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7,11-DIARYL-2,4-DIAZASPIRO[5.5]UNDECANE-1,5,9-TRIONES: A NEW SERIES OF SPIROHETEROCYCLES

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Abstract- A novel two step synthesis of 7,11-diaryl-2,4-diazaspiro[5.5]undecane-1,5,9-triones has been reported based on double Michael addition of 2-thiobarbiturates or *N,N'*-diaryl-2-thiobarbiturates with dibenzalacetones followed by reductive desulfurization with nickel boride.

The multifaceted display of biological activities by spiroheterocyclic units has been the driving force for their synthesis during the last few decades. Spiro compounds are known to exhibit various biological activities like fungicidal,[1] herbicidal,[2] bactericidal,[3] anticonvulsant,[4] anti-inflammatory, narcotic,[5] hypotensive, skeletal muscle relaxant and antianxiety.[6] Barbituric acid and thiobarbituric acid derivatives are also well known sedatives, herbicides,[7] fungicides[8] and antiviral[9] agents. Inspite of the synthesis of numerous compounds containing spiroheterocyclic moieties by various research groups, synthesis of 2,4-diazaspiro[5.5]undecane-1,5,9-triones has not received any attention. Thus there is a sufficient scope to develop synthetic protocols for these compounds. We have attempted to achieve the desired synthesis by first condensing 2-thiobarbituric acid with dibenzalacetones followed by reductive desulfurization with nickel boride.

We report herein a novel and efficient synthesis of 7,11-diaryl-2,4-diazaspiro[5.5]undecane-1,5,9-triones(**4a-4j**) in two convenient steps. The first step involves double Michael addition of thiobarbituric acid or *N,N'*-diaryl-2-thiobarbituricacids (**2**) to dibenzalacetones (**1**) by a reported procedure[10] to give 7,11-diaryl-3-thioxo-2,4-diazaspiro[5.5]undecane-1,5,9-triones (**3a-3j**) (Scheme 1). Though compounds (**3a-3e**)[11]are reportedly known, a number of new spiroheterocycles (**3f-3j**) have been synthesized and characterized by their NMR, IR and Mass spectra. These results are summarized in Table 1.

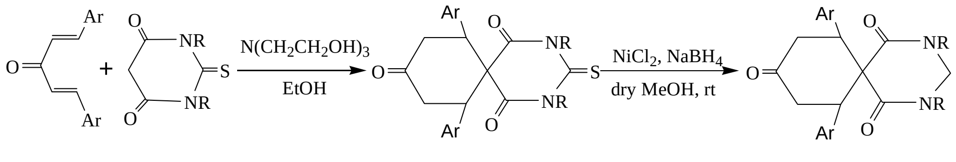
Reductive desulfurization of 7,11-diaryl-3-thioxo-2,4-diazaspiro[5.5]undecane-1,5,9-triones with *in situ* generated nickel boride in dry methanol at ambient temperature resulted in the formation of a new series of spiroheterocycles i.e., 7,11-diaryl-2,4-diazaspiro[5.5]undecane-1,5,9-triones. Our group has been

Table 1. Preparation of 7,11-diaryl-3-thioxo-2,4-diazaspiro[5.5]undecane-1,5,9-triones.

S. No	Dibenzalacetones (**1**) Ar	2-Thiobarbituric acid (**2**) R	7,11-Diaryl-3-thioxo-2,4-diazaspiro[5.5]undecane-1,5, 9-triones (**3**)	Yield (%)
1.	C_6H_5	H	**3a**	82
2.	4-$MeOC_6H_4$	H	**3b**	83
3.	2-$MeOC_6H_4$	H	**3c**	89
4.	4-ClC_6H_4	H	**3d**	81
5.	2-ClC_6H_4	H	**3e**	87
6.	4-MeC_6H_4	H	**3f**	90
7.	2-MeC_6H_4	H	**3g**	86
8.	C_6H_5	C_6H_5	**3h**	84
9.	4-MeC_6H_4	C_6H_5	**3i**	87
10.	4-MeC_6H_4	4-MeC_6H_4	**3j**	87

