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Synthesis and Cyclization of some N-(2-Pyridyl) Anthranilic Acids

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ABSTRACT

A series of N-(2-Pyridyl) anthranilic acids (Ia-f) have been synthesized by Ullmann reaction. Cyclization of (Ib,d,f) by phosphorusoxy chloride ($POCl_3$) gives substituted 5-chlorobenzo [b][1,8] naphthyridine compounds. The reaction progress was followed by thin layer chromatography (TLC), rate flow (R_f) values was recorded, spectral data (IR) and (U.V) were recorded. Elemental analysis (CHNS) and gas chromatography-mass spectrometery (GC/MS) were carried out for some of the synthesized compounds.

تحضير وحولقة بعض مركبات N- (2-بريديل) حامض الانثرانيليك

الملخص

يتضمن البحث تحضير سلسلة من حوامض الانثرانليك(Ia-f) باستخدام تفاعل المان المعـروف يتبعهـا عملية الحولقة لبعض تلك الحوامض (Ib,d,f) باستخدام اوكسي كلوريد الفسفور($POCl_3$) بصفة عامل حولقة للحصول على مركبات 5-كلوروبنزو [b][1,8] نفثاريدين المعوضة. ولقد تم تتبع نواتج جميـع التفـاعلات بوساطة كروموتوكرافيا الطبقة الرقيقة (TLC) حيث سجلت قيم (R_f)، وتم استخدام الطرائق الطيفية المتوفرة مثل طيف الأشعة تحت الحمراء (I.R) وطيف الأشعة فوق البنفسجية (U.V) في عملية التـشخيص، وتـم أيضاً استخدام التحليل الدقيق للعناصر (CHNS) وكروموتوكرافيا غـاز-طيـف الكتلـة (GC/MS) فـي تشخيص واثبات بعض هذه المركبات.

INTRODUCTION

Biochemistry of anthranilic acid was reported (Nelson, 2000). Some anthranilic acid derivatives show anticancer activity (Maria *et al*., 2004; Cenzo *et al*., 2005). The "Ullmann type" reactions include copper – catalyzed nucleophilic aromatic substitution between various nucleophiles (e.g. substituted aromatic amines) with aryl halides to give substituted anthranilic acids (Kwong *et al*., 2002**;** Wolf *et al*., 2006). Cyclization of anthranilic acid derivatives gave different types of heterocyclic compounds (Per, 2004). Many of naphthyridine derivatives were synthesized by researchers and their biological activity was evaluated and used in different fields. It was used as antimalarial (Zheng *et al*., 1979),

treatment of diseases involving enzymes tissues destruction (Skotnicki and Gilman, 1989), Antihypertensive (Ferrarini *et al*., 1990), antimicrobial (Antoni *et al*., 2003), antitumor (Tsuzuki *et al*., 2004), antiinflammatory; analgesic; Antipyretic (Glancarlo *et al*., 2005) agents, and chemotherapy of infection diseases of human including aids and some of new 1, 8-naphthyridine derivatives including benzo [b]1,8] naphthyridine have recently been patented as growth regulator, fungicides, bactericides, herbicides, insecticides (Tangali *et al*., 2006).

This work presents successful cyclization method of the new N-(2-Pyridyl) anthranilic acids by ($POCl_3$) to give 5-Chlorobenzo [b][1,8] naphthyridine compounds.

EXPERIMENTAL

Uncorrected melting point was determined using electrothermal IA9000 digital-series melting point (1988) apparatus. I.R spectra were recorded on FTIR –Tensor 27- Burker Co., Germany 2003, using KBr discs. U.V Spectra were measured on Shimadzu UV-1650Pc, U.V –Visible recording spectrophotometer. Elemental analysis was measured on Elementer Vario EL III (CHNS) (I.I.T Roorkee, India). Mass Spectra measured on perkin Elmer Clarus 500 Gas chromatography mass spectrometer (I.I.T Roorkee, India).

Synthesis of N-(2-Pyridyl) anthranilic acids (Vogel, 1972).

Two methods are used to prepare these acids: The first method include using of chloropyridine compounds and anthranilic acid to prepare of: Ia = N-(2-pyridyl)anthranilic acid. Ib = N-(6-Methoxy-2-pyridyl)anthranilic acid.

