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Ring Size Preference in the Intramolecular Cyclisation of Amines with Esters. Synthesis of Aminoacid Derived Hexahydropyrimidines and Tetrahydroimidazoles

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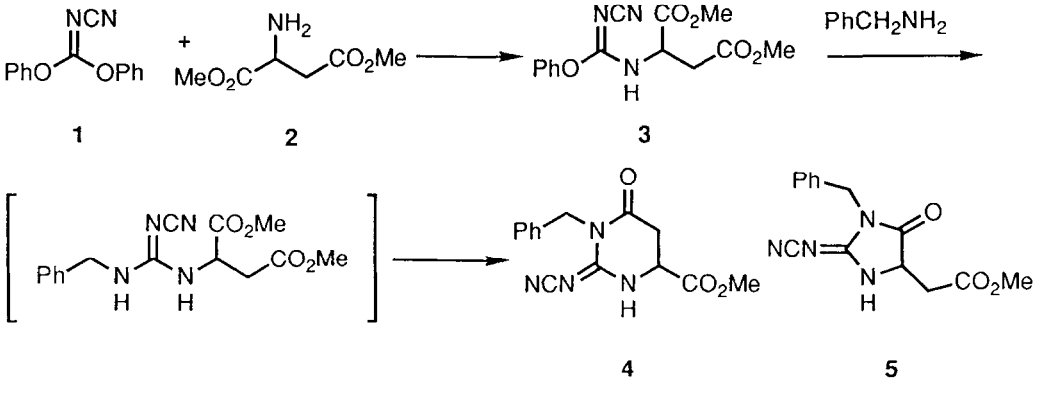
Abstract. In the sequential addition of β-aminoesters and amines to diphenyl cyanocarbonimidate it has been shown that, if there is a choice, the intramolecular cyclisation of the amine to the esters gives a 5-membered rather than a 6-membered diazaheterocycle. ^{13}C NMR and IR spectroscopic assignments were made in cases in which the ring size was unequivocal and these assignments were then used to determine the size of the ring in cyclisations in which rings of either size could be formed. A previous structural assignment has been revised on the basis of this spectroscopic analysis. A number of the newly prepared tetrahydroimidazoles and hexahydropyrimidines are conceptually derived from dipeptides.

We have recently reported that sequential nucleophilic addition to diphenyl cyanocarbonimidate (**1**), first demonstrated by Webb and co-workers,[1] can be adapted to allow subsequent reaction between the functional groups on the nucleophiles such that cyclisation to hydropyrimidines and hydroquinazolines occurs.[2] A problem arose in the case where dimethyl (R)-aspartate was one of the nucleophiles since cyclisation was then possible at either ester group, leading respectively to a five or a six membered heterocycle. The compound so obtained was converted to a derivative of orotic acid, a pyrimidine, and applying 'Ockham's Razor',[3] we assigned a 6-membered ring structure to the original product. We were aware, however, that the interconversion of 5- to 6-membered rings occurred readily in this area [4] and considered it essential, before proceeding further with the attempted development of the synthesis to prepare chiral derivatives, to establish definitively the ring size at initial closure. Spectroscopic differentiation between the 5- and 6-membered ring compounds was not possible with the amount of information available and we

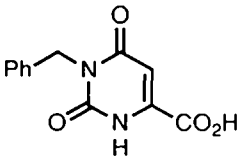
therefore prepared compounds of known ring size and compared the properties of these with those of compounds prepared by reactions that could lead to two possible products. Characteristic spectroscopic values can now be assigned to functional groups and ring atoms in the two ring sizes and thus we are able to elucidate the structures of new systems. The problems that remain are largely concerned with the effect of substituents on these assigned spectral values.

Results and Discussion

The reaction of compound (**1**) with dimethyl (R)-aspartate (**2**) followed by benzylamine gave a cyclic product that was either (**4**) or (**5**).[2] The 6-membered ring structure was eventually preferred because the product could be converted in a series of transformations to the known 3-N-benzylorotic acid (**6**), although it was realised that interconversion between a 5- and a 6-membered ring could readily have occured during these procedures. The need to define the regiospecificity of this ring closure became more urgent with the observation that the precursors of (**6**) were not optically active, the chiral centre having racemised in the process of ring formation.[5] Since we had hoped to develop this synthetic route as a means of preparing chiral hexahydropyrimidines, this would clearly founder if racemisation occurred on cyclisation. Racemisation, however, appeared much more likely in the process leading to 5-membered ring closure and we therefore decided to prepare a series of compounds with unequivocal structures, hoping that spectral differences might be sufficient to enable us to probe those reactions in which ring size would be equivocal.



