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Novel Synthesis of *cis*-3,5-Disubstituted Morpholine Derivatives

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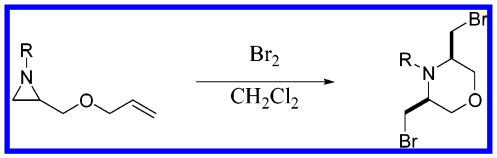

1-*tert*-Butyl-2-(allyloxymethyl)aziridine has been transformed for the first time diastereoselectively into *cis*-3,5-di(bromomethyl)-4-*tert*-butylmorpholine via an electrophile-induced ring closure using bromine in dichloromethane. The latter morpholine has been used as a substrate for the synthesis of the corresponding 3,5-di(methoxymethyl)morpholine and 3,5-di(cyanomethyl)morpholine upon nucleophilic displacement of both bromo atoms. Further evaluation of this protocol toward the synthesis of 4-arylmethyl- and 4-alkylmethyl-3,5-di(bromomethyl)morpholines showed that the premised cyclization of the corresponding 2-(allyloxymethyl)aziridines into 3,5-di(bromomethyl)morpholines only proceeded well for the *N*-neopentylmorpholine, which was subsequently transformed into a 3-oxa-7-thia-9-azabicyclo-[3.3.1]nonane derivative. Also, in some other cases, the desired 3,5-di(bromomethyl)morpholines were isolated in low yields and transformed into the corresponding 3,5-di(cyanomethyl)morpholines.

Introduction

Although morpholines are frequently used in organic synthesis as bases or as *N*-alkylating agents, less attention has been devoted to the development of novel carbon-substituted morpholine derivatives. However, the latter class of compounds has gained much interest in recent years as a result of the pronounced biological activities ascribed to many representatives and their use as chiral reagents in asymmetric synthesis, which explains the current increase in new methods for the synthesis of *C*-substituted morpholines.[1−7] The applications of biologically relevant carbon-substituted morpholines vary from medicinal use to agricultural use.[8] For example, reboxetine **1** is an antidepressant drug used in the treatment of clinical depression, panic disorder, attention deficit disorder, and attention deficit hyperactivity disorder,[9] and fenpropimorph **2** is a widely used leaf fungicide whose major use is to control fungal diseases in cereals (Figure 1).[10] Furthermore, the growing importance of asymmetric synthesis has led to the development of several *trans*-disubstituted morpholines as a novel class of C_2-symmetric auxiliaries.[1,11]

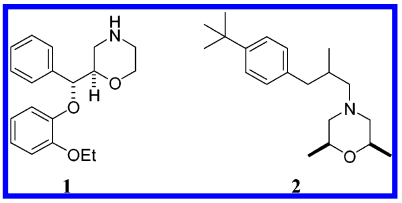

FIGURE 1. Biologically relevant morpholines reboxetine **1** and fenpropimorph **2**.

In the past decade, the interest of the pharmaceutical industry in *cis*-3,5-disubstituted morpholine derivatives as biologically active compounds and as substrates for further elaboration has increased significantly, and a large number of patents describing such compounds have been published since then.[12] However, synthetic approaches toward this type of morpholines in the conventional literature are scarce and usually long (several steps) and rather cumbrous or starting from commercially available morpholine.[11a,13] In almost all cases, the morpholine synthesis is based on the cyclization of an acyclic precursor. In the present report, a new and diastereoselective approach toward *cis*-3,5-

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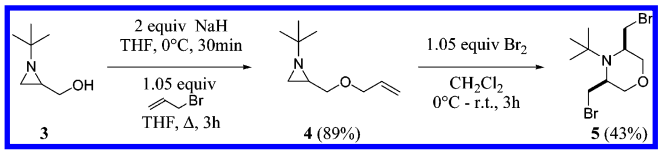
SCHEME 1



disubstituted morpholine derivatives is disclosed based on a ring enlargement of a 2-(allyloxymethyl)aziridine via an electrophile-induced ring closure.

