hydrochloride, urea and thiourea and the isoxazolines *V*, pyrimidinones *VI* and pyrimidinthiones *VII* were obtained, respectively, as shown in Scheme 1. Compounds *IX* and *XI* were prepared using benzal derivative *VIII* as shown in Scheme 2.

EXPERIMENTAL

All melting points are uncorrected. Elemental analyses were performed on Perkin–Elmer 240E analyzer. IR spectra (given in cm^{-1}) were recorded on Pye–Unicam SP-200 G in KBr pellet. ^1H NMR spectra (given in δ ppm) were recorded on 90 MHz Varian NMR spectrometer in $(CD_3)_2SO$ using TMS as internal standard. Physico-chemical data are given in Table I.

N-(*p*-Acetophenonyl)quinolinimide *I*

This compound was prepared from quinolinic anhydride (0·01 mol, 1·5 g) and 4-aminoacetophenone (0·01 mol, 1·4 g) in glacial acetic acid under reflux for one hour. ^1H NMR spectrum: 2·60 s, 3 H (CH_3); 7·50–8·20 m, 5 H (phenyl protons and 1 H of pyridine); 8·16 d, 1 H (pyridine); 8·83 d, 1 H (pyridine). IR spectrum: 1 680 (C=O), 1 600 (C=N–).

N-Quinolimido-*p*-substituted Chalcones *IIa–IId*

To an ethanolic solution of *I* (0·01 mol, 2·7 g) and respective aromatic aldehyde (0·01 mol), 0·1 ml of piperidine was added. The reaction mixture was refluxed for 2 h. The products were crystallized from ethanol. IR spectra: 1 730–1 720 (C=O of quinolimide), 1 690–1 660 (C=O of chalcones) 1 640–1 605 (C=C). ^1H NMR spectrum of *IIb*: 3·70 s, 3 H (CH_3O); 6·95 d, 2 H (CH=CH); 8·75–7·50 m, 11 H (phenyl and pyridine protons). For compound *IIc*: 2·50 s, 3 H (CH_3); 8·65 to 7·45 m, 11 H (aromatic and pyridine protons); 7·00 d, 2 H (CH=CH).

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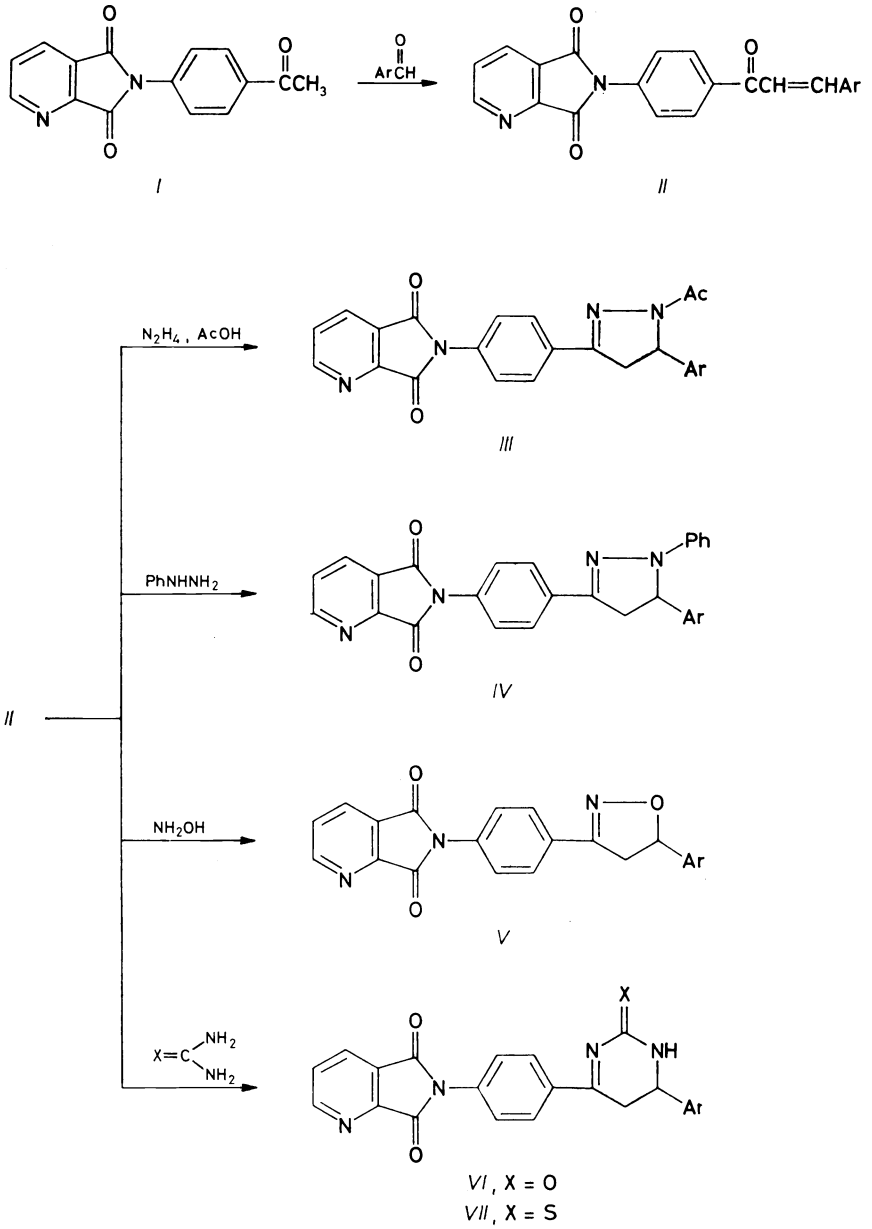