1 **2** **3** **4** **5**



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A number of compounds were accordingly prepared in which the constitution of the product was unequivocal. Compound (**1**) was treated with glycine methyl ester (**7**) in propan-2-ol to give (**8**) in 70% yield. Compound (**8**) was then treated with the hydrochloride of (**7**) in propan-2-ol containing slightly more than one equivalent of triethylamine to give the tetrahydroimidazole (**9**), a dipeptide derivative, in 31% yield. The analytical results were in accord with the assigned structure and the ^{1}H NMR, ^{13}C NMR and IR spectroscopic data are given in Tables 1, 2 and 3, respectively. Compound (**1**) was treated similarly, first with β-alanine methyl ester (**10**) to give (**11**) and then with the hydrochloride of (**10**) to give the analogous β-alanine dipeptide derivative (**12**) in 45% yield as the hexahydropyrimidine. The analytical data was in accord with the assigned structure and the spectroscopic data are shown in the tables. Both (**9**) and (**12**) have unequivocal ring sizes and a number of other compounds with unequivocal structures were also synthesised. Compound (**13**) was prepared by the reaction of the isourea (**8**) with benzylamine, as previously described.[2] No details of this preparation have been reported and these are provided in the experimental part. Compound (**16**) was prepared in 29% yield by treatment of (**14**) with isourea (**15**) in boiling propan-2-ol. Compound (**17**) was prepared as described previously.[2]

With a number of compounds of certain structure now available, attention was turned to compounds in which the direction of ring closure was equivocal. The previously described β-alanine derivative (**11**) was treated with the hydrochloride of glycine (**7**) to give a crystalline product in 30% yield. This glycine-β-alanine dipeptide derivative could have the 5-membered ring structure (**18a**) or the 6-membered ring structure (**18b**). The analytical results were in accord with the molecular formulae of these isomers and the spectroscopic data are shown in the tables. The same product could be obtained from treatment of (**8**) with the hydrochloride of (**10**), but only in 18% yield.

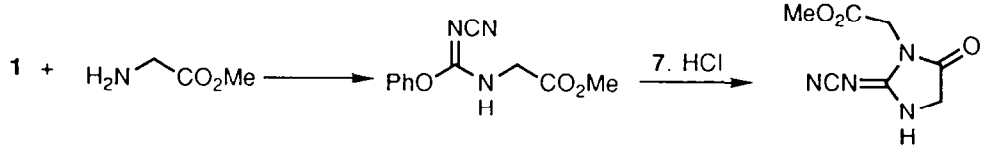

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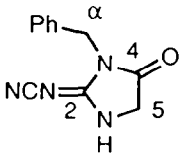
Table 1. ^{1}H NMR Spectra of Tetrahydroimidazoles and Hexahydropyrimidines.[a]

Compound	H-5 δ	H-6 δ	H-α δ	H-β δ	Other δ
9	4.27 (4.29)			4.27 (4.29)	3.69 (Me)
13	4.22		4.60		7.27-7.34 (Ph)
16	4.45		4.51	3.25, 3.16	7.00-7.27 (Ph)
12	2.68	3.36	3.91		3.59 (Me), 2.51 ($C\underline{H}_2CO_2Me$)
17	2.80	3.45	4.90		7.25 (Ph)
18	4.11		3.65		3.60 (Me), 2.60 ($C\underline{H}_2CO_2Me$) 9.73 (NH)
5	4.44		4.70	3.02, 2.79	7.30-7.41 (Ph)

a Spectra taken in DMSO-d_6



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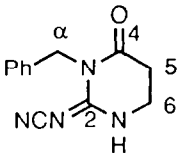