N-(2-Pyridyl)anthranilic acid (Ia) : (General procedure)

In (1) liter round bottomed flask equipped with air condenser a mixture of (0.14 mole,16 g) of 2-chloropyridine, (0.075 mole,10.3 g) of anthranilic acid, (0.075 mole,10.35 g) of anhydrous potassium carbonate and (1g) of cupric oxide was placed. The mixture was refluxed in an oil bath at (120 -130 ^{o}C) for (15 hrs.). Allowed to cool, the excess of chloropyridine was removed by steam distillation and (1g) of charcoal was added to the residual solution. The mixture was boiled for (30 min) and filtered at the pump. Mixture of (1:1) hydrochloric acid and water was added to the filtrate with stirring until neutral-acidic medium was achieved. Then the precipitated acid was filtered with suction and washed with cold water for many times, and dried in the air. Recrystallization from ethanol gave pale green acid (Ia), m.p = 210-212 ^{o}C ; (yield, 47%), (Table 1).

Using the above procedure, by reacting of 2-Chloro-6-methoxypyridine with anthranilic acid, gave N-(6-Methoxy-2-pyridyl)anthranilic acid (Ib), m.p =196-198 ^{o}C; (yield, 31%), (Table 1), (Figure 1), (Scheme 1).

The second method includes the use of 2-Aminopyridine and halo benzoic acid compounds for preparation of:

Ic = N-(6-Methyl-2-pyridyl)anthranilic acid .

Id = 4-Chloro-N-(6-methyl-2-pyridyl)anthranilic acid .

Ie = N-(4-Methyl-2-pyridyl)anthranilic acid .

If = 4-Chloro-N-(4-methyl -2-pyridyl)anthranilic acid .

Ia = N-(2-Pyridyl)anthranilic acid.

N- (6-Methyl-2-pyridyl) anthranilic acid (Ic): (General procedure)

(0.1 mole, 10.8 g) of 2-Amino-6-picoline, (0.05 mole, 10.05 g.) of o-bromo benzoic acid, (0.05 mole, 6.9 g) of anhydrous potassium carbonate and (1g) of cupric oxide were mixed together in appropriate flask. The mixture was refluxed in oil bath for (3.5 hrs.) at (130-140 ^{o}C). The mixture was steam distilled to remove the excess amine and (1g) of charcoal was added. The mixture was boiled for (30 min.) and filtered. A mixture of (1:1) hydrochloric acid: water was added, until pH ≈ 4 (Besly and Goldberg, 1954). The solid product was recrystallized from methanol to give greenish white acid (Ic). m.p =125-127^{o}C; (yield, 63%); (Table 1); CHNS analysis (%), calculated (found) for $C_{13}H_{12}N_2O_2$, C:68.42(67.83), H:5.26(5.64), N:12.28 (12.79).

The above procedure was used to prepare the compound (Id) from (2-Amino-6-picoline) and (2,4-Dichlorobenzoic acid); (Ie) from (2-Amino-4-picoline) and (o-bromobenzoic acid); (If) from (2-Amino-4-picoline) and (2,4-Dichlorobenzoic acid), while compound (Ia) was prepared from (2-Amino pyridine) and (o-bromobenzoic acid). The physical constants and the spectral data (IR) of these acids were listed in table (1); mass spectra of the compound (Id) was given, (figure 2) and the fragmentation pattern was showed in scheme (2).

Synthesis of substituted 5-chlorobenzo [b][1,8] naphthyridine (Besly and Goldberg, 1954; Adrine and Bruce, 1955,1942) .

5-Chloro-2-methoxybenzo [b][1,8] naphthyridine (IIa): (General procedure)

In a round-bottomed flask fitted with water condenser (calcium chloride drying tube was used), (1.2 g, 0.0049 mole) of (Ib) was placed , (10 ml, 0.107 mole) of phosphorusoxy chloride ($POCl_3$) was slowly added. The mixture was heated for (30 min.) in an water bath. The mixture was heated in oil bath at (130 - 140^{o}C) for (5 hrs.), then the excess of ($POCl_3$) was removed by vacuum distillation in an oil bath (80 -100 mm Hg)/50-60^{o}C). The residue was slowly poured on a well-stirred mixture of (25 ml.) conc. ammonia solution, (50 g.) of ice and (50 ml.) of chloroform. With continuous cooling a little ice and conc. ammonia solution was added until the solution become basic. The final mixture was allowed to stay in ice bath (over night), when no more undissolved solid remain, the organic layer was separated, and the aqueous layer was extracted with an additional (20 ml) of chloroform. The organic layer was dried by calcium chloride. After filtration the solvent was removed by vacuum distillation until dryness. 5-chloro-2-methoxybenoz [b][1,8] naphthyridine (IIa), m. p =118 -120 ^{o}C; (yield, 39%); (Table 1,2). CHNS, analysis (%), calculated (found): C: 63.8 (65.94), H: 3.68 (3.43), N: 11.45 (11.07) was obtained.

