Research Article

Synthesis and Study of Biological Activity of Some 1, 6-Naphthyridinic acid Derivatives

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ABSTRACT
4-Aminopyridine was treated with aromatic aldehyde derivatives to give the imine intermediate, which then treated with pyruvic acid to give a series of 1,6-naphthyridine derivatives. The products were characterized by physical and spectral analyses. The biological activities of these heterocyclic compounds were examined against different type of microorganisms and they found to have considerable activity in comparison with the most commonly used antibiotics.

Key words: Synthesis, Aminopyridine, Naphthyridine, Biological activity.

INTRODUCTION

The fusion of two six-membered aromatic heterocyclic rings through a carbon single bond results in the formation of heterocyclic analogs of naphthalene. These heterocycles are planar and possess 10 π- electrons required for the aromaticity according to (4n+2) π rule.
Six-membered aromatic heterocycles are related to benzene as these derived by the replacement of one or more CH group(s) of the benzene ring by the trivalent heteroatom(s). Benzo-fused aromatic heterocycles are considered to be analogs of naphthalene.
Bicyclic six-membered heteroaromatics with nitrogen atom in both rings are called naphthyridines, these compounds can exist in six possible isomers[1]. The synthetic methods of these compounds are similar to those of the synthesis of quinoline. The first successful synthesis was reported by Hart[2], and then many researchers have attempted to synthesize some of these compounds through modification of Skraup method[3, 4]. Many studies were also concerned with the reactions and properties of these compounds and they were found to be similar to those of quinoline too[5].
The importance of these compounds lies in their uses in drug industries and it has been established that they are biologically active in many aspects[6-8]. These findings encourage many other scientists to concentrate no modifying these compounds for the purpose of using them in treatment of many different diseases[9, 10].
Naphthyridinic acids in particular are the most important derivatives of the naphthyridine series; they have many applications through the possibility of converting them into other substances readily[11, 12].
Naphthridinic acid derivatives have been prepared by many authors and from a wide variety of compounds[13, 14].
In the foregoing publications[15, 16], 1, 8-and 1, 5-naphthyridinic acid derivatives were obtained from 2-aminopyridine and 3-aminopyridine respectively. In the same way, starting from 4-aminopyridine a number of substituted phenyl-1, 6-naphthyridinic acid were also prepared.

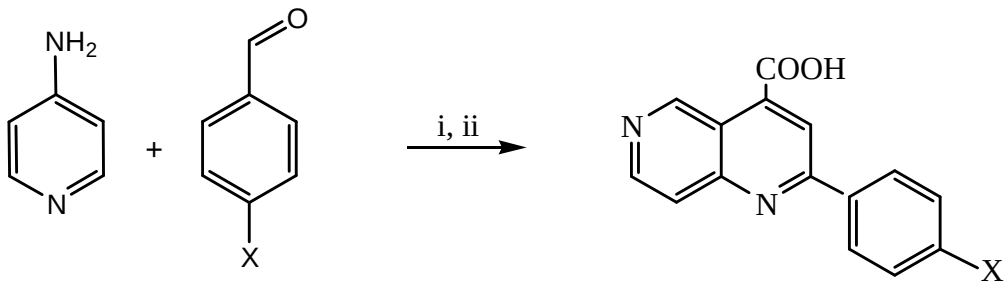
Experimental

Melting points were measured on a Gallen-Kamp apparatus and are uncorrected, IR spectra were recorded by Perkin-Elmer 580 B spectrophotometer, ^{1}H-NMR were recorded by Hitashi 300 MHz spectrometer in $CDCl_3$ with TMS as internal standard, chemical shifts (δ) were given in ppm. Elemental analyses were performed on Carlo Erba type 1106 analyzer. All of the above measurements were carried out at Cairo University, Egypt.
Solvents and chemicals used were of reagent grade and they were purified (when necessary) by standard procedurs[17]. The compositions of the reaction mixtures and the purities of the products were monitored by TLC on silica gel plates.

General procedure for preparation of 2-(p-substituted phenyl)-1, 6-naphthyridinic acids (II_{a-h})
Benzaldehyde (0.025 mol) was placed in a round bottomed flask fitted with reflux condenser protected with $CaCl_2$ tube. Absolute ethanol (10mL) was added and the mixture was heated in a water bath for 10 minutes, 4-aminopyridine (0.025 mol) in absolute ethanol (5mL) was added in one portion followed by drop wise addition of pyruvic acid (0.025 mol) with vigorous stirring and maintaining the temperature at 40-50^{o}C, the addition lasts one hour. The reaction mixture then refluxed in water bath for further 6 hours, then left to stand overnight. The solvent was removed under vacuum and the oily residue was treated with water to give solid material which after crystallization from ethanol gave a pale yellow crystals. The physical and spectral data of the compounds prepared are given in tables 1 and 2 below.

