Synthesis of Nicotinoyl Hydrazones, Their *N*-Oxide Analogues and the Corresponding 3-(5-Aryl-1,3,4-oxadiazol-2-yl)pyridine Derivatives as Potential Hypoglycemic Agents

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A series of nicotinoyl hydrazones and their *N*-oxide analogues have been synthesized. Subsequent ring closure afforded the 3-(5-aryl-1,3,4-oxadiazol-2-yl)pyridine derivatives. The structures of the prepared compounds were established by means of spectral data. Fourteen of the hitherto prepared compounds, when screened on the albino rats at an oral dose of 100 mg/kg, reduced the blood sugar level to a significant extent.

Oxadiazoles constitute one of the very significant classes of compounds which possess a variety of biological activity including antiinflammatory, bactericidal, fungicidal, herbicidal, analgesic, anti-proteolytic, hypoglycemic, tranquilizing and CNS depressant [1—9] properties. Recently, hydrazones have been found [10, 11] to be mildly active in producing hypoglycemia. The pharmacological activity associated with those hydrazones was attributed [12] to the presence of —CONH—N=C— moiety. In addition, *N*-oxide derivatives usually have high polarity and consequently high solubility in aqueous solution which in turn facilitates their use for *in vivo* biological investigations.

Perusal of literature revealed sufficient scope for further studies on the synthesis of new heterocyclic ring systems containing oxadiazole moiety *via* oxidative cyclization of the corresponding hydrazones. Thus, in continuation of our research program [13—17] directed for the synthesis of novel heterocycles of potential biological applications, we report herein on the synthesis of the previously unreported series of 3-(5-aryl-1,3,4-oxadiazol-2-yl)pyridine derivatives *Va—Ve* and their *N*-oxide analogues *VIa—VIe* together with their precursors *IIIa—IIIe* and *IVa—IVe*, respectively aiming to synthesize more potent and less toxic hypoglycemic agents.

EXPERIMENTAL

Melting points of the analytical samples were determined using Fisher—Johns apparatus. IR spectra were recorded on a spectrophotometer Specord M 80 using KBr pellets, ^{1}H NMR spectra ($CDCl_3$) on a spectrometer EM 360 (Varian, 60 MHz) with TMS as an internal standard, mass spectra (15 and 70 eV) on spectrometer 711 (Varian). The homogeneity and purity of the prepared compounds were tested by TLC.

Nicotinoyl hydrazine *N*-oxide (*II*) was obtained by the reaction of 3-ethoxycarbonylpyridine *N*-oxide with hydrazine hydrate (100 %) and following the method of *Clemo* and *Koening* [18].

Complete details of the biological screening together with pharmacological findings, including ALD_{50} values (higher than 1000 mg/kg body mass), for these possible hypoglycemic agents will be published separately.

Nicotinoyl Hydrazone Derivatives *IIIa—IIIe* and Their *N*-Oxide Analogues *IVa—IVe*

To a solution of nicotinoyl hydrazine (*I*) or its *N*-oxide (*II*) (0.01 mol in each case) in glacial acetic acid (20 cm^3), aromatic aldehyde (0.012 mol) was added and the mixture heated under reflux for about 4 h and cooled. The precipitated solid, obtained on pouring onto crushed ice (200 g), was filtered and crystallized to give the products as white to yellow crystals in 62—98 % yield. The pertinent data of the compounds thus prepared are recorded in Table 1.