exploring the reducing and desulfurizing properties of nickel boride.[12] We have already reported reductive desulfurization of 2-thiobarbiturates, 2-thioxo-4(3*H*)–quinazolonones and 4-oxo-2-thioxo-5*H*-pyrano[2,3-*d*]pyrimidines.[13] Therefore, we envisioned the possibility of reductive desulfurization of 7,11-diaryl-3-thioxo-2,4-diazaspiro[5.5]undecane-1,5,9-triones with nickel boride generated *in situ*. The reactions of 7,11-diphenyl-3-thioxo-2,4-diazaspiro[5.5]undecane-1,5,9-trione (**3a**) were carried out with nickel boride by changing the molar ratios of substrate : nickel chloride : sodium borohydride and by changing the solvents. Methanol was the solvent of choice as reactions in other solvents either did not proceed at all or were incomplete even after prolonged reaction times. The reaction of **3a** in dry methanol using a molar ratio of 1: 3: 9 (S: $NiCl_2$: $NaBH_4$) was complete in 5 min and a new product was formed having R_f lower than the starting material as observed on TLC. The product (**4a**) was characterized by its NMR, IR and Mass spectra. IR spectra showed the absence of C=S stretch at 1534 cm^{-1} which was observed in the IR spectra of **3a,** NMR spectra showed the appearance of 2 new doublets (*J*=4.3 Hz) at 3.83 and 4.84 for 2 protons at C-3 position. FAB MS spectra gave M^{+}+1 molecular ion peak at 349 confirming the formation of 7, 11-diphenyl-2,4-diazaspiro[5.5]undecane-1,5,9-trione (**4a**).

The reaction was found incomplete in lower molar ratios of substrate: nickel chloride: sodium borohydride. The desulfurization was undoubtedly proceeding due to the *in situ* generated nickel boride because when the reactions of **3a** were performed with nickel chloride and sodium borohydride alone, starting material was recovered unchanged in the former case and a mixture of products was obtained in the latter case. Other 7,11-diaryl-3-thioxo-2,4-diazaspiro[5.5]undecane-1,5,9-triones (**3b-3j**) with different aryl substitutions and N-substitutions also underwent complete reductive desulfurization by using either 1: 3: 9 or 1: 5: 15 (S: $NiCl_2$: $NaBH_4$) molar ratios and yielded the corresponding 7,11-diaryl-2,4-diazaspiro[5.5]undecane-1,5,9-triones in high yields (Scheme 1). Spiroheterocycles (**4a-j**) were all new compounds and were characterized by their NMR, IR and Mass Spectra. These results are summarized in Table 2. Nickel boride showed complete selectivity towards desulfurization as no effect was observed on the carbonyl groups as well as on the halogen in the case of halogenated substrates (**3d** and **3e**).

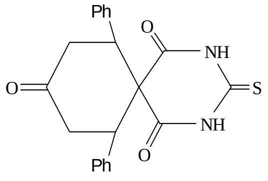
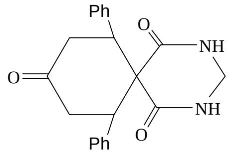
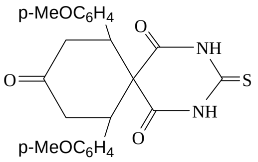
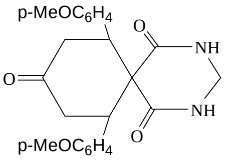
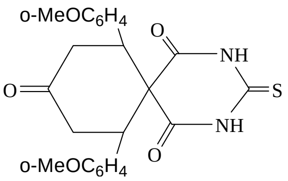
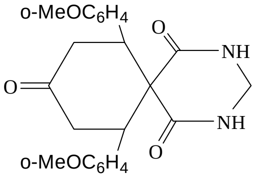


