

Cycloadditions of Indolizine-3-carbonitriles with Dimethyl Acetylenedicarboxylate: Formation of [2.2.3]Cyclazines and 1:2 Adducts

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Reactions of indolizine-3-carbonitriles with dimethyl acetylenedicarboxylate (DMAD), in the presence of Pd-C, gave the corresponding [2.2.3]cyclazines in low to moderate yields, whereas, in the absence of Pd-C, the same reactions afforded the 1:2 molar products. The X-ray analysis of one of the 1:2 adducts established that the structure was dimethyl 2-cyano-3-styrylpyrrole-1,4-dicarboxylate. A possible mechanism is presented.

Several indolizines¹⁻⁴ are known to undergo $[8 + 2]\pi$ cycloadditions with electron-deficient alkynes to afford [2.2.3]cyclazines^{5,6} and addition of acetylenic esters to nitrogen-containing heterocycles has often produced novel types of compounds.^{7,8} Previously, we have reported the synthesis of 1,2-unsubstituted indolizine-3-carbonitriles by 1,3-dipolar cycloadditions of heteroaromatic dicyanomethylides with phenyl vinyl sulfoxide and bis(trimethylsilyl)acetylene.⁹

We now describe details of the reactions of 1,2-unsubstituted indolizine-3-carbonitriles with dimethyl acetylenedicarboxylate (DMAD) both in the presence and absence of Pd-C.¹⁰

Indolizine-3-carbonitrile **1a** when heated with an excess of DMAD in toluene in the presence of 5% Pd-C for 24 h gave the [2.2.3]cyclazine **3a** (40% yield)[†] (Table 1, entry 1), which was identical with authentic material.² Analogous reactions of the indolizine-3-carbonitriles **1b-f** with DMAD in the presence of Pd-C produced the corresponding cyclazines in low to moderate yields (see Table 1; entries 3, 8, 9, 10 and 12). However, indolizine-3-carbonitriles possessing an electron-withdrawing substituent (CN, MeO₂C), reacted only sluggishly with DMAD to give very low yields of the cyclazine **3f** and the 1:1 adduct **2g** (Table 1, entries 13 and 14 respectively). Pyrrolo[1,2-*b*]isoquinoline-3-carbonitrile **1h** was also quite unreactive to DMAD forming only a trace of the 1:1 adduct **2h** (Table 1, entry 15), which was identified by mass spectral analysis. Data including melting points, elemental analyses, mass, IR, ¹H, and ¹³C NMR spectra are presented in Tables 2-4. The above reactions provide a method for the synthesis of [2.2.3]cyclazines complementary to Boekelheide's method² albeit with limited scope.

In contrast to these results, indolizine-3-carbonitrile **1a** when heated under reflux with DMAD in toluene in the absence of Pd-C, gave a 1:2 adduct (18% yield). Similarly, the indolizine-3-carbonitrile **1b-d** gave the 1:2 adducts in up to 42% yield in which the molar ratio of **1b** and DMAD was 1:5. Even in the presence of Pd-C, the use of an excess of DMAD gave a considerable amount of the 1:2 adduct (22 and 35% yields for molar ratios **1b**/DMAD = 1:5 and 1:8 respectively; Table 1, entries 5 and 8). Initially, we assumed that the compounds had the primary structure **5**, and could be formed by successive Michael type additions and subsequent cyclization. There are many precedents for this type of 1:2 structure being formed

