Indolizine Derivatives. IX. Preparation of 1-Acylpyrrolo[2,1,5-*cd*]indolizines *via* Cycloaddition of 3-Acyloxyindolizines to Active Ethylenes and Acetylenes

Esko K. Pohjala

Department of Chemistry, Helsinki University of Technology, Otaniemi, 02150 Espoo 15, Finland

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3-Indolizinyl acetates and propionates **4** react with ethylenic and acetylenic ketones or carboxylic esters to give 1-acylpyrrolo[2,1,5-*cd*]indolizines **5-12** in excellent yields.

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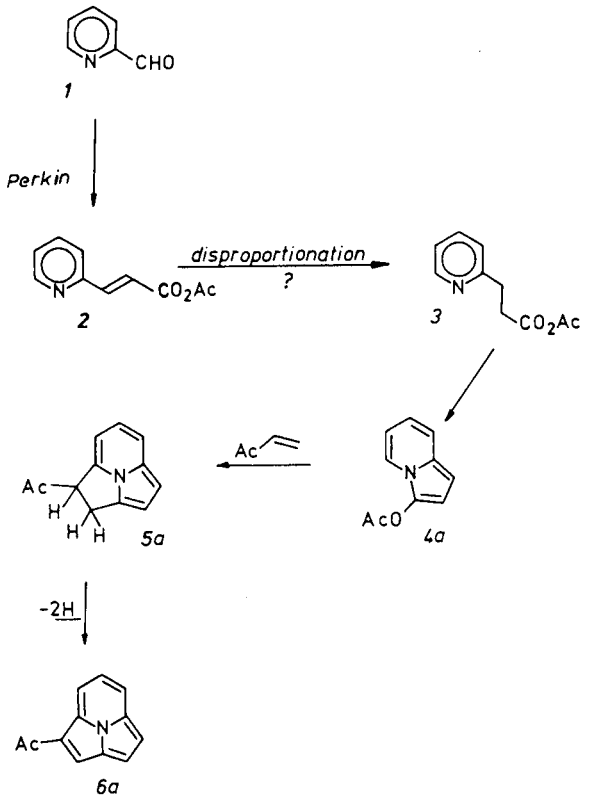
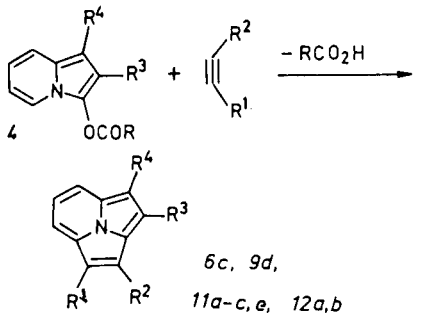
Introduction.

A few years ago a novel approach to 1-acylpyrrolo-[2,1,5-*cd*]indolizines exploiting the Perkin reaction of 2-pyridinecarbaldehyde (**1**) in the presence of vinylic ketones and esters was introduced (1). In a later communication (2) the reaction was shown to proceed through 3-acyloxyindolizine precursors, as illustrated below:



The subsequent and outstanding availability of various 3-acyloxyindolizines (3,4) prompted us to study their applicability to the preparation of pyrrolo[2,1,5-*cd*]-indolizines, especially *via* reaction with acetylenes:



It is shown here that the various pyrrolo[2,1,5-*cd*]-indolizine minor products encountered in the Perkin reaction of **1** in the presence of α,β-unsaturated carbonyl compounds (1) also arise from the corresponding 3-acyloxyindolizine intermediates.

The structures of the new compounds were assigned on the basis of spectral data (uv, ir, ^{1}H nmr, ms), and by comparison with structures of known pyrrolo[2,1,5-*cd*]-indolizines (3-6). Particularly the nature and site of the substituents of pyrrolo[2,1,5-*cd*]indolizines are easily determined by ^{1}H nmr spectroscopy (Table II).

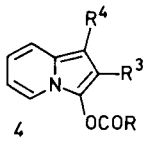
Scope of the Cyclization and Results.