For *IVc* IR spectrum, $\tilde{\nu}$/cm^{-1}: 3200—3500 ν(NH), 1655 ν(CONH—N), 1600 ν(C=N), 1560 ν(C=C), 1320 ν(N$^+$—O$^-$). ^{1}H NMR spectrum, δ: 9.97 (s, 1H,

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Table 1. Characterization of the Prepared Compounds *III**—*VI***

Compound	Formula	w_i(calc.)/%			M.p.	Solvent
		w_i(found)/%				
	M_r	C	H	N	°C	
IIIa	$C_{13}H_{10}N_3OBr$	51.34	3.31	13.82	179—182	Ethanol—water
	304.1	51.51	3.36	13.79		
IIId	$C_{13}H_{10}N_3OF$	64.19	4.14	17.28	195—196	Ethanol—water
	243.2	64.30	4.26	17.41		
IVa	$C_{13}H_{10}N_3O_2Br$	48.77	3.15	13.13	218—221	Ethanol
	320.1	48.94	3.01	13.32		
IVb	$C_{13}H_{10}N_4O_4$	54.55	3.52	19.57	279—281	Acetic acid
	286.2	54.39	3.41	19.42		
IVc	$C_{14}H_{13}N_3O_3$	61.99	4.83	15.49	211—213	Ethanol
	271.3	62.20	4.91	15.61		
IVd	$C_{13}H_{10}N_3O_2F$	60.23	3.89	16.21	219—221	Ethanol
	259.2	60.10	3.75	16.32		
IVe	$C_{15}H_{13}N_3O_2$	67.40	4.90	15.72	215—217	Ethanol
	267.3	67.31	5.20	15.56		
Va	$C_{13}H_8N_3OBr$	51.68	2.67	13.91	86—87	Ethanol—water
	302.1	51.81	2.76	13.72		
Vb	$C_{13}H_8N_4O_3$	58.21	3.01	20.89	185—186	Ethanol
	268.2	58.03	2.88	20.97		
Vc	$C_{14}H_{11}N_3O_2$	66.39	4.38	16.59	170—173	Ethanol—water
	253.3	66.04	4.39	16.65		
Vd	$C_{13}H_8N_3OF$	64.73	3.34	17.42	101—103	Ethanol—water
	241.2	64.98	3.51	17.60		
Ve	$C_{15}H_{11}N_3O$	72.27	4.45	16.86	146—148	Ethanol
	249.3	72.09	4.59	16.69		
VIa	$C_{13}H_8N_3O_2Br$	49.08	2.54	13.21	174—176	Acetic acid
	318.1	48.93	2.69	13.43		
VIb	$C_{13}H_8N_4O_4$	54.93	2.84	19.71	114—116	Acetic acid
	284.2	54.77	2.92	19.59		
VIc	$C_{14}H_{11}N_3O_3$	62.45	4.12	15.61	128—130	Ethanol
	269.3	62.68	4.31	15.44		
VId	$C_{13}H_8N_3O_2F$	60.70	3.14	16.34	140—142	Ethanol
	257.2	60.85	3.24	16.58		
VIe	$C_{15}H_{11}N_3O_2$	67.91	4.18	15.84	118—121	Acetic acid
	265.3	68.20	4.28	15.69		

*Compounds *IIIb*, *IIIc*, *IIIe* have melting points in accordance with Ref. [23].
**No depression in melting points was observed on admixing samples prepared by the methods *A*, *B*, and *C*.

CONH, exchanged with D_2O), 8.15 (s, 1H, CH=N), 7.2—8.0 (m, 8H, H_{arom} and $H_{heteroarom}$), 4.18 (s, 3H, OCH_3).

