# Optically Active Silicon in 2-Siloxazolidones-5. An Asymmetric Synthesis[1]

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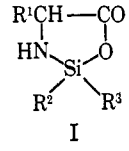
**Abstract:** A general synthesis of the new 2-siloxazolidone-5 ring system was found in the reaction of N-substituted amino acids with diamidosilanes. N-Phenylalanine, -valine, -$\beta$-phenylalanine, and -phenylglycine were allowed to react with bis(N-methylacetamido)methylphenylsilane giving nearly quantitative yields of diastereomeric pairs of siloxazolidones. The individual diastereomers were formed in unequal amounts as detected by nmr; crystallization was accompanied by a rearrangement of the less abundant into the predominant diastereomer, resulting in optical activity associated with silicon in those cases where the amino acid was optically active. Cleavage reactions of siloxazolidones with two different hydroxylic reagents in successive steps yielded the original amino acid and new silane derivatives in which silicon was retained in optically active form. Silanes of opposite configuration were obtained by identical cleavage reactions of siloxazolidones derived from (+)-(*R*)-N-phenylalanine and (+)-(*R*)-N-phenylvaline, respectively.

Condensation reactions of amino acids with reactive carbonyl compounds leading to oxazolidinediones or oxazolidones have been studied for many years. Well-known products of reactions of this kind are the N-carboxy amino acid anhydrides (Leuch's anhydrides), mainly of interest as intermediates for polypeptide synthesis, and more recently, the 2,2-bis(trifluoromethyl)-oxazolidones-5[2] which have been used for gas chromatographic analysis of amino acids as well as peptide synthesis.

It occurred to us that another class of five-membered cyclic derivatives of amino acids I containing a silane moiety in place of the carbonyl or bis(trifluoromethyl) function, respectively, should exhibit interesting stereochemical and reaction properties.



I

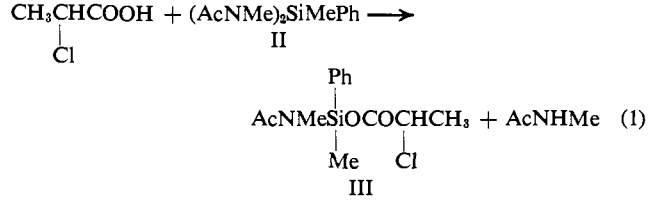
Since the preparation of N-trimethylsilyl amino acid trimethyl silyl esters from amino acids and trimethylsilyl halides,[3] -amines,[4] or -amides[5] is well known, a synthetic approach using corresponding difunctional silanes appeared promising. The silylamine and the silyl ester bond in 2-siloxazolidones-5 would be expected to be subject to displacement reactions, one with greater ease than the other, allowing successive reactions with two different reagents. In addition, a polymerization of the amino acid portion in a fashion similar to that of Leuch's anhydrides or the 2,2-bis(trifluoromethyl)oxazolidones-5[2] appeared possible. By proper choice of the substituents $R^2$ and $R^3$, the silicon could be made chiral, and the effect of an asymmetric carbon on the reactions of an asymmetric silicon could be studied.

(1) A preliminary account of this work has appeared: J. F. Klebe and H. Finkbeiner, *J. Am. Chem. Soc.*, **88**, 4740 (1966).
(2) F. Weygand, K. Burger, and K. Engelhardt, *Chem. Ber.*, **99**, 1461 (1966).
(3) J. Hils and K. Rühlmann, *ibid.*, **100**, 1638 (1967).
(4) K. Rühlmann, *ibid.*, **94**, 1876 (1961).
(5) J. F. Klebe, H. Finkbeiner, and D. M. White, *J. Am. Chem. Soc.*, **88**, 3390 (1964).

## Results and Discussion

**Synthesis.** Bis(N-methylacetamido)methylphenylsilane (II) was chosen as the difunctional silyl donor because of the high reactivity of silylamides toward proton-active compounds and the convenience of avoiding amine hydrochlorides as by-products associated with silyl chloride reactions. Equimolar mixtures of the diamidosilane and glycine, alanine, $\beta$-phenylalanine, sarcosine, and proline, respectively, in benzonitrile were stirred at 30–40° for several hours until clear solutions were obtained. The nmr spectra of the solutions showed in all cases that 2 equiv of N-methylacetamide had been formed, as expected; however, the numerous signals associated with the silicon–methyl and the amino acid protons indicated a multitude of products containing these two moieties.

Reactions of II with model compounds showed that the carboxyl group of, *e.g.*, 2-chloropropionic acid displaces N-methylacetamide and forms the amido silyl ester III in a clean reaction, whereas attempts to displace the amide group from III with aliphatic amines like benzylamine or ethyl glycinate led to a variety of products. However, reaction of III with aniline yielded the anilino silyl ester IV and N-methylacetamide as the only products. Consequently, N-phenyl-substituted amino acids were prepared and allowed to react with II and similar diamidosilanes. The reactions were found to proceed rapidly at room temperature in a variety of solvents, yielding 2-sila-3-phenyl-4-alkyl(aryl)-oxazolidones-5 (V) in generally nearly quantitative



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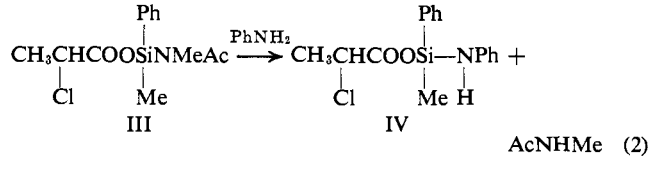

