1,6- and 1,7-Naphthyridines. I. Rearrangement of Quinolinimidoacetic Acid Derivatives

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The reaction of *N*-substituted quinolinimides **1a-d** with sodium alkoxides afforded a mixture of 1,6-naphthyridines **2** and 1,7-naphthyridines **3** which were isolated by chromatographic methods. Structure assignment for each pair of isomers was made by comparison of their ^{1}H nmr spectra with those of picolinamide and nicotinamide. When esters **1a-c** were treated with alkoxides from primary alcohols, other than that of the ester, total transesterification took place. Experimental results suggest that transesterification occurs in open intermediary species.

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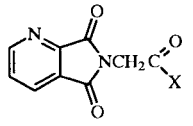
Introduction.

The alkoxide-induced rearrangement of *N*-substituted phthalimides (Gabriel-Colman reaction), has been widely described [1-8] and seems to be the method of choice to prepare 3-substituted 4-hydroxy-1(2*H*)-isoquinolones, but there are only scanty reports on this reaction in the case of *N*-substituted 5*H*-pyrrolo[3,4-*b*]pyridine-5,7(6*H*)-diones (*N*-substituted quinolinimides). Assuming that in such compounds, as in phthalimide derivatives, the rearrangement reaction takes place by alcoholysis of the carboxamide linkage followed by a Dieckmann cyclization [8,9] and given the molecular asymmetry conferred by the pyridine nitrogen, it is not unreasonable to expect the production of two isomers derived from 1,6-naphthyridine (**2**) and 1,7-naphthyridine (**3**) (Scheme I). However, in 1904 Fels [10] studied the rearrangement of quinolinimidoacetic acid ethyl ester (**1b**) with sodium methoxide to obtain a sole product ambiguously assigned either the **2a** or **3a** structure (as the diketone). Years later, Ochiai *et al.* [11] showed that the methyl ester obtained by Fels' procedure was actually the 1,6-naphthyridine **2a** since it proved identical to a specimen previously prepared by an unequivocal route [12]. Still later, Albert [13] reported that the reaction afforded a more water-soluble substance identified as the 1,7-naphthyridine **3a**, in addition to **2a**. The physical properties described by the authors for compound **2a** are in disagreement, and there are no spectroscopic data available to confirm the proposed structures. It is this lack of information which has prompted us to study the reaction of some *N*-substituted quinolinimides (Table I) with alkoxides in order to investigate the scope of the above synthetic approach. Accordingly, a series of quinolinimidoacetic acid alkyl esters **1a-c** as well as the related α-quinolinimidoacetophenone **1d** were treated with alkoxides in alcoholic solution.

Table 1
N-Substituted Quinolinimides Derivatives



Compound	X
1a	OCH_3
1b	OC_2H_5
1c	$OCH(CH_3)_2$
1d	C_6H_5

Scheme I

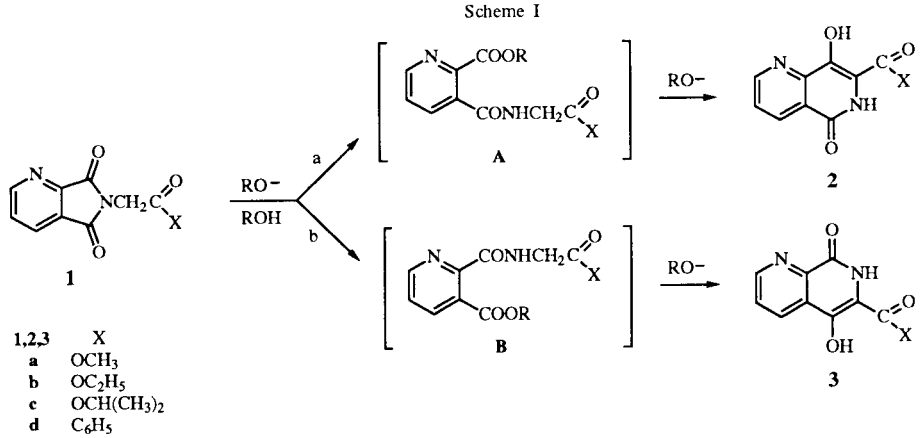
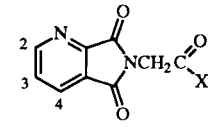