In formulae *II*–*VII*: *a*, Ar = C_6H_5; *b*, Ar = *p*-$CH_3OC_6H_4$; *c*, Ar = *p*-$CH_3C_6H_4$; *d*, Ar = *p*-$O_2NC_6H_4$

SCHEME 1

TABLE I

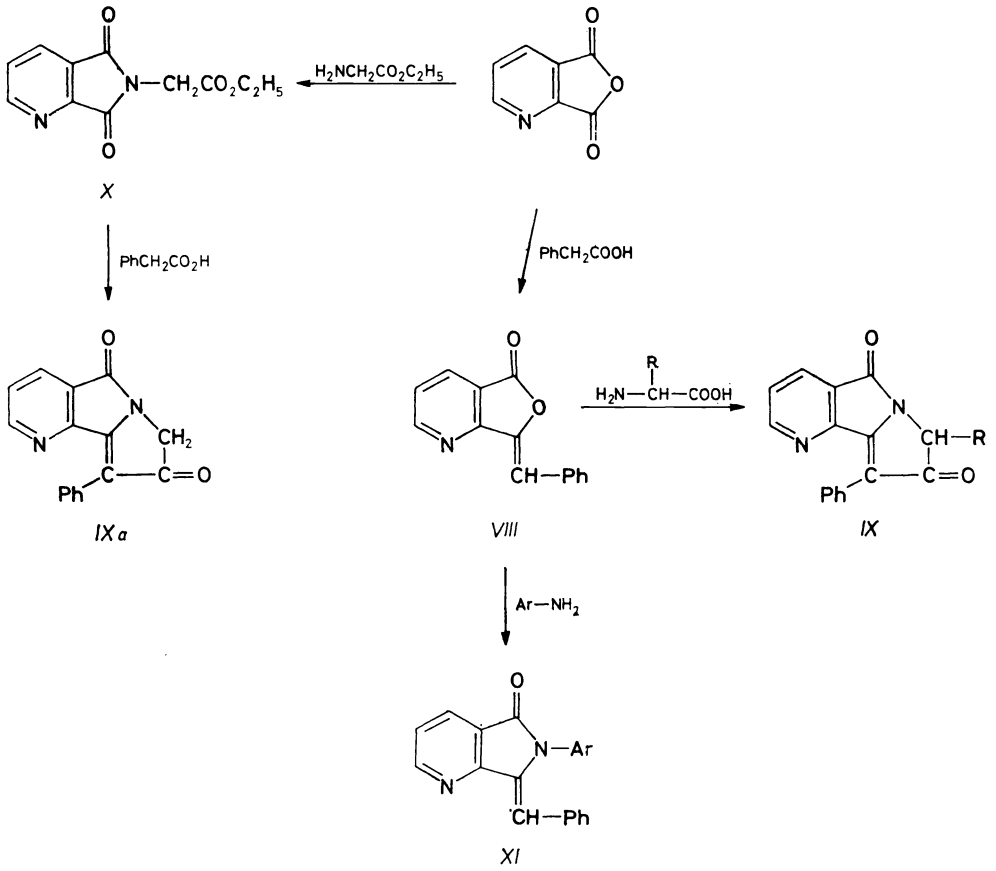
Physico-chemical data of compounds *I*—*XI*