The above procedure, by using (3 g , 0.0114 mole) of (Id) and (21 ml, 0.228 mole) of ($POCl_3$) gave the compound 5,8-dichloro-2-methyl benzo [b][1,8] naphthyridine (IIb); m.p =158 – 160 ^{o}C; (yield, 54%); (Table 1 and 2); (Fig. 3); (Scheme 3). While the compound 5,8-dichloro-4-methylbenzo [b][1,8] naphthyridine (IIc) was prepared from (0.3 g. 0.0011 mole) of (If) and (5 ml, 0.0536 mole) of ($POCl_3$). M.p = 175-177^{o}C; (yield, 30%), (Table 1 and 2).

Table 1: Physical properties and spectral data (I.R , cm^{-1}, KBr) for compounds (Ia-f, IIa-c).

Comp. No.	m.p,°C	R_f	Color	Yield (%)	OH Str. (br.)	NH Str. (br.)	C=O Str.	C=N Str.	C=C Str. (arm.)	Others
Ia	210-212	0.425	Pale green	47	3546	3414	1697	1640	1609	---------
Ib	196-198	0.429	Brown	31	3547	3414	1667	1639	1616	δ $CH(CH_3)$=1414 υ R-O-Ar =1235
Ic	125-127	0.478	Greenish white	63	3430	3329	1687	1640	1609	δ $CH(CH_3)$=1371
Id	108-109	0.122	Brown	38	3367	3318	1682	1633	1588	δ $CH(CH_3)$=1372 δ C-Cl =735
Ie	128-130	0.153	Brown	59	3445	3280	1682	1640	1598	δ $CH(CH_3)$=1390
If	206-208 Sub.	0.465	White	25	3550	3414	1690	1649	1597	δ $CH(CH_3)$=1382 δ C-Cl =700
IIa	118-120	0.658	Greenish brown	39	-------	----------	-------	1647	1604	δ C-H(CH_3)= 1374 δ C-Cl =689 υ R-O-Ar=1249
IIb	158-160	0.607	Dark brown	54	-------	----------	-------	1652	1621	δ C-H(CH_3)= 1370 δ C-Cl =697
IIc	175-177	0.940	Yellowish brown	30	-------	----------	-------	1638	1617	δ C-H(CH_3)= 1390 δ C-Cl =697

Table 2: U.V Spectral data (in [MeOH]) of compounds (IIa-c).

Comp. No.	λmax[nm] (logЄ)
IIa	216(4.394), 270(4.114), 344(4.425), 366(4.117)
IIb	216(4.396), 238(4.316), 270(4.35), 350(3.707)
IIc	209(4.287), 230(4.36), 270(4.03), 348(4.02)

1, 8-naphthyridine λmax[nm] (logЄ):
257(3.60), 295(3.65),302(3.79), 307(3.80).

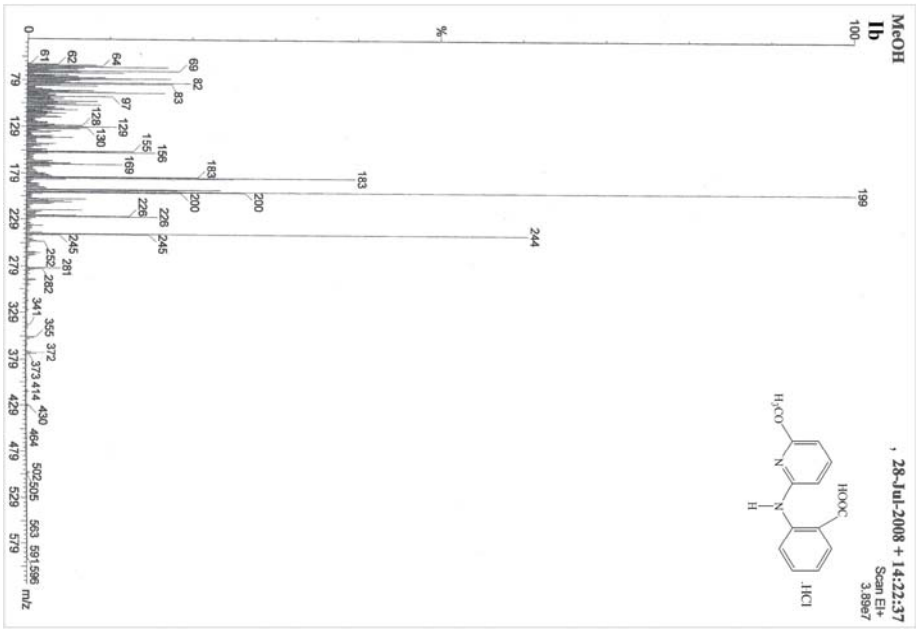


Fig. 1: Mass spectrum of (Ib).