Results and Discussion

1-(*tert*-Butyl)-2-(hydroxymethyl)aziridine **3**, prepared from methyl acrylate and *tert*-butylamine according to the procedure of Deyrup and Moyer,[14] was converted into the corresponding 2-(allyloxymethyl)aziridine **4** in excellent yield by means of a Williamson ether synthesis, using 2 equiv of sodium hydride and 1.05 equiv of allylbromide in THF (Scheme 1). In this way, a versatile substrate **4** was prepared in high yield, suitable for various transformations in organic synthesis due to the high reactivity of the constrained aziridine ring. The presence of a double bond in the ϵ,φ-position with respect to the nitrogen atom allows intramolecular reactions upon activation of this alkene moiety. Activation of the double bond in compound **4** by the addition of 1.05 equiv of bromine in CH_2Cl_2 afforded 3,5-di(bromomethyl)-4-*tert*-butylmorpholine **5** as one stereoisomer in good yield (88% crude yield), which was purified by means of column chromatography on silica gel (Scheme 1). This ring transformation proceeds through an electrophile-induced formation of the intermediate bicyclic aziridinium salt **7**, followed by regioselective ring opening of the aziridinium moiety by bromide at the unsubstituted aziridine carbon atom (Scheme 2).

No conclusive information regarding the relative stereochemistry of this 3,5-disubstituted morpholine could be obtained from spectroscopic analysis, although some data pointed in the direction of a *cis*-relationship. For all *trans*-2,6- and *trans*-3,5-disubstituted morpholines reported in the literature, the difference in δ-value, $\Delta\delta$ (^{1}H NMR), between the axial and the equatorial protons of the unsubstituted, morpholine carbon atoms is small (always < 0.33 ppm),[15,11c] whereas for *N*-tosyl-*cis*-3,5-diphenylmorpholine a very large $\Delta\delta$ (1.61 ppm) value has been reported.[15] In the case of 3,5-di(bromomethyl)morpholine **5**, a large $\Delta\delta$ of 0.91 ppm was observed for C*H*$_2$O, which could indicate a *cis*-stereochemistry of the substituents resulting in a considerable difference in shielding between the axial and equatorial protons on the carbon next to the oxygen atom (Figure 2).

To obtain conclusive evidence for the relative stereochemistry in morpholine **5**, an X-ray analysis of these colorless crystals was performed, confirming the anticipated chairlike conformation of the morpholine ring with the two bromomethyl substituents in a cisoid relationship (see Supporting Information). In fact, two rotamers were observed in the asymmetric unit, with only a rotational difference in the orientation of the *tert*-butyl

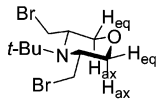


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FIGURE 2. Relative stereochemistry of morpholine **5**.

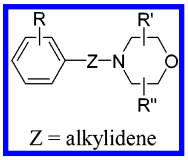


FIGURE 3. General structure of morpholines with fungicidal activity.

substituent of 11.7(2)°. This relative *cis*-stereochemistry can be explained considering an equatorial orientation of both the bromomethyl substituent and the aziridinium ring in the intermediate **7** (Scheme 2).

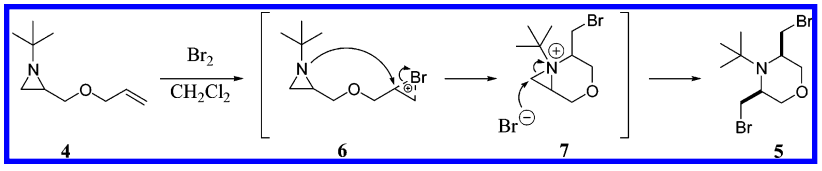
Only one analogous compound has been reported in the literature, that is, 3,5-di(chloromethyl)-4-(4-fluorobenzyl)morpholine, which was used for the synthesis of a bridged piperazine derivative useful against inflammatory diseases.[16] However, this compound was obtained as a 1/1 mixture of cis/trans isomers, although only the cis isomer was desired and used toward the 3-oxa-7,9-diazabicyclo[3.3.1]nonane scaffold.[17] The present methodology offers a suitable alternative for the preparation of such compounds, because *cis*-dibromoamine **5** is obtained diastereoselectively in good yield.