Table II

N-Substituted Quinolinimides **1a-d**

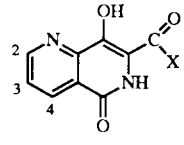


Compound No.	Conditions Temp. (°C)	Time (hs)	Yield (%)	Mp (°C)	Recrystallization solvent	Formula	Analyses (Calcd./Found) %C	%H	%N	IR ν (cm^{-1})		δ (ppm)	^{1}H-NMR [a] Multiplicity	Assignment
1a	70-80	12	80	103	methanol	$C_{10}H_8N_2O_4$	54.54	3.64	12.73	3055	(OH)	9.00	dd	H2
							54.34	3.82	12.60	2939	(CH)	8.70	dd	H4
										1750	(CO)	7.65	dd	H3
										1721	(CO)	4.50	s	CH_2
										1595	(CN)	3.80	s	CH_3
1b [b]	70-80	14	82	121	ethanol	$C_{11}H_{10}N_2O_4$				3062	(CH)	9.00	dd	H2
										2985	(CH)	8.70	dd	H4
										1758	(CO)	7.65	dd	H3
										1730	(CO)	4.50	s	CH_2
										1596	(CN)	4.20	c	CH_2CH_3
												1.30	t	CH_3
1c	70-80	12	84	125	ethanol	$C_{12}H_{12}N_2O_4$	58.06	4.84	11.29	3042	(CH)	9.00	dd	H2
							58.25	4.99	11.22	2985	(CH)	8.70	dd	H4
										1784	(CO)	7.65	dd	H3
										1731	(CO)	5.10	m	CH
										1600	(CN)	4.50	s	CH_2
												1.25	d	CH_3
1d	50	17	78	131	2-propanol	$C_{15}H_{10}N_2O_3$	67.67	3.76	10.53	3060	(CH)	9.00	dd	H2
							67.82	3.94	10.40	2924	(CH)	8.20	dd	H4
										1750	(CO)	8.0	dd	C_6H_5 (2 *ortho* H)
										1723	(CO)	7.65	m	H_3, C_6H_5 (*para* H)
										1700	(CO)	7.5	t	C_6H_5 (2 *meta* H)
										1595	(CN)	5.2	s	CH_2

[a] Spectra were performed in deuteriochloroform. [b] Previous reference [10,11].

Table III

7-Substituted 8-Hydroxy-1,6-naphthyridin-5(6*H*)-ones **2a-d**



Compound No.	Mp (methanol) (°C)	Yield (%)	Formula	Analyses (Calcd./Found) %C	%H	%N	Mass M$^+$ (%)	IR ν (cm^{-1})	UV in 0.1*N* HCl λ max (nm)	in ethanol λ max (nm)	in 0.1*N* NaOH λ max (nm)	^{1}H-NMR [a] δ (ppm)	Multiplicity	Assignment
2a [b]	220 dec	42	$C_{10}H_8N_2O_4$	54.54	3.64	12.73	220	3450	340	376	374	10.75 and		
				54.32	3.85	12.80	(71.10)	2900	262	268	268	10.25	bs [c]	NH, OH
								1650	216	225	223	9.10	dd [d]	H2
								1600				8.60	dd [d]	H4
								1582				7.70	dd [d]	H3
								1560				3.90	s	CH_3
2b	209 dec	40	$C_{11}H_{10}N_2O_4$	56.41	4.27	11.97	234	3450	338	373	375	10.90 and		
				56.19	4.49	11.70	(84.53)	2950	261	263	268	10.40	bs [c]	NH, OH
								1640	226	229	226	9.10	dd [e]	H2
								1580				8.60	dd [e]	H4
								1560				7.75	dd [e]	H3
												4.35	c	CH_2
												1.35	t	CH_3

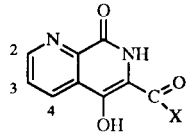
Table III (Contin'd)