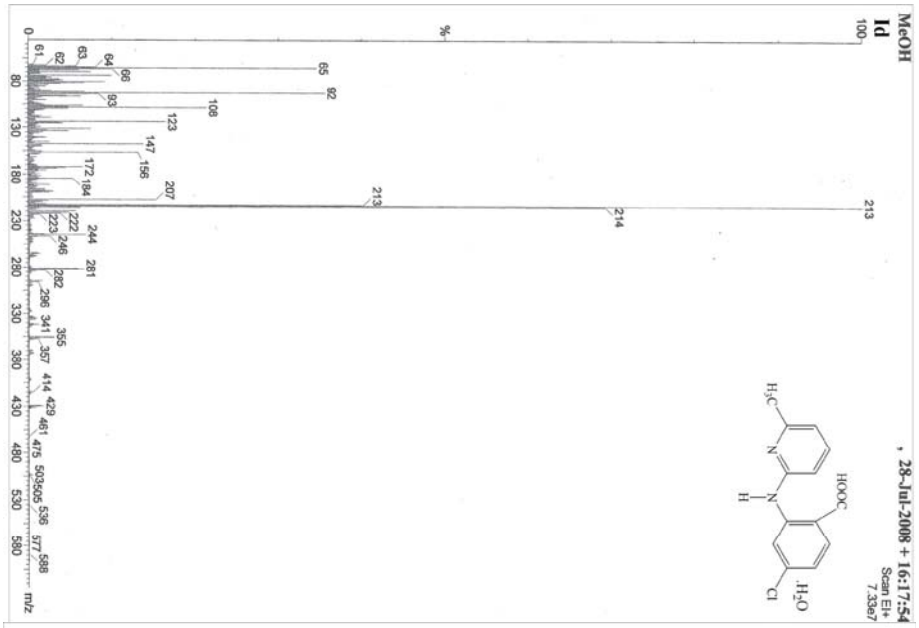


Fig . 2 : Mass spectrum of (Id).

