Reduction of Pyridine Dicarboximide as a Facil Rout to Synthesis of Isomeric Pyridine Lactones

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Abstract

Four isomers of pyridine lactone were synthesized by reduction of readily available pyridine dicarboximides to the corresponding amides by sodium borohydride in acidic ethanolic solution to give the two isomers of hydroxyl methyl pyridine amide. Lactonisation of the later was best achieved using either hydrochloric acid or heating in toluene.
The structure of all compounds were identified by the available physical, chemical and spectroscopic methods.

Key words: Pyridine dicarboximide, pyridine lactones

Introduction

In spite of the importance of pyridine, lactones (azaphthalide) as useful precursor in indole alkaloide synthesis namely apparicine[1-5]. Pyridine lactones have received little attention[6-8] due to the difficulties encountered in their synthesis, including long sequence (no satisfactory yield) and tedious purification[9,10].
Accordingly, we sought to develop a more useful method, new and efficient for the construction of such compounds from the points of view, ease of working or high yields and to evolve a route which at least compares favourably with others for the synthesis of lactones, in addition to isolate and illustrate the structure of the four isomers produced from the reduction of pyridine dicarboximide[11,17]. Furthermore, these lactone isomers could be used as a novel synthone to prepare pyridine aldehydic acid.

Experimental

Uncorrected melting points were determined using Gallnkampe melting point apparatus. I.R spectra were recorded by using Pye Unicam SP 1100 Spectrophotometer as KBr disc. U.V-Visible spectra were performed on double beam Shimadzu U.V-160 Spectrophotometer. Reactions progress were monitored by T.L.C technique. Column chromatography was carried out on silica (BDH-60-120).

Synthesis of pyridine 2,3-dicarboxylic anhydride [1]

Pyridine 2,3-dicarboxylic acid (16.7 g, 0.1 mole) in acetic anhydride (50 ml) was heated under reflux for 30 min. On cooling, the residue was filtered and recrystallized from acetic acid to give white crystals (10.5 g, 80%), m.p = 136-138 °C (Lit.[13] 138 °C).

Synthesis of pyridine 3,4-dicarboxylic anhydride [2]

Pyridine 3,4-dicarboxylic acid (16.7 g, 0.1 mole) in acetic anhydride (50 ml) and anhydrous sodium sulphate (5 g) were heated under reflux for 1 hr. On cooling, the precipitate was dissolved with acetic acid. The crystalline material was filtered and washed with acetic acid-followed by water to afford the title product as white crystals (11.6 g, 88%), m.p = 75 °C (Lit.[14] 77).

Synthesis of pyridine dicarboximides [3,4]

Pyridine 2,3-or 3,4-dicarboxylic anhydride (6.0 g, 0.04 mole) and appropriate amines (0.04 mole) were refluxed in acetic acid (30 ml) for one hour. The reaction mixture were filtered while hot and allowed to cool. The solvent was evaporated off and product was recrystallized using acetic acid-water to give the desired product. Physical properties and spectral data for [3,4] were listed in Table (I and II).

Table (I): Physical and spectroscopic data of imides [3,4]

Comp. No.	R	Molecular formula	m.p. (°C)	Yield (%)	I.R ν (cm^{-1}) KBr disc				U.V. EtOH λ_{max} (nm)
					Ar C-H	C=O	C=N	C=C	
3a	C_2H_5	$C_9H_8N_2O_2$	46-47	72	3020	1725	1600	1590	275,244,222
3b	C_3H_7	$C_{10}H_{10}N_2O_2$	99-100	82	3010	1740	1605	1598	280,278,225
3c	C_4H_9	$C_{11}H_{12}N_2O_2$	77-78	85	3000	1720	1600	1590	280,278,225
3d	$C_6H_5CH_2$	$C_{13}H_{10}N_2O_2$	160-162	84	3005	1740	1600	1590	300,254,222
4a	C_2H_5	$C_9H_8N_2O_2$	41-42	75	300	1725	1600	1590	272,223,221
4b	n-C_3H_7	$C_{10}H_{10}N_2O_2$	54-56	84	3010	1730	1600	1595	280,270,220
4c	iso-C_3H_7	$C_{11}H_{12}N_2O_2$	93-94	90	3005	1720	1610	1590	280,230,220
4d	$C_6H_5CH_2$	$C_{13}H_{10}N_2O_2$	100-102	92	3000	1715	1610	1598	285,2272,224