As displayed in Table I, the 3-acyloxyindolizines **4c,f,g** carrying various substituents at position 1 were each transformed into a single pyrrolo[2,1,5-*cd*]indolizine **7**, **9-12** and/or the corresponding dihydro-precursor **5** in excellent yields, when added to unsaturated carbonyl species in acetic anhydride. If **4** was unsubstituted at C-1, a side-product was formed *via* substitution addition at this position with unsaturated ketones. Besides the ethylenes and acetylenes shown in Table I, similar cycloadditions were attempted with styrene, methyl 2-methacrylate, mesityloxide, and benzylideneacetone, which failed to react, and with acrylonitrile and maleic anhydride, which in turn produced too much tar to be investigated more closely. Acetic anhydride proved the best cyclization medium. The reactions were completed in acetic anhydride within a few minutes, except in the case of *O*-acetylated β-dicarbonyl compounds, where the actual polarophiles are probably 3-pentyne-2-ones (*e.g.*, to produce **9d**). The reaction with 3-buten-2-one could also be performed in chloroform or toluene, though much more slowly. Dimethyl acetylenedicarboxylate effected cycloaddition of **4b** in chloroform at room temperature, whereas heating in acetic anhydride was required for the cyclization of **4f**. Under the conditions used, 1-phenyl-2-propen-1-one was the only unsaturated species showing an appreciable tendency to polymerize. Acetophenone was also isolated from the reactions of 1-phenyl-2-propen-1-one.

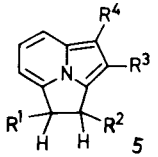
In the above transformations, equivalent compounds can be used successfully as well: *e.g.*, 4-hydroxy-2-butanone and 4-dimethylamino-2-butanone hydrochloride in the place of 3-buten-2-one.

Table I

Pyrrolo[2,1,5-*cd*]indolizines from 3-Acyloxyindolizines and α,β-Unsaturated Ketones



4



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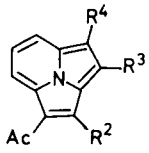
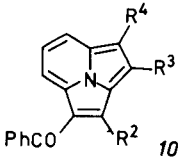


	R^3
6	H
7	Me
8	Ph
9	CO_2Et



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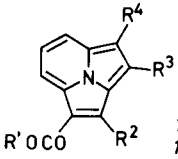


	R'
11	Me
12	Et

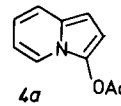
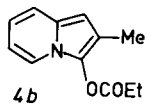
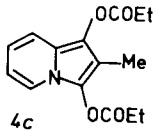
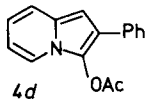
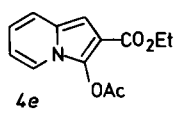
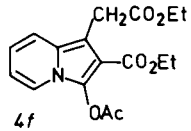
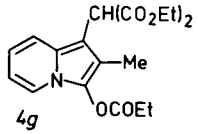
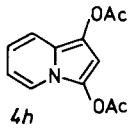
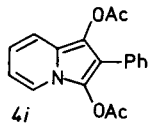
Indolizines	Ketones and Esters	Pyrrolo[2,1,5-*cd*]indolizines	R^2	R^3	R^4	M.p. (°C)	Yields (%) From 4	Yields (%) From 1
	$AcCH=CH_2$	**5a** (R^1 = Ac)	H	H	H			
		6a(9)	H	H	H	40	94	50
		6b	H	H	CH_2CH_2Ac	87 (a)	1	1
	$AcCH=CHMe$ $AcCH=C(OAc)Me$	**6c**(3)	Me	H	H	79	95 76	45
 4a	$PhCOCH=CH_2$	**10a**	H	H	H	93	75	40
	$MeOCOCH=CH_2$ $MeOCOC\equiv CH$	**11a**(9)	H	H	H	64	83 86	35
	$EtOCOCH=C(OAc)Me$ (c)	**12a**(3)	Me	H	H	64	74	
	$AcCH=CH_2$	**7a**	H	Me	H	73	81	30
		7b	H	Me	CH_2CH_2Ac	149 (a)	16	10
		7c	H	Me	2-Pyridylmethyl	160 (a)		5
 4b	$AcCH=CHMe$	**7d**(3)	Me	Me	H	70	92	45
	$PhCOCH=CH_2$	**10b**	H	Me	H	101	62	20
		10c	H	Me	Me	150		15
	$MeOCOC\equiv CCO_2Me$	**11b**(10)	CO_2Me	Me	H	117	≈100	
 4c	$AcCH=CH_2$	**5b** (R^1 = Ac)	H	Me	OCOEt			
		7e	H	Me	OCOEt	118	≈100	25
	$AcCH=CHMe$	**7f**	Me	Me	OCOEt	121	95	10
	$PhCOCH=CH_2$	**10d**	H	Me	OCOEt	94	88	20
	$AcCH=CH_2$	**8a**(5)	H	Ph	H	103	81	35
		8b	H	Ph	CH_2CH_2Ac	137	13	5
 4d	$MeOCOC\equiv CCO_2Me$	**11c**(5)(11)	CO_2Me	Ph	H	135	90	