The presence of two bromomethyl groups in morpholine **5** offers prospects for the synthesis of a large variety of *cis*-3,5-disubstituted morpholine derivatives, because the halogenated carbon atoms might undergo substitution reactions by different types of nucleophiles. The treatment of morpholine **5** with 3 equiv of sodium methoxide in methanol (2 N) afforded the novel corresponding 3,5-di(methoxymethyl)morpholine **8** in 92% yield after reflux for 2 h (Scheme 3), and the reaction of the same substrate **5** with 3 equiv of potassium cyanide in DMSO furnished β-amino nitrile **9** in 77% yield after heating at 60 °C for 3 h (Scheme 3). Di(cyanomethyl)morpholines such as **9** can be considered as precursors for the synthesis of the corresponding β-amino acid derivatives with potential use in peptide chemistry.[18] Their monosubstituted counterparts, 3-(alkoxycarbonyl)morpholines, and the enzymatic resolution of these substrates toward the corresponding β-amino acids have been reported previously, pointing to the importance of this type of compounds.[19]

On the basis of the well-known fungicidal activity of morpholines with a general structure as depicted in Figure 3,[8] and to evaluate the scope of the above-described ring transformation, a synthesis of different novel *N*-arylmethyl-3,5-di(bromomethyl)morpholines and *N*-alkylmethyl-3,5-di(bromomethyl)morpholines was elaborated.

Thus, a variety of different 1-(arylmethyl)- and 1-(alkylmethyl)-2-(allyloxymethyl)aziridines **11** were prepared in excellent yield starting from the corresponding 2-(bromomethyl)-

SCHEME 2



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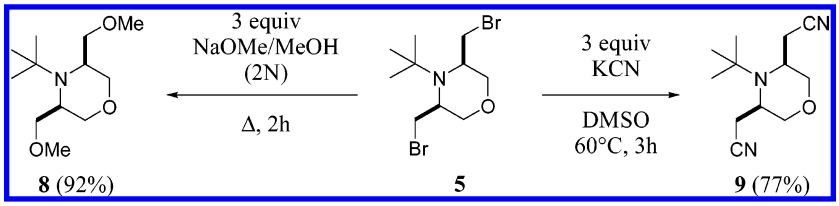
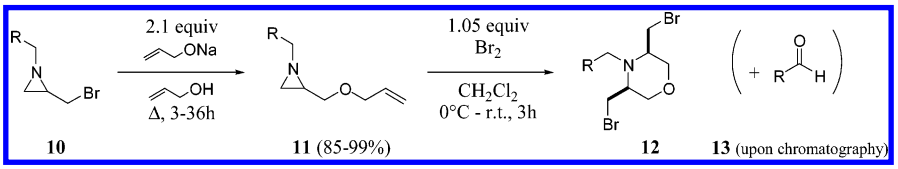


SCHEME 4



aziridines **10**[20] upon treatment with 2.1 equiv of sodium allyloxide in allyl alcohol and reflux for 12−36 h (Scheme 4). This methodology offers an efficient and straightforward approach toward a versatile class of novel substrates **11** suitable for different transformations in organic synthesis, as different methods for ring-opening reactions of aziridines are available. The treatment of these aziridines **11** with 1.05 equiv of bromine in CH_2Cl_2 toward the synthesis of morpholines **12** did not proceed as smoothly as it did for 4-*tert*-butylmorpholine **5** (Scheme 1), and rather complex reaction mixtures were obtained, although, based on ^{1}H NMR and GC-MS, the premised morpholines **12a**−**h** were present in these reaction mixtures (30−40% for morpholines **12a**−**e** and 40−87% for morpholines **12f**−**g**). Only in the case of the *N*-neopentyl derivative **11g**, the corresponding 3,5-di(bromomethyl)morpholine **12g** was obtained as the major compound (87%) and could be purified by means of column chromatography on silica gel. The major bottleneck appeared to be the purification and isolation of these reactive *β*-bromo amines **12** because they decomposed partially upon column chromatography, and the corresponding aldehydes **13** were isolated in high quantities (65−90% for the benzaldehydes **13a**−**e** and 76% for cyclohexanecarboxaldehyde **13f**), without the detection of other degradation products. Only for R = *tert*-Bu (entry 7, Table 1), the corresponding *N*-neopentyl morpholine **12g** was obtained in a good yield (40% after chromatography).