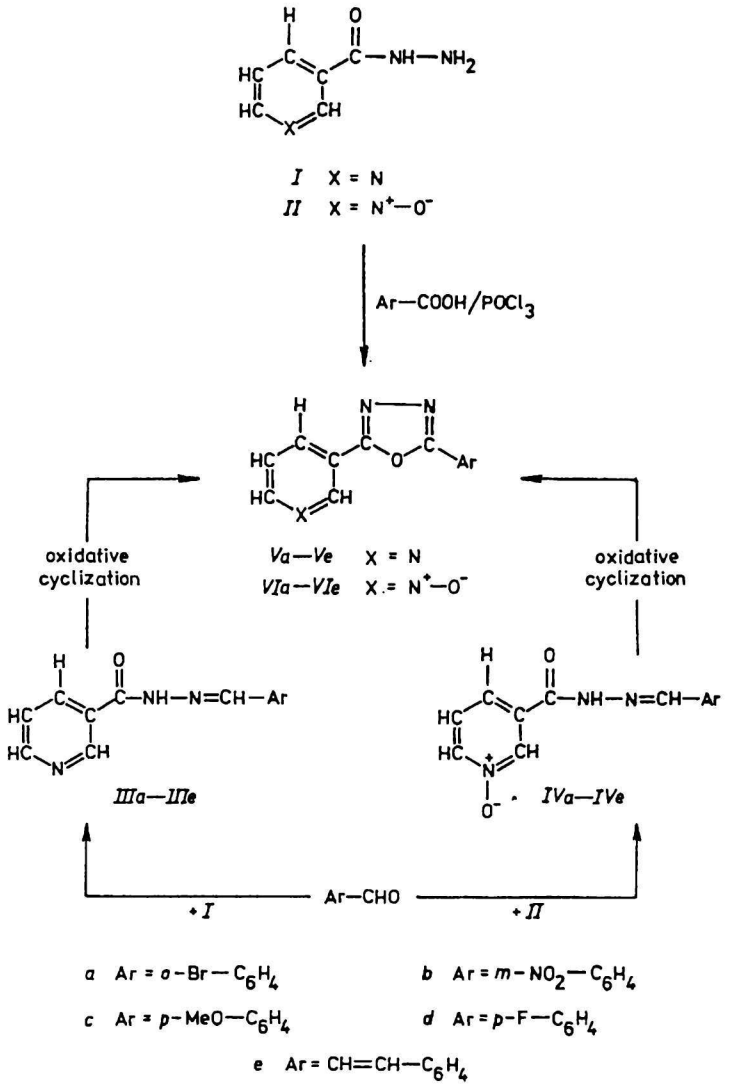
For *IVb* mass spectrum, *m/z* (I_r/%): 286, M^+ (37), 270 (6.18), 164 (17.19), 148 (4.17), 138 (62), 122 (74), 106 (100), 94 (10.15), 78 (74).

3-(5-Aryl-1,3,4-oxadiazol-2-yl)pyridine Derivatives *Va—Ve* and Their *N*-Oxide Analogues *VIa—VIe*

Method A. To a solution of *III* or *IV* (0.01 mol in each case) in glacial acetic acid (30 cm^3), lead dioxide (2.4 g; 0.01 mol) was added, while stirring at room temperature, over a period of 90 min. The solid product that formed on dilution with ice-cold water (200 g ice/200 cm^3 water) was filtered, washed with water, dried and recrystallized to give the products *V* and *VI* as white to yellow crystals in 18—27 % yield. Characterization data for these products are given in Table 1.

Method B. A solution of *III* or *IV* (0.01 mol in each case) in glacial acetic acid (20 cm^3) was treated while stirring with the solution of ferric chloride (10 g) in water (10 cm^3) over a period of 90 min, then it was kept at ambient temperature for 3 d. The products were obtained as before in an average 22—34 % yield.

Method C. A mixture of *I* or *II* (0.01 mol in each case), carboxylic acid (0.01 mol), and phosphorous trichloride oxide (8 cm^3) was heated at reflux temperature for 8 h and left to cool. The unreacted $POCl_3$ was removed under reduced pressure and the residue triturated with ice-cold water. Extraction of the residue with ether gave a solid which on recrystallization furnished the required products as white to yellow crystals in 55—90 % yield.



