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Mercaptothioalkanoic Acids. III.

Reactions of Mercaptothioalkanoic Acids with Isocyanates

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メルカプトチオカルボン酸 Ⅲ
メルカプトチオカルボン酸と イソシアナートとの反応

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概　　要

メルカプトチオ酢酸（1）およびメルカプトチオプロピオン酸（2）は著者等の一人により1973，1977年にはじめて合成発表された化合物で，分子内にメルカプト基，チオカルボキシル基および活性メチレン基をもつ反応性に富んだ特異的化合物である。したがって，化合物 1，2 は反応および合成有機化学的にみて非常に興味深い化合物であると考えられる。この点において，著者等はこれらメルカプト酸とカルボニル化合物との反応またC＝N 結合をもつ化合物との反応をおこない，1,3-ジチオラン-4-オン（4），4-オキソテトラハイドロチアゾール（6）等の新種ヘテロ環化合物の合成や4-チアゾリジノン（5）の新しい製法の開発をおこなってきた。今回メルカプト酸の特異性，有為性を更に拡げるためにイソシアナートとの反応をおこない種々の知見をえたので報告する。

化合物 1 はアルキルイソシアナートとの反応で，N-アルキル-2-メルカプトアセトアミド（7）と N-アルキル-2,4-チアゾリジンジオン（8）とを与えた。これは Scheme 1 に記載のように，1 のチオカルボキシル基がまず N＝C 結合に付加し，ついで COS が脱離するか，1 のメルカプト基が N＝C に付加し，ついで H_2S がとれるかによるものと考えられる。一方，芳香族イソシアナートとの反応では，チアゾリジンジオン誘導体はえられず，アセトアミド誘導体のみがえられた。アルキル基とアリル基の電子作用の強弱によりイソシアナートの窒素の電子密度が異なり，このような反応性のちがいを示すもの

と推察される。

化合物 2 とイソシアナートとの反応においては，7型化合物である N-置換-3-メルカプトプロピオンアミド (9) が Scheme 2 のような機構により高収率でえられた。この場合，8 のような環状ヘテロ化合物はえられなかったが，これは5員環と6員環の生成難易性に基づくものと考えられる。

ここに得られた化合物の多くは文献に記載されていない物質であり，そのために，元素分析，マススペクトル，赤外吸収，核磁気吸収等により構造の確実なる同定をおこなった (Table 2, 3, 4)。

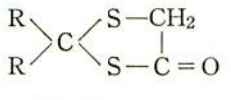
Mercaptothioalkanoic Acids. III.

Reactions of Mercaptothioalkanoic Acids with Isocyanates

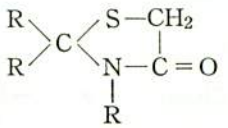
Mercaptothioacetic acid (**1**) and 3-mercaptothiopropionic acid (**2**) are interesting compounds which have reactive functional groups (mercapto, active methylene and thiocarboxyl groups), therefore, it is expected that many useful organic compounds will be readily prepared from these mercaptothio acids. The acid (**1**) was first synthesized in 1973 by one of the authers in a good yield from the reaction of chloroacetyl chlorides with hydrogen sulfide, followed by treatment with potassium hydrogen sulfide.[1] The acid (**2**) was also prepared in 1977 by the same way as the acid (**1**).[2] Since the compounds (**1**,**2**) are now easily accessible and expected to be useful synthetic intermediates, it is of interest to investigate expansions of the reactions of **1** and **2**.

$$Cl(CH_2)_nCOCl \longrightarrow Cl(CH_2)_nCOSH \longrightarrow HS(CH_2)_nCOSH$$

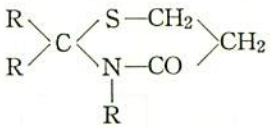
Previously, one of the authers have reported on the reactions of these acids (**1**, **2**) with compounds containing C=O bond to afford 1,3-dithiolanone derivatives (**4**), and with compounds containing C=N bond to afford 4-thiazolidinone derivatives (**5**) and 4-thiazanone derivatives (**6**). In relation to the reactions, we report the reactions of these acid with several isocyanates, heterocumulene compounds, in this paper.