Small quantities of morpholines **12d** and **12g** could be isolated in pure form and in a sufficient amount to be used for further elaboration. Treatment of these compounds with 3 equiv of KCN in DMSO afforded the corresponding 3,5-di(cyanomethyl)-morpholines **14d** and **14g** after heating at 60 °C for 3 h in good yields (Scheme 5).

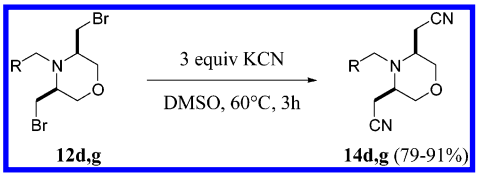
The *cis*-relationship of both bromomethyl groups in morpholines **12** enables the synthesis of bridged bicyclic compounds such as the 3-oxa-7-thia-9-azabicyclo[3.3.1]nonane scaffold. The

TABLE 1. Synthesis of 2-(Allyloxymethyl)aziridines 11 and Morpholines 12

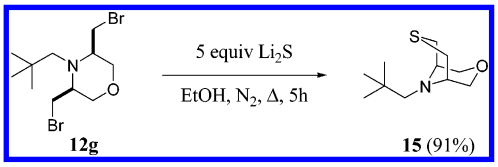
entry	starting compound	R	compounds **11** (% yield)	compounds **12** (% yield)[a]
1	**10a**	Ph	**11a** (90)	**12a** (1%)
2	**10b**	2-ClC_6H_4	**11b** (88)	**12b** (0)
3	**10c**	4-$MeOC_6H_4$	**11c** (93)	**12c** (0)
4	**10d**	4-BrC_6H_4	**11d** (85)	**12d** (6)
5	**10e**	4-MeC_6H_4	**11e** (90)	**12e** (1%)
6	**10f**	C_6H_{11}	**11f** (99)	**12f** (0)
7	**10g**	*t*-Bu	**11g** (89)	**12g** (40)

[a] Isolated yields after column chromatography.

SCHEME 5



SCHEME 6



treatment of morpholine **12g** with 5 equiv of Li_2S in EtOH under a nitrogen atmosphere afforded 9-(2,2-dimethylpropyl)-3-oxa-7-thia-9-azabicyclo[3.3.1]nonane **15** in excellent yield after reflux for 5 h (Scheme 6). This bridged morpholine **15** represents a hitherto novel class of heterobicyclic compounds.

In conclusion, the diastereoselective ring expansion of 1-*tert*-butyl-2-(allyloxymethyl)aziridine into pseudo C_2-symmetric *cis*-3,5-di(bromomethyl)-4-*tert*-butylmorpholine via an electrophile-induced ring closure has been described for the first time as an elegant approach toward *cis*-3,5-disubstituted morpholine derivatives. Furthermore, some 4-arylmethyl- and 4-alkylmethyl-3,5-di(bromomethyl)morpholines have been synthesized, although the yields were mostly low, and a novel heterocyclic scaffold has been described, that is, a 3-oxa-7-thia-9-azabicyclo-[3.3.1]nonane derivative.