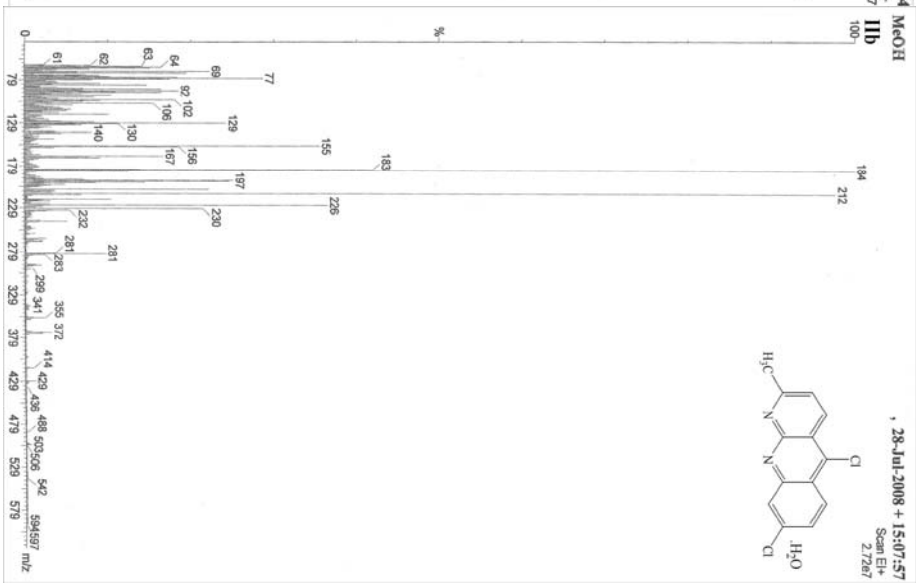
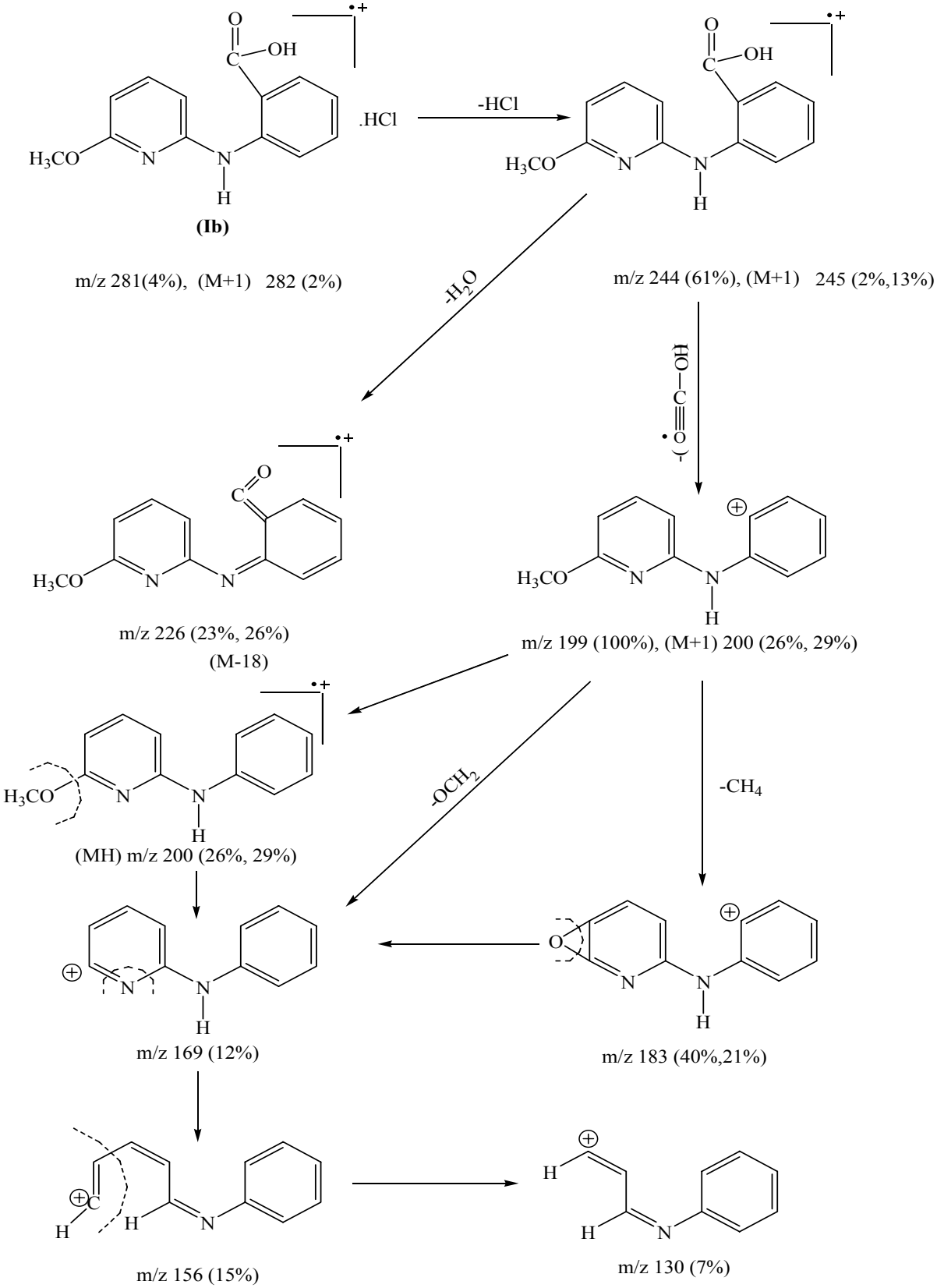
