CHEMISTRY LETTERS, pp. 391-394, 1977. Published by the Chemical Society of Japan

SYNTHESES OF 1,4-DIHYDROPYRIDINES CONTAINING AMINO ACIDS AND REDUCTION OF ETHYL BENZOYLFORMATE

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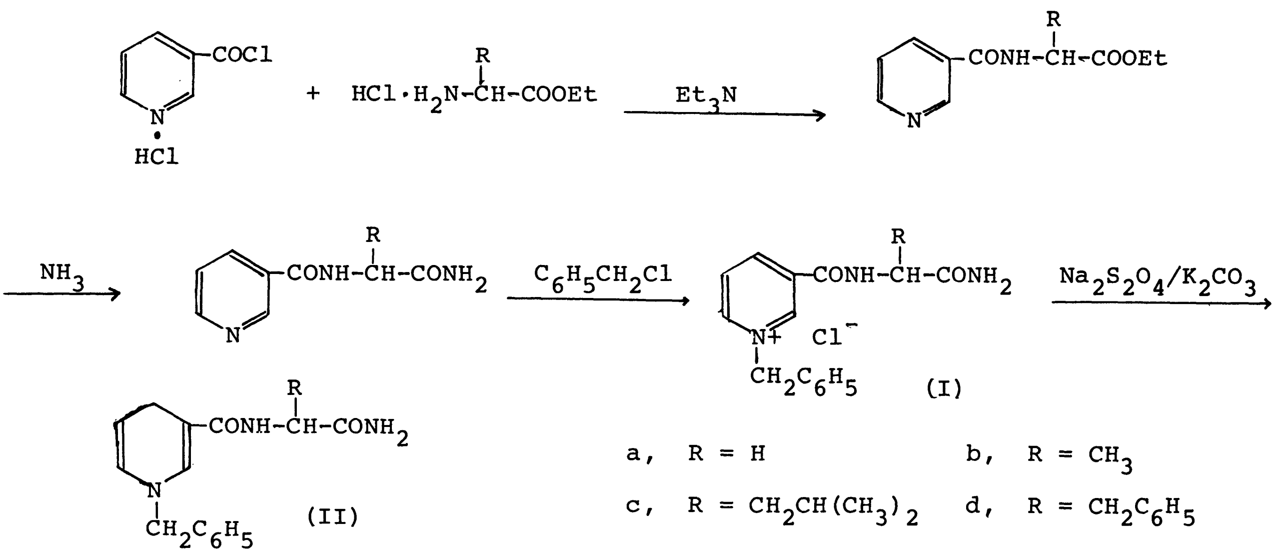
1-Benzyl-1,4-dihydronicotinamide derivatives(IIa-IId) containing amino acid moieties such as glycine, L-alanine, L-leucine and L-phenylalanine were prepared, and the asymmetric reduction of ethyl benzoylformate by use of IIa-IId was examined.

The reactions of 1-alkyl-1,4-dihydronicotinamide derivatives as a model for the reduced nicotinamide-adenine dinucleotide have been investigated because of their biochemical significance.1-2) For instance, the reductions of activated carbonyl compounds3) or olefines4) by 1-benzyl-1,4-dihydronicotinamide(BNAH) have been reported. Further, syntheses and reactions of polymers containing BNAH structure have been reported.5-7)

We, in this communication, wish to report the syntheses of 1-benzyl-1,4-dihydronicotinamide derivatives(IIa-IId) containing amino acids structure such as glycine, L-alanine, L-leucine and L-phenylalanine as a model of polymer catalysts, and the reduction of ethyl benzoylformate as an example of redox reaction by use of IIa-IId in the presence of magnesium perchlorate.

Syntheses of pyridinium salts(Ia-Id) and 1,4-dihydronicotinamides(IIa-IId) were carried out by the method, as shown in scheme 1. Ia-Id and IIa-IId were identified by infrared, uv, nmr and elemental analysis. The results were indicated in Tables 1 and 2.