Reduction of N-substituted pyridine dicarboximides [3,4] with sodium borohydride:

Sodium borohydride (3 g) was added to the cooled stirred solution (0-5 °C) of N-substituted pyridine dicarboximides (0.025 mole) in ethanol. Hydrochloric acid (2N) (50 ml) was added dropwise to this mixture every 15 minutes during five hours. The reaction mixture was acidified with hydrochloric acid and neutralized with sodium carbonate solution. Extraction of the mixture with ethyl acetate and evaporation of the solvent gave dark residue. This was loaded on a silica gel and eluated with ethyl acetate to give the isomers [5a-d, 6a-d] and [7a-d, 8a-d].

Table (II): Physical and spectroscopic data of imides [5-8]

Comp. No.	R	Molecular formula	m.p. (°C)	Yield (%)	I.R ν (cm^{-1}) KBr disc				U.V. EtOH λ_{max} (nm)
					N-H	O-H	Ar C-H	C=O	
5a	C_2H_5	$C_9H_{12}N_2O_2$	Oily	42	3450	3300	3000	1630	196,278,265
5b	C_3H_7	$C_{10}H_{14}N_2O_2$	Oily	44	3420	3320	3010	1635	390,380,326
5c	C_4H_9	$C_{11}H_{16}N_2O_2$	Oily	39	3500	3340	3000	1640	297,270,215
5d	$C_6H_5CH_2$	$C_{14}H_{14}N_2O_2$	86-87	37	3440	3310	3000	1660	298,265,232
6a	C_2H_5	$C_9H_{12}N_2O_2$	Oily	35	3450	3310	3000	1685	300,282,222
6b	n-C_3H_7	$C_{10}H_{14}N_2O_2$	Oily	37	3460	3250	3000	1690	298,281,222
6c	iso-C_3H_7	$C_{11}H_{16}N_2O_2$	Oily	38	3480	3300	3000	1680	295,278,222
6d	$C_6H_5CH_2$	$C_{14}H_{14}N_2O_2$	99-100	33	3400	3250	3000	1690	297,227,222
7a	C_2H_5	$C_9H_{12}N_2O_2$	Oily	41	3600	3600	3000	1680	320,270,220
7b	iso-C_3H_7	$C_{10}H_{14}N_2O_2$	Oily	38	3450	3450	3000	1675	310,278,222
7c	C_4H_9	$C_{11}H_{16}N_2O_2$	Oily	35	3450	3450	3000	1670	320,270,215
7d	$C_6H_5CH_2$	$C_{14}H_{14}N_2O_2$	85-86	42	3600	3600	3000	1670	300,264,222
8a	C_2H_5	$C_9H_{12}N_2O_2$	Oily	40	3600	3600	3000	1680	310,272,215
8b	iso-C_3H_7	$C_{10}H_{14}N_2O_2$	Oily	39	3450	3450	3000	1675	300,282,222
8c	C_4H_9	$C_{11}H_{16}N_2O_2$	Oily	34	3425	3425	3000	1670	305,270,232
8d	$C_6H_5CH_2$	$C_{14}H_{14}N_2O_2$	138-140	38	3550	3550	3010	1685	320,270,232

For physical and spectroscopic data see Tables (III and IV).