Experimental Section

1-*tert*-Butyl-2-(allyloxymethyl)aziridine 4. To an ice-cooled solution of 1-*tert*-butyl-2-(hydroxymethyl)aziridine **3**[14] (0.2 g, 1.6

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mmol) in THF (5 mL) was added NaH (0.09 g, 2 equiv, 60% dispersion in oil), and the resulting suspension was stirred for 30 min at room temperature. Subsequently, allyl bromide (0.20 g, 1.05 equiv) was added at 0 °C, followed by reflux for 3 h. Extraction with water (10 mL) and Et_2O (3 × 10 mL), drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent in vacuo afforded 1-*tert*-butyl-2-(allyloxymethyl)aziridine **4**, which was filtered through a pad of silica (hexane/EtOAc, 5/4) to obtain an analytically pure sample. Yield 89% of light-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.99 (9H, s); 1.41 (1H, d, J = 3.3 Hz); 1.58 (1H, d, J = 6.3 Hz); 1.83−1.93 (1H, m); 3.35 and 3.43 (2H, 2 × d × d, J = 10.2, 6.1, 5.8 Hz); 3.96−4.08 (2H, m); 5.15−5.32 (2H, m); 5.86−5.98 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.2, 26.5, 31.0, 52.7, 72.0, 73.4, 116.8, 134.9. IR (NaCl, cm^{-1}): ν_{max} 3044, 2968, 2928, 2857, 1647, 1363, 1099. MS (70 eV, %): *m*/*z* 170 (M^+ + 1, 100). Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.28. Found: C, 71.13; H, 11.45; N, 8.10. R_f = 0.27, hexane/EtOAc, 5/4.

***cis*-3,5-Di(bromomethyl)-4-*tert*-butylmorpholine 5.** To an ice-cooled solution of 1-*tert*-butyl-2-(allyloxymethyl)aziridine **4** (0.17 g, 1 mmol) in CH_2Cl_2 (5 mL), was added dropwise bromine (0.17 g, 1.05 equiv) in CH_2Cl_2 (2.5 mL), and the resulting solution was stirred for 3 h at room temperature. Evaporation of the solvent afforded 3,5-di(bromomethyl)-4-*tert*-butylmorpholine **5**, which was purified by means of column chromatography on silica gel (hexane/EtOAc 9/1). Yield 88% (crude), 43% (after column chromatography) of colorless crystals, mp 58.4−59.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 (9H, s); 3.10−3.18 (4H, m); 3.29−3.33 (2H, m); 3.45−3.53 (2H, m); 4.22 (2H, d, J = 11.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.9, 35.7, 51.3, 56.2, 66.7. IR (NaCl, cm^{-1}): ν_{max} 2970, 1462, 1368, 1204, 1141, 1043, 899. HRMS calcd for $C_{10}H_{19}Br_2NO$, 326.9828/328.9807/330.9787; found, 326.9830/328.9808/330.9790 (M^+, 100). Anal. Calcd for $C_{10}H_{19}Br_2NO$: C, 36.50; H, 5.82; N, 4.26. Found: C, 36.66; H, 5.94; N, 4.18. R_f = 0.36, hexane/EtOAc, 9/1.

4-*tert*-Butyl-3,5-di(methoxymethyl)morpholine 8. To 3,5-di(bromomethyl)-4-*tert*-butylmorpholine **5** (0.1 g, 0.3 mmol) was added NaOMe (0.45 mL, 3 equiv, 2 N in MeOH), and the mixture was heated at reflux for 2 h. Extraction with water (5 mL) and CH_2Cl_2 (3 × 5 mL), drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent in vacuo afforded 4-*tert*-Butyl-3,5-di(methoxymethyl)morpholine **8**, which was purified by flash chromatography on silica gel (hexane/EtOAc, 9/1). Yield 92% of colorless crystals, mp 34.4−35.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (9H, s); 2.91−2.98, 3.06−3.10 and 3.28−3.45 (2H, 2H and 4H); 3.34 (6H, s); 3.94 (2H, d, J = 11.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.8, 48.6, 55.9, 58.8, 67.1, 75.6. IR (NaCl, cm^{-1}): ν_{max} 2974, 2925, 2893, 2853, 1460, 1117, 1097. MS (70 eV, %): *m*/*z* 231 (M^+, 1); 216 (10); 186 (84); 130 (100); 98 (37); 68 (24); 57 (17). Anal. Calcd for $C_{12}H_{25}NO_3$: C, 62.30; H, 10.89; N, 6.05. Found: C, 62.49; H, 11.03; N, 5.88. R_f = 0.08, hexane/EtOAc, 9/1.