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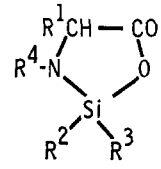
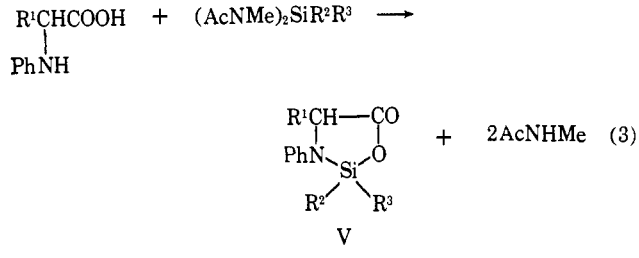
Table I. Siloxazolidones



| Compd | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Mp, °C | $[\alpha]^{25}D$, deg | $CH_3$—Si nmr shifts[a] ($\tau$) of diastereomers Stable | Unstable | Calcd, % C | H | N | Si | Found, % C | H | N | Si |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Va | H | $CH_3$ | $C_6H_5$ | $C_6H_5$ | 84–86 | | 9.53 | | 66.9 | 5.6 | 5.2 | | 66.7 | 5.7 | 5.2 | |
| Vb | $CH_3$ | $CH_3$ | $C_6H_5$ | $C_6H_5$ | 115–117 | | | | 67.8 | 6.1 | 5.0 | 9.9 | 67.7 | 6.1 | 5.0 | 9.9 |
| $Vb_1$ | $CH_3$ | $CH_3$ | $C_6H_5$ | $C_6H_5$ | 125–128 | −27.5[b] | 9.57 | 9.40 | 67.8 | 6.1 | 5.0 | 9.9 | 68.2 | 6.1 | 5.0 | 9.4 |
| $Vb_2$ | $CH_3$ | $CH_3$ | $C_6H_5$ | $C_6H_5$ | 129–132 | +27.7 | | | 67.8 | 6.1 | 5.0 | 9.9 | 67.6 | 6.3 | 5.2 | 9.7 |
| Vc | $C_6H_5CH_2$ | $CH_3$ | $C_6H_5$ | $C_6H_5$ | 128–130 | | 10.07 | 9.68 | 73.5 | 5.9 | 3.9 | 7.8 | 73.5 | 6.1 | 4.0 | 7.6 |
| Vd | $(CH_3)_2CH$ | $CH_3$ | $C_6H_5$ | $C_6H_5$ | 109–112 | | | | 69.5 | 6.8 | 4.5 | 9.0 | 69.0 | 7.0 | 4.3 | |
| $Vd_1$ | $(CH_3)_2CH$ | $CH_3$ | $C_6H_5$ | $C_6H_5$ | 120–125 | −37.9[c] | 9.31 | 9.62 | 69.5 | 6.8 | 4.5 | 9.0 | 69.1 | 6.9 | 4.2 | 8.9 |
| $Vd_2$ | $(CH_3)_2CH$ | $CH_3$ | $C_6H_5$ | $C_6H_5$ | 115–118 | +37.3 | | | 69.5 | 6.8 | 4.5 | 9.0 | 69.7 | 6.96 | 4.83 | 8.82 |
| Ve | $C_6H_5$ | $CH_3$ | $C_6H_5$ | $C_6H_5$ | 171–175 | | 9.30 | 9.45 | 73.0 | 5.5 | 4.1 | 8.1 | 73.3 | 5.6 | 3.8 | |
| Vf | $CH_3$ | $CH_3$ | $CH_3$ | $C_6H_5$ | 78–81 | | 9.36 | | 59.6 | 6.8 | 6.3 | 12.7 | 59.8 | 7.1 | 6.6 | 13.3 |
| | | | | | | | 9.52 | | | | | | | | | |
| Vg | $CH_3$ | $C_6H_5$ | $C_6H_5$ | $C_6H_5$ | 156–160 | | | | 73.0 | 5.5 | 4.1 | 8.1 | 73.1 | 5.8 | 4.2 | 8.7 |
| | | | | | | | 9.38 | | | | | | | | | |
| VIa | $CH_3$ | $CH_3$ | $C_6H_5$ | $CH_3$ | | | 9.39 | | 59.7 | 6.8 | 6.3 | 12.7 | 59.7 | 7.0 | 6.6 | 12.7 |
| VIb | $C_6H_5$ | $CH_3$ | $C_6H_5$ | $CH(CH_3)_2$ | 113–122[d] | | 9.08 | | 69.5 | 6.8 | 4.5 | 9.0 | 69.2 | 6.9 | 9.3 | 8.7 |
| | | | | | | | 9.19 | | | | | | | | | |

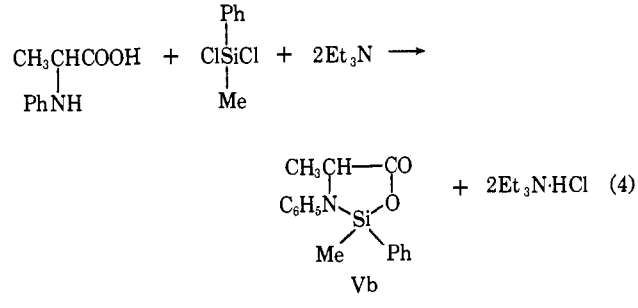
[a] Va–Ve, 15% in $C_6H_6$; Vf, VIa, VIb, 15% in $DCCl_3$. No stability differences were detected between diastereomers of Vf, Vg, VIa, and VIb. [b] From (+)-(*R*)-N-phenylalanine. Rotation of the unstable diastereomer of $Vb_1$: $[\alpha]^{25}D$ −96°. [c] From (+)-(*R*)-N-phenylvaline. Rotation of the unstable diastereomer of $Vd_1$: $[\alpha]^{25}D$ +28°. [d] Mixture of two diastereomers.

yield as determined by nmr (see Table I). Siloxazolidones were also formed with N-phenylalanine derivatives having substituents on the aromatic ring in the



3 or 4 position; however, 2,4-dinitro-N-phenylglycine and N-(2-nitrophenyl)valine formed only the open-chain analogs of III, presumably due to steric hindrance.

A single experiment was carried out with N-phenylalanine, methylphenyldichlorosilane, and an acid acceptor in order to demonstrate the accessibility of siloxazolidones by this route. Compound Vb was indeed



formed in good yield; however, the work-up requiring filtration from a voluminous precipitate of triethylamine hydrochloride resulted in an appreciable loss of the hydrolytically very sensitive product. Reaction 3, on the other hand, simply requires the vacuum distillation of N-methylacetamide which leaves essentially pure V as pot residue. This reaction is preferable as a synthetic method.

The silicon and the carbon in the 4 position of Vb–e are centers of asymmetry, and these compounds are thus formed as diastereomeric pairs. The individual diastereomers, which were present in unequal amounts in the product mixtures, could readily be distinguished by shift differences of protons of the amino acid moieties and particularly of the silicon–methyl signals in the nmr spectra. All those siloxazolidones having unsubstituted N-phenyl substituents crystallized upon removal of solvent and N-methylacetamide from the crude reaction mixtures.