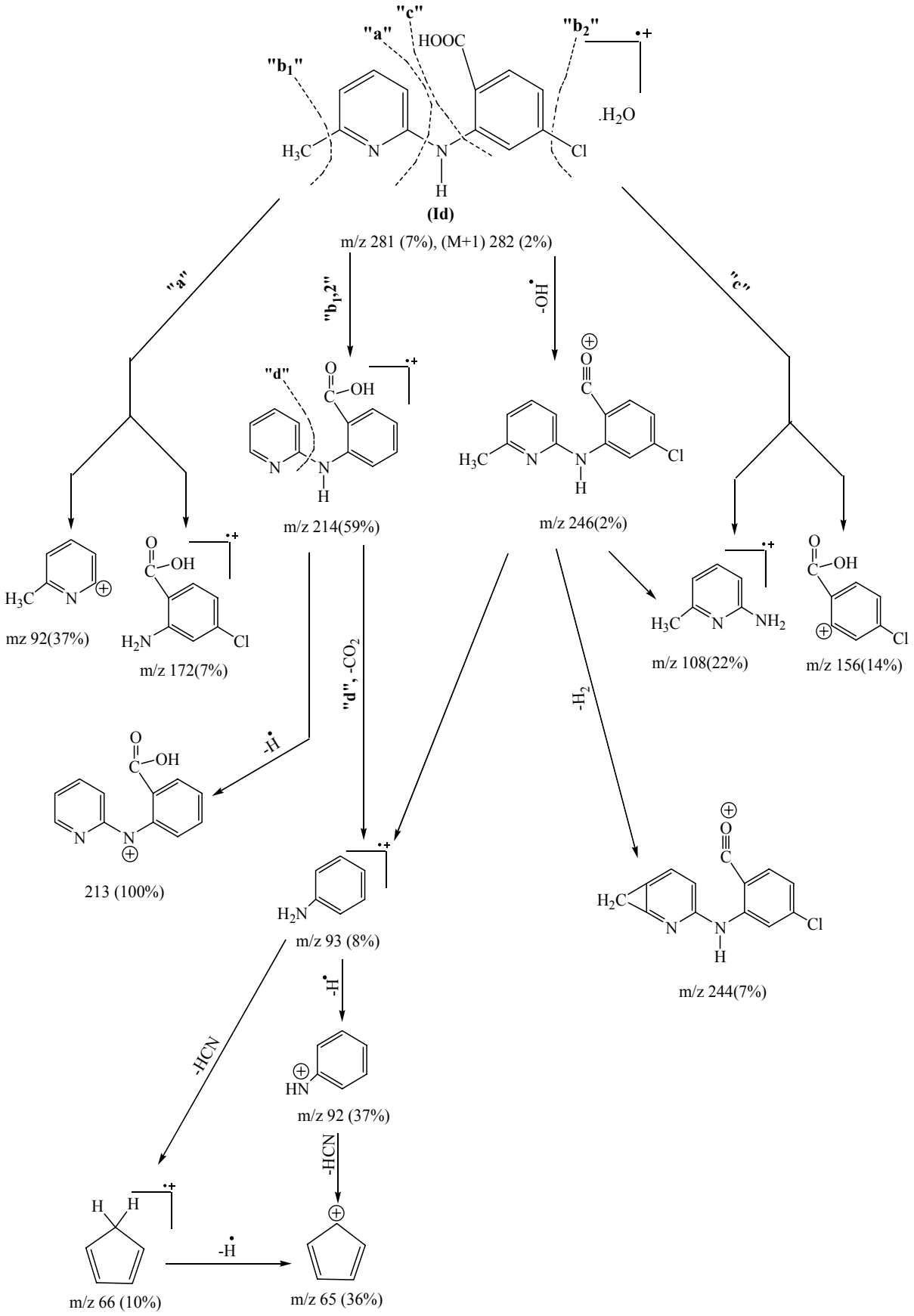