Scheme 1

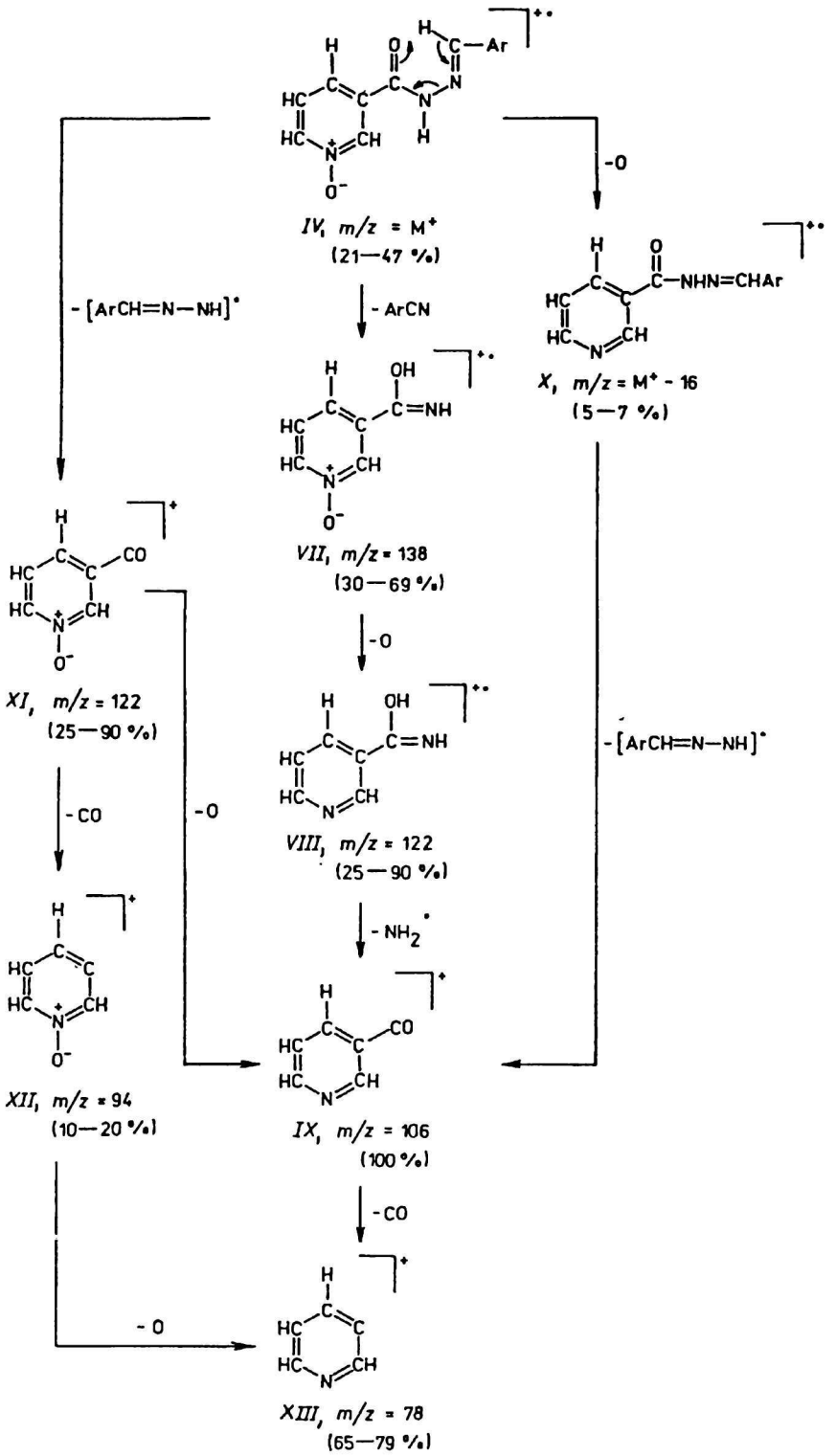
For *Vc* IR spectrum, $\tilde{\nu}$/cm^{-1}: 1610 ν(C=N), 1560 ν(C=C), 1030 ν(C—O of oxadiazole). ^{1}H NMR spectrum, δ: 7.30—8.25 (m, 8H, H_{arom} and $H_{heteroarom}$), 4.05 (s, 3H, OCH_3).