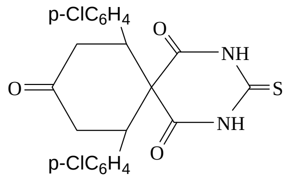
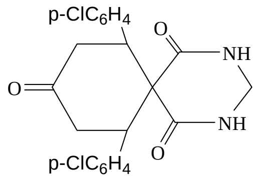
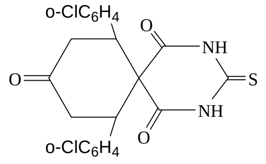
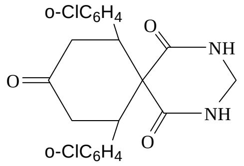
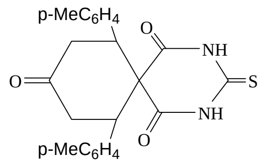
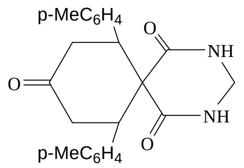
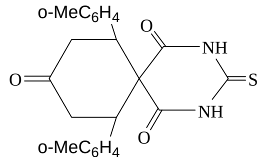
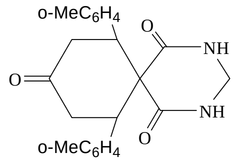
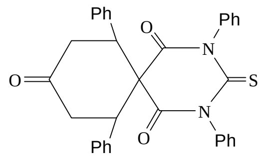
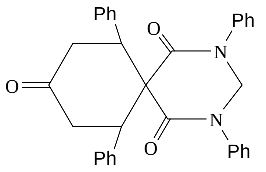
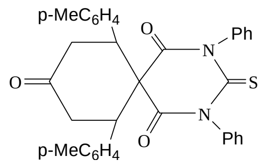
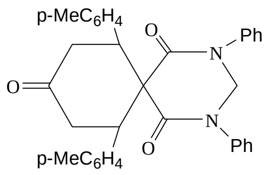
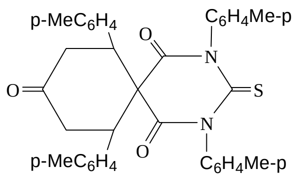
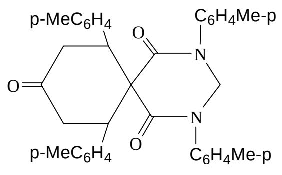
1 **2** **3 a-j** **4 a-j**

	Ar	R		Ar	R
a:	C_6H_5	H	f:	4-MeC_6H_4	H
b:	4-$MeOC_6H_4$	H	g:	2-MeC_6H_4	H
c:	2-$MeOC_6H_4$	H	h:	C_6H_5	C_6H_5
d:	4-ClC_6H_4	H	i:	4-MeC_6H_4	C_6H_5
e:	2-ClC_6H_4	H	j:	4-MeC_6H_4	4-MeC_6H_4

Scheme 1

Table 2. Preparation[a] of 7,11-diaryl-2,4-diazaspiro[5.5]undecane-1,5,9-triones

S.No.	Substrate (**3**)	Molar Ratio S: $NiCl_2$: $NaBH_4$	Time (min)	Product (**4**)	Yield (%)
1.		1: 3: 9	5		87
2.		1: 5: 15[b]	60		84
3.		1: 5: 15[b]	10		81

4.		1: 5: 15[b]	30		81
5.		1: 5: 15[b]	10		89
6.		1: 3: 9	30		92
7.		1: 3: 9	10		97
8.		1: 5: 15[b]	20		89
9.		1: 5: 15[b]	10		83
10.		1: 5: 15[b]	10		77

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[a] 5 mL of dry methanol was used for 0.1 g of substrate.

[b] Reaction was incomplete with lower molar ratios.

We conclude that 7,11-diaryl-2,4-diazaspiro[5.5]undecane-1,5,9-triones (**4**) can be easily synthesized by following a simple protocol which requires a base catalysed double Miachel addition of thiobarbiturates to dibenzalacetone followed by reductive desulfurization of the resulting compounds with nickel boride**.**

EXPERIMENTAL

The melting points were determined on a Tropical Labequip apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer FT-IR Spectrum 2000 and NMR spectra were recorded on Bruker Avance Spectrospin dpx-300 MHz instrument. The FAB mass spectra were recorded on JOEL SX 102/DA-6000 Spectrometer using Argon/Xenon as the FAB gas.

STARTING MATERIALS

Methanol (Speckpure) was used after drying by the reported procedure. Nickel (II) chloride hexahydrate (S.D.Fine) was dried by heating in a crucible till golden yellow, it was then allowed to cool at room temperature and stored over calcium chloride in a dessicator. Sodium borohydride (E. Merck) was used in all the reactions. Dibenzalacetones were prepared by the literature reported procedure.[14] 1,3-Diaryl-2-thiobarbituric acids were prepared by the condensation of malonic acid and *N, N'*-diarylthioureas.[15] 2-Thiobarbituric acid (Spectrochem) was used as such.