Scheme 1. Preparation of 1-Benzyl-1,4-Dihydronicotinamides



a, $R = H$ b, $R = CH_3$

c, $R = CH_2CH(CH_3)_2$ d, $R = CH_2C_6H_5$

Table 1. Syntheses of Pyridinium Salts (I)

Compounds	R	Yield$^{a)}$ (%)	mp. (°C)	λmax$^{b)}$ (nm)	$[\alpha]_D^{23 c)}$
Ia	H	91	150-152	264	0
Ib	CH_3	84	83-85	264	9.5
Ic	$CH_2CH(CH_3)_2$	97	70-72	263	-7.7
Id	$CH_2C_6H_5$	80	58-60	264	-26.8

a) Benzylation, b) 99.5% EtOH, c) 99.5% EtOH, c=5

Table 2. Preparation of 1,4-Dihydronicotinamides (II)

Compounds	R	Yield (%)	λmax$^{a)}$ (nm)	$[\alpha]_D^{23 b)}$
IIa	H	82	354	0
IIb	CH_3	84	355	40.8
IIc	$CH_2CH(CH_3)_2$	64	354	-3.1
IId	$CH_2C_6H_5$	70	355	-38.5

a) 99.5% EtOH, b) 99.5% EtOH, c=5

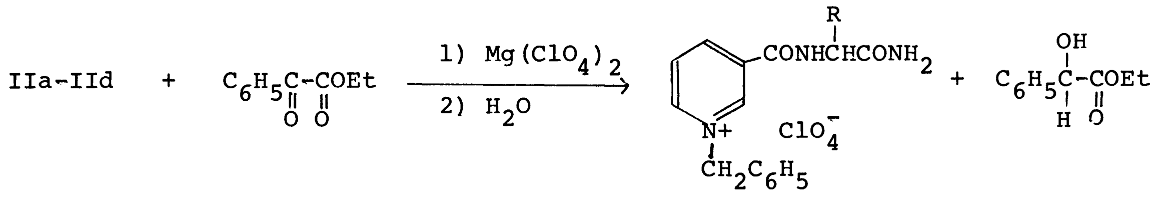
Stereospecific reduction of pyruvate to D- or L-lactate by NADH is catalyzed by lactate dehydrogenase.[8] It has been reported[9~10] that stereoselective nonenzymatic reduction of esters of pyruvic acid and benzoylformic acid in the presence of magnesium perchlorate or zinc perchlorate and 1,4-dihydronicotinamide derivatives. For example, the reduction of ethyl benzoylformate with R-(-)-N-methylbenzyl-1,4-dihydronicotinamide as chiral model for NAD(P)H at room temperature proceeded quantitatively to give ethyl(R)-(-)-mandelate with an optical purity of 19%.

The reduction of ethyl benzoylformate with IIa-IId was attempted. A mixture of 2 mmole each of ethyl benzoylformate, IIa-IId and magnesium perchlorate in 50 ml of acetonitrile was allowed to react for 72 hrs at 26°C. After removing acetonitrile, 20 ml of water was added. The solution was extracted 3 times with ether. Ether was removed in vacuo and the residue was column-chromatographed on silica gel and eluted with benzene. Ethyl mandelate was obtained quantitatively and 1-benzyl-3-carbamoylpyridinium perchlorate was recovered from the aqueous solution in 80-90% yields. The configuration and optical purity of obtained ethyl mandelate were shown in Table 3.

Table 3. Reduction of Ethyl Benzoylformate by IIa-IId

1,4-Dihydronicotinamides		Product(Ethyl mandelate)			
	R	Yield (%)	$[\alpha]_D^{23}$ a)	Configuration	Optical purity(%) b)
IIa	H	100			0
IIb	CH_3	100	-48.7	R	47
IIc	$CH_2CH(CH_3)_2$	100	-27.3	R	26
IId	$CH_2C_6H_5$	97	5.1	S	5

a) 99.5% EtOH, c=2. b) pure ethyl mandelate $[\alpha]_D^{24}$ = -104°[11]



Almost quantitative yields based on isolated ethyl mandelate and enantio-differentiating reaction with high optical yield by L-alanine derivative(IIb) were observed. It is extremely interesting that R-configuration was predominantly obtained in the case of $R=CH_3$ (optical purity; 47%) and $R=CH_2CH(CH_3)_2$ (optical purity; 26%), on the other hand, in the case of $R=CH_2C_6H_5$(optical purity; 5%) S-configuration was given.

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(Received February 14, 1977)