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# Stereochemical Studies. XV.[1] 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[2]

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Detailed examinations of nitrous acid deaminations of L-phenylalanine (VIb) and its *p*-nitro (VIa) and *p*-methoxy (VIc) derivatives in 1N sulfuric acid, acetic acid, and trifluoroacetic acid have shown that the reaction patterns (yields of products and their stereochemical results) differ considerably both with the solvent employed and with the substituent attached to the aromatic ring. These results were explained as due to effects of both the neighboring carboxylate group and the neighboring aryl group.

Successful conversion of L-phenylalanine to naturally occurring (*S*)-tropic acid ((*S*)-VIIIb X=OH) is also described by the application of the present results.

Studies on deamination of optically active α-amino acids and their derivatives are a matter of considerable interest,[4] mainly in relation to establishing methods for D-L interconversion of optically active α-amino acids. The reaction of nitrous acid or of nitrosyl halides on optically active α-amino acid (I) having a hydrogen and having no aryl group at the asymmetric α-carbon atom leads to the corresponding α-substituted acid (III) as the sole product with retention of configuration, while the reaction on its ester (IV) leads to the corresponding α-substituted ester (V) with inversion accompanied by much racemization.[4,5] The striking difference in the stereochemical cuorses of these reactions is attributed to a difference in the ability of the neighboring carboxylate group in the former and the neighboring alkoxycarbonyl group in the latter to participate. Thus, it has been proposed[4]

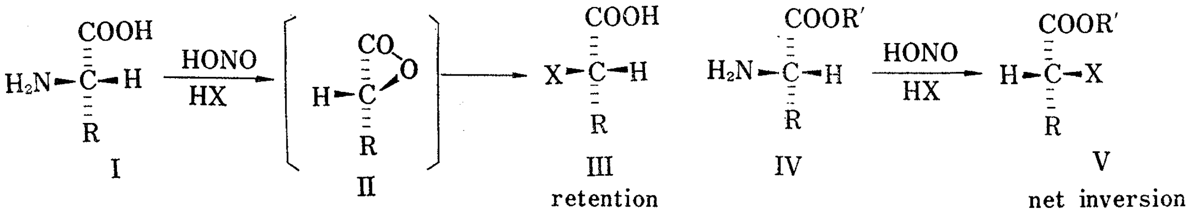

Chart 1

that deamination of α-amino acid (I) proceeds by the initial formation of an α-lactone intermediate (II) with inversion by intramolecular participation of the neighboring carboxylate group, followed by intermolecular attack of the solvent nucleophile from the backside of the oxygen of the α-lactone (II), resulting in the formation of the α-substituted product (III) with retention. In deamination of its ester (IV), participation by the alkoxycarbonyl group

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[1] Part XIV: K. Koga, C.C. Wu, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **20**, 1272 (1972).,

[2] A preliminary report has been published: K. Koga, C.C. Wu, and S. Yamada, *Tetrahedron Letters*, **1971**, 2287.

[3] Location: *Hongo, Bunkyo-ku, Tokyo.*

[4] *a*) A. Neuberger, "Advances in Protein Chemistry," Vol. 4, ed. by M.L. Anson and J.T. Edsall, Academic, Press, New York, 1948, pp. 327—338; *b*) N. Izumiya, *Bull. Chem. Soc. Japan*, **72**, 26 (1951).

[5] P. Brewster, F. Hiron, E.D. Hughes, C.K. Ingold, and P.A.D.S. Rao, *Nature*, **166**, 179 (1950).