Antibacterial activity tests
The antibacterial activity tests were performed according to the disk diffusion method using Ampicillin and Gentamycin as the reference compounds. The sterile disks were impregnated with the synthesized compounds (600 µg/disk). A nutrient agar medium was used and the disks were incubated at 37ºC for 24 hours. After incubation, the relative susceptibility of the microorganisms to the potential antibacterial agent is demonstrated by a clear zone of growth inhibition around the disk. The inhibition zones caused by the various compounds on the microorganisms were measured and the activity rated on the basis of the size of the inhibition zone. The results of the biological activities were shown in table 3.

Results and discussion
Synthesis of 2-(p-substituted phenyl)-4-carboxy-1, 6-naphthridine derivatives (II_{a-h}) was accomplished according to the reaction scheme outlined below:



I_{a-h} II_{a-h}

i = EtOH, ii = $CH_3COCOOH$

ii = H; Me; OH; OMe; $N(Me)_2$; NO_2; COOH; Cl

Reaction scheme

The first step of this reaction involve the condensation of 4-aminopyridine with the aromatic aldehyde derivatives (I_{a-h}) through nucleophilic addition then dehydration of the carbinol amine to give the expected imines, which then undergo cyclization when treated with pyruvic acid followed by aromatization to give the final products, the reaction was completed in about 6 hours, then the reaction mixture was left to stand overnight at room temperature. Compounds (II_{a-h}) were easily isolated by conventional work up in reasonable yields.

Table 1: The physical data of compounds (II_{a-h})

Compd.	Molecular Formula	Yield (%)	M.P. (°C)	% Analysis Found (Calc.) C	H	N	Cl
II_a	$C_{15}H_{10}N_2O_2$	66	153	72.0 (71.4)	4.0 (3.6)	11.2 (10.5)	--
II_b	$C_{16}H_{12}N_2O_2$	68	140	72.7 (72.1)	4.5 (4.8)	10.6 (10.2)	--
II_c	$C_{15}H_{10}N_2O_3$	70	168	67.6 (67.2)	3.7 (3.2)	10.5 (11.1)	--
II_d	$C_{16}H_{12}N_2O_3$	65	148	68.5 (67.8)	4.2 (3.6)	10.0 (10.6)	--
II_e	$C_{17}H_{15}N_3O_2$	69	158	69.6 (69.1)	5.1 (4.7)	14.3 (14.9)	--
II_f	$C_{15}H_9N_3O_4$	63	136	61.0 (61.7)	3.0 (3.4)	15.9 (15.2)	--
II_g	$C_{16}H_{10}N_2O_4$	70	164	65.3 (65.8)	3.4 (3.9)	9.5 (9.1)	--
II_h	$C_{15}H_9N_2O_2Cl$	60	187	63.2 (63.8)	3.1 (3.7)	9.8 (9.2)	12.4 (11.9)

Table 2: The spectral data of compounds (II_{a-h})

Compd.	IR (υ cm^{-1}) OH	C=O	C=N	C—O	C—N	^{1}H-NMR (δ ppm)
II_a	3300	1700	1650	1200	--	7.2-9.2(m,Ar-H); 10.2(s,1H)
II_b	3200	1705	1625	1100	--	2.3(s,3H);7.1-9.2(m,Ar-);10.5(s,1H)
II_c	3500	1700	1630	1150	--	5.0(s,1H);6.8-9.1(m,Ar-H);11.0(s,1H)
II_d	3300	1710	1650	1100	--	3.7(s,3H);6.8-9.2(m,Ar-H);11.0(s,1H)
II_e	32001715	1630	1150	2200		2.4(s,6H);7.1-9.0(m,Ar-H);11.5(s,1H)
II_f	3100	1710	1640	1200	2100	7.9-9.2(m,Ar-H);11.0(s,1H)
II_g	3300	1730	1650	1150	--	7.9-9.1(m,Ar-H),10.5(s,1H);11.0(s,1H)
II_h	3200	1710	1640	1200	--	7.3-9.2(m,Ar-H);11.0(s,1H)

Table 3: Results of antibacterial activity tests of the synthetic compounds

Compound	Microorganism		
	E. coli	*S.aureus*	*p. aeruginosa*
Ampicillin	+++	+++	+++
Gentamycin	+++	+++	+++
II_a	+	-	-
II_b	+	+	+
II_c	+++	+++	+++
II_d	++	++	++
II_e	+	+	+
II_f	+	+	+
II_g	++	++	++
II_h	+	-	-

Key to symbols:
Highly active = +++ (inhibition zone >12 mm)
Moderately active = ++ (inhibition zone 9-12 mm)
Slightly active = + (inhibition zone 6-9 mm)
Inactive = - (inhibition zone <6 mm)

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