(**4**)



(**5**)



(**6**)

The reaction of **1** with methyl isocyanate (**3a**) was carried out in tetrahydrofuran under an anhydrous condition. The reaction temperature was maintained at about −30°C by regulating the rate of addition of the isocyanate and by external cooling. Two kinds of oily products were obtained by fractional distillation, boiling at 85–86°C/0.2mm and 81–82°C/0.2mm. The values of elemental analyses and

mass spectrum of the former are well in accord with the formula C_3H_7NOS, formed by the elimination of 1 mol of COS from the adduct of 1 mol of **1** and 1 mol of **3a**. Spectral data suggest the structure as N-methyl 2-mercaptoacetamide (**7a**). The infrared spectrum displays the characteristic absorption bands of -NH-CO- at 3290 and 1640cm^{-1}, and of S-H at 2545cm^{-1}. The nuclear magnetic resonance spectrum exhibits a broad singlet at δ 7.69 assignable to an amide proton, a methyl doublet at δ 4.01, a methylene doublet at δ 3.29 and a mercapto triplet proton at δ 2.11 ppm. The analytical values and the mass spectrum of the latter are in good agreement with the formula $C_4H_5NO_2S$, formed by the elimination of 1 mol of hydrogen sulfide from the adduct of **1** and **3a**. The infrared spectrum displays two strong carbonyl absorptions at 1745 and 1670cm^{-1}, and no absorption exhibits in the N-H and S-H regions at about 3300 and 2550cm^{-1}, respectively. The nuclear magnetic resonance spectrum exhibits two singlet at δ 4.03 and 3.66ppm in area ratio of 3:2. On the bases of these evidences, the structure of the latter is assumed to be N-methyl 2,4-thiazolidinedinedione (**8a**). It seems that the addition of thiocarboxyl group of **1** to -N=C=O group of **3a**, followed by the elimination of COS, results to give the former. On the other hand, the latter is formed by attack of mercapto group of **1** upon -N=C=O group of **3a** followed by the cyclization with the elimination of hydrogen sulfide.

The possible pathways for the formations of **7a** and **8a** by the reaction of **1** with **3a** are shown in Scheme 1, and the yields of **7a** and **8a** are also presented in

Scheme 1.

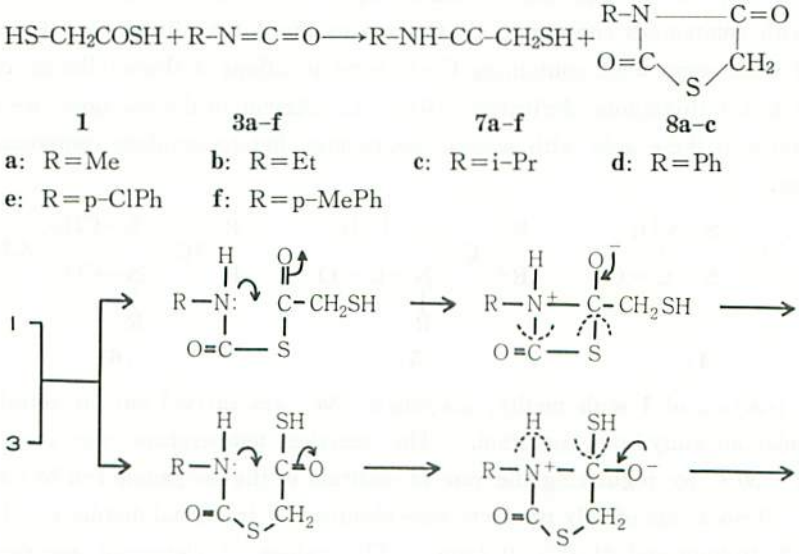


Table 1.

R	1+3⟶7+8 Yield, %			2+3⟶9
	7	**8**	**7+8**	Yield %
Me	43	30	73	72
Et	45	26	71	65
i-Pr	48	26	74	68
Ph	76	—	76	88
p-ClPh	86	—	86	74
p-MePh	80	—	80	83

Table 1.

Ethyl isocyanate (**3b**) reacted with **1** under the similar condition to give the expected products, N-ethyl 2-mercaptoacetamide (**7b**) and N-ethyl 2,4-thiazolidinedione (**8b**). The reaction of **1** with i-propyl isocyanate (**3c**) was also carried out to obtain the amide (**7c**) and the dione (**8c**). The structure of the product **7b**, **7c**, **8b** or **8c** was equally confirmed by a mass, an infrared and a nuclear magnetic resonance spectrum, and elemental analyses, as seen in Table 2 and 3.