The examination of the crystalline products by nmr showed that the initially predominant diastereomer was now exclusively present. In some cases, crystallization started before all solvent was removed, particularly if hexane was added to the mixture; the ratio of diastereomers in the mother liquors was found the same as in the original mixture before crystallization, showing that one of the diastereomers had disappeared upon crystallization. Further concentration of the mother liquors yielded more of the predominant diastereomer.

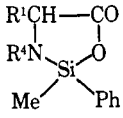
Evidently, a rearrangement of the less stable into the thermodynamically more stable diastereomer had taken place during the crystallization. Such a rearrangement can only take place by cleavage of either the Si–N or the Si–O bond, rotation, and ring closure with inversion of configuration of the silicon moiety. Figure 1 shows the pertinent parts of the nmr spectra of four siloxazolidones before and after the rearrangement.

In solution, the stable diastereomers reverted to equilibrium mixtures of the two forms; the equilibria in nonpolar solvents like benzene or chloroform were reached in periods ranging from 2 days to 3 weeks, depending on the substituent R. In solvents like acetone

or acetonitrile, or in the presence of traces of tertiary amines, the equilibria were established in less than 30 min.

A mixture of the two diastereomers of Vb in pure benzene yielded the same ratio of diastereomers in crystalline form when the solvent was removed. Addition of a small amount of N-methylacetamide to the same solution of diastereomers caused the "unstable" diastereomer to disappear upon crystallization. Apparently, N-methylacetamide is sufficiently basic to catalyze the diastereomer rearrangement, which explains the disappearance of the "unstable" diastereomers when the crude reaction mixtures crystallized.

Key to the siloxazolidone diastereomer rearrangement appears to be the phenyl group on nitrogen. The reaction of N-methylalanine with II afforded equal amounts of the two diastereomeric forms of VIa which could not be obtained crystalline and did not undergo rearrangement over a period of several months. The crystalline VIb, obtained from N-isopropylphenyl-



VIa, $R^1 = CH_3$; $R^4 = CH_3$
b, $R^1 = Ph$; $R^4 = CH(CH_3)_2$

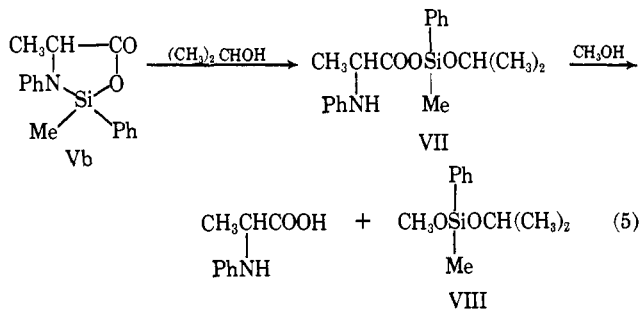
glycine and II, was formed as a diastereomeric mixture which could be enriched in one isomer by repeated recrystallizations; again, no diastereomer rearrangement was observed.[6]

Stuart–Briegleb models of the siloxazolidones V show considerable crowding of the substituents in the 2, 3, and 4 position; the stability differences between the members of any given pair of diastereomers are presumably due to steric reasons.

The experiments described above were initially conducted with racemic N-phenyl-substituted amino acids so that each diastereomer consisted of a pair of spectrally indistinguishable enantiomers. Subsequently, (+)-N-phenylalanine[7] and (+)-N-phenylvaline were prepared by resolution of their quinine salts. The siloxazolidones were synthesized therefrom and the specific optical rotations of the respective "stable" diastereomers measured. The reversion to diastereomer equilibrium mixtures was now accompanied by mutarotation; the specific rotations of the "unstable" diastereomers could be calculated from the optical rotations of the equilibrium mixtures and the relative amounts of the two diastereomers present (Table I).

**Reactions.** The diastereomer rearrangement of siloxazolidones prepared from optically active N-phenyl-substituted amino acids is equivalent to an asymmetric synthesis resulting in optically active silicon. It was of interest to learn if the optical activity associated with the difunctional silicon moiety could be retained in reactions performed on this center of asymmetry.

Silylamines and silyl esters undergo displacement reactions with alcohols and phenols under mild conditions. Of the two classes of compounds, the silylamines are considerably more reactive; carboxyl displaces amine from a silylamine very readily.[8] The reaction of Vb with isopropyl alcohol and methanol in consecutive steps produced the asymmetric silicon derivative VIII without difficulty (eq 5). Optically ac-



(5)

tive $Vb_1$ gave racemic VIII when the methanol addition was carried out approximately 1 hr after the formation of the isopropoxy silyl ester VII was complete.

The ring opening of $Vb_1$ with isopropyl alcohol was associated with a change of rotation from $[\alpha]^{25}D$ −27.5 to +32.8° within the first 15 min, a time found sufficient by nmr for essentially complete formation of VII. During the next 60 min, the rotation changed to +40° and remained unchanged thereafter. We assumed that the change of rotation after 15-min reaction time was mainly associated with racemization of VII; addition of methanol to VII 15 min after mixing isopropyl alcohol with Vb in benzene solution did indeed afford VIII with a weak specific rotation of $[\alpha]^{25}D$ +0.4°.

By using 1-naphthol instead of isopropyl alcohol, we obtained a system in which the ring-opening reaction as well as any racemization of the naphthoxy silyl ester IX could be monitored by nmr. Racemization of the silicon atom leads to diastereomers with a 3-cps shift difference of the $CH_3$–Si signals in the case of IX. By working in concentrated solutions with carefully purified starting materials, it was possible to carry the ring opening to over 90% conversion with less than 10%