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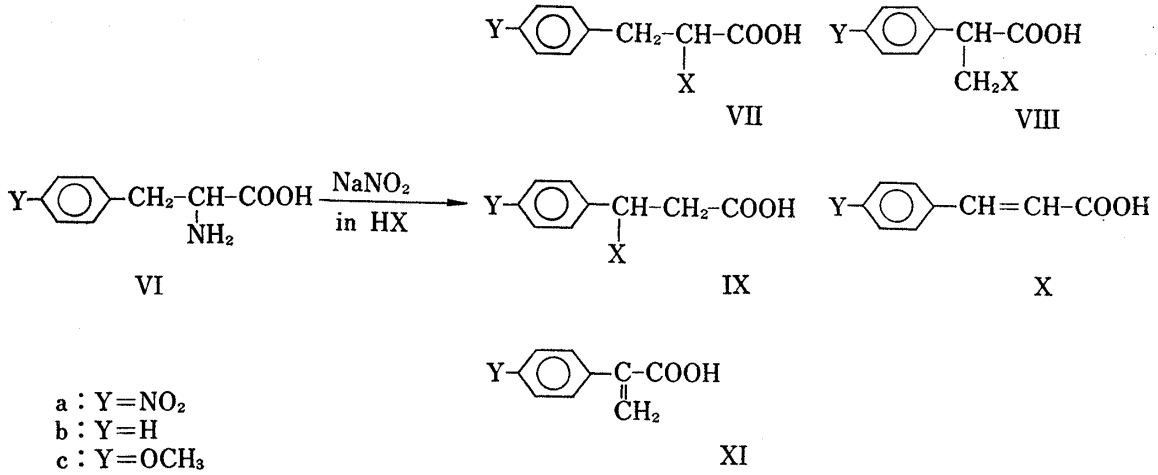
seems to be impossible, resulting in formation of α-substituted products (V) with inversion accompanied by much racemization.

Detailed examinations[1] of nitrous acid deaminations of L-phenylalanine ethyl ester and its *p*-nitro and *p*-methoxy derivatives, however, have shown that the reactions are highly dependent both on the solvent employed and on the substituent attached to the aromatic ring; due to differences in the degree of participation of the neighboring aryl group. We, therefore, examined whether the reaction patterns (yields of products and their stereochemical results) of nitrous acid on L-phenylalanine (VIb) and its *p*-nitro (VIa) and *p*-methoxy (VIc) derivatives might change with the solvent (1N sulfuric acid, acetic acid, and trifluoroacetic acid) and with the aryl group (*p*-nitrophenyl, phenyl, and *p*-methoxyphenyl) by nucleophilic competition between the neighboring carboxylate and aryl groups, and the solvent at the cationic center.



a : Y=$NO_2$
b : Y=H
c : Y=$OCH_3$

HX: 1N $H_2SO_4$, $CH_3COOH$, $CF_3COOH$

Chart 2

Deamination reactions, determinations of the products ratios, and analyses of their stereochemical consequences were carried out analogously to methods reported in a previous paper.[1] Results are shown in Table I.

Table I. Reaction Patterns of VIa, VIb, and VIc

| Starting material (Y) | Product | Solvent (HX)<br>1N $H_2SO_4$ ($X=OH$)<br>Yield (%) | Stereo-chemistry[a] | $CH_3COOH$ ($X=OCOCH_3$)<br>Yield (%) | Stereo-chemistry[a] | $CF_3COOH$ ($X=OCOCF_3$)<br>Yield (%) | Stereo-chemistry[a] |
|---|---|---|---|---|---|---|---|
| VIa ($NO_2$) | VIIa | 56 | 97 ret | 74 | 70 ret | 72 | 90 ret |
| VIb (H) | VIIb | 78 | 91 ret | 81 | 84 ret | 25 | 65 ret |
|  | VIIIb | 2 |  | <0.1 |  | 63 | 27 ret |
|  | IXb |  |  | <0.1 |  | 10 |  |
|  | Xb | 1 |  |  |  | 2 |  |
| VIc ($OCH_3$) | VIIc | 53 | 80 ret | 71 | 76 ret | 5 |  |
|  | VIIIc | 31 | 93 ret | 14 |  | 78 | 60 ret |
|  | IXc |  |  | 3 |  |  |  |
|  | XIc |  |  |  |  | 15 |  |

[a] Values represent optical purities in net. Inv=Inversion, ret=retention.

We clearly demonstrated that considerable amounts of migration products are produced in the present deamination reactions; depending on the solvent employed and on the substituent attached to the aromatic ring. Thus, while a migration product is absent in deaminations of VIa in the solvents used, the aryl migration product becomes the main product in deaminations of VIb and VIc in trifluoroacetic acid. It is particularly noteworthy that the stereochemical results of aryl migration products are net retention of configuration in all cases examined, in contrast to net inversion of configuration in deaminations of their corresponding esters under the same reaction conditions.[1]

Trifluoroacetic acid is a unique solvent due to its very low nucleophilicity, and its relatively high ionizing power; and, therefore, for its high ability to enhance neighboring group participation in solvolysis reactions.[6] The substituent at *p*-position of the aromatic ring is, however, remote from the reaction site, and is thought to have little steric effects, but rather to show considerable electronic effects in changing the nucleophilic character of the aryl group. Table I, shows that the ratio of the aryl migration product becomes larger in proportion; 1) to the increase in nucleophilicity of the aryl group and 2) to the decrease in nucleophilicity of the solvent.