Compound	M.p. °C	Yield °C	Formula (M.w.)	Calculated/Found			
				% C	% H	% N	% S
I	182—185	90	$C_{15}H_{10}N_2O_3$ (266·3)	67·66 67·25	3·75 4·12	10·52 10·86	—
IIa	192—197	74	$C_{22}H_{14}N_2O_3$ (354·4)	74·57 74·18	3·95 4·22	7·90 7·76	—
IIb	194	76	$C_{23}H_{16}N_2O_4$ (384·4)	71·87 71·43	4·16 4·32	7·29 7·78	—
IIc	185	69	$C_{23}H_{16}N_2O_3$ (368·4)	75·00 75·43	4·34 4·52	7·60 7·27	—
IId	194	75	$C_{22}H_{13}N_3O_5$ (399·4)	66·16 66·52	3·25 3·12	10·52 10·95	—
IIIa	214	65	$C_{24}H_{18}N_4O_3$ (410·4)	70·24 70·65	4·39 4·21	13·65 13·44	—
IIIb	228	67	$C_{25}H_{20}N_4O_4$ (440·5)	68·16 67·83	4·54 4·77	12·72 12·55	—
IIIc	305	55	$C_{25}H_{20}N_4O_3$ (424·5)	70·74 70·28	4·71 4·89	13·20 12·69	—
IIId	275	60	$C_{24}H_{17}N_4O_5$ (441·4)	65·30 65·72	3·85 3·54	12·69 12·73	—
IVa	215	62	$C_{28}H_{20}N_4O_2$ (444·5)	75·76 75·28	4·50 4·23	12·61 12·14	—
IVb	218	71	$C_{29}H_{22}N_4O_3$ (474·5)	73·41 73·12	4·64 4·69	11·81 12·33	—
IVc	191	84	$C_{29}H_{22}N_4O_2$ (458·5)	75·98 76·24	4·80 4·15	12·22 12·61	—
IVd	220	68	$C_{28}H_{19}N_5O_4$ (489·5)	68·71 68·28	3·88 4·16	14·31 14·76	—
Va	270	70	$C_{22}H_{15}N_3O_3$ (369·3)	71·54 71·16	4·06 3·83	11·38 11·24	—
Vb	263	71	$C_{23}H_{17}N_3O_4$ (399·4)	69·17 68·87	4·26 4·35	10·52 10·72	—
Vc	255	75	$C_{23}H_{17}N_3O_3$ (383·4)	71·13 70·83	4·38 3·29	10·82 10·41	—
Vd	222	73	$C_{22}H_{14}N_4O_5$ (414·6)	63·76 63·28	3·38 3·43	13·52 13·64	—

TABLE I
(*Continued*)

Compound	M.p. °C	Yield %	Formula (M.w.)	Calculated/Found			
				% C	% H	% N	% S
VIa	285	50	$C_{23}H_{16}N_4O_3$ (396·6)	69·69 64·87	4·04 3·65	14·14 14·63	—
VIb	248	63	$C_{24}H_{18}N_4O_4$ (426·00)	67·60 67·14	4·22 4·43	13·14 13·56	—
VIc	272	55	$C_{24}H_{18}N_4O_3$ (410·00)	70·24 70·64	4·39 4·25	13·65 13·19	—
VId	312	49	$C_{23}H_{15}N_5O_5$ (441·00)	62·58 62·88	3·40 3·27	15·87 15·45	—
VIIa	283	65	$C_{23}H_{16}N_4O_2S$ (412·00)	66·95 67·35	3·88 4·12	13·59 13·86	7·76 7·35
VIIb	320	67	$C_{24}H_{18}N_4O_3S$ (442·7)	65·15 65·47	4·07 3·75	12·66 12·18	7·23 7·65
VIIc	385	62	$C_{24}H_{18}N_4O_2S$ (426·70)	67·60 67·83	4·22 4·62	13·14 12·85	7·51 7·42
VIId	205	59	$C_{23}H_{15}N_5O_4S$ (457·00)	60·39 60·24	3·28 3·68	15·31 15·52	7·00 6·85
VIII	207	84	$C_{14}H_9NO_2$ (223·00)	75·33 75·14	4·03 3·94	6·27 6·46	—
IXa	210	90	$C_{16}H_{10}N_2O_2$ (262·00)	73·28 73·14	3·81 3·42	10·68 10·24	—
IXb	225	88	$C_{17}H_{12}N_2O_2$ (276·00)	73·91 74·32	4·34 4·48	10·14 9·86	—
IXc	230	70	$C_{19}H_{16}N_2O_2$ (304·00)	75·00 75·36	5·26 5·24	9·21 9·55	—
IXd	235	75	$C_{20}H_{18}N_2O_2$ (218·00)	75·47 75·66	5·66 5·49	8·80 8·65	—
X	122—125	65	$C_{11}H_{10}N_2O_4$ (234·00)	56·41 56·84	4·27 4·22	11·96 12·29	—
XIa	187	87	$C_{20}H_{14}N_2O$ (298·20)	80·53 80·19	4·69 4·35	9·39 9·22	—
XIb[a]	167	76	$C_{20}H_{13}N_2OCl$ (332·00)	72·18 72·55	3·90 4·14	8·42 8·83	—
XIc	122—124	82	$C_{21}H_{16}N_2O_2$ (328·00)	76·82 77·14	4·87 4·65	8·53 8·27	—