Table 2. N-Substituted 2-Mercaptoacetamides (**7a–f**)

Compd	R	Mp°C or Bp°C/mm	Formula	Calcd, %			Found, %			Mass
				C	H	N	C	H	N	M^+
7a	Me	85–86/0.2	C_3H_7NOS	34.28	6.71	13.33	34.01	6.98	13.57	105
7b	Et	81–82/0.5	C_4H_9NOS	40.33	7.62	11.76	40.12	7.86	11.91	119
7c	i-Pr	85–86/0.5	$C_5H_{11}NOS$	45.10	8.33	10.52	44.88	8.52	10.80	133
7d	Ph	106–107	C_8H_9NOS	57.48	5.43	8.38	57.19	5.70	8.53	167
7e	p-ClPh	129–131	C_8H_8NOSCl	47.64	4.00	6.95	47.37	4.22	7.17	201, 203
7f	p-MePh	124–125	$C_9H_{11}NOS$	59.66	6.12	7.73	59.46	6.25	8.00	181

	IR, cm^{-1}			^1H-NMR ($CDCl_3$) δ, ppm					
	N-H	C=O	S-H						
7a	3290	1640	2545	7.69 (b, 1)	4.01 (d, 3)	3.29 (d, 2)	2.11 (t, 1)		
7b	3280	1640	2545	7.60 (b, 1)	4.3–4.1 (m, 2)	3.27 (d, 2)	2.08 (t, 1)	1.30 (t, 3)	
7c	3280	1640	2540	7.62 (b, 1)	4.01 (m, 1)	3.30 (d, 2)	2.10 (t, 1)	0.9–1.4 (m, 6)	
7d	3300	1650	2555	8.65 (b, 1)	7.8–7.1 (m, 5)	3.30 (d, 2)	2.41 (t, 1)		
7e	3300	1660	2560	8.78 (b, 1)	7.8–7.1 (m, 4)	3.36 (d, 2)	2.45 (t, 1)		
7f	3280	1650	2550	8.52 (b, 1)	7.5–7.0 (m, 4)	3.33 (d, 2)	2.40 (t, 1)	2.27 (s, 3)	

Table 3. 3-Alkyl-1,3-thiazolidine-2,5-diones (**8a-c**)

Compd	R	Bp°C/mm	Formula	Calcd, %			Found, %		
				C	H	N	C	H	N
8a	Me	81-82/0.2	$C_4H_5NO_2S$	36.65	3.84	10.69	36.33	4.01	10.82
8b	Et	69-70/0.5	$C_5H_7NO_2S$	41.38	4.86	9.65	41.24	4.99	9.78
8c	i-Pr	75-79/0.5	$C_6H_9NO_2S$	45.28	5.70	8.80	45.01	5.96	8.92

	MW	Mass IR, cm^{-1}			^1H-NMR ($CDCl_3$)		
		M^+	C=O	C=O	δ, ppm		
8a	131.2	131	1745	1670	4.03 (s, 3H)	3.66 (s, 2H)	
8b	145.2	145	1740	1660	4.12 (q, 2H)	3.60 (s, 2H)	1.30 (t, 3H)
8c	159.2	159	1740	1660	4.01 (m, 1H)	3.50 (s, 2H)	1.4-0.9 (m, 6H)