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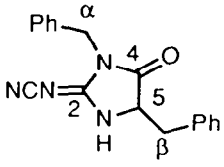


16

Table 2. ^{13}C NMR Spectra of Tetrahydroimidazoles and Hexahydropyrimidines.[a]

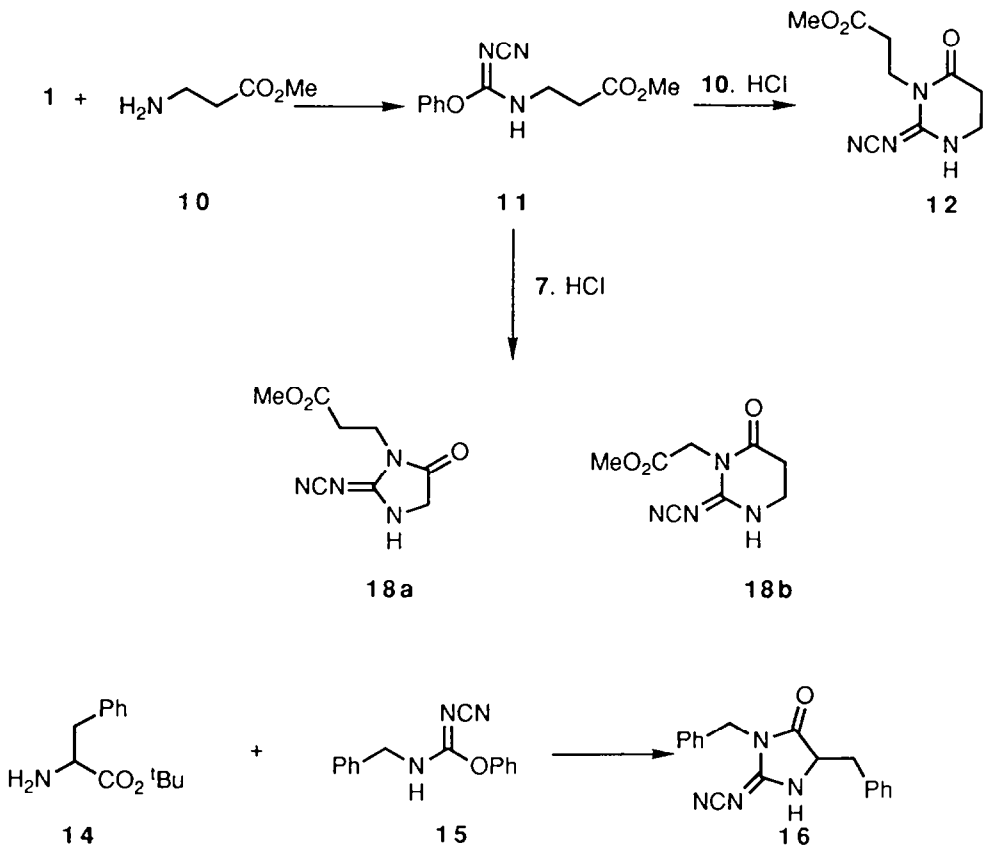
Compound	C-2 δ	C-4 δ	C-5 δ	C-6 δ	NCN δ	C-α δ	C-β δ	C=O δ
9	161.5	171.3	48.0		114.9	39.9		167.4
13	162.3	171.9	48.0		115.4	42.2		
16	162.1	172.4	59.7		115.6	42.9	36.4	
12	158.6	168.2[b]	30.4	35.7	115.5	37.2	32.1	171.2[b]
17	158.7	168.4	30.5	35.7	115.4	44.3		
18a	162.2	171.5[b]		47.8	115.3	34.8	31.5	170.8[b]
5	162.4	169.3[b]		55.1	115.4	42.4	35.0	172.2[b]

[a]Spectra taken in DMSO-d_6. [b] These assignments can be interchanged.

Table 3. Infrared Spectra of Tetrahydroimidazoles and Hexahydropyrimidines.[a]

Compound	C N cm^{-1}	C = N cm^{-1}	C = O ester cm^{-1}	C = O ring cm^{-1}
9	2200	1651	1738	1768
13	2201	1651		1748
16	2180	1639		1749
12	2182	1631	1732	1710
17	2184	1628		1716
18a	2202	1631	1737	1760
5	2190	1650	1740	1760

[a] All spectra taken as KBr discs except **12** as a nujol mull.