Compound No.	Mp (methanol) (°C)	Yield (%)	Formula	Analyses (Calcd./Found) %C	%H	%N	Mass M+ (%)	IR ν (cm-1)	in 0.1N HCl λ max (nm)	in ethanol λ max (nm)	in 0.1N NaOH λ max (nm)	δ (ppm)	1H-NMR [a] Multiplicity	Assignment
2c	180	40	$C_{12}H_{12}N_2O_4$	58.06	4.84	11.29	248	3400	338	375	375	10.75 and		
				57.83	4.99	11.04	(33.14)	2900	262	267	267	10.20	bs [c]	NH, OH
								1640	226	229	227	9.05	dd [f]	H2
								1580				8.60	dd [f]	H4
								1560				7.75	dd [f]	H3
												5.15	m	CH
												1.35	d	CH_3
2d	222	45	$C_{15}H_{10}N_2O_3$	67.67	3.76	10.53	266	3430	370	373	428	11.00 and		
	dec			67.90	3.98	10.30	(100.00)	2840	261	259	264	9.70	bs [c]	NH, OH
								1650	218	220	220	9.05	dd [g]	H2
								1610				8.65	dd [g]	H4
								1578				7.85	dd [g]	H3
								1550				7.45	m	aromatics

[a] Spectra were performed in dimethyl sulfoxide-d_6. [b] Lit 203-205° [10], 219-220° [11,13]. [c] Exchangeable. [d] $J_{H2,H3}$ = 4.45 Hz, $J_{H2,H4}$ = 1.58 Hz, $J_{H3,H4}$ = 8.12 Hz. [e] $J_{H2,H3}$ = 4.51 Hz, $J_{H2,H4}$ = 1.62 Hz, $J_{H3,H4}$ = 8.03 Hz. [f] $J_{H2,H3}$ = 4.47 Hz, $J_{H2,H4}$ = 1.60 Hz, $J_{H3,H4}$ = 7.98 Hz. [g] $J_{H2,H3}$ = 4.46 Hz, $J_{H2,H4}$ = 1.59 Hz, $J_{H3,H4}$ = 7.97 Hz.

Table IV

6-Substituted 5-Hydroxy-1,7-naphthyridin-8(7*H*)-ones **3a-d**



Compound No.	Mp (ethanol) (°C)	Yield (%)	Formula	Analyses (Calcd./Found) %C	%H	%N	Mass M+ (%)	IR ν (cm-1)	UV in 0.1N HCl λ max (nm)	in ethanol λ max (nm)	in 0.1N NaOH λ max (nm)	δ (ppm)	1H-NMR [a] Multiplicity	Assignment
3a [b]	204	18	$C_{10}H_8N_2O_4$				220	3450	342	345	373	10.90 and		
	dec						(42.36)	3160	264	258	268	10.30	bs [c]	NH, OH
								2920	214	216	222	9.00	dd [d]	H2
								2820				8.45	dd [d]	H4
								1657				7.85	dd [d]	H3
								1610				3.90	s	CH_3
								1595						
3b	198	18	$C_{11}H_{10}N_2O_4$	56.41	4.27	11.97	234	3500	335	340	374	10.90 and		
	dec			56.20	4.42	12.08	(100.00)	3050	264	258	267	10.40	bs [c]	NH, OH
								2920	228	219	229	8.95	dd [e]	H2
								2800				8.45	dd [e]	H4
								1640				7.85	dd [e]	H3
								1600				4.40	c	CH_2
												1.35	t	CH_3
3c	190	20	$C_{12}H_{12}N_2O_4$	58.06	4.84	11.29	248	3480	335	341	373	10.90 and		
	dec			58.30	5.10	11.50	(35.71)	3100	263	260	265	10.50	bs [c]	NH, OH
								2920	229	220	229	9.00	dd [f]	H2
								2800				8.45	dd [f]	H4
								1645				7.85	dd [f]	H3
								1605				5.20	m	CH
												1.40	d	CH_3
3d	170	19	$C_{15}H_{10}N_2O_3$	67.67	3.76	10.53	266	3500	374	400	425	11.10	bs [c]	NH, OH
				67.50	3.92	10.70	(50.25)	3190	264	259	256	9.00	dd [g]	H2
								2890	227	229	228	8.50	dd [g]	H4
								2810				7.90	dd [g]	H3
								1640				7.8-7.5	m	aromatics
								1600						