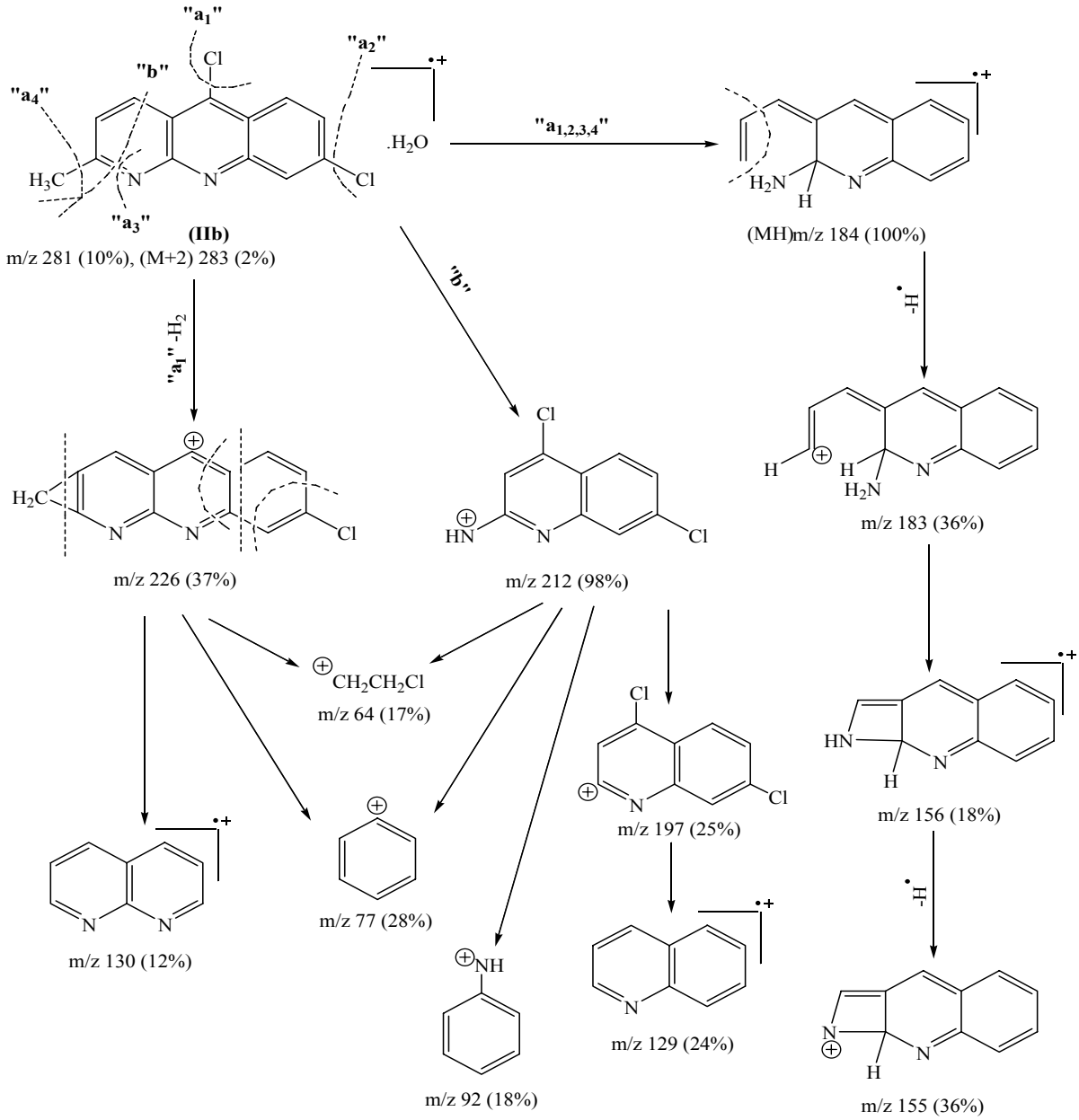
Fig . 3: Mass spectrum of (IIb).