4-*tert*-Butyl-3,5-di(cyanomethyl)morpholine 9. To a solution of 3,5-di(bromomethyl)-4-*tert*-butylmorpholine **5** (0.1 g, 0.3 mmol) in DMSO (2 mL) was added KCN (0.06 g, 3 equiv), and the mixture was heated at 60 °C for 3 h. Extraction with water (5 mL) and Et_2O (3 × 5 mL), washing of the organic extracts with brine (2 × 5 mL), drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent in vacuo afforded 4-*tert*-Butyl-3,5-di(cyanomethyl)-morpholine **9**, which was purified by flash chromatography on silica gel (hexane/EtOAc, 5/4). Yield 77% of colorless crystals, mp 92.2−92.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (9H, s); 2.62 and 2.67 (4H, 2 × d × d, J = 16.7, 8.3, 7.4 Hz); 3.40−3.50 (4H, m); 3.84 (2H, d, J = 11.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.8, 28.9, 47.0, 56.6, 68.7, 118.4. IR (NaCl, cm^{-1}): ν_{CN} 2254. MS (70 eV, %): *m*/*z* 221 (M^+, 6); 206 (45); 181 (23); 165 (7); 125 (100); 84 (37); 57 (38). Anal. Calcd for $C_{12}H_{19}N_3O$: C, 65.13; H, 8.65; N, 18.99. Found: C, 65.34; H, 8.83; N, 18.84. R_f = 0.34, hexane/EtOAc, 5/4.

9-(2,2-Dimethylpropyl)-3-oxa-7-thia-9-azabicyclo[3.3.1]nonane 15. To a solution of lithium sulfide (80 mg, 1.75 mmol, 5 equiv) in absolute EtOH (60 mL) was added via a syringe a solution of 4-(2,2-dimethylpropyl)-3,5-di(bromomethyl)morpholine **12g** (120 mg, 0,35 mmol) in EtOH (20 mL) under nitrogen atmosphere. The resulting mixture was heated under reflux for 5 h. Extraction with water (80 mL) and Et_2O (3 × 40 mL), drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent in vacuo afforded 9-(2,2-dimethylpropyl)-3-oxa-7-thia-9-azabicyclo[3.3.1]nonane **15**, which was filtered through a pad of silica gel to obtain an analytically pure sample (hexane/EtOAc, 2/3) after crystallization from EtOH. Yield 91% of colorless crystals, mp 42.6−43.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84 (9H, s); 2.17−2.31 (2H, m); 2.38 (2H, s); 2.66 (2H, br s); 3.41 (2H, d × d × d, J = 13.3, 3.7, 2.2 Hz); 3.91−3.95 and 4.04−4.10 (4H, 2 × m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.2, 29.4, 34.0, 53.0, 65.5, 69.3. IR (NaCl, in $CDCl_3$, cm^{-1}): ν_{max} 2951, 2924, 2853, 1479, 1459, 1359, 1180, 1089, 965. MS (70 eV, %): *m*/*z* 215 (M^+; 9); 200 (4); 158 (100); 128 (3); 112 (5); 73 (5); 56 (4). Anal. Calcd for $C_{11}H_{21}NOS$: C, 61.35; H, 9.83; N, 6.50. Found: C, 61.54; H, 9.97; N, 6.41.

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Supporting Information Available: General information and all spectroscopic data of compounds **10f**,**g**, **11a**−**g**, **12a**,**d**,**e**,**g**, and **14d**,**g**. Crystallographic data of compound **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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