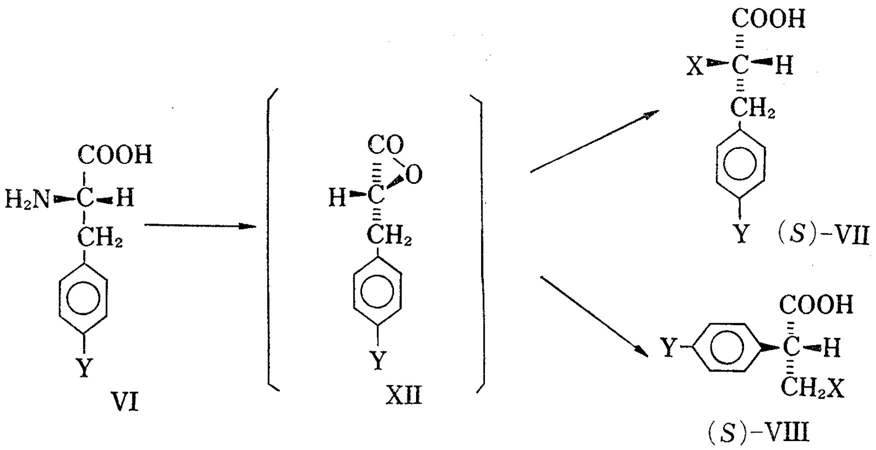


Chart 3

Based on results of a previous paper,[1] the data in Table I seem to be explainable by the following mechanism. The first step of the reaction is formation of the $\alpha$-lactone intermediate (XII) with inversion of configuration by the backside attack of the neighboring carboxylate group.[4] In cases where a solvent of high nucleophilicity and an aryl group of low nucleophilicity are employed, nucleophilic attack by the solvent occurs from the backside of the oxygen of XII, preferentially, to predominantly give substitution products ((*S*)-VII) of retained configuration. In cases where a solvent of low nucleophilicity and an aryl group of high nucleophilicity are employed, nucleophilic attack by the aryl group occurs from the backside of the oxygen of XII, preferentially, to predominantly give an aryl migration product ((*S*)-VIII) of retained configuration. From Table I we deduced that the latter case operates partially in deaminations of VIb in trifluoroacetic acid and of VIc in 1N sulfuric acid and acetic acid; and predominantly in deamination of VIc in trifluoroacetic acid.

(*S*)-Tropic acid ((*S*)-VIIIb, X=OH), the acid moiety of the ester alkaloid hyoscyamine and scopolamine, is known to be biosynthesized from L-phenylalanine (VIb) by migration of carboxyl group in *Datura* species.[7] (*R*)-Tropic acid is also synthesized chemically from

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[6] *a*) J.E. Nordlander and W.G. Deadman, *J. Am. Chem. Soc.*, **90**, 1590 (1968); *b*) I. Lazdins Reich, A. Diaz, and S. Winstein, *ibid.*, **91**, 5635 (1969).

[7] M.L. Louden and E. Leete, *J. Am. Chem. Soc.*, **84**, 4507 (1962).

L-phenylalanine ethyl ester by migration of a phenyl group *via* nitrous acid deamination in acetic acid.[8] It now becomes possible to synthesize (*S*)-tropic acid chemically from L-phenylalanine by migration of a phenyl group *via* nitrous acid deamination in trifluoroacetic acid.