Scheme 1: The fragmentation of compound (I b).



Scheme 2: The fragmentation of compound (I d).

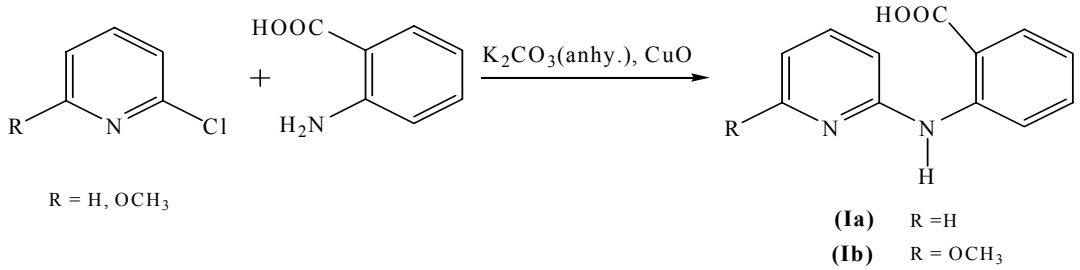


Scheme 3: The fragmentation of compound (I I b).

RESULTS AND DISCUSSION

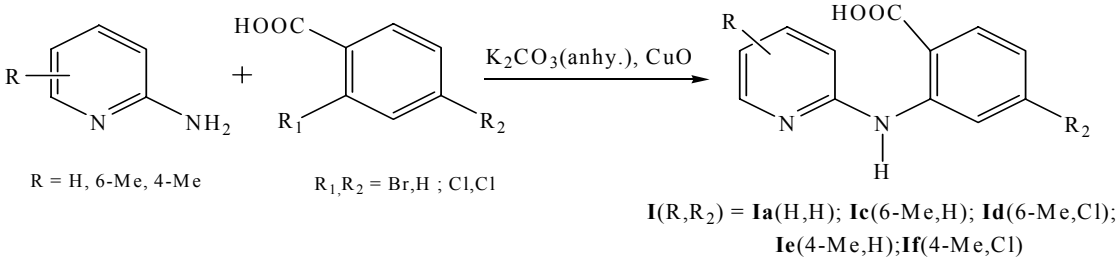
Synthesis of N-(2-Pyridyl)anthranilic acids (Ia-f):

N-(2-pyridyl)anthranilic acids (Ia,b) were prepared by mixing 2-chloropyridine derivatives with anthranilic acid, anhydrous potassium carbonate as a base and cupric oxide as a catalyst, Equation (1).



Equation (1)

N-(2-pyridyl)anthranilic acids (Ia,c-f) were prepared by mixing 2-Amino pyridine derivatives with 2,4-Dichloro or 2-Bromo benzoic acid, anhydrous potassium carbonate as a base and cupric oxide as catalyst , (Equation 2).



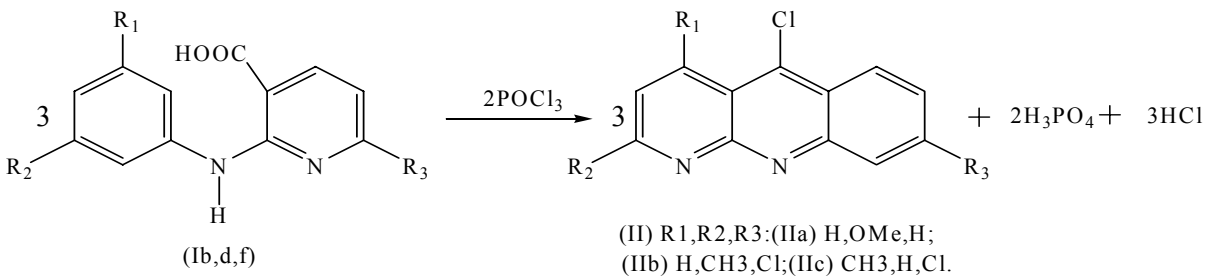
Equation (2)

The structure of acids (Ia-f) was identified by iodate-iodide test (cheronis, 1963) and I.R spectra which showed a main absorption bands at ν (3550 - 3280) cm^{-1} assigned to (O-H) and (N-H) groups, (1697 - 1667) cm^{-1} assigned to (C=O) and (1649 - 1633) cm^{-1} assigned to (C=N), (Table 1). Elemental analysis were used to identify some of these acids (Ia,c) (see the values in the experimental part), GC/MS for the compounds (Ib, d) showed that the two acid are formed, figures (1,2); schemes (1 and 2).

The figure (1) gave peak bar (m/z 244, 61%) and (m/z 281, 4%), which were assigned to the compound (Ib) (M.Wt = 244) and (M + HCl), while the figure (2) gave peak bar (m/z 281, 7%) that assigned to the compound (Id) containing one water molecule (M+18). The suggested fragmentations pattern for both acids (Ib,d) were given in the schemes (1 and 2).

Synthesis of 5-Chlorobenzo [b] [1,8] naphthyridine compounds.

The compounds (IIa-e) were prepared by cyclization of substituted anthranilic acids (Ib,d,f) respectively by using ($POCl_3$), (Equition 3).



Equation (3)

The structure of the compounds (IIa-c) was identified by elements test, (Cheronis; 1963) and I.R spectra which shows a main absorption bands at ν(1652 - 1638) cm^{-1} assigned to (C=N), (1621 - 1604) cm^{-1} assigned to (C=C aromatic), and disappearance of (C=O) band. A new bands at (679 - 689) cm^{-1}assigned to (C-Cl) and (749, 830, 1048, 1124) cm^{-1} assigned to naphthyridine cycles (Mohammad, 1994). U.V spectra showed absorption values (λ max) at (209-366) nm and (logε) values at (4.425-3.707), (Table 2). (The values that fitted 1, 8-naphthyridine moiety given by (katritzky, 1984).

Elemental analysis of the compound (IIa) showed that this compound may contain water or hydrogen chloride molecule. GC/MS of (IIb), Figure (3) shows a peak bar of (m/z 281, 10%) which assigned to this compound with water molecule i.e. M + 18. The suggested fragmentation for this compound was given in the scheme (3).

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