Synthesis of pyridine lactones [9-12]

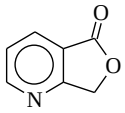
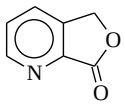
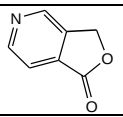
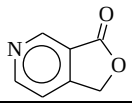
Method a

An appropriate N-substituted hydroxyl methyl pyridine amides [5,8] (0.01 mole) in hydrochloric acid (3N) (10 ml) was refluxed for 1 hr. The reaction mixture was neutralized with sodium carbonate (10%), extraction with ethyl acetate gave lactones [9-12]. For physical and spectral data see Table (V).

Method b

An appropriate N-substituted hydroxyl methyl pyridine amides [5-8] in toluene was heated in dean stark apparatus for 1 hr. The resulting residue was purified by chromatographed on silica gel column using ethyl acetate as eluent to give lactones [9-12] which were identical to the lactones prepared in method a

Table (V): Physical and spectroscopic data of azaphthalide

Comp. No.	Structure	Molecular formula	m.p. (°C)	Yield (%)	I.R ν (cm^{-1}) KBr disc		U.V. EtOH λ_{max} (nm)	S.E	H.F
					C=O	C-O			
9		$C_7H_5NO_2$	140-142	45	1710	1150	222	20.196	-30.8
10		$C_7H_5NO_2$	113-114	39	1025	1153	217	23.661	-33.665
11		$C_7H_5NO_2$	139-141	36	1720	1070	223	22.855	-32.892
12		$C_7H_5NO_2$	158-160	42	1720	1080	217	22.762	-32.025

Results and Discussion

As a key intermediate in projected synthesis of various heterocyclic compounds of pyridine-dicarboximides which attracted considerab;e synthetic interests in recent years[15], as a number of fascinating artificial bioactive compounds, a number of pyridine lactones (azaphthalide) was synthesized via pyridine dicarboximide. We have

previously reported the condensation of phthalic anhydride or pyridine dicarboxylic anhydride with amines[17,18], the results of which where reported herein.

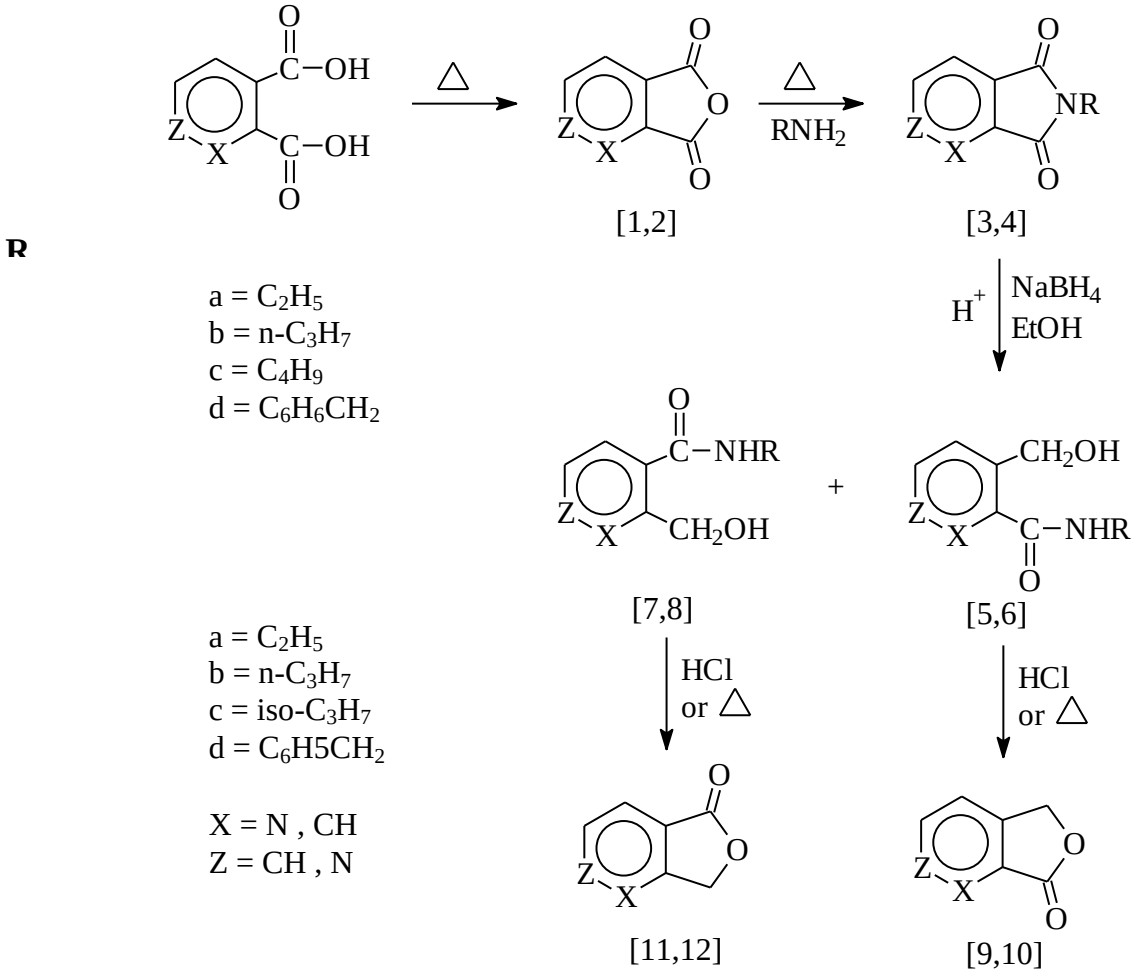
When an equimolar of 2,3-or 3,4-pyridine dicarboxylic anhydride with appropriate amines were refluxed in acetic acid, N-substituted pyridine-dicarboximide were obtained. Structural elucidation of compounds [3 and 4] were based on physical and spectroscopic evidences.