[a] Spectra were performed in dimethyl sulfoxide-d_6. [b] Previous reference [13]. [c] Exchangeable. [d] $J_{H2,H3}$ = 4.37 Hz, $J_{H2,H4}$ = 1.60 Hz, $J_{H3,H4}$ = 8.19 Hz. [e] $J_{H2,H3}$ = 4.38 Hz, $J_{H2,H4}$ = 1.62 Hz, $J_{H3,H4}$ = 8.22 Hz. [f] $J_{H2,H3}$= 4.43 Hz, $J_{H2,H4}$ = 1.48 Hz, $J_{H3,H4}$ = 8.18 Hz. [g] $J_{H2,H3}$ = 4.40 Hz, $J_{H2,H4}$ = 1.52 Hz, $J_{H3,H4}$ = 8.20 Hz.

Results and Discussion.

Compounds **1** were prepared starting from quinolinimide, lithium hydroxide and the corresponding halogen derivative in dimethylformamide. Analytical and spectroscopic data are listed in Table II and agree with the proposed structures.

The reaction of compounds **1a-d** with hot alkoxides followed a common behavior. Without exception, a mixture of two products was obtained, with a predominance of the one having the lower Rf value, which were isolated by chromatographic methods. Elemental analysis, a positive reaction with ferric chloride and spectroscopic properties (as discussed below) indicated that the low Rf compounds derived from 8-hydroxy-1,6-naphthyridin-5(6*H*)-one (**2**) and those of high Rf from 5-hydroxy-1,7-naphthyridin-8(7*H*)-one (**3**) (Tables III and IV).

When esters **1a-c** were treated with alkoxides from primary alcohols other than that of the ester, total transesterification took place [14]. Thus, compounds **1b-c** reacted with sodium methoxide to yield a mixture of **2a** and **3a** alone. Following the reaction by tlc, the presence of **1a** could not be detected at any time, which indicates that transesterification fails to occur in the starting quinolinimide; neither are the non-transesterified compounds **2b-c** and **3b-c** observed. Furthermore, when treatment with sodium methoxide was carried out on expanded products **2b** or **3b**, transterification proved to be partial. Such findings suggest that, in common with related reactions [15], transesterification takes place in open intermediary species (**A** and **B** in our case), supporting the proposed reaction mechanism (Scheme I). However, as in the rearrangement of *N*-sustituted phthalimides [8,9] no such open intermediaries could be detected. The predominant yield of compounds **2** in all cases is understandable bearing in mind that alkoxide attack should occur more readily on the carbonyl in the position of lower electronic density (route *a*).

Spectroscopic Characterization of Naphthyridines **2** and **3**.

The ^{1}H nmr spectra of compounds **2** and **3** (Tables III and IV) show an enol hydroxyl and the carboxamide hydrogen at 9.7-11.1 ppm as broad signals. All three aromatics protons are sharply differentiated with the expected multiplicity, observing H2 at 8.9-9.1, H3 at