The reaction of aromatic isocyanate with **1** was also examined. Phenyl isocyanate (**3d**) was added to **1** in ether solution at about −20°C, and then the mixture was stirred for 8 hr at the same temperature. In this case, only one crystalline product was obtained. The infrared bands at 3300, 2555 and 1650cm^{-1} indicate the presence of a N-H group, a mercapto group and a carbonyl group, respectively. There are five aromatic protons in the region of δ 7.8-7.1ppm as multiplet, a methylene doublet centred at δ 3.30ppm and a mercapto proton triplet centred at δ 2.41ppm. A remaining broad absorption appeared at 8.65ppm is assigned to an amide proton. The values of elemental analyses and mass spectrum are in accord with the calculated values of the formula C_8H_9NOS. On the bases of these data, the structure of the crystalline product is confirmed to be N-phenyl 2-mercaptoacetamide (**7d**). The reaction of **1** with p-chlorophenyl (**3e**) or p-methylphenyl (**3f**) isocyanate was also carried out and the expected N-p-chlorophenyl (**7e**) or N-p-methylphenyl (**7f**) 2-mercaptoacetamide was obtained in a good yield (Table 1). As stated above, alkyl isocyanate reacted with **1** to give both 3-alkyl-2,4-thiazolidinedione and N-alkyl 2-mercaptoacetamide, but the reaction of aryl isocyanate with **1** gave only N-aryl 2-mercaptoacetamide. The reason why no 3-aryl-2,4-thiazolidinedione is formed in the reaction of **1** with aryl isocyanate is not clear, but is subject to the influence of the electron density on the nitrogen atom in isocyanate.

The parent compound, thiazolidine-2,4-dione, was the first compound in which the thiazole ring system was recognized. It was first prepared by the isomerization of thiocyanatoacetic acid in aqueous acid and for some time was thought to be isothiocyanatoacetic acid. Treatment of esters of α-thiocyanato acids with aqueous

acid constitutes a general method for the preparation of both the dione and many its derivatives. However, perhaps the most widely applicable method is the acid hydrolysis of the 2-imino analogs which are so readily prepared by the reaction of α-halo acids or esters with thioureas or N-substituted thioureas.[3)]

The dione is weak acid, is soluble in aqueous alkali, and can be alkylated. The N-substituted derivative may also dissolve slowly in alkali, but this acid property is due to opening of the ring. The methylene carbon atom at the 5-position of a 4-thiazolidinone possesses nucleophilic activity and attacks an electrophilic center. If it is structurally possible, the reaction product loses water, forming a 5-unsaturated derivative. Most frequently, the reaction occurs in the presence of a base and the anion of the 4-thiazolidinone is the attacking species. The ease of formation of the anion and hence the degree of the nucleophilic activity is dependent not only on the electron-withdrawing effect of the adjacent carbonyl group, but also on the presence of other electron-withdrawing groups such as those attached to the 2-carbon atom. The electron attraction of the sulfur of a 2-thione group is greater than that of the oxygen of a 2-carbonyl group.

Several oxazolidinedione derivatives protect against metrazole-induced convulsions and are used in the treatment of petit mal epilepsy[4)], the corresponding thiazolidinedione analogs were examined and found to afford less protection[5)]. 5-Phenyl-2,4-thiazolidinedione protects mice against metrazole-induced convulsions and also potentiates the hypnotic action of pentobarbital[6)].

In place of 2-mercaptothioacetic acid (**1**), 3-mercaptothiopropionic acid (**2**) was used and was allowed to react with **3a-f**. Treatment of **3a** with **2** in tetrahydrofuran for 8 hr at about $-20°C$ gave an oily product. By the informations of elementary analyses and mass spectroscopy, the oil was found to be the compound, formed by the elimination of 1 mol of hydrogen sulfide from the adduct of **2** and **3a**. The infrared bands at 3280 and 1640cm^{-1} indicate the presence of an acid amide group, and at 2550cm^{-1} points a mercapto group. The nuclear magnetic resonance spectrum shows the absorptions at δ 7.32ppm assignable to amide proton, at 3.2-2.3ppm corresponding to two methylene groups which is situated between a nitrogen atom and a sulfur atom, and at 1.67ppm due to mercapto proton, in area ratio of 1:4:1. The methyl protons appear at 3.18ppm as a triplet. These spectral data suggest the structure of the reaction product of **2** with **3a** as N-methyl 3-mercaptopropionamide (**9a**).

Other aliphatic isocyanates (**3b**, **3c**) also reacted with **2** to give N-ethyl (**9b**) and N-i-propyl (**9c**) 3-mercaptopropionamide. The pathway to yield **9** is set forth in Scheme 2. The results of the reactions of aliphatic isocyanates with **2** are summarized in Table 1 and Table 4.