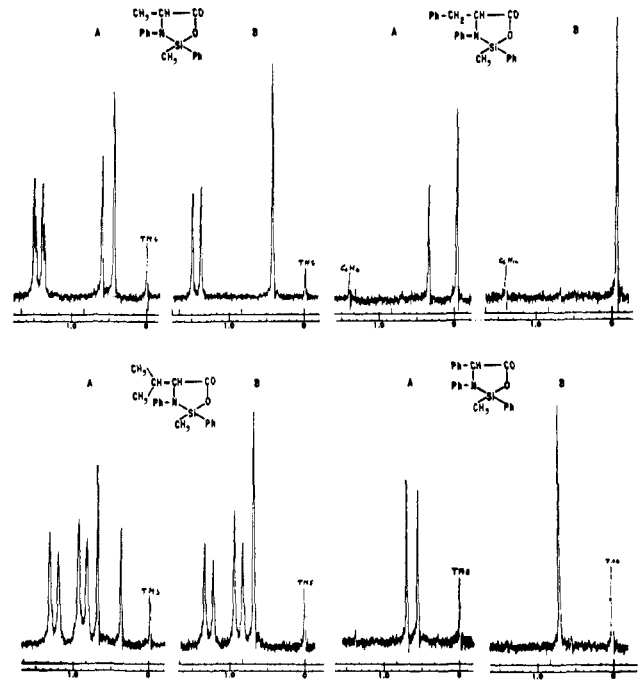


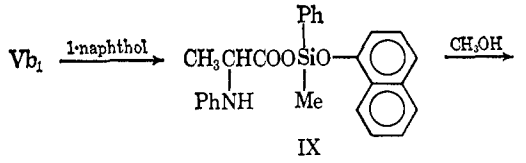
Figure 1. Nmr spectra of 2-siloxazolidones-5, 15% in benzene: A, mixture of diastereomers; B, stable diastereomer obtained by rearrangement during the crystallization.

(6) The only satisfactory solvent found for the preparation of VIa from II and N-methylalanine was pyridine; several unidentified products were formed in solvents such as benzene, chloroform, and benzonitrile. No difficulty arose in the analogous preparation of VIb in benzene.

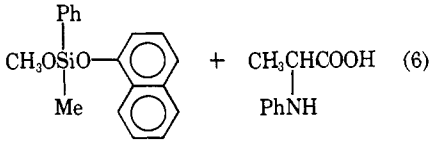
(7) P. S. Portoghese, *J. Med. Chem.*, **8**, 147 (1965).

(8) K. Rühlmann and J. Hils, *Ann. Chem.*, **683**, 211 (1965).

racemization. Addition of a threefold excess of methanol at this point afforded methoxynaphthoxymethylphenylsilane (X) with a specific rotation $[\alpha]^{25}D$ +21.9°.



IX

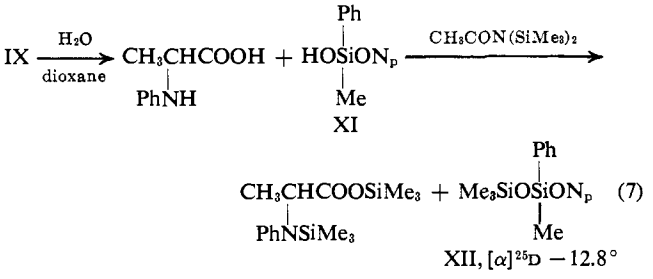


X, $[\alpha]^{25}D$ + 21.9

The analogous reaction with the siloxazolidone $Vd_1$, prepared from (+)-N-phenylvaline, yielded X with a weaker specific rotation of opposite sign, $[\alpha]^{25}D$ −4.9°. The significance of this result is discussed below.

The N-phenyl-substituted amino acids reclaimed from any of the displacement reactions on optically active siloxazolidones had retained their full original optical activity as could be expected since none of the reactions involved the asymmetric carbon.

The fairly fast racemization rates of silyl esters VII and IX limited the choice of the hydroxylic agent for the ester cleavage. The higher alcohols were found to be unsuitable; for instance, extensive racemization of IX occurred when ethanol was used for the cleavage since the reaction was rather slow. Water was found to displace N-phenylalanine from IX in a rapid reaction without appreciable racemization prior to the cleavage, provided the reaction was carried out in dioxane solution (a multitude of products was formed in several other solvents). However, dioxane as the reaction medium posed the problem that the formation of IX from $Vb_1$ with 1-naphthol (reaction 6) is slow in this solvent and racemization is appreciable before the reaction is complete. A further complication is that the silanol resulting from reaction of IX with water is chemically unstable, forming a number of condensation products within a period of several hours at room temperature. The reaction sequence 7 was finally carried out successfully by preparing IX in benzene, removing the solvent *in vacuo* at low temperature, cleaving the silyl ester bond with water in dioxane, and converting the reactive XI into the stable silyl ether XII, which was obtained in optically active form, $[\alpha]^{25}D$ −12.8°. The



XII, $[\alpha]^{25}D$ −12.8°

ring opening of $Vb_1$ with phenol, *o*- and *p*-cresol, *p*-methoxyphenol, *p*-nitrophenol, and methyldiphenylsilanol and the subsequent racemization of the resulting silyl esters were studied by measuring the change of optical rotation. The initial slopes of the curves, representing the ring opening, followed second-order kinetics. The racemization of the esters is acid and base catalyzed, and the rates appeared to be dependent on the concentration of the phenols. This was pronounced in the case of *p*-nitrophenol where the rate of racemization exceeded the rate of ring opening. The racemization is apparently subject to steric hindrance as shown by a retardation of the racemization of the *o*-cresoxysilyl ester by a factor of 3 as compared with the *para*-substituted or unsubstituted phenols.

The configurational instability of the open-chain silyl esters of the type VII and IX is almost certainly due to a lability of the Si–OCO bond; the aryloxyalkoxy- and aryloxysiloxysilanes X and XII did not show any sign of racemization over a period of weeks at room temperature. The same bond is likely to be responsible for the less pronounced configurational lability of the siloxazolidones.

Sommer and coworkers have extensively investigated the stereochemistry of optically active silyl esters with three hydrocarbon groups on silicon[9] and report no comparable configurational instability. Electron donation from oxygen or nitrogen could conceivably stabilize a positive charge on silicon; however, a mechanism of racemization involving the formation of a siliconium ion starting from tetrahedral silicon seems very unlikely. Pentacoordinated siliconium ions have been described by Corey and West;[10] Sommer suggests expanded-octet return for the racemization of optically active fluorosilane in the presence of methanol.[9] A related mechanism may be operative in the present case, but definite conclusions cannot be drawn from the available data.