For *VIb* mass spectrum, *m/z* (I_r/%): 284, M^+ (21), 268 (100), 212 (20.17), 162 (0.7), 150 (3.16), 118 (2), 106 (66).

RESULTS AND DISCUSSION

The synthesis of the title compounds was accomplished in accordance with the sequence of reactions depicted in Scheme 1. Condensation of nicotinoyl hydrazines *I* or *II* with aromatic aldehydes gave the corresponding nicotinoyl hydrazones *IIIa—IIIe* and *IVa—IVe*, respectively. The assigned structures for these products were inferred from spectral analysis. Besides absorption bands characteristic of >C=N— group and —CO—NH—N= moiety, the *N*-oxide analogues *IVa—IVe* revealed an absorption band of medium intensity at $\tilde{\nu}$ = 1320 cm^{-1} characteristic of $N^+—O^-$ group. The appearance of the latter absorption band at a relatively higher wavenumber may be attributed to the electron-withdrawing effect of the substituent in pyridine moiety [19].

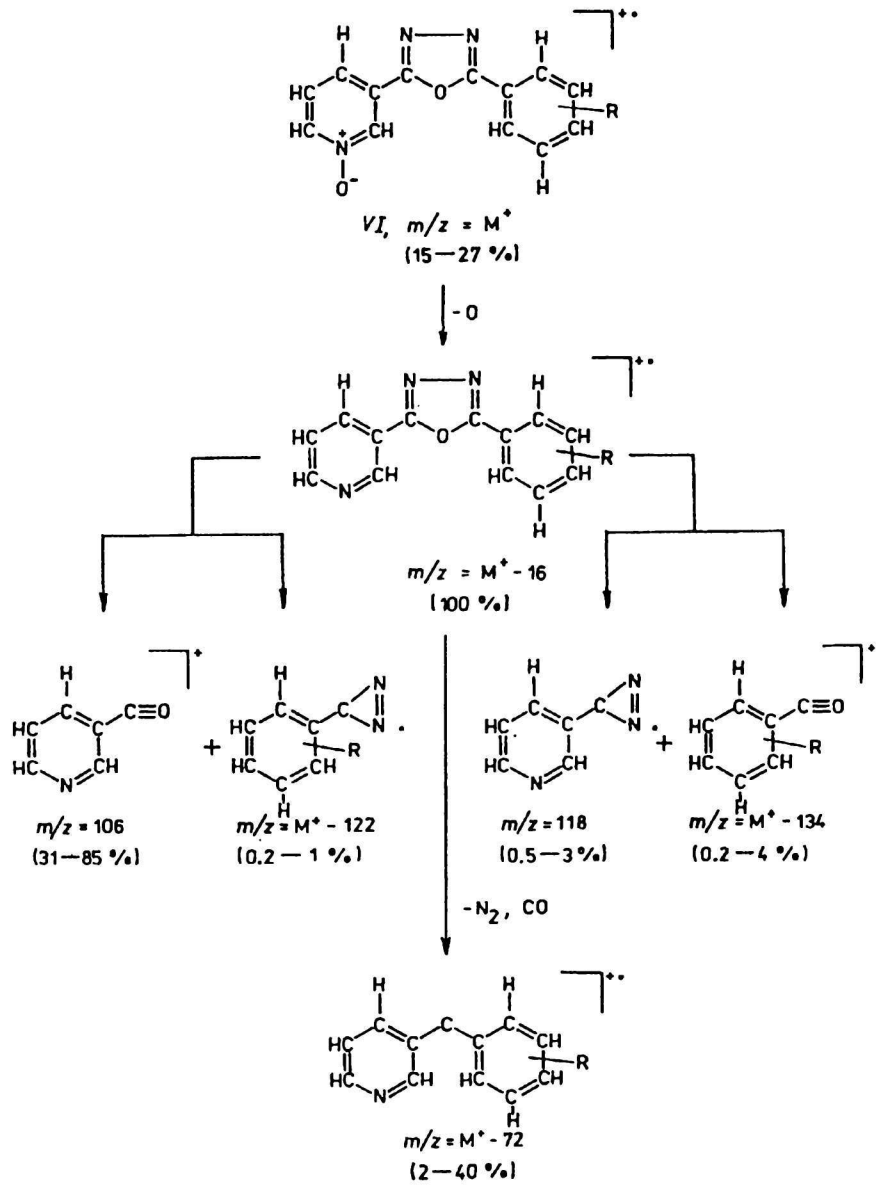
The ^{1}H NMR spectra of hydrazones *III* and *IV* revealed the absence of signals near δ = 4.50 due to NH_2 protons of the hydrazide moiety. Further support was gathered from mass spectral data of molecular ion M^+ peaks at *m/z*: 304 (*IIIa*), 243 (*IIId*), 286 (*IVb*), and 271 (*IVc*) corresponding to their relative molecular masses. In all cases, the base peak was due to the produced cation *IX*, formed by the successive loss of oxygen atom and [Ar—CH=N—NH]$^\cdot$ radical or loss of [Ar—CH=N—NH]$^\cdot$ radical followed by oxygen atom. A third possible



