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EXAMINATIONS ON THE NEIGHBORING ARYL GROUP PARTICIPATION IN NITROUS ACID DEAMINATIONS OF L-PHENYLALANINE AND ITS p-NITRO AND p-METHOXY DERIVATIVES. CONVERSION OF L-PHENYLALANINE TO NATURALLY OCCURRING S-TROPIC ACID

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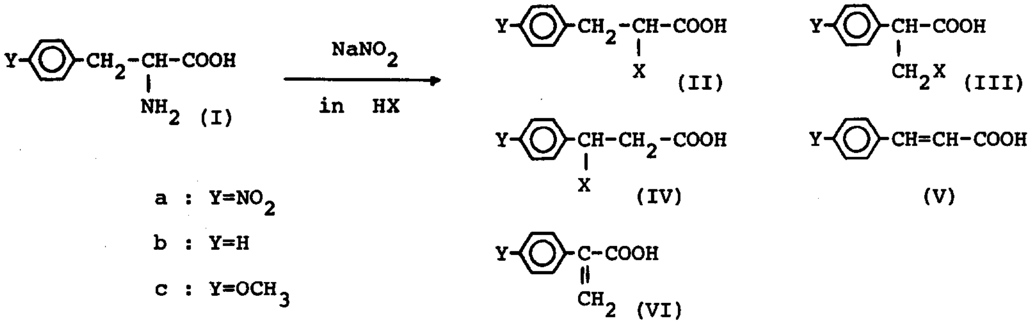
The reactions of nitrous acid or of nitrosyl halides on optically active α-amino acids having a hydrogen and having no aryl group on the asymmetric α-carbon atom are reported to give exclusively α-hydroxy or α-halo acids with retention of configuration, due to the participation of the neighboring carboxylate group.1) For example, nitrous acid deamination of phenylalanine in aqueous surfuric acid is known to produce α-hydroxy-β-phenylpropionic acid with high retention of configuration.2) Detailed examinations on nitrous acid deaminations of L-phenylalanine ethyl ester and its p-substituted derivatives, however, have shown that the reactions are highly dependent both on the solvent employed and on the substituent attached on the aromatic ring, due to the participation of the neighboring aryl group.3) It was examined, therefore, whether the pattern of the reaction (products and their stereochemical results) of nitrous acid on L-phenylalanine (Ib) and its p-substituted derivatives (Ia and Ic) might change with solvent (N-H_2SO_4, CH_3COOH, and CF_3COOH) and p-substituent (NO_2, H, and OCH_3) by nucleophilic competition between neighboring carboxylate group, neighboring aryl group, and the solvent on the cationic center.

The reactions were carried out as follows: To a solution of optically pure L-amino acids (Ia, Ib, or Ic) in N-H_2SO_4, CH_3COOH, or CF_3COOH were added 1.1 molar equivalents of sodium nitrite in portions within ca. 5 hours and the whole was allowed to stand at room temperature overnight. The determinations of the product ratios and their stereochemical consequences were made analogously to the previous paper3) and the results are shown in the Table.

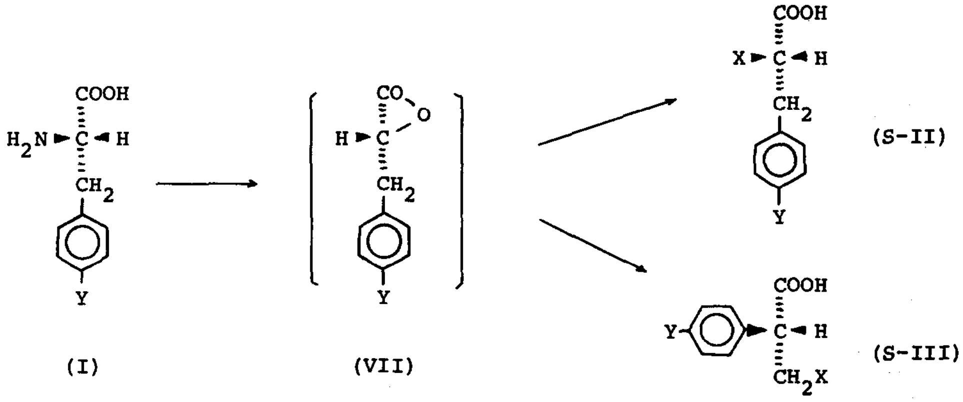


Starting Material Y	Solvent (HX) / Product	$N-H_2SO_4$ (X=OH) Yield (%)	$N-H_2SO_4$ (X=OH) Stereo-chemistry[3)]	CH_3COOH ($X=OCOCH_3$) Yield (%)	CH_3COOH ($X=OCOCH_3$) Stereo-chemistry[3)]	CF_3COOH ($X=OCOCF_3$) Yield (%)	CF_3COOH ($X=OCOCF_3$) Stereo-chemistry[3)]
NO_2 (Ia)[1)]	IIa	56	97 Ret	74	70 Ret	72	90 Ret
H[2)] (Ib)	IIb	78	91 Ret	81	84 Ret	25	65 Ret
	IIIb	2		<0.1		63	27 Ret
	IVb			<0.1		10	
	Vb	1				2	
OCH_3[2)] (Ic)	IIc	53	80 Ret	71	76 Ret	5	
	IIIc	31	93 Ret	14		78	60 Ret
	IVc			3			
	VIc					15	

1) Yields of products were determined by nmr. 2) Yields of products were determined by vpc. 3) Values represent optical purity in net. Inv=Inversion. Ret=Retention.

It has become apparent that considerable amounts of migration products are also produced in the deamination reaction, depending on the nature of the solvent employed and on the substituent attached on the aromatic ring. Thus, while aryl migration product is not observed in the deamination of p-nitro-L-phenylalanine (Ia) in solvents employed, aryl migration product becomes the main product in the deamination of p-methoxy-L-phenylalanine (Ic) in CF_3COOH. The ratio of aryl migration product seems to become larger in proportion to the increase in the nucleophilicity of the aryl group and also to the decrease in the nucleophilicity of the solvent employed. Moreover, it is particularly noteworthy that the stereochemical results of aryl migration products are retention of configuration in all cases examined, in contrast to inversion of configuration in nitrous acid deaminations of their corresponding amino acid ethyl esters.$^{3)}$

These results may be tentatively rationalized by the following mechanism. The first step of the reaction is the formation of the unstable intermediate (VII) with inversion of configuration by the backside attack of the neighboring carboxylate group.$^{1)}$ In cases where solvent of high nucleophilicity and aryl group of low nucleophilicity are employed, nucleophilic attack by solvent occurs from the backside of the oxygen of VII to give substitution product (S-II) of retained configuration. In cases where solvent of low nucleophilicity and aryl group of high nucleophilicity are employed, nucleophilic attack by aryl group occurs from the backside of the oxygen of VII to give aryl migration product (S-III) of retained configuration. It may be said from the Table that the latter case operates partially in the deaminations of L-phenylalanine in CF_3COOH, of p-methoxy-L-phenylalanine in N-H_2SO_4 and CH_3COOH, predominantly in the deamination of p-methoxy-L-phenylalanine in CF_3COOH.



It is well known that S-tropic acid (S-III, X=OH, Y=H), the acid moiety of the ester alkaloid hyoscyamine and scopolamine, is synthesized from L-phenylalanine in Datura species by migration of carboxyl group.[4] It now becomes possible to achieve this biosynthetic reaction chemically by migration of phenyl group, even though R-tropic acid is produced from L-phenylalanine ethyl ester.[3,5]

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