**Configuration.** The optical rotatory dispersion curves of $Vb_1$ and $Vb_2$ (from (+)- and (−)-N-phenylalanine, respectively) and of $Vd_1$ and $Vd_2$ (from (+)- and (−)-N-phenylvaline, respectively) were recorded in chloroform solution, showing strong Cotton effects whose first extrema could be measured.[11] The curves of siloxazolidones derived from enantiomeric pairs of amino acids are virtual mirror images of each other, with troughs for $Vb_1$ and $Vd_1$ and peaks for $Vb_2$ and $Vd_2$ at about 300 mμ. The curves prove the expected structural relationship of the pairs Vb and Vd, showing that they are enantiomeric in all parts of the molecule contributing to the optical rotation.

The nmr spectra of the siloxazolidones V provide clues to the relative configuration of the two asymmetric centers. The shielded position at τ 10.07 of the $CH_3$–Si signal of the "stable" diastereomer of Vc stands out from the respective signals of the other siloxazolidones and suggests an interaction of the silylmethyl group with the benzyl group on the asymmetric carbon. Indeed, Stuart–Briegleb models of the two diastereomers of Vc show that the $CH_3$–Si group can readily assume a position over the center of the aromatic ring if these two groups are in *cis* configuration, which should produce strong shielding of the silylmethyl protons. No such interaction is possible in the other diastereomer with the silylmethyl and the benzyl group on opposite sides of the hetero ring which should thus be associated with the $CH_3$–Si signal at τ 9.68. Confirmation of this

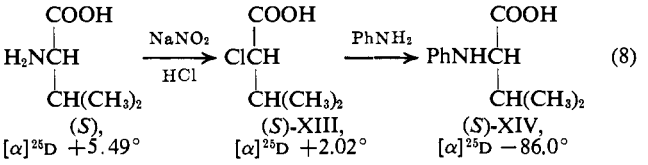
(9) L. H. Sommer, "Stereochemistry, Mechanism and Silicon," McGraw-Hill Book Co., Inc., New York, N. Y., 1965.
(10) J. Y. Corey and R. West, *J. Am. Chem. Soc.*, **85**, 4034 (1963).
(11) We are very grateful to Professor C. G. Overberger, University of Michigan, for the ORD measurements.

tentative conclusion must await X-ray crystallographic analysis; the connection with other siloxazolidones could then be made by reactions like 6 and 7 described above.

Figure 1 shows that on crystallization of the siloxazolidones Vb and Vc, prepared from N-phenylalanine and N-phenyl-$\beta$-phenylalanine respectively, the more upfield one of the original two $CH_3$–Si signals remains, whereas the thermodynamically more stable diastereomers of Vd and Ve, derived from N-phenylvaline and N-phenylphenylglycine, are associated with the respective downfield $CH_3$–Si signals. It appeared attractive to associate the relative position of the signals with the configuration of the silicon moiety. Identical displacement reactions with $Vb_1$ and $Vd_1$ indeed yielded silane X of opposite configuration (reaction 6). It remained to show that the precursors of $Vb_1$ and $Vd_1$, (+)-N-phenylalanine and (+)-N-phenylvaline, respectively, have the same configuration.

(+)-N-Phenylalanine has been shown to have the *R* configuration by Portoghese, who first resolved this compound.[7] We prepared (+)-N-phenylvaline by resolution of the quinine salts. Its enantiomer was obtained by reaction of aniline with $\alpha$-chloroisovaleric acid, which in turn was prepared from L-valine with $NaNO_2$–HCl in a manner similar to the preparation of optically active $\alpha$-chloropropionic acids described by Fu, *et al.*[12]

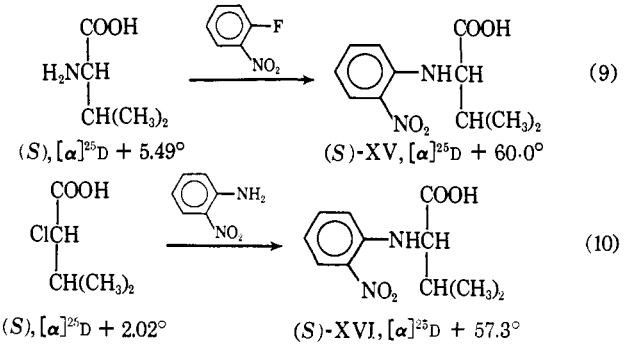
The conversion of amino acids into $\alpha$-chloro acids with $NaNO_2$–HCl is generally assumed to proceed with retention of configuration.[12,13] Reaction of the latter with amines normally proceeds with inversion of configuration; however, $\alpha$-haloisovaleric acids are an exception, yielding valine of the same configuration.[13] We assume that retention of configuration also pertains in reaction sequence 8, and this can be substantiated



(8)

with the following two reactions. L-Valine was treated with *o*-fluoronitrobenzene which yielded N-2-nitrophenylvaline with a + rotation. This product must have the same *S* configuration as the starting material since the asymmetric carbon was not involved in the reaction. The same product was then prepared by reaction of (*S*)-$\alpha$-chloroisovaleric acid with *o*-nitroaniline. Again, (+)-N-2-nitrophenylvaline was obtained, showing that the latter reaction had proceeded with retention of configuration.

We think that these experiments show beyond reasonable doubt that both (+)-N-phenylalanine and (+)-N-phenylvaline have the same *R* configuration. Provided that the displacement reactions shown in eq 6 proceed by the same mechanism with Vb and Vd, it follows that the silicon moieties have opposite configuration in the thermodynamically more stable diastereomers of these two siloxazolidones. This conclusion is in accord with the fact that the "stable" diastereomer of $Vb_1$ has a less negative specific rotation than the "unstable" one, whereas the opposite obtains for the two diastereomers of $Vd_1$ (Table I).



(9) (10)

We conclude that the relative position of the $CH_3$–Si nmr signals is indeed indicative of the configuration of the asymmetric silicon, at least in the case of the two siloxazolidones investigated, although the absolute configuration has not been determined. Moreover, the configuration of the silicon moiety appears to be determined by the steric requirements of the substituent on the $\alpha$-carbon of the amino acid. It is a new phenomenon in asymmetric synthesis, to our knowledge, that the size of a substituent on the existing asymmetric atom has a directing influence on the newly created center of asymmetry.