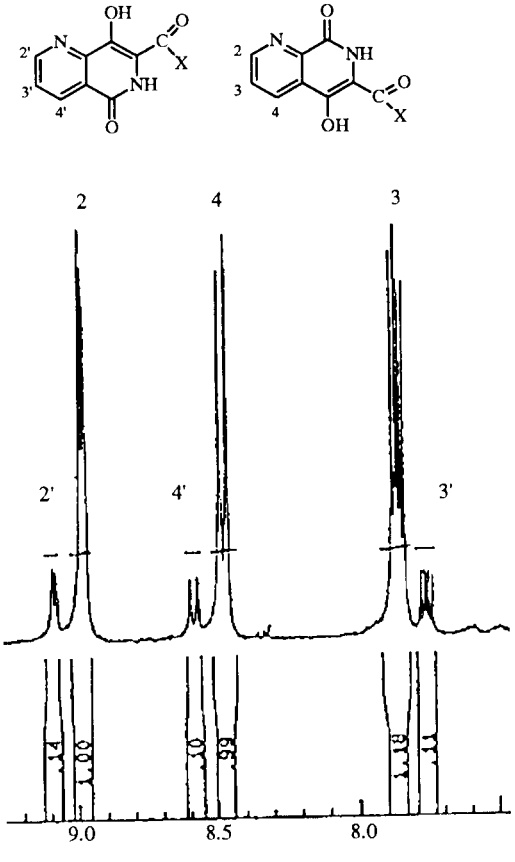


Figure 1. ^{1}H nmr chemical shift assignments for aromatic protons of a mixture of **2a** and **3a** (1:10).

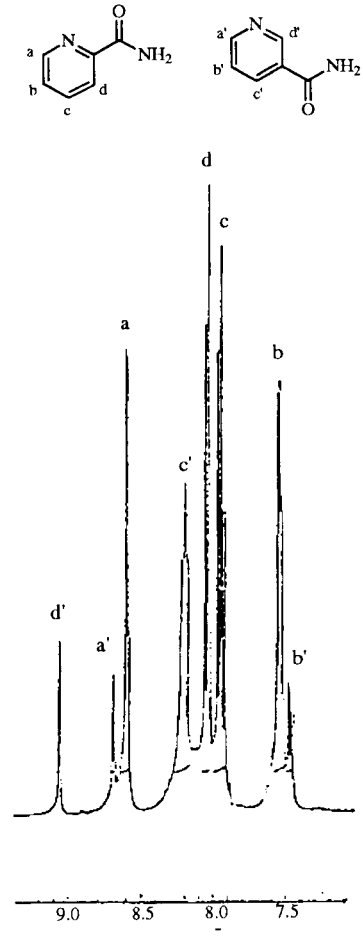
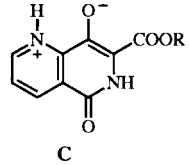


Figure 2. ^{1}H nmr chemical shift assignments for aromatic protons of a mixture of nicotinamide and picolinamide (1:4).

7.7-7.9 and H4 at 8.4-8.7 ppm. Structure assignment for each pair of isomers was made by comparison of their ^{1}H nmr spectra with those of picolinamide and nicotinamide, with which there is a close structural relation. As shown in Figure 1, all low Rf compounds presented greater chemical shifts for H2' and H4', but a lower shift for H3', versus the corresponding protons in high Rf compounds. Such a relationship was also observed in the corresponding aromatic protons in nicotinamide versus those of picolinamide (Figure 2). On the basis of these findings, for low Rf compounds the structure of 1,6-naphthyridin-5(6*H*)-one derivatives (**2**) and for high Rf compounds that of 1,7-naphthyridin-8(7*H*)-one (**3**) were assigned.

Characteristically, ir spectra of compounds **2** show a single broad band between 3450-2840 cm^{-1}and two sharp bands in the 1580-1500 cm^{-1} range. On the other hand, ir spectra of compounds **3** exhibit a broad absorption band extending from 3500 to 2800 cm^{-1} with several well defined maxima, whereas the bands in the 1580-1500 cm^{-1} region are absent.

The uv spectra of compounds **2** and **3** invariably exhibit three strong bands with two at 216-223 and 258-268 nm and a third in the blue-violet region at 340-373 nm. Observed variations are related to the structure of such compounds in solution. Thus, in alcoholic solution, compounds **2a-c** present a predominance of the zwitterion structure C, as shown by the stricking similarity of their spectra in alcoholic solution with those in basic medium (enolate anion), as well as by the significant difference with spectra of acidic solution with the longest wavelength band exhibiting a strong hypsochromic shift. In contrast, spectra of compounds **2d** and **3a-d** in alcoholic solution show a predominance of the normal covalent structure **3** (Scheme I), all proving very similar to those in acidic solution, which as expected exhibit a batochromic shift in the longest wavelength band in basic solutions.