Scheme 2.

$$HS\text{-}CH_2CH_2COSH + R\text{-}N{=}C{=}O \longrightarrow R\text{-}NH\text{-}CO\text{-}CH_2CH_2SH$$

2 **3a–f** **9a–f**

a: R=Me **b**: R=Et **c**: R=i-Pr

d: R=Ph **e**: R=p-ClPh **f**: R=p-MePh

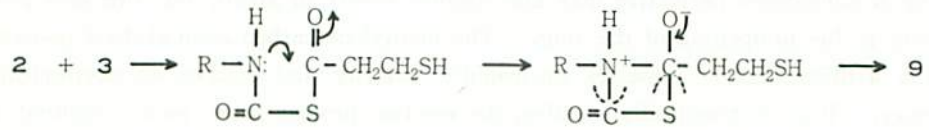


Table 4. N-Substituted 3-Mercaptopropionamide (**9a-f**)

Compd	R	Mp°C or Bp°C/mm	Formula	Calcd, %			Found, %			Mass
				C	H	N	C	H	N	M^+
9a	Me	93–95/1	C_4H_9NOS	40.33	7.62	11.76	40.07	7.86	11.71	119
9b	Et	102–103/1	$C_5H_{11}NOS$	45.10	8.33	10.52	44.81	8.54	10.80	133
9c	i-Pr	116–118/2	$C_6H_{13}NOS$	48.96	8.90	9.52	48.72	9.17	9.64	147
9d	Ph	87–88	$C_9H_{11}NOS$	59.66	6.12	7.73	59.39	6.40	7.89	181
9e	p-ClPh	106–107	$C_9H_{10}NOSCl$	50.11	4.67	6.49	49.90	4.72	6.72	215, 217
9f	p-MePh	85–86	$C_{10}H_{13}NOS$	61.52	6.71	7.18	61.28	6.85	7.33	195

	IR, cm^{-1}			^1H-NMR ($CDCl_3$) δ, ppm				
	N-H	S-H	C=O					
9a	3280	2550	1640	7.32 (b, 1)	3.18 (d, 3)	3.2-2.3 (m, 4)	1.67 (t, 1)	
9b	3285	2550	1650	7.23 (b, 1)	3.5-3.0 (m, 2)	2.9-2.3 (m, 4)	1.70 (t, 1)	1.13 (t, 3)
9c	3285	2545	1640	7.30 (b, 1)	3.4-3.0 (m, 1)	2.9-2.3 (m, 4)	1.87 (t, 1)	1.6-0.9 (m, 6)
9d	3295	2560	1660	8.00 (b, 1)	7.6-6.8 (m, 5)	3.3-2.6 (m, 4)	1.80 (t, 1)	
9e	3295	2565	1670	8.25 (b, 1)	7.6-7.1 (m, 4)	3.4-2.8 (m, 4)	1.80 (t, 1)	
9f	3290	2555	1660	7.90 (b, 1)	7.5-6.9 (m, 4)	3.3-2.5 (m, 4)	2.25 (s, 3)	1.83 (t, 1)

Phenyl isocyanate (**3d**) added to **2** in diethyl ether for 10 hr in the same manner as **3a–c** to give an white solid. The nuclear magnetic resonance spectrum of this product closely resemble to that of **9a**, except that the signals of aromatic protons appear at 7.6-6.8ppm and the absorptions of methyl protons disappear. The values of elemental analyses and mass spectrum are well in accord with the calculated values of the formula, formed by the elimination of H_2S from the 1 : 1 adduct of **2** and **3d**. The infrared spectrum displays characteristic absorption bands at 3295, 2560 and 1660cm^{-1}, assignable to amino, mercapto and carbonyl group, respe-

ctively. Therefore the structure of this product is confirmed to be N-phenyl 3-mercaptopropionamide (**9d**). Other aromatic isocyanates such as **3e** and **3f** also reacted with **2** to give N-p-chlorophenyl (**9e**) and N-p-methylphenyl (**9f**) 3-mercaptopropionamide. The yields of the amides (**9**) from the reactions of **2** with **3** are summarized in Table 1, and the analytical and spectral data are shown in Table 4.

Mercaptoalkanoic acid amides are generally made by acylation of amines with the corresponding esters or acid chlorides in which the mercapto group is protected as the acyl derivative [7]. Another reaction used is the addition of thiol acid to olefinic double bond followed by ammonolysis with aqueous ammonia. The mercapto amides are employed for colored cheleting agents that is applied to the detection or determination of inorganic materials in non-aqueous solutions.