[a] Calculated: 10·67% Cl; found: 10·29% Cl.



X IXa VIII IX XI

In formula *IX*: *a*, R = H; *b*, R = CH_3; *c*, R = $CH(CH_3)_2$; *d*, R = $CH_2CH(CH_3)_2$
XI: *a*, Ar = C_6H_5; *b*, Ar = *p*-ClC_6H_4; *c*, Ar = *p*-$CH_3OC_6H_4$

SCHEME 2

N-4-(1′-Acetyl-5′-aryl-2′-pyrazolin-3′-yl)phenylquinolimides *IIIa*—*IIIc*

To a solution of chalcones *IIa*—*IId* (0·03 mol) in ethanol (30 ml), hydrazine hydrate (98%, 4 ml) was added first, then 5 ml glacial acetic acid, followed by heating for 5 h to give *IIIa*—*IIIc*. IR spectrum: 1 720—1 705 (C=O), 1 660—1 640 (C=N), absence of NH band. ^{1}H NMR spectrum of *IIIb*: 2·60 s, 3 H (CH_3—CO); 3·70 s, 3 H (CH_3O); 3·55 d, 2 H (–CH_2–); 5·70 t, 1 H (N—CH—Ar); 8·70—7·50 m, 11 H (aromatic and pyridine protons). For compound *IIIc*: 2·30 s, 3 H (CH_3—Ar); 2·60 s, 3 H (CH_3—CO); 8·85—7·55 m, 11 H (phenyl and pyridine protons).

N-[4-(4′-Phenyl-5′-aryl-2′-pyrazolin-3′-yl)phenyl]quinolimides *IVc—IVd*

To an ethanolic solution of chalcones *IIa—IId* (0·03 mol) and phenylhydrazine (1·1 ml, 0·01 mol), piperidine (0·1 ml) was added and refluxed for 5 h to give *IVa—IVd*. IR spectra: 1 720 (C=O); 1 615—1 600 (C=N), 1 260—1 250 (C—H). ^{1}H NMR spectrum of *IVc*: 2·40 s, 3 H (CH_3—Ar); 8·75—7·55 m, 19 H (aromatic protons).

N-[4(5′-Aryl-2′-isoxazolin-3′-yl)phenyl]quinolimides *Va— Vd*

A solution of equimolar quantities (0·01 mol) of *IIa—IId* and hydroxylamine hydrochloride (6·69 g) in ethanol (20 ml) and (0·5 g, 0·00125 mol) of NaOH was refluxed for 6 h giving compounds *Va— Vd*. IR spectrum: 1 720 (C=O), 1 660—1 605 (C=N). ^{1}H NMR spectrum of *Vc*: 2·15 s, 3 H (CH_3—Ar); 3·60 d, 2 H (–CH_2–); 5·60 t, 1 H (O—CH—Ar); 8·70—7·95 m, 11 H (phenyl and pyridine protons).