The infrared spectra showed absorption at around 1740-1725 cm^{-1} to C=O group and also show the disappearance of absorption at about 3400 – 3500 cm^{-1} for the NH2 group. The U.V absorption of the imides [3,4] were very similar in shape and positions of absorption maximam (λ_{max} 300, 275 nm).

Reduction of the imides [3,4] was carried out using sodium borohydride in ethanol under acidic medium at room temperature ture to produce a mixture of two components which was separated by passing through silica gel column using ethyl acetate as eluent to afford of the isomers hydroxyl methyl N-substituted-pyridine amides [5,6] and [7,8]. The structure of isomeric of amides [5-8] were elucidated from spectroscopic evidence and acid hydrolysis with hydrochloric acid (3N) or pyrolytic deamination in toluene.

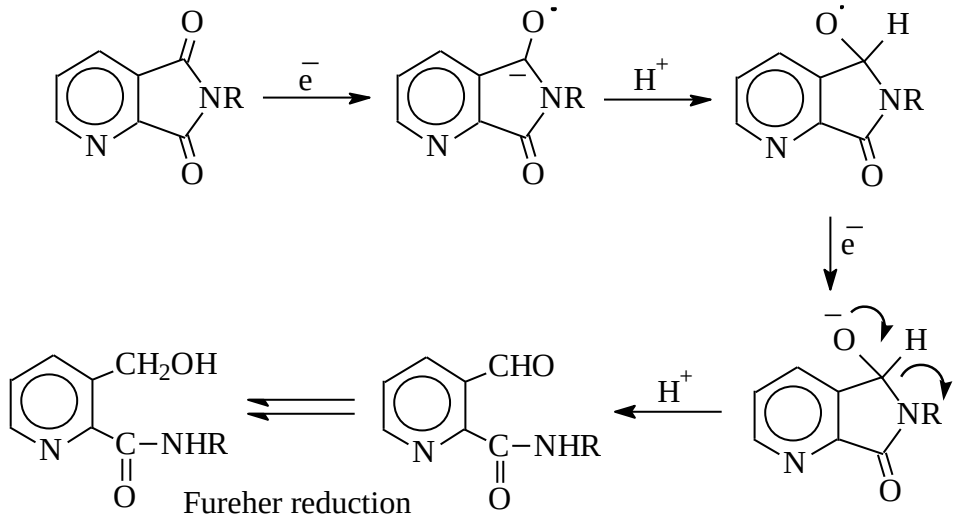
The infrared spectra exhibited characteristic peaks at 3500, 3400 and 1680 cm^{-1} due to NH, OH and C=O groups, respectively. Further evidence for the structures of isomers [5,6] was obtained from deamination of hydroxyl methyl pyridine amides [5,6] to give lactones [9,10], the physical and spectroscopic data of which distinguishing[11] unambiguously which isomer is which.