Considerable structural information may be obtained by consideration of the spectral data shown in the tables Inspection of the ^{1}H NMR spectra (Table 1) shows that in the 6-membered ring systems, H^5 and H^6 are coupled as two triplets, J = 6.9 Hz, with H^6 at ca. δ 3. 4 and H^5 at ca. 2.7. In the 5-membered ring, H^5 is a singlet at ca. δ 4.2. Inspection of the ^{1}H NMR spectrum of compound (**18**) shows a singlet at δ 4.11 and triplets at δ 3.65 and 2.60. Clearly there is a problem in deciding the structure of (**18**), which is compounded by the position of the exocyclic carbon in compound (**9**) at δ 4.27 (4.29), and ^{1}H NMR spectroscopy thus does not seem satisfactory for this purpose.

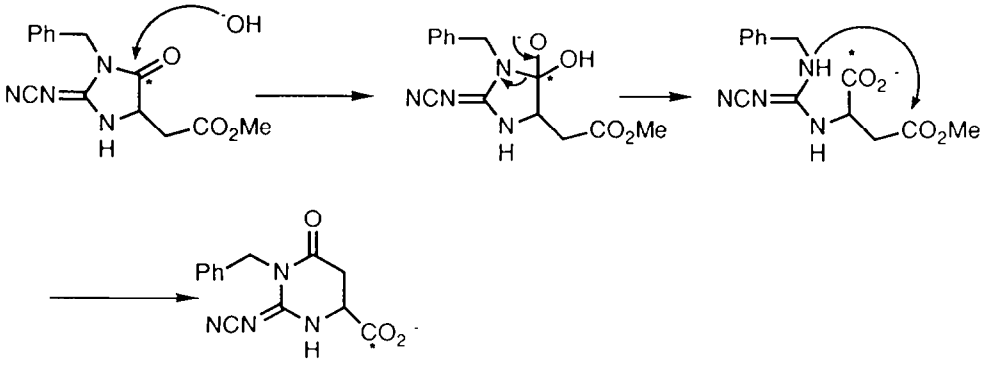
The ^{13}C NMR spectra (Table 2) are more diagnostic of ring size. In the 6-membered ring, C-5 is at ca. δ 30 and C-6 at ca. δ 36, while in the 5-membered ring C-5 is at ca. δ 48. There is also a difference between the ring carbonyl and ring carbonimine carbons: in the 6-membered rings C-4 is at ca. δ 168 while in the 5-membered rings is at ca. δ 171, and C-2 in the 6-membered rings is at ca. δ 159 while in the 5-membered rings it is at ca. δ 162. Inspection of the ^{13}C NMR spectrum of (**18**) shows C-5 at δ 47,8, C-4 at δ 171.5 (170.8) and C-2 at δ 162.6. The side chain carbons are at δ 31.5 and 34.8, at similar positions to those they would have as ring atoms in a 6-membered

ring, but in this case the single side chain carbon should be at ca. δ 40 [see compound (**9**)] rather than at δ 48.

Confirmation that the structure of (**18**) is (**18a**) comes from the IR spectrum (Table 3). The ring carbonyl stretching frequency is between 1748 and 1768 cm^{-1} for the 5-membered ring compounds and between 1710 and 1716 cm^{-1} for the 6-membered ring compounds. The carbonimine stretching frequency, which might also have been expected to show some correlation with ring size, appears much more variable, although it is usually higher in the 5-membered rings. Interestingly, the nitrile stretching frequency, which might have been expected to be less influenced by ring size because more remote, although still in conjugation, is diagnostic for the ring size in the C-unsubstituted derivatives, appearing at ca. 2180 cm^{-1} in the 6-membered rings and at 2200 cm^{-1} in the 5-membered rings.

We can now apply our analysis to our original problem, the reaction of compound (**3**) with benzylamine to give either (**4**) or (**5**). The ^{13}C NMR data best fit the 5-membered ring structure and the assignments that would be made in this case are those given in Table 2. The IR spectrum (Table 3) conclusively supports the 5-membered ring structure, the ring carbonyl group C=O stretching band appearing at 1760 cm^{-1} rather than at 1715 cm^{-1} as in the 6-membered rings.