General procedure for preparation of 7,11-diaryl-3-thioxo-2,4-diazaspiro[5.5]undecane-1,5,9-triones (3)

In a typical procedure, a mixture of dibenzalacetone (**1a**) (2.34 g, 10 mmol), 2-thiobarbituric acid (**2a**) (1.44 g, 10 mmol) and EtOH (30 mL) was taken in a 100 mL RB flask and 3-4 drops of triethanolamine were added to the solution. The contents of the flask were refluxed for 7 h with constant stirring. The mixture was filtered hot at pump, cooled and poured onto ice-cold water (200 mL). The solid thus separated was filtered at pump, washed with water, dried and crystallized from $CHCl_3$ to give **3a** as white crystals. Yield**:** 82 %, mp 250-252 °C (Lit., mp 249-250 °C).[10] Compounds **3b-3j** were obtained in a similar way. Spectroscopic data of the new compounds (**3f-3j**) is reported herein.

3f: Crystallized from $CHCl_3$, white crystals. Yield: 90 %. mp 234-235 °C; ^{1}H-NMR (DMSO-d_6): δ 2.27 (s, 6H, 2 x CH_3), 2.43- 2.49 (dd, *J* = 4.19,14.6, 2H, 8-H/10-H equatorial), 3.54-3.63 (t, *J* = 14.76, 2H, 7-H/11-H), 3.87-3.93 (dd, *J*= 4.19, 14.1, 2H, 8-H/10-H axial), 7.01-7.08 (m, 8H, Ar-H)); IR (Nujol) ν_{max}: 1525 (C=S), 1681, 1713 (C=O), 3188 (NH), 819 (p-substituted aromatic); FAB MS: 407 (M^++1).

3g: Crystallized from $CHCl_3$, white crystals. Yield: 86 %. mp 232-233 °C; ^{1}H-NMR (DMSO-d_6): δ 2.21 (s, 6H, 2 x CH_3), 2.34- 2.41 (dd, *J* = 4.86,15.17, 2H, 8-H/10-H equatorial), 3.01-3.12 (t, *J* = 14.15, 2H, 7-H/11-H), 4.29-4.35 (dd, *J*= 4.90, 13.51, 2H, 8-H/10-H axial), 7.03 (m, 8H, Ar-H)); IR (Nujol) ν_{max}: 1550 s(C=S), 1696, 1717 (C=O), 3172 (NH); FAB MS: 407 (M^++1).

3h: Crystallized from $CHCl_3$, yellow crystals. Yield: 84 %. mp 245 °C; ^{1}H-NMR (DMSO-d_6): δ 2.30-2.38 (q, 2H, 8-H/10-H equatorial), 3.25-3.34 (t, *J* = 14.34, 2H, 7-H/11-H), 3.99-4.05 (dd, *J*= 4.35, 13.64, 2H, 530 (M^+).

3i: Crystallized from $CHCl_3$, yellow crystals. Yield: 87 %. mp 240-242 °C; ^{1}H-NMR (DMSO-d_6): δ 2.36 (s, 6H, 2 x CH_3), 2.49-2.53 (d, *J*=12.26, 2H, 8-H/10-H equatorial), 3.43-3.48 (t, *J* = 12.95, 2H, 7-H/11-H), 4.15 (d, 2H, 8-H/10-H axial), 6.41-7.11 (m, 8H, Ar-H)), 7.36-7.50 (m, 10H, Ar-H); IR (Nujol) ν_{max}: 1593 (C=S), 1698, 1725 (C=O), 841 (p-substituted aromatic); FAB MS: 558 (M^+).

3j: Crystallized from $CHCl_3$, yellow crystals. Yield: 87 %. mp 250 °C; ^{1}H-NMR (DMSO-d_6): δ 2.36 (s, 12H, 4 x CH_3), 2.47-2.54 (q, 2H, 8-H/10-H equatorial), 3.44-3.54 (t, *J* = 14.46, 2H, 7-H/11-H), 4.10-4.16 (dd, *J*=4.57, 13.85, 2H, 8-H/10-H axial), 6.27-7.33 (m, 16H, Ar-H); IR (Nujol) ν_{max}: 1693, 1723 (C=O), 1511 (C=S); FAB MS: 586 (M^+).