C

EXPERIMENTAL

Melting points were taken on a Büchi capillary apparatus and are uncorrected. The ir spectra were recorded on a Beckman 180A spectrometer. Samples were run as potassium bromide pellets. The ^{1}H nmr spectra were recorded on a Bruker MSL 300 Hz. Chemical shifts are quoted in parts per million (δ) downfield from an internal TMS reference. The presence of exchangeable protons was confirmed by use of deuterium oxide. Proton signals are quoted as: s (singlet), d (doublet), dd (doublet of doublet), t (triplet), c (quartet) and bs (broad signal). Mass spectra were performed on a MS Shimadzu QP-1000 instrument at 70 eV. The uv spectra were recorded on a Jasco 7850 UV-VIS spectrophotometer. Analytical tlc was carried out on aluminium sheets Silica Gel 60 F_{254}. Preparative thin layer separations were carried out by centrifugally accelerated, radial chromatography using Chromatotron model 8924. The rotors were coated with Silica Gel 60 PF_{254} and the layer thickness was 2 mm. Reagents, solvents and starting materials were purchased from standard sources and purified according to literature procedures.

N-Substituted 5*H*-Pyrrolo[3,4-*b*]pyridine-5,7(6*H*)-diones (*N*-Substituted Quinolinimides) **1a-d**. General Procedure.

A mixture of 1 g of quinolinimide (0.007 mole), 0.77 g of lithium hydroxide (0.008 mole), 0.010 mole of the corresponding halogen derivative and 5 ml of dimethylformamide was heated in an oil bath at the appropriate temperature and monitored by tlc (benzene-methanol, 9:1). When the reaction was completed, the reaction mixture was poured into ice-water and the resulting solid filtered, washed with water and recrystallized. Details of reaction (temperature, time, yields), melting points, recrystallization solvents, analyses and spectroscopic data of the compounds are given in Table II.

Reaction of Compounds **1a-d** with Sodium Alkoxides. General Procedure.

A solution of sodium alkoxide was prepared from 0.23 g of sodium (0.01 mole) in 5 ml of the corresponding absolute alcohol (methanol for **1a,d**, ethanol for **1b** and 2-propanol for **1c**). The solution was heated in an oil bath (90-100°) and 0.0025 mole of **1a-d** was added all at once as the powder. After 30 minutes the reaction was quenched by pouring in 10% oxalic acid. If the product crystallized (reaction of compounds **1a,d**) the resulting solid was filtered, washed with water and air dried. If not (reaction of compounds **1b,c**) the solution was extracted three times with chloroform. The organic layer was washed with water, dried and concentrated *in vacuo*. In all cases, the crude product showed two spots by tlc (Rf *ca.* 0.2 and 0.4, 9:1 chloroform-methanol). Separation of the two products was achieved by centrifugal tlc by a solvent system selected after trial on a qualitative tlc plate. The reaction mixture in chloroform-methanol (50:50) was applied, the rotor dried and then eluted with chloroform and increasing percentages of methanol. The first band eluted gave a solid which was recrystallized affording 6-substituted 5-hydroxy-1,7-naphthyridin-8(7*H*)-ones **3a-d**. The slower moving band afforded 7-substituted 8-hydroxy-1,6-naphthyridin-5(6*H*)-ones **2a-d**. Yields, melting points, recrystallization solvents, analyses and spectroscopic data of the compounds are given in Tables III and IV. Following the reaction at different times by tlc (9:1 chloroform-methanol) no intermediate was observed.

Transesterifications

When esters **1a-c** were treated with alkoxides from primary alcohols other than that of the ester, total transesterification took place. In a typical procedure compound **1b** was treated with sodium methoxide in the same conditions as above affording only **2a** and **3a**. Monitoring the reaction by tlc neither **1a** nor a mixture of **2b** and **3b** were detected. When **2b** or **3b** were treated with sodium methoxide in the same conditions, they remained almost unchanged and only traces of **2a** or **3a** respectively were observed.

Acknowledgements.

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