Table I (Continued)

Indolizines	Ketones and Esters	Pyrrolo[2,1,5-*cd*]indolizines	R^2	R^3	R^4	M.p. (°C)	Yields (%) From 4	Yields (%) From 1
 *4e*	$AcCH{=}CH_2$	**9a**	H	CO_2Et	H	149	38	
		9b	H	CO_2Et	CH_2CH_2Ac	132	58	
 *4f*	$AcCH{=}CH_2$	**5c** (R^1 = Ac)	H	CO_2Et	CH_2CO_2Et	109	75	
		9c	H	CO_2Et	CH_2CO_2Et	112 (a)	20	
	AcCH=C(OAc)Me (b)	**9d** (4)	Me	CO_2Et	CH_2CO_2Et	148 (a)	89	
	$MeOCOCH{=}CH_2$	**11d**	H	CO_2Et	CH_2CO_2Et	148	≈100	
	$MeOCOC{\equiv}CCO_2Me$	**11e**	CO_2Me	CO_2Et	CH_2CO_2Et	129 (a)	≈100	
	EtOCOCH=C(OAc)Me (c)	**12b** (4)	Me	CO_2Et	CH_2CO_2Et	167	66	
 *4g*	$MeOCOCH{=}CH_2$	**5d** (R^1 = CO_2Me)	H	Me	$CH(CO_2Et)_2$	79	≈100	
		11f	H	Me	$CH(CO_2Et)_2$	93	0	
 *4h*	$AcCH{=}CH_2$	**6d**	H	H	OAc	119		1
 *4i*	$AcCH{=}CH_2$	**8c**	H	Ph	OAc	187		20

(a) From ethanol. (b) *In situ* from acetylacetone. (c) *In situ* from ethyl acetoacetate.