Experimental

Mercaptothioacetic Acid (1). Hydrogen sulfide was passed into a mixture of chloroacetyl chloride (79g, 0.7mol) and anhydrous aluminum chloride (2.0g) at 0°C for 30hr. The reaction mixture was filtered and the filtrate was distilled to obtain chlorothioacetic acid (56.2g, 73%), bp 34–36° (5mm).

A solution of potassium hydroxide (90g) in ethanol (90%, 270ml) was saturated with hydrogen sulfide at 0°C, and chlorothioacetic acid (30g, 0.27mol) was added slowly at about −5°C. After potassium chloride was removed by precipitation, the filtrate was concentrated to about 100ml, acidified with cold 3N-HCl, and extracted with ether. Distillation gave the product **1**: bp 61–62° (8mm); yield 24.6g, 84%; nmr (CCl_4) δ 5.18 (s, 1H), 3.60 (d, 2H), 2.37 (t, 1H); ir bands at 2550, 1680cm^{-1}.

Anal. Calcd for $C_2H_4OS_2$: C, 22.23; H, 3.73; S, 59.23. Found: C, 22.45; H, 3.77; S, 58.97.

3-Mercaptothiopropionic Acid (2). A solution of potassium hydroxide (90g) in ethanol (90%, 300ml) was saturated with hydrogen sulfide at 0°C, and 3-chloropropanoyl chloride (25g, 0.2mol) was added slowly at about −10°C. After the precipitated potassium chloride was removed, the filtrate was concentrated to about 100ml, acidified with 3N-HCl, and extracted with ether. Distillation gave the product **2**: bp 60–61° (4mm); yield 16g, 67%; nmr ($CDCl_3$) δ 5.06 (s, 1H), 3.17–2.55 (m, 4H), 1.82 (t, 1H); ir bands at 2550, 1695cm^{-1}.

Anal. Calcd for $C_3H_6OS_2$: C, 29.51; H, 4.95; S, 52.42. Found: C, 29.22; H, 5.11; S, 52.19.

N-Alkyl-2-mercaptoacetamide (7a–c) and **3-Alkyl-1,3-thiazolidine-2,5-dione**

Derivatives (8a–c). To a solution of 0.1mol of **1** in 150ml of tetrahydrofuran, 0.1 mol of alkyl isocyanate (**3a**, **3b** or **3c**) in 30ml of the same solvent was added with good agitation under an anhydrous condition. The temperature of the content was maintained at about −30°C by regulating the rate of addition of isocyanate and by external cooling with dry ice and acetone. After the reaction mixture was stirred for 5 hr at the same temperature, the solvent was removed under reduced pressure. Fractional distillation of the residue gave the products **7** and **8**. The results obtained are summarized in Table 2 and 3.

N-Aryl-2-mercaptoacetamides (7d–f). To a solution of 0.1mol of **1** in 150 ml ether, 0.1mol of aromatic isocyanate (**3d**, **3e** or **3f**) was added dropwise at about −20°C. The mixture was then stirred for 8 hr at the same temperature. After a small amount of precipitated diaryl urea was filtered off, the solvent was evaporated to dryness under reduced pressure. Recrystallization of the residue from toluene gave the results presented in Table 2.

N-Alkyl-3-mercaptopropionamides (9a–c). Aliphatic isocyanate (**3a**, **3b** or **3c**; 0.1mol) dissolved in 30ml of tetrahydrofuran was added slowly to a solution of 0.1mol of **2** in 150ml of the same solvent at about −20°C. After the mixture obtained was stirred for 8hr at the same temperature, the solvent was removed, and the residue was distilled to give **9a–c** The yields and the spectral data are given in Table 1 and 4.

N-Aryl-3-mercaptopropionamides (9d–e). To a solution of 0.1mol of **2** in 150ml of diethyl ether, 0.1mol of aromatic isocyanate in 30ml of the same solvent was added dropwise at about −10°C. The mixture was then stirred for 10 hr at the same temperature. After the solvent was evaporated under reduced pressure, the residual white solid was recrystallized from trichloroethylene to give **9d–f**. The results obtained are summarized in Table 1 and 4.

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