General procedure for preparation of 7,11-diaryl-2,4-diazaspiro[5.5]undecane-1,5,9-triones (4)

In a typical procedure, **3a** (0.25g, 0.6613 mmol) and dry MeOH (12 mL) were placed in a 100 mL round bottomed flask fitted with a condenser and a calcium chloride guard tube. The flask was mounted over a magnetic stirrer and the contents were stirred vigorously. Anhyd. $NiCl_2$ (0.2559 g, 1.9841 mmol) was added to the flask followed by the addition of $NaBH_4$ (0.2261 g, 5.9524 mmol) cautiously at rt. $NaBH_4$ addition resulted in an exothermic reaction but the reaction mixture slowly cooled down. The contents of the flask were stirred. Complete disappearance of the starting material (**3a**) was observed by TLC (EtOAc: petroleum ether: 70: 30 ; v/v) in 5 min. After the completion of the reaction, the reaction mixture was filtered through a celite pad (~ 1 inch). Nickel boride precipitate was washed with MeOH (2 x 10 mL). The combined filtrate was diluted with water (~ 30 mL) and extracted with EtOAc (3 x 50 mL). The combined extract was dried over anhyd. $MgSO_4$, filtered and concentrated to afford **4a** as white powder. Yield: 87 %. mp 272 °C; ^{1}H-NMR (DMSO-d_6): δ 2.72-2.84 (q, *J*=12.11, 2H, 8-H/10-H equatorial), 2.95 (s, 2H, 7-H/11-H), 3.50-3.56 (dd, *J*=2.72, 13.33, 2H, 8-H/10-H axial), 3.83-3.85 (d, *J*= 4.39, 1H, 3-H), 4.84-4.86 (d, *J*=4.23, 1H, 3-H), 7.11-7.28 (m, 10H, Ar-H)); IR (Nujol) ν_{max}: 1679 (C=O), 3263 (NH); FAB MS: 349 (M^++1).

Compounds (**4b-4j**) were obtained in a similar way. The spectroscopic data of all these compounds is reported herein.

4b: White powder. Yield: 84 %. mp 255-256 °C; ^{1}H-NMR (DMSO-d_6): δ 2.76-2.81 (q, *J*=12.41, 2H, 8-H/10-H equatorial), 3.12 (s, 2H, 7-H/11-H), 3.49-3.53 (d, *J*=12.02, 2H, 8-H/10-H axial), 3.74 (s, 6H, 2 x OCH_3), 3.87-3.89 (d, *J*=4.725, 1H, 3-H), 4.43-4.44 (d, *J*=4.389, 1H, 3-H), 6.71-7.23 (m, 8H, Ar-H)); IR (Nujol) ν_{max}: 1674 (C=O), 3238 (NH), 830 (p-substituted aromatic); FAB MS: 409 (M^++1).

4c: White powder. Yield: 81 %. mp 258-260 °C; ^{1}H-NMR (DMSO-d_6): δ 2.50-2.54 (q, *J*=11.64, 2H, 8-H/10-H equatorial), 3.00 (s, 2H, 7-H/11-H), 3.72 (s, 6H, 2 x OCH_3), 3.95-4.00 (m, 3H, 8-H/10-H axial, 3-H), 4.68 (s, 1H, 3-H), 6.78-7.30 (m, 8H, Ar-H)); IR (Nujol) ν_{max}: 1686 (C=O), 3259 (NH); FAB MS: 410 (M^++2).

4d: White powder. Yield: 81 %. mp 286-287 °C; ^{1}H-NMR (DMSO-d_6): δ 2.64-2.76 (q, *J*=12.26, 2H, 8-H/10-H equatorial), 3.05 (s, 2H, 7-H/11-H), 3.48-3.51 (d, *J*=12.49, 2H, 8-H/10-H axial), 3.78 (br s, 1H, 3-H), 4.79-4.81 (d, *J*=4.11, 1H, 3-H), 7.21-7.27 (m, 8H, Ar-H)); IR (Nujol) ν_{max}: 1707 (C=O), 3255 (NH), 823 (p-substituted aromatic); FAB MS: 419 (M^++2).