The evidence thus shows that the cyclic product in the reaction of (**3**) with benzylamine is (**5**). Where, then, does the rearrangement to the 6-membered ring occur to provide 3-N-benzylorotic acid? We suggest that this is in the hydrolysis of the ester to the acid . This hydrolysis is extremely facile, and we believe it occurs by nucleophilic addition of the hydroxyl ion to the ring C=O followed by ring cleavage. The resulting half-ester can now undergo cyclization, but preferentially to the ester function, leading to the formation of the 6-membered ring, cleavage of the ester and interchange of the two carbonyl carbon atoms from cyclic to acyclic (Scheme). The facile ring cleavage is presumably enhanced by the NCN substituent at C-2 which can accommodate the incipient negative charge.



Scheme

It appears, both from the reaction of (**11**) with (**7**) to give (**18a**) and from the reaction of (**3**) to give (**5**), that there is a preference for the formation of the 5-membered over the 6-membered ring. This would seem reasonable in terms of a kinetic effect, fewer degrees of freedom being lost on forming the 5-membered ring. The crude reaction times, however, suggest that the 6-membered rings are formed faster. Similar anomalies have been observed in the Dieckmann reaction.[6] Modifications are now being sought so that the 6-membered ring may be formed regiospecifically to allow the enantioselective synthesis of 6-substituted hexahydropyrimidines.

Compounds (**9**), (**12**), and (**18a**) are dipeptide derivatives with the N-terminal and amide nitrogen functions contributing to a heterocyclic ring and, as such, are of potential biological interest. The cyanoimine function is known to be physicochemically very similar to the carbonyl group[7] and the pharmacology of these compounds is being examined.

Experimental

^{1}H NMR and ^{13}C NMR spectra were taken on a Varian VXR-400 spectrometer in $CDCl_3$ as solvent with Me_4Si as internal standard. IR spectra were taken on a Perkin-Elmer PE-983 spectrophotometer as KBr discs. Melting points were recorded on a Kofler Hot-stage apparatus and are uncorrected. Thin layer chromatography was carried out on Merck Kieselgel 60 F_{254} plates. Flash chromatography was carried out on silica using the method of Rigby and Hunt.[8] Solvents were dried by standard methods.

General preparation of Heterocycles

Preparation of Isourea (**8**)

Glycine methyl ester hydrochloride (7.0g, 0.56 mol) was suspended in propan-2-ol (120 mL) and triethylamine (6.24 g, 0.06 mol) was added. A precipitate formed which was removed by filtration. Diphenyl cyanocarbonate (**1**) (13.30 g, 0.056 mol) was then added in portions and the mixture was stirred overnight. The solid precipitate was removed and the filtrate reduced to a quarter volume and allowed to stand overnight at 4 °C. A second crop of solid was obtained which was combined with the first and the whole washed with water and then ether and dried. Recrystallization from EtOH: H_2O (1:1) gave (**8**), 9.10 g (0.039 mol, 70%), mp 131 - 132 °C., ms *m/e* 233; ^{1}H NMR δ 3.70 (s,) 3.72 (s), OCH_3), 3.98 (bs), 4.13 (bs, H-1), 7.10 (d), 7.28 (d), 7.35 (t), 7.42 (m), 7.49 (m, Ph); ^{13}C NMR δ 43.3, 43.6, 52.2, 52.3, 113.8, 114.4, 120.0, 121.6, 126.5, 126.6, 129.7, 130.5, 151.0, 151.4, 160.6, 163.3, 169.0, 169.5; IR 2186, 1742, 1636 cm^{-1}. Anal. Calcd for $C_{11}H_{11}O_3N_3$: C, 56.65; H, 4.72; N, 18.03. Found: C, 56.61; H, 4.68; N, 18.12.

The preparation of the isourea (**11**) was described previously.[2]

Preparation of the Heterocycles (**9**), (**12**) and (**18a**)

The isourea (13 mmol) was dissolved in propan-2-ol (100 mL) and the aminoacid methyl ester hydrochloride (13 mmol) was added and the mixture heated to reflux under N_2 for 7 h. The solvent was removed by evaporation and the products separated by flash chromatography on silica gel, eluting with CH_2Cl_2: MeOH 95:5.