Table II

Selected Spectral Data of Representative Cyclization Products

Product	^{1}H Nmr (Deuteriochloroform) δ (Protons and Substituents) At: C-1	C-2	C-3	C-4	C-5	C-6	C-7 (a)	Coupling Constants (Hz)	Ir (Potassium bromide) ν (C=O), cm^{-1}	
5c	4.66 (1H, br. dd) 2.31 (3H, s)	3.80 (1H, dd) (H_a) 3.68 (1H, dd) (H_b)	4.27 (2H, q) 1.37 (3H, t)	4.14 (2H, q) 3.97 (2H, s) 1.26 (3H, t)	6.95 (1H, dt)	6.51 (1H, dd)	6.30 (1H, dt)	$J_{1,2a}$ = 5.5 $J_{1,2b}$ = 9.5 $J_{2a,2b}$ = 18.5 $J_{5,6}$ = 8.7 $J_{5,7}$ = 1.0 $J_{6,7}$ = 6.4	1730 1710 1690	C-4 ester ketone C-3 ester
5d	4.73 (1H, br. dd) 3.74 (3H, s)	3.65 (1H, dd) (H_a) 3.56 (1H, dd) (H_b)	2.22 (3H, s)	4.76 (1H, s) 4.22 (4H, q) 1.24 (6H, t)	7.12 (1H, dt)	6.43 (1H, dd)	6.33 (1H, dt)	$J_{1,2a}$ = 6 $J_{1,2b}$ = 12 $J_{2a,2b}$ = 16 $J_{5,6}$ = 8.5 $J_{5,7}$ = 1.0 $J_{6,7}$ = 6.3	1740 1720	C-1 ester C-4 ester
6d	2.61 (3H, s)	7.83 (1H, s)	7.49 (1H, s)	2.40 (3H, s)	7.95-7.75 (2H, m)		8.48 (1H, sext)	$J_{5,7}$ = 2.5 $J_{6,7}$ = 6	1740 1640	ester ketone
7a	2.65 (3H, s)	7.77 (1H, s)	2.62 (3H, d)	6.92 (1H, q)	7.67 (1H, dd)	7.72 (1H, dd)	8.34 (1H, sext)	$J_{3,4}$ = 1 $J_{5,6}$ = 8 $J_{5,7}$ = 3 $J_{6,7}$ = 6	1630	ketone
7c	2.71 (3H, s)	7.88 (1H, s)	2.65 (3H, s)	8.60 (1H, br. d) 7.3-7.0 (3H, m) 4.52 (2H, s)	7.68 (1H, dd)	7.71 (1H, dd)	8.40 (1H, sext)	$J_{5,6}$ = 7.5 $J_{5,7}$ = 2.5 $J_{6,7}$ = 6.5	1635	ketone
7e	2.61 (3H, s)	7.76 (1H, s)	2.51 (3H, s)	2.79 (2H, q) 1.42 (3H, t)	7.67 (1H, dd)	7.71 (1H, dd)	8.35 (1H, sext)	$J_{5,7}$ = 3.5 $J_{6,7}$ = 6	1755 1640	ester ketone
8c	2.73 (3H, s)	8.08 (1H, s)	8.0-7.7 (2H, m) 7.7-7.3 (3H, m)	2.46 (3H, s)	8.0-7.7 (2H, m)		8.49 (1H, br. t)		1760 1635	ester ketone
9b	2.61 (3H, s)	7.83 (1H, s)	4.46 (2H, q) 1.52 (3H, t)	3.53 (2H, t) 2.88 (2H, t) 2.03 (3H, s)	8.12 (1H, d)	7.79 (1H, t)	8.47 (1H, d)	$J_{5,6}$ = 7.5 $J_{6,7}$ = 7.5	1710 1700 1640	C-4 ketone ester C-1 ketone
10a	8.0-7.7 (2H, m) 7.5-7.25 (3H, m)	7.76 (1H, s)	7.47 (1H, d)	7.18 (1H, d)	7.9-7.6 (2H, m)		8.40 (1H, dd)	$J_{3,4}$ = 4.8 $J_{5,7}$ = 2.1 $J_{6,7}$ = 6.3	1615	ketone

Table II (Continued)

Product	^{1}H Nmr (Deuteriochloroform) δ (Protons and Substituents) At: C-1	C-2	C-3	C-4	C-5	C-6	C-7 (a)	Coupling Constants (Hz)	Ir (Potassium bromide) ν (C=O), cm^{-1}	
10b	8.05-7.7 (2H, m) 7.7-7.35 (3H, m)	7.80 (1H, s)	2.69 (3H, d)	7.06 (1H, q)	8.0-7.6 (2H, m)		8.35 (1H, sext)	$J_{3,4}$ = 1	1620	ketone
11a	3.94 (3H, s)	7.96 (1H, s)	7.49 (1H, d)	7.21 (1H, d)	7.79 (1H, dd)	7.72 (1H, dd)	8.31 (1H, dd)	$J_{3,4}$ = 4.7 $J_{5,6}$ = 7.0 $J_{5,7}$ = 2.4 $J_{6,7}$ = 6.5	1690	ester
11d	4.04 (3H, s)	8.18 (1H, s)	4.52 (2H, q) 1.51 (3H, t)	4.48 (2H, s) 4.20 (2H, q) 1.27 (3H, t)	8.06 (1H, dd)	7.84 (1H, dd)	8.45 (1H, dd)	$J_{5,6}$ = 7.6 $J_{5,7}$ = 1.2 $J_{6,7}$ = 7.0	1720 1700 1690	C-4 ester C-3 ester C-1 ester
11e	4.08 (3H, s)	3.99 (3H, s)	4.43 (2H, q) 1.42 (3H, t)	4.45 (2H, s) 4.16 (2H, q) 1.23 (3H, t)	8.08 (1H, dd)	7.88 (1H, t)	8.47 (1H, dd)	$J_{5,6}$ = 7.2 $J_{5,7}$ = 1.0 $J_{6,7}$ = 7.2	1735 1715 1700	C-2 ester C-4 ester C-1 ester C-3 ester
11f	3.98 (3H, s)	8.04 (1H, s)	2.68 (3H, s)	5.11 (1H, s) 4.22 (4H, q) 1.23 (6H, t)	7.93 (1H, dd)	7.82 (1H, dd)	8.28 (1H, dd)	$J_{5,6}$ = 7.2 $J_{5,7}$ = 1.2 $J_{6,7}$ = 7.6	1740 1720 1690	C-4 ester C-1 ester