## Experimental Section

**Bis(N-methylacetamido)methylphenylsilane (II).** Methylphenyldichlorosilane, 192 g, was added dropwise to the mechanically stirred solution of 146 g of N-methylacetamide and 250 g of triethylamine in about 1 l. of dry benzene. Anhydrous conditions were maintained throughout the reaction. The mixture warmed up to near reflux temperature and triethylamine hydrochloride precipitated. Stirring was continued for 2 hr after the addition was complete. The salt was filtered off and the filtrate concentrated on a rotary evaporator. A pale yellow fluid remained which was mixed with about twice its volume of dry hexane and allowed to crystallize overnight in the refrigerator. A yield of 240 g of nearly colorless crystals was obtained, mp 66–68°, after recrystallization from benzene–hexane. *Anal.* Calcd for $C_{13}H_{20}N_2O_2Si$: C, 59.1; H, 7.6; N, 10.6; Si, 10.6. Found: C, 59.5; H, 7.8; N, 10.7; Si, 10.7.

**Bis(N-methylacetamido)dimethylsilane** was prepared in the same way as II; colorless liquid, bp 70–75° (0.05 mm). *Anal.* Calcd for $C_8H_{18}N_2O_2Si$: C, 47.5; H, 8.9; N, 13.8; Si, 13.9. Found: C, 47.8; H, 8.7; N, 13.9; Si, 14.2.

**2-(Methylphenylsila)-3-phenyl-4-methyloxazolidone.** The following procedure (a) is an example for the general preparation of siloxazolidones from N-phenyl-substituted amino acids. Analytical data and (uncorrected) melting points are shown in Table I. All solvents used for the preparation and recrystallization of siloxazolidones were dried by conventional means.

(a) A mixture of 8.2 g of N-phenylalanine and 13.2 g of bis(N-methylacetamido)methylphenylsilane in about 50 cc of benzene was stirred at room temperature under anhydrous conditions. (Other solvents like carbon tetrachloride, chloroform, pyridine, acetone, and benzonitrile could be used equally well.) A clear, light yellow solution was formed after a few minutes. An nmr spectrum taken about 20 min later indicated that the reaction was complete. Benzene and N-methylacetamide were removed *in vacuo*, the latter by heating at 70–80° (0.5 mm) for about 1 hr. The product crystallized during this procedure and was recrystallized from benzene–hexane, yield 13 g (92%).

(b) To a mixture of 3.3 g of N-phenylalanine, 10 g of triethylamine, and 22 cc of benzene was added dropwise with stirring under anhydrous conditions 3.8 g of methylphenyldichlorosilane. Triethylamine hydrochloride precipitated immediately in slightly exothermic reaction. Stirring was continued for 1 hr, the mixture then filtered under a blanket of dry nitrogen, the filter cake washed several small portions of dry hexane, and the filtrate concentrated. A light yellow liquid remained which crystallized on

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trituration with hexane. The product was identical by nmr with the material prepared by method a, yield 3.2 g (57%).

**2-(Methylphenylsila)-3-isopropyl-4-phenyloxazolidone.** α-Bromophenylacetic acid, 20 g, was heated at reflux with 20 g of isopropylamine in 50 cc of ethanol. The product was dissolved in water and neutralized with concentrated hydrochloric acid which furnished a white precipitate of N-isopropylphenylglycine. The nmr spectrum of the infusible compound in $CF_3COOH$ shows a doublet at $\tau$ 8.45, multiplets at $\tau$ 6.4 and 4.7, and an aromatic signal at $\tau$ 2.4 in the required ratio of 6:1:1:5.

A mixture of 1.93 g of N-isopropylphenylglycine and 2.64 g of bis(N-methylacetamido)methylphenylsilane in about 15 cc of pyridine was stirred under anhydrous conditions; after about 3 hr at 30° all of the amino acid was dissolved and a clear solution obtained. Solvent and N-methylacetamide were distilled off *in vacuo* at 60–80°, the remaining light tan syrup crystallized on trituration with hexane, mp 113–122° (mixture of diastereomers), yield 2.9 g (93%).

**2-(Methylphenylsila)-3,4-dimethyloxazolidone.** Stirring of 520 mg of N-methylalanine with 1.4 g of bis(N-methylacetamido)-methylphenylsilane in about 5 cc of anhydrous pyridine yielded a clear solution after 1 hr at 35°. Pyridine and N-methylacetamide were removed at 0.5-mm pressure at room temperature overnight. The remaining brown liquid was distilled in a microstill; a colorless fluid distilled at a bath temperature of 55–60° (0.1 mm). For the nmr spectrum, see Table I. The product did not crystallize.

**Methylphenylmethoxynaphthoxysilane (X) (from $Vb_1$).** 1-Naphthol, 2.70 g, was added to a solution of 5.59 g of $Vb_1$ in 15 cc of anhydrous benzene. The mixture was stirred magnetically under anhydrous conditions at 30° for 15 min. The solution was then kept in Dry Ice while an nmr spectrum of a sample was taken which showed the conversion to IX over 90% complete with less than 10% racemization. Methanol, 3.2 g, was added after thawing and the mixture stirred for 15 min at room temperature; N-phenylalanine precipitated during this period of time. The solvent and excess methanol were removed *in vacuo* and the residue extracted with several portions of dry hexane, totaling 30 cc. Removal of hexane left a colorless oil which was distilled, bp 130–136° (0.5 mm), $[\alpha]^{25}D$ +21.9° (9% in benzene). *Anal.* Calcd for $C_{18}H_{18}O_2Si$: C, 73.45; H, 6.16; Si, 9.45. Found: C, 73.21; H, 6.08; Si, 9.75.

**Methylphenylmethoxynaphthoxysilane (X) from $Vd_1$.** A mixture of 1.29 of $Vd_1$ and 570 mg of 1-naphthol in 2.0 g of dry benzene was stirred at 30° for 25 min. Nmr indicated nearly complete reaction after this time; about 20% of the resulting silyl ester had racemized. The solution was divided into two equal portions, each containing about 2 mmol of the silyl ester, and to one (A) was added 320 mg of methanol (10 mmol), to the other (B), 2.0 g of methanol (62 mmol). Nmr indicated complete reaction after 15 min; both solutions were concentrated in a stream of nitrogen, and X was extracted with dry hexane; N-phenylvaline was left as residue. The extracts were distilled after removal of the solvent at 150° bath temperature (0.1-mm pressure). The distillates were identical with X from the previous experiment as determined by vpc and nmr. Experiment A gave $[\alpha]^{25}D$ −2.5° (15% in $C_6H_5$); B gave $[\alpha]^{25}D$ −4.9° (20% in $C_6H_5$).