## Experimental[9]

**Materials**——L-(*p*-Nitrophenyl)alanine of $[\alpha]^{25}_{\mathrm{D}}+8.9^\circ$ ($c=2.0$, 1 N HCl) (reported[10] $[\alpha]^{25}_{\mathrm{D}}+9.8^\circ$ ($c=1.77$, 1 N HCl)), L-phenylalanine of $[\alpha]_{\mathrm{D}}-31.6^\circ$ ($c=1.02$, $H_2O$) (reported[11] $[\alpha]_{\mathrm{D}}-33^\circ$ ($H_2O$)), and L-(*p*-methoxyphenyl)alanine of $[\alpha]^{23}_{\mathrm{D}}-5.5^\circ$ ($c=2.0$, 1 N HCl) (reported[12] $[\alpha]^{29}_{\mathrm{D}}-5.9^\circ$ ($c=2$, 1 N HCl)) were used in the present study. These amino acids are considered optically pure. Standard samples[1] used in stereochemical determinations are as follows. (*S*)-VIIa (X=OAc) of mp 50—51°, $[\alpha]^{20}_{\mathrm{D}}-9.26^\circ$ ($c=2.31$, 95% EtOH); (*S*)-VIIb (X=OAc) of bp 138° (4 mmHg), $\alpha^{23}_{\mathrm{D}}-0.825^\circ$ ($l=0.1$, neat), $[\alpha]^{25}_{\mathrm{D}}+15.6^\circ$ ($c=2.89$, EtOH); (*S*)-VIIc (X=OAc) of bp 131° (0.04 mmHg), $[\alpha]^{25}_{\mathrm{D}}-8.3^\circ$ ($c=1.052$, 95% EtOH), $[\alpha]^{29}_{450}-12.8^\circ$ ($c=1.052$, 95% EtOH): (*S*)-VIIIb (X=OAc) of bp 126° (3 mmHg), $\alpha^{23}_{\mathrm{D}}-6.185^\circ$ ($l=0.1$, neat); (*S*)-VIIIc (X=OAc) of bp 132° (0.03 mmHg), $[\alpha]^{25}_{\mathrm{D}}-35.5^\circ$ ($c=1.28$, 95% EtOH), $\alpha^{25}_{450}-101.6^\circ$ ($c=1.28$, 95% EtOH).

**General Procedure of Nitrous Acid Deamination**——1.1 Molar equivalents of $NaNO_2$ were added in portions over *ca.* 5 hr at room temperature to a stirred solution (suspension in the reaction of VIa in AcOH) of L-amino acid (VIa, VIb, or VIc) in ten-fold volume (thirty-five-fold volume in the reaction of VIa in AcOH, twenty-six-fold volume in the reaction of VIa in 1 N $H_2SO_4$, and twenty-fold volume in the reaction of VIb in AcOH) of 1 N $H_2SO_4$, AcOH, or $CF_3COOH$, then the whole was stirred at the same temperature overnight. When AcOH and $CF_3COOH$ were used, the solvent was evaporated *in vacuo* to dryness and the residue was mixed with $H_2O$. The aqueous mixture was extracted several times with AcOEt. The AcOEt extracts were washed with sat. *aq.* NaCl, then dried over anhyd. $Na_2SO_4$. Evaporation of the solvent gave a residue, which was treated with excess diazoethane in ether. A mixture of reaction products obtained by the usual work up was treated as reported previously[1] in determinations of product yields and of stereochemical results.

**Determination of Product Yields**——Determination of product yields was carried out as described previously.[1] Results are shown in Table I.

**Determination of Stereochemical Results**——Determination of stereochemical results was carried out as described previously.[1] The compounds separated were identified, with the corresponding authentic samples described above, by spectral comparisons. Data obtained on separated compounds are as follows.

i) The Reaction of VIa in 1 N $H_2SO_4$: VIIa (X=OAc): pale yellow solid of mp 46—49°, $[\alpha]^{20}_{\mathrm{D}}-9.0^\circ$ ($c=2.04$, 95% EtOH), corresponding to 97% net retention.

ii) The Reaction of VIa in AcOH: VIIa (X=OAc): pale yellow solid of mp 49—53.5°, $[\alpha]^{20}_{\mathrm{D}}-6.5^\circ$ ($c=2.40$, 95% EtOH), corresponding to 70% net retention.

iii) The Reaction of VIa in $CF_3COOH$: VIIa (X=OAc): pale yellow solid of mp 45—48.5°, $[\alpha]^{20}_{\mathrm{D}}-8.3^\circ$ ($c=2.176$, 95% EtOH), corresponding to 90% net retention.

iv) The Reaction of VIb in 1 N $H_2SO_4$: VIIb (X=OAc): colorless liquid of bp 137° (3 mmHg), $\alpha^{23}_{\mathrm{D}}-0.752^\circ$ ($l=0.1$, neat), corresponding to 91% net retention.

v) The Reaction of VIb in AcOH: VIIb (X=OAc): colorless liquid of bp 137° (3 mmHg), $\alpha^{23}_{\mathrm{D}}-0.692^\circ$ ($l=0.1$, neat), corresponding to 84% net retention.

vi) The Reaction of VIb in $CF_3COOH$: VIIb (X=OAc): colorless liquid of bp 137° (3 mmHg), $[\alpha]^{32}_{\mathrm{D}}-10.2^\circ$ ($c=1.0$, EtOH), corresponding to 65% net retention; VIIIb (X=OAc): colorless liquid of bp 137° (3 mmHg), $\alpha^{23}_{\mathrm{D}}-1.688$ ($l=0.1$, neat), corresponding to 27% net retention.