(a) In some cases an additional complexity is due to virtual coupling (5).

Dihydropyrrolo[2,1,5-*cd*]indolizine Intermediates.

The cycloadditions were carried out in nitrogen atmosphere, but at later stages, *e.g.*, during crystallizations, the products were exposed to atmospheric oxygen, which can assist aromatization. Only two of the pyrrolo[2,1,5-*cd*]indolizines **5** could be isolated without difficulty, namely **5c** and **5d**. Thin layer chromatography of the product mixtures revealed the probable presence of other dihydrointermediates as well, *e.g.*, the precursors of **7e** and **9b**, but these are so readily oxygenated that possible isolation requires a more rigorous elimination of air contact at all purification stages. The dihydrocompound **5c** was aromatized to give **9c** when heated in benzene in the presence of air, whereas **5d** was so stable that it required boiling with palladium in benzene to give the aromatic **11f**.

Since the observed stabilities of the dihydroprecursors were in the order: **5d** (R^4 = $CH(CO_2Et)_2$) > **5c** (R^4 = CH_2CO_2Et) > **5b** (R^4 = OCOEt) > **5a** (R^4 = H), it is believed that C-4 of compounds **5** is the point of oxygen attack. Furthermore, the larger the substituent at C-4, the greater is the resistance to attack.

Side-products of the Related Perkin Reactions.

The Perkin reactions of **1** in the presence of 3-buten-2-one, catalyzed by acetic anhydride/potassium acetate, gave **6a** as the main product, accompanied by very small amounts of **6b** and **6d**. In the many other reactions of **1**, more complicated mixtures of various pyrrolo[2,1,5-*cd*]-indolizines were obtained. Compounds **7e** and **10d**, among others (**7a-c** and **10b,c**), were formed from **1** with propionic anhydride/potassium propionate and 3-buten-2-one or 1-phenyl-2-propen-1-one, respectively. At the same time, one of the products of the Perkin reactions of **1** with propionic anhydride/potassium propionate (without unsaturated carbonyl species) has been shown to be **4c** (3), which with the vinylic ketones gave the 4-propionyloxy derivatives **7e** and **10d**.

It is accordingly assumed that the 4-acetoxy derivatives **6d** and **8c** are formed *via* the respective diacetates **4h** and **4i**, although the latter (3) were not isolated from the corresponding Perkin reactions. The otherwise rather unstable indolizinediacetates **4h** and **4i** are trapped as **6d** and **8c** when 3-buten-2-one is present. Since the 4-(3-oxobutyl) derivative **6b** is obtained from **4a** with acetic anhydride and 3-buten-2-one in addition to **6a**, the acetate **4a** is almost certainly the precursor of **6b** also in the corresponding Perkin reaction in the presence of the butenone. All other 4-(3-oxobutyl)pyrrolo[2,1,5-*cd*]-indolizines **7b**, **8b** and **9b** are assumed to be formed similarly from the corresponding 3-acyloxyindolizines **4b**, **4d** and **4e**, respectively. The 4-(2-pyridyl)methyl derivative **7c** was found among other products when **1** was allowed to interact with 3-buten-2-one in a propionate system. Possibly it formed *via* **4b**, since **4b** gave with **1**,