The method of deamination of [5,6] to lactones [9,10] was extrapolated on [7,8] isomers to give lactones [11,12] (Scheme I). The U.V spectra of the lactones [9-12] were very similar in shape and positions of absorption maxima. I.R evidence showed the presence of C=O group at around 1720-1725 cm^{-1}. Scheme (I) shows the reduction of pyridine dicarboximide with sodium borohydride and the product assignments.



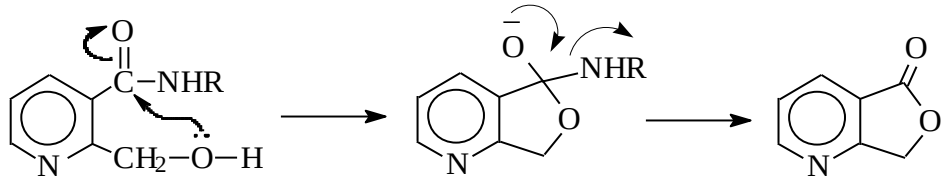
Scheme (I)

The possible pathway accounting for the formation of hydroxyl methyl pyridine amide and its isomer is shown in Scheme (II).



Scheme (II)

The formation of lactone from amide probably proceed by nucleophilic attack at carbonyl group of amide to give the intermediate followed by deamination to give the lactone (Scheme III).



Scheme (III)

Further information about the isolated products (5-12) were obtained from calculated heat of formation and steric energy using molecular mechanic and quantum mechanic methods (MOBAC), on addition to 3D-configuration which was shown in Table (I , II , III ,VI) and Figures (1,2).

Table (VI)

Comp. No.	R	S.E	H.F	Comp. No.	R	S.E	H.F
5a	C_2H_5	5.8502	-58.5506	7a	C_2H_5	4.6879	-60.567
5b	C_3H_7	6.5344	-66.4928	7b	C_3H_7	10.9532	-65.740
5c	C_4H_9	11.634	-65.9909	7c	C_4H_9	9.6487	-65.8171
5d	$C_6H_5CH_2$	1.9986	-26.107	7d	$C_6H_5CH_2$	0.4880	-27.3170
6a	C_2H_5	3.1669	-60.9443	8a	C_2H_5	8.9204	-58.595
6b	C_3H_7	7.5187	-64.852	8b	C_3H_7	10.4067	-62.945
6c	C_4H_9	10.0065	-70.17	8c	C_4H_9	12.0113	-68.3973
6d	$C_6H_5CH_2$	-6.1060	-28.517	8d	$C_6H_5CH_2$	10.0910	-27.011

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اختزال البريدين ثنائي الكاربوكساميد كطريق سهل لتحضير ايزومرات لاكتون البريدين

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الملخص

تم تحضير اربعة ايزومرات للاكتونات البريميدين من اختزال بريدين ثنائي الكاربوكسيميد الى الامايد المقابل بواسطة هيدريد صوديوم بورون في الايثانول بوجود حامض الهيدروكلوريك لتعطي ايزومرات هيدروكسي مثيل بريدين اميد. تمت عملية الاسترة الحلقية لنواتج الاختزال اما باستعمال حامض الهيدروكلوريك او بواسطة التسخين في التولوين. شخصت المواد الناتجة بالطرائق الكيمياوية والفيزياوية والطيفية المتوافرة.

الكلمات المفتاحية: البريدين ثنائي الكاربوكساميد، لاكتون البريدين