Compound (**9**), 20% [57% based on recovered (**8**)] , mp 195 -196 °C, ms *m/e* 210 (7%), 179 (16), 152 (31), 151 (17), 125 (34) 124 (31), 99 (28), 94 (27), 82 (13), 80 (28), 70 (10), 68 (22), 59 (18), 56(12), 55 (100); ^{1}H NMR see Table 1; ^{13}C NMR see Table 2; IR see Table 3. Anal. Calcd for $C_7H_8O_3N_4$: C, 45.70; H, 4.79; N, 26.67. Found: 45.70, H, 4.57; N, 26.36.

Compound (**12**), 45% [93.5% based on recovered (**11**)], mp 154 -155 °C, ms *m/e* 224 (3%), 193 (13), 166 (11), 166 (23), 110 (12), 85 (22), 69 (16), 68 (12), 55 (100); ^{1}H NMR see Table 1; ^{13}C NMR see Table 2; IR see Table 3. Anal. Calcd for $C_9H_{12}O_3N_4$: C, 48.21; H, 5.39; N, 24.98. Found: C, 47.85; H, 5.35; N, 24.62.

Compound (**18a**), 14% [36.8% based on recovered (**8**)], mp 149 -150 °C, ms *m/e* 210 (4%), 208 (6), 181 (13), 180 (115), 179 (21) , 154 (19), 153 (37), 152(39), 151 (18), 139 (16), 125 (49), 124 (37), 123 (12), 99 (14), 98 (13), 97 (15), 95 (10), 94 (39), 82 (15), 81 (11), 80 (20), 70 (14), 69 (47), 68 (25), 59 (13), 57 (18), 56 (22), 55 (100); ^{1}H NMR see Table 1; ^{13}C NMR see Table 2; IR see Table 3; Anal: Calcd for $C_8H_{10}O_3N_4$: C, 45.71; H, 4.80; N, 26.64. Found: C, 45.70; H, 4.57; N, 26.36.

Preparation of Compound (**13**)

The isourea (**8**) (2.50 g, 11 mmol) was dissolved in propan-2-ol (100 mL). Benzylamine (1.30 g, 12 mmol) was added and the mixture heated to reflux under N_2 for 3 h. On cooling, (**13**) crystallized from the reaction mixture as colourless needles which were collected and washed with cold propan-2-ol and then ether, 1.70 g (73%), mp 238 - 243 °C (dec)., ms *m/e* 214 (M+ , 84%), 185 (58), 157 (18), 145 (5), 116 (3), 104 (12), 91 (100); ^{1}H NMR see Table 1; ^{13}C NMR see Table 2; IR see Table 3. Anal. Calcd for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.71; N, 26.15. Found: C, 61.67; H, 4.66; N, 26.15.

Preparation of Compound (**16**)

(S)-Phenylalanine tert-butyl ester (**14**) (76%) was obtained from (S)-phenylalanine hydrochloride by the method of Goodson et al [9] Compound (**14**) (1.30 g, 5.87 mmol) and the isourea (**15**) (1.38 g, 5.50 mmol) were added to propan-2-ol (50 mL) and the mixture stirred and heated to reflux under N_2 for 60 h. The cooled solution was allowed to stand for 72 h at room temperature when a white solid had precipitated which was removed by filtration, washed with ether and dried. Flash chromatography of this material, eluting with CH_2Cl_2: EtOAc (7:3) gave (**16**), 0.49 g (1.6 mmol,

29%), mp 184 - 186 °C, ms *m/e* 304 (M^+, 48%), 118 (76), 94 (74), 91 (100); ^1H NMR see Table 1; ^{13}C NMR see Table 2; IR see Table 3. Anal. Calcd for $C_{18}H_{16}N_4O$: C, 71.04; H, 5.30; N, 18.41. Found: C, 71.06, H, 5.17; N, 18.32.

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[3] William of Ockham, "frustra fit per plura, quod potest fieri per pauciora".

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