Table III

Analyses of the New Pyrrolo[2,1,5-*cd*]indolizines

Compound	Formula	Calcd.			Found		
		C	H	N	C	H	N
6b	$C_{16}H_{15}NO_2$	75.85	5.95	5.55	76.10	5.85	5.85
6d	$C_{14}H_{11}NO_3$	69.70	4.60	5.80	69.50	4.70	5.70
7a	$C_{13}H_{11}NO$	79.15	5.60	7.10	79.10	5.40	6.90
7b	$C_{17}H_{17}NO_2$	76.40	6.40	5.25	76.45	6.30	5.15
7c	$C_{19}H_{16}N_2O$	79.15	5.60	9.70	79.40	5.60	9.80
7e	$C_{16}H_{15}NO_3$	71.35	5.60	5.20	71.00	6.00	5.50
7f	$C_{17}H_{17}NO_3$	72.05	6.05	4.95	72.05	6.15	4.90
8b	$C_{22}H_{19}NO_2$	80.20	5.80	4.25	80.10	5.80	4.45
8c	$C_{20}H_{15}NO_3$	75.70	4.75	4.40	75.55	4.95	4.70
9a	$C_{15}H_{13}NO_3$	70.60	5.15	5.50	70.80	5.30	5.45
9b	$C_{19}H_{19}NO_4$	70.15	5.90	4.30	70.05	6.00	4.35
9c	$C_{19}H_{19}NO_5$	66.85	5.60	4.10	66.70	5.70	4.10
10a	$C_{17}H_{11}NO$	83.25	4.50	5.70	82.95	4.55	5.55
10b	$C_{18}H_{13}NO$	83.35	5.05	5.40	83.30	5.30	5.75
10c	$C_{19}H_{15}NO$	83.50	5.55	5.15	83.55	5.35	5.20
10d	$C_{21}H_{17}NO_3$	76.10	5.15	4.25	76.00	5.15	3.90
11d	$C_{19}H_{19}NO_6$	63.85	5.35	3.90	63.60	5.45	3.70
11e	$C_{21}H_{21}NO_8$	60.70	5.10	3.35	60.55	5.05	3.45
11f	$C_{20}H_{21}NO_6$	64.70	5.70	3.75	64.35	5.35	3.40
5c	$C_{19}H_{21}NO_5$	66.45	6.15	4.10	66.85	6.25	4.15
5d	$C_{20}H_{23}NO_6$	64.35	6.20	3.75	64.60	6.20	3.80

acetic anhydride/potassium acetate and 3-buten-2-one, small amounts of **7c**. In this case, aromatization does not occur *via* dehydrogenation but *via* elimination of the carboxylic acid. Analogously, the formation of **10c** may be due to elimination of acetophenone.

Mechanism of the Cyclization Step.

Cycloadditions of indolizines unsubstituted at C-3 to electron deficient ethylenes (6) and acetylenes (5) have been assumed to occur *via* a concerted [8+2] cycloaddition (7). The same might be true for the 3-acyloxyindolizines, at least when chloroform or toluene is used as the solvent. With acid anhydride, however, a stepwise ionic mechanism is very probable (2), as is indicated by the accelerated reaction rates. In order to elucidate the matter, relevant experiments with other substituted indolizines are now in progress.

EXPERIMENTAL

The general conditions of related cyclizations, as well as separation procedures and instruments used, have been described in the earlier papers of this series (3,8).

General Procedure for the Cyclizations of 3-Acyloxyindolizines with Active Ethylenes and Acetylenes.

The 3-acyloxy derivative (**4a-d** (3), **4e-g** (4)) (0.010 mole) and an unsaturated carbonyl compound (0.015 mole) were heated in an excess of acetic anhydride (25 ml.) for 0.5 hours at 120° under nitrogen (Table I). After the reaction, all volatile materials were removed *in vacuo*, the temperature not exceeding 30°. The residue was fractionated when necessary by column chromatography (Woelm silica, benzene containing increasing amounts of dichloromethane as eluent) and the components purified by recrystallization from light petroleum (b.p. 40-60°) if not otherwise stated.

General Procedure for the Perkin Reaction of **1** in the Presence of Unsaturated Carbonyl Compounds.

2-Pyridinecarbaldehyde (**1**) (0.10 mole) and a vinylic ketone or ester (0.15 mole) were refluxed in an acid anhydride (0.5 mole) together with the corresponding potassium salt (0.25 mole) for 15 minutes (Table I). The cooled acylating mixture was stirred with water until the hydrolysis was completed. The dark precipitated product mixture was extracted in ether, washed and dried. The residue was fractionated and the components purified as above.

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