**Tetramethylphenylnaphthoxydisiloxane (XII).** To a solution of 3.11 g of $Vb_1$ in 6 g of dry benzene was added 1.50 g of 1-naphthol (6% molar deficiency); the mixture was stirred until a clear solution was obtained (about 5 min) and then concentrated in a stream of dry nitrogen. The reaction was essentially complete after 35 min, as shown by nmr. The concentrated silyl ester IX was chilled in a Dry Ice bath and 5.5 g of dioxane containing 216 mg of water (10% excess) was added and the mixture stirred magnetically at 30° for 30 min. Nmr showed after this time that all silyl ester was consumed; essentially one new Me–Si signal was present attributed to the silanol XI. Bis(trimethylsilyl)acetamide, 5.1 g, was now added and allowed to stand at room temperature for several hours. N-Trimethylsilylacetamide was removed at 40° (0.1 mm) overnight. Ethanol, 3 cc, was added in order to hydrolyze the silylated N-phenylalanine, volatile material removed *in vacuo* at room temperature, and XII extracted with hexane. Distillation afforded XII, bp 122–130° (0.1 mm); $[\alpha]^{25}D$ −12.8° (12% in $C_6H_5$). *Anal.* Calcd for $C_{20}H_{24}O_2Si_2$: C, 68.20; H, 6.86; Si, 15.95. Found: C, 68.44; H, 6.86; Si, 15.91.

**N-Phenylvaline.** A solution of 2-bromoisovaleric acid (0.166 *m*) in 35 ml of methanol was titrated at 0° to the phenolphthalein end point with methanolic sodium hydroxide. The solvent was then removed, aniline (100 g) added, and the mixture heated on a steam bath for 2 hr. After adding 100 ml of 0.1 *N* sodium hydroxide, the aniline was removed by extraction with ether, and the aqueous phase was acidified to a pH of 4. The precipitated solid was filtered off and recrystallized from aqueous ethanol, yield 15.8 g, mp 129–131.5° (lit.[14] 125°). *Anal.* Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25; mol wt, 193. Found: C, 67.0; H, 7.5; N, 7.2; mol wt, 199.

**N-Phenylphenylglycine.** α-Bromophenylacetic acid (50 g) was dissolved in 200 ml of aniline and 100 ml of methanol. The solution was stirred overnight at room temperature, then the precipitated product was removed and the product, after recrystallization from methanol, had a melting point of 178–179° (lit.[15] 174–175°). The infrared and nmr spectra were in agreement with the assigned structure. *Anal.* Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16; mol wt, 227. Found: C, 73.4; H, 5.5; N, 6.0; mol wt, 220.

**1,3-Diphenylhydantoin.** A solution of potassium hydroxide (68 g) and N-phenylglycine (151 g) was vigorously stirred as phenyl isocyanate (132 g) was added over a 1-hr period. The reaction was carried out in a nitrogen atmosphere to minimize the oxidation of the N-phenylglycine. After stirring for 16 hr at room temperature, the reaction mixture was filtered to remove the N,N′-diphenylurea, and the filtrate was acidified with hydrochloric acid. The gummy precipitate was refluxed with a mixture of ethanol (100 ml), water (100 ml), and concentrated hydrochloric acid (200 ml) for 2 hr. On cooling, the crystallized product was removed and dissolved in benzene and the benzene extracted several times with 5% sodium hydroxide to remove any unreacted N-phenylglycine and the highly colored oxidation products. After drying over magnesium sulfate, the benzene was removed under vacuum and the product recrystallized from acetone, yield 100.8 g; mp 136.5–137.5° (lit.[16] 135°). *Anal.* Calcd for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.80; N, 11.11. Found: C, 71.1; H, 4.0; N, 11.0.

**N-Phenyl-β-phenylalanine.** A solution of 1,3-diphenylhydantoin (0.1 mol) in 100 ml of 2 *M* magnesium methylcarbonate[17] was heated at 100° for 2 hr. Benzyl chloride (0.1 mol) was added and the heating continued for 4 hr. The reaction mixture was poured into 200 g of ice and 40 ml of hydrochloric acid. After the ice had melted, the product was extracted with ether and dried, and on evaporating the ether, a thick oil was obtained. This oil was added to a solution of 16 g of sodium hydroxide in 50 ml of water and stirred overnight at room temperature. The sodium hydroxide was heated to 80° and enough ethanol added to obtain a homogeneous solution. Refluxing was continued for 24 hr, and the solution was cooled to room temperature, extracted with ethyl acetate, and acidified to a pH of 4. The precipitated solid was recrystallized from methanol–water, mp 165–167° (lit.[14] 165°). *Anal.* Calcd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81; mol wt, 241. Found: C, 76.3; H, 6.5; N, 5.8; mol wt, 248.

**(+)-N-Phenylvaline.** A solution of 9.1 g of racemic N-phenylvaline in 35 cc of warm methanol was mixed with the warm solution of 15.3 g of quinine in 5 cc of methanol and 220 cc of acetone. Fine white needles began to form soon after the solution had cooled to room temperature. The crystals were filtered off after about 5 hr and decomposed by shaking with 20 cc of 1 *N* NaOH solution and 20 cc of chloroform. The aqueous layer was extracted twice with chloroform and then acidified with concentrated hydrochloric acid (pH 4). The precipitate of N-phenylvaline was washed with water and dried; 2.2 g was obtained, $[\alpha]^{25}D$ +67.0° (3.5% in EtOH). The procedure was repeated by combining the 2.2 g of N-phenylvaline in 7 cc of $CH_3OH$ with the solution of 3.7 g of quinine in 3 cc of $CH_3OH$ and 55 cc of acetone. The salt was filtered after standing overnight at room temperature and decomposed to give 1.32 g of N-phenylvaline, $[\alpha]^{25}D$ +83.8° (4.3% in EtOH). The highest rotation obtained for this compound by repetitions of this procedure was +86.0°.