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8) *a*) S. Yamada, T. Kitagawa, and K. Achiwa, *Tetrahedron Letters*, **1967**, 3007; *b*) E. Leete, *ibid.*, **1968**, 5793.

9) All melting and boiling points are uncorrected. IR spectra were measured with a Koken DS-402G Spectrometer. NMR spectra were measured with a JNM 3H-60 Spectrometer operating at 60 MHz or with a JNM-PS-100 Spectrometer operating at 100 MHz using tetramethylsilane as an internal standard. Optical rotations were measured with a Yanaco OR-50 Automatic Polarimeter or with a JASCO ORD/UV-5 Spectrometer. Separations of compounds by GLC were carried out with a Perkin-Elmer F-21 Präparative Gaschromatograph equipped with columns containing 20% carbowax 20M on chromosorb WAW. Spectral measurements were carried out by members of the Central Analysis Room of this faculty.

10) R. Bergel and J.A. Stock, *J. Chem. Soc.*, **1954**, 2409.

11) J.P. Greenstein and M. Winitz, "Chemistry of Amino Acids," Vol. 3, John Wiley & Sons, Inc., New York, 1961, pp. 2172.

12) L.D. Behr and H.T. Clarke, *J. Am. Chem. Soc.*, **54**, 1630 (1932).

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vii) The Reaction of VIc in 1N $H_2SO_4$: VIIc (X=OAc): colorless liquid of bp 133° (0.03 mmHg), $[\alpha]^{25}_{D}$ −5.59° ($c$=2.184, 95% EtOH), $[\alpha]^{31}_{450}$ −10.2° ($c$=2.184, 95% EtOH), corresponding to 80% net retention; VIIIc (X=OAc): colorless liquid of bp 132° (0.03 mmHg), $[\alpha]^{25}_{D}$ −30.8° ($c$=1.722, 95% EtOH), $[\alpha]^{31}_{400}$ −94.1° ($c$=1.722, 95% EtOH), corresponding to 93% net retention.

viii) The Reaction of VIc in AcOH: VIIc (X=OAc): colorless liquid of bp 132° (0.03 mmHg), $[\alpha]^{25}_{D}$ −6.47° ($c$=2.38°, 95% EtOH), $[\alpha]^{31}_{450}$ −9.7° ($c$=2.38, 95% EtOH), corresponding to 76% net retention.

ix) The Reaction of VIc in $CF_3COOH$: VIIIc (X=OAc): colorless liquid of bp 133° (0.02 mmHg), $[\alpha]^{25}_{D}$ −18.6° ($c$=2.23, 95% EtOH), $[\alpha]^{31}_{400}$ −61.3° ($c$=2.23, 95% EtOH), corresponding to 60% net retention.

**Synthesis of (*S*)-Tropic Acid ((*S*)-VIIIb, X=OH) from L-Phenylalanine (VIb)**——$NaNO_2$ (3.04 g, 44 mmoles) was added in portions during 5 hr at room temperature to a stirred solution of VIb (6.60 g, 40 mmoles) in $CF_3COOH$ (66 ml) and stirring was continued overnight. Evaporation of the solvent left a reddish-brown oil, which was mixed with 10% aq. HCl (130 ml), then the whole was refluxed for 1 hr. The hot reaction mixture was filtered to remove insoluble oily materials, after which the cooled filtrate was extracted three times with AcOEt. AcOEt extracts were combined, washed with sat. aq. NaCl then dried over anhyd. $Na_2SO_4$. Evaporation of AcOEt left a pale brown oil, which solidified on trituration in the presence of ether. Recrystallizations, once from ether–hexane and twice from benzene, afforded (*S*)-VIII (1.6 g, 24.2% yield) as colorless leaflets of mp 116—119°. IR $\nu^{\text{THF}}_{\text{max}}$ $\text{cm}^{-1}$: 3440 (OH), 1740 (COOH), $[\alpha]^{20}_{D}$ −37.9° ($c$=1.687, $H_2O$), corresponding to 49.7% optical purity based on the authentic sample1) obtained by hydrolysis of scopolamine. NMR and IR(THF) spectra were superimposable on spectra of the authentic sample.

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