Scheme 2

fragmentation pathway depends on loss of Ar—C≡N, oxygen atom and $NH_2^{\cdot}$ radical, respectively from the molecular ion M^+ (Scheme 2). The greater stability (100 % intensity) of *IX* is probably due to a higher degree of resonance stabilization.

Oxidative cyclization of hydrazones *III* and *IV* in the presence of lead dioxide [20] or ferric chloride [21] gave 3-(5-aryl-1,3,4-oxadiazol-2-yl)pyridines *Va—Ve* and *VIa—VIe*, respectively. The latter products were alternatively prepared in one pot synthesis *via* reaction of nicotinoyl hydrazines *I* or *II* with the corresponding aromatic acids in the presence of phosphorous trichloride oxide as illustrated in Scheme 1. The formation of compounds



Scheme 3

Va—Ve and *Vla—Vle* was supported by lacking absorption due to —CO—NH—N= moiety in the region of $\tilde{\nu}$ = 1650—1700 cm^{-1} in IR spectra and the appearance of new absorption band at $\tilde{\nu}$ = 1020—1050 cm^{-1} due to the stretching vibration of C—O bond in oxadiazole moiety. IR spectra of *Vla—Vle* revealed the presence of an absorption band at $\tilde{\nu}$ = 1320—1325 cm^{-1} characteristic of $N^+—O^-$ group [19]. The absence of signals due to the proton of —CONH—N= moiety in ^1H NMR spectra for these products is considered as a further support for the assigned structures. The fragmentation of *Vlb* as an illustrative example for oxadiazole derivatives under electron impact was generally found to follow the general pattern anticipated for oxadiazole derivatives (Scheme 3).

The new compounds prepared in this manner were screened out for their hypoglycemic activity using albino rats which were kept fasting for eighteen hours. The percentage change in glucose level before and after oral administration of the tested compounds was calculated following the method of *Somogyi* [22]. The average maximum reduction of blood sugar level was found to be in the range 11—22 %.

The synthesized products were also tested *in vitro* for their antimicrobial activities: the microorganisms and the minimum inhibitory concentrations (MIC/(μg cm^{-3})) are given, unless they exceed 100 μg cm^{-3}: *Staphylococcus albus*, *IVa* 25, *Vd* 100, *Ve* 25, *Vlb* 25, *Vld* 50, *Vle* 12.5; *Staphylococcus aureus*, *Va* 50, *Vc* 50, *Vd* 12.5, *Ve* 50, *Vla* 100, *Vle*

50; *Escherichia coli*, *IVd* 12.5, *IVe* 100, *Vc* 12.5, *Ve* 50, *Vla* 50, *Vlc* 25, *Vle* 12.5; diplococcal *Neisseria catarrhalis*, *Ille* 12.5, *Vd* 25, *Vlc* 100.

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