N-[4-(5′-Aryl-5′,6′-dihydro-1′*H*-pyrimidin-2′-one-4′-yl)-phenyl]quinolimides *VIa— VId* and Respective 2′-Thiones *VIIa— VIId*

A mixture of *IIa—IId* (0·005 mol) and urea (0·005 mol, 0·38 g) in aqueous ethanolic potassium hydroxide solution (2%) refluxed for 3 h afforded compound *VIIa— VIId*. IR spectrum of compounds *VIa— VId*: 1 720—1 680 (C=O), 1 605—1 600 (C=N), 3 380—3 360 (NH); compounds *VIIa— VIId*: 1 720 (C=O), 1 640—1 625 (C=N), 1 505—1 490 (N—C=S), 1 290 (C=S), 3 380 (NH). ^{1}H NMR spectrum of *VIIb*: 3·50 s, 1 H (NH); 3·85 s, 3 H (CH_3O); 3·60 d, 2 H (–CH_2–); 5·60 t, 1 H (N—CH—Ar); 8·50—7·25 m, 11 H (aromatic and pyridine protons).

2-Benzal Quinolinic Anhydride *VIII*

A mixture of quinolinic anhydride (0·1 mol, 14·9 g), phenylacetic acid (0·1 mol, 13·6 g) and fused potassium acetate (0·008 mol, 0·784 g), was heated to 230—240°C for 2 h and the product was crystallized from dioxane to give *VIII*. IR spectrum: 1 720 (C=O), 1 605 (C=C), 1 590 (C=N). ^{1}H NMR spectrum: 7·20 s, 1 H (CH=C); 8·70 d, 1 H (pyridine proton); 8·72 d, 1 H (pyridine proton); 7·45 m, 6 H (phenyl and pyridine protons).

General Method for the Reaction of 2-Benzal Quinolinic Anhydride *VIII* with α-Amino Acids *IXa—IXd*

A mixture of equimolar quantities (0·01 mol) of compound *VIII* and respective α-amino acid was heated in a Pyrex tube to 220°C for 5 min to give compounds *IXa—IXd*.

Compound *IXa* was synthesized also by an independent route: A mixture of quinolinic anhydride (0·01 mol, 1·49 g), ethylglycinate ester (0·01 mol, 1·03 g) and fused sodium acetate (0·01 mol, 0·82 g) was refluxed in glacial acetic acid for 2 h and the product was crystallized from diluted acetic acid to afford *X*. IR spectra: 1 720 (C=O), 1 735 (C=O of ester group). ^{1}H NMR spectrum of *X*: 1·20 t, 3 H (CH_3); 4·15 q, 2 H (ester CH_2); 4·40 s, 2 H (N—CH_2); 7·75 q, 1 H (pyridine proton); 8·32 d, 1 H (pyridine proton); 8·95 d, 1 H (pyridine proton).

Equimolar amounts of compound *X* and phenylacetic acid in presence of fused potassium acetate were fused as mentioned previously to give compound *IXa* identical to that prepared previously.

2-Benzal-N-(*p*-substituted phenyl)quinolimide *XIa*—*XIc*

A mixture of 2-benzal quinolinic anhydride (*VIII*) (0·002 mol, 0·446 g), respective aromatic amine (0·002 mol) and sodium acetate (0·025 mol, 0·2 g) was refluxed in glacial acetic acid (15 ml) for 10—12 h to give compounds *XIa*—*XIc*. ^{1}H NMR spectrum of *XIc*: 3·70 s, 3 H (CH_3O); 6·95 s, 1 H (CH=C); 7·50 m, 10 H (two phenyl and pyridine protons); 8·25 d, 1 H (pyridine proton); 8·75 d, 1 H (pyridine proton).

Screening for Antibacterial Activity

The biological screening was studied by the usual cup-plate agar diffusion technique[2], 1% dimethyl formamide solutions of these compounds were prepared. The antibacterial activities of the compounds *I*—*XI* have been screened in vitro against nine Gram-positive and Gram-negative bacteria. Compounds *IV*—*XI* showed a strong activities (inhibition zones 70—110 mm) against *Klebsiella pneumonia* only. The test compounds were potent against *Klebsiella pneumonia, Staphylococcus aureus, Escherichia coli* and *Anthrax bacilli*. Comparison between the activities of the different compounds showed that compounds *IVa* and *IVc* were highly potent (inhibition zones 70—210 mm) against all bacteria used. The majority of the other compounds showed strong activities (inhibition zones 60—190 mm) against *Escherichia coli* and *Staphylococcus aureus*.

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