4e: White powder. Yield: 89 %. mp 298 °C; ^{1}H-NMR (DMSO-d_6): δ 2.50-2.52 (q, 2H, 8-H/10-H equatorial), 3.14 (s, 2H, 7-H/11-H), 3.74 (br s, 1H, 3-H), 4.01-4.07 (dd, *J*=2.75, 13.14, 2H, 8-H/10-H axial), 4.89-4.90 (d, *J*=4.28, 1H, 3-H), 7.21-7.51 (m, 8H, Ar-H)); IR (Nujol) ν_{max}: 1701 (C=O), 3234 (NH); FAB MS: 419 (M^++2).

4f: White powder. Yield: 92 %. mp 272-273 °C; ^{1}H-NMR (DMSO-d_6): δ 2.26 (s , 6H, 2 x CH_3), 2.69-2.81 (q, *J*=11.72, 2H, 8-H/10-H equatorial), 3.00 (s, 2H, 7-H/11-H), 3.45-3.49 (d, *J*=11.49, 2H, 8-H/10-H axial), 3.80 (br s, 1H, 3-H), 4.64 (s, 1H, 3-H), 6.98-7.16 (m, 8H, Ar-H)); IR (Nujol) ν_{max}: 1705 (C=O), 3238 (NH), 813 (p-substituted aromatic); FAB MS: 377 (M^++1).

4g: White powder. Yield: 97 %. mp 295-296 °C; ^{1}H-NMR (DMSO-d_6): δ 2.33 (s , 6H, 2 x CH_3), 2.62-2.70 (q, 2H, 8-H/10-H equatorial), 3.08 (s, 2H, 7-H/11-H), 3.71-3.80 (m, 3H, 8-H/10-H axial, 3-H), 4.52-4.54 (d, *J*=4.30, 1H, 3-H), 7.04-7.44 (m, 8H, Ar-H)); IR (Nujol) ν_{max}: 1696 (C=O), 3233 (NH); FAB MS: 377 (M^++1).

4h: Yellow powder. Yield: 89 %. mp 248 °C; ^{1}H-NMR (DMSO-d_6): δ 2.26-2.39 (q, *J*=11.70, 2H, 8-H/10-H equatorial), 3.10 (s, 2H, 7-H/11-H), 3.52-3.56 (d, *J*=11.87, 2H, 8-H/10-H axial), 3.74-3.75 (d, *J*=4.16, 1H, 3-H), 4.83-4.85 (d, *J*=4.26, 1H, 3-H), 6.31-7.31 (m, 20H, Ar-H)); IR (Nujol) ν_{max}: 1711, 1695 (C=O); FAB MS: 501 (M^++1).

4i: Yellow powder. Yield: 83 %. mp 242-244 °C; ^{1}H-NMR (DMSO-d_6): δ 2.35 (s , 6H, 2 x CH_3), 2.45-2.53 (q, *J*=10.3, 2H, 8-H/10-H equatorial), 3.43 (s, 2H, 7-H/11-H), 3.69-3.72 (d, *J*=10.75, 2H, 8-H/10-H axial), 3.95 (br s, 1H, 3-H), 5.07-5.09 (d, *J*=4.29, 1H, 3-H), 6.55-7.45 (m, 18H, Ar-H)); IR (Nujol) ν_{max}: 1714, 1697 (C=O); FAB MS: 529 (M^++1).

4j: Yellow powder. Yield: 77 %. mp 258-260 °C; ^{1}H-NMR (DMSO-d_6): δ 2.31 (s , 12H, 4 x CH_3), 2.45-2.53 (q, *J*=12.64, 2H, 8-H/10-H equatorial), 3.34 (s, 2H, 7-H/11-H), 3.67-3.71 (d, *J*=12.74, 2H, 8-H/10-H axial), 3.93 (br s, 1H, 3-H), 5.01-5.03 (d, *J*=3.5, 1H, 3-H), 6.41-7.30 (m, 16H, Ar-H)); IR (Nujol) ν_{max}: 1676, 1710 (C=O), 813 (p-substituted aromatic); FAB MS: 557 (M^++1).

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