**(−)-N-Phenylvaline (XIV).** A solution of 19.5 g of L-valine ($[\alpha]^{25}D$ 5.49° (2.5% in $H_2O$)) in 210 cc of 6 *N* HCl was cooled to 0° and finely powdered $NaNO_2$, 19 g, was added in small portions to the stirred solution within a period of 3 hr while keeping the temperature at 0–5°. The solution was then extracted with ether and the ether extract dried with $CaCl_2$ and distilled. A yield of 15 g of α-chloroisovaleric acid (XIII) was obtained, bp 53–55° (0.1 mm), $[\alpha]^{25}D$ +2.12° (8.7% in EtOH). Sodium α-chloroisovalerate was prepared by dissolving 7.8 g of XIII in 10 cc of methanol and titrat-

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ing the solution at −15° with 1 *N* methanolic NaOH solution (phenolphthalein). The salt was recovered by evaporation of the solvent and vacuum drying overnight at 60°. The finely powdered salt, 3.5 g, was heated with 60 cc of aniline in an oil bath at 100–105° for 5 hr. After cooling, 10 cc of 1 *N* NaOH solution was added and excess aniline extracted three times with ether. The aqueous phase was acidified with concentrated HCl to pH 4. Crystals mixed with oil separated; the oil was found to be unreacted XIII. The crystals were filtered off and recrystallized from EtOH–water. A yield of 310 mg of colorless crystalline XIV was obtained, $[\alpha]^{25}D$ −86.0° (1.2% in EtOH).

**N-2-Nitrophenylvaline (XV).** 2-Fluoronitrobenzene, 10 g, was suspended in a solution of 5 g of L-valine and 10 g of $NaHCO_3$ in 200 cc of EtOH and 100 cc of water and the mixture heated at reflux for about 3 hr. The solution was filtered, excess 2-fluoronitrobenzene extracted with ether, and the filtrate acidified with concentrated HCl. A dark yellow oil was obtained which was extracted with ether. The ether solution was dried and the solvent evaporated. The product crystallized on standing at room temperature for several hours, mp 85°, $[\alpha]^{25}D$ +60.0° (2.5% in EtOH). *Anal.* Calcd for $C_{11}H_{14}N_2O_4$: C, 55.5; H, 5.9; N, 11.8. Found: C, 55.4; H, 6.0; N, 11.7.

**N-2-Nitrophenylvaline (XVI).** A mixture of 0.5 g of XIII and 4 g of 2-nitroaniline was heated in an oil bath at 100–105° for 1 hr. A clear, red solution was obtained after this time. After cooling 6 cc of 1 *N* NaOH solution was added and excess 2-nitroaniline extracted three times with ether. Concentrated HCl was added until the initially dark yellow solution was nearly colorless and a yellow oil separated. The oil was extracted with ether, the ether solution dried, and the solvent evaporated. The yellow oily residue was trimethylsilylated with bis(trimethylsilyl)acetamide and was found to be a mixture of XVI and unreacted XIII as determined by vpc (comparison with authentic samples). The more volatile silylated XIII was removed by heating at 40–50° (0.1 mm) for 30 min. At a bath temperature of 80°, a yellow liquid distilled which was identical with silylated XV by vpc. The product was hydrolyzed with EtOH; concentration gave crystalline XVI, $[\alpha]^{25}D$ +57.3 (1.2% in EtOH).

# The Mechanism of Reaction of Benzylboronic Esters with Mercuric Chloride, a Concerted Electrophilic Displacement[1a]

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**Abstract:** The kinetics of the reaction of benzylboronic esters with mercuric chloride have been followed by a titration method involving complexing of the remaining mercuric chloride with EDTA. In aqueous ethanol in the presence of glycerol, sodium acetate, sodium chloride, and acetic acid, the rate law appears to be $-d[HgCl_2]/dt = k[RB(OR)_2][HgCl_2][OH^-]$. We have also prepared benzylboronic esters with *p*-$CH_3$, *p*-Cl, and *m*-$CF_3$ substituents. A Hammett correlation of the four rates yielded $\rho \cong +0.93$. If the relative acidities of the boronic esters are taken into account so that reactions of their hydroxide complexes with mercuric chloride are correlated, $\rho$ becomes $\sim -0.5$. These results are consistent with a concerted electrophilic displacement mechanism.

Electrophilic displacements of boron from saturated carbon by mercury have convenient characteristics for mechanistic studies. We have found previously that the transannular displacement of boron from norborneneboronic acids by mercuric chloride proceeds with preferential inversion of the configuration of the carbon from which the boron departs[2] and we have studied the mechanism.[3] Direct displacement of boron from 1-phenylethaneboronic acid by mercuric chloride proceeds with retention.[4] Attempts to study the mechanism of this reaction yielded disappointing results, due to the inaccuracy of the analytical method and the instability of the product, 1-phenylethylmercuric chloride.[5]

In the present work we have obtained much more accurate kinetics by the use of the simpler benzylboronic acids and an improved analytical technique. The effects of substituents in the benzene ring have provided information about the electron density at the benzyl carbon in the transition state.

$$ArCH_2B(OH)_2 + HgCl_2 \xrightarrow[\text{glycerol}]{OAc^-} ArCH_2HgCl + B(OH)_3$$

## Results

Our analytical method was based on the fact that mercuric chloride forms a strong complex with ethylenediaminetetraacetic acid (EDTA), but benzylmercuric chloride does not. We were thus able to follow the concentration of unconsumed mercuric chloride by a simple titration method.[6]

The reaction conditions were those which had evolved from earlier experience with related reactions.[3,5] The solvent consisted of 8% water, 4% glycerol, and the remainder ethanol, and the solution was buffered with sodium acetate and acetic acid. Sodium chloride was included to prevent ionization of the mercuric chloride, which would lead to more complicated kinetics. The reactions were run under nitrogen, and the butyl ester of the boronic acid was injected into the reaction flask through a rubber septum, as described previously.[3] Samples were withdrawn at intervals by means of a hypodermic needle and were added to a solution of EDTA, which stops the reaction immediately, and then titrated.

(1) (a) Supported by National Science Foundation Grant GP 6069. (b) Alfred P. Sloan Foundation Research Fellow, 1966–1968.
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