from nitrogen heterocycles such as pyridines, azapentalenes, and azaazulenes.⁷ However, the 11-12 Hz coupling constant between two of the lower-field protons is too large for these protons to be placed in vicinal positions on a double bond within a five-membered ring. The ¹³C value of δ 103 (Table 5) does not correspond to an sp³ carbon. Furthermore, all attempts to convert the compound into the corresponding [2.3.4]cyclazine failed. The ¹⁵N NMR spectrum of the 1:2 adduct from **1b** gave two signals at δ -243 and -145 (from ¹⁵N chemical shift of nitromethane as an external standard). The former signal is evidently due to a cyano group, while the latter seems to suggest a pyrrole nitrogen¹¹ if it is assumed that the 1:2 adduct possesses any heterocyclic unit. The use of [4,5,6,7-²H₄]indolizine-3-carbonitrile did not help solve the problem since the ¹H NMR spectrum of the 1:2 adduct indicated an AB quartet and a singlet at δ 6.96, 6.72 and 7.28, respectively in the lower field region. An X-ray analysis of the 1:2 adduct from **1b** established the pyrrole structure though it proved difficult to assign the position of nitrogen unambiguously. While structure **6** appeared to accommodate the ¹³C and ¹H NMR data acceptably, some of the reactions involved were atypical.^{10b} The crystal structure analysis was, therefore, repeated with further refinement (see footnote in Table 7), and this served to confirm the isomeric pyrrole structure **4** (Fig. 1). Furthermore, since, in the parent pyrrole,¹² the distances C(2)-C(3) [and C(4)-C(5)], N(1)-C(2) [and C(5)-N(1)], and C(3)-C(4) have been shown by microwave studies to be 1.371, 1.383 and 1.429 Å, respectively, structure **4** [N(1)-C(2), 1.404; C(2)-C(3), 1.368 Å; C(3)-C(4), 1.427; C(4)-C(5), 1.359; C(5)-N(1), 1.367 Å] seems more consistent with the evidence than **6** [N(1)-C(2), 1.427; C(2)-C(3), 1.359; C(3)-C(4), 1.367; C(4)-C(5), 1.404; C(5)-N(1), 1.368 Å]. This new structure is consistent with all the NMR data (Tables 3 and 5).

Formation of the product **4** can be envisaged as arising as follows: an $[8 + 2]\pi$ cycloaddition of **1** with DMAD forms the 1:1 adduct **2**; this undergoes a Diels-Alder reaction with a further molecule of DMAD to give the primary 1:2 adduct; the latter then undergoes an intramolecular retro-Diels-Alder reaction followed by three consecutive [1,5]-sigmatropic rearrangements of the ester group (Scheme 1). Indeed, thermal [1,5]-sigmatropic rearrangements of 2*H*-pyrroles to give ultimately 1*H*-pyrroles are well documented, sometimes via 3*H*-pyrrole intermediates.¹³ The present results show that an ester group migrates in preference to styryl, and the styryl group in preference to cyano because the products **7** and **8** could not be isolated. It is not clear why the styryl group migrates preferentially to carbon rather than to nitrogen.

[†] Only in this case, lower yields (1-10%) of **3a** was isolated in later runs. The reason was not clear.

Table 1 Reaction of indolizine-3-carbonitriles with dimethyl acetylenedicarboxylate

Entry no.	Indolizine	Substituents			Reaction conditions			Products [yields(%)]		
		R ¹	R ²	R ³	Mol. ratio ^a	Pd/C	Reflux time (h)	2	3	4
1	1a	H	H	H	1:5	add.	24	—	40	—
2	1a	H	H	H	1:5	none	70	—	—	18
3	1b	H	Me	H	1:1	add.	47	—	7	—
4	1b	H	Me	H	1:1	none	45	—	—	7
5	1b	H	Me	H	1:5	add.	10	—	8	22
6	1b	H	Me	H	1:5	none	10	—	—	29
7	1b	H	Me	H	1:5	none	25	—	0.3	42
8	1b	H	Me	H	1:8	add.	25	—	10	35
9	1c	H	CH ₂ Ph	H	1:5	add.	30	—	5	6
10	1d	H	Ph	H	1:5	add.	215	—	13	—
11	1d	H	Ph	H	1:5	none	71	—	—	9
12	1e	Me	H	Me	1:5	add.	77	—	25	—
13	1f	H	CN	H	1:5	add.	260	—	7	—
14	1g	H	CO ₂ Me	H	1:5	add.	336	2	13	—
15	1h	H	—(CH=CH) ₂ —	H	1:5	add.	90	1	—	—

^a Molar ratio of the indolizine and dimethyl acetylenedicarboxylate.**Table 2** Melting points, IR spectra and analytical data for the products 2, 3 and 4

Product	M.p. (°C)	IR spectra v(KBr disk)/cm ⁻¹		Mass spectra (m/z)		Microanalysis (%), Found (required)			Formula (mol. wt.)
		C=O	CN	M ⁺	Other	C	H	N	
3a ^a	88–91			257	226				C ₁₄ H ₁₁ NO ₄ (257)
4a	147–148	1725, 1770	2220	426	384	58.8 (59.3)	4.4 (4.3)	6.4 (6.6)	C ₂₁ H ₁₆ N ₂ O ₈ (426)
3b	123–125	1705, 1740		271	240	66.2 (66.4)	4.9 (4.8)	5.2 (5.2)	C ₁₅ H ₁₃ NO ₄ (271)
4b	152–154	1710, 1770	2250	440	396	60.0 (60.0)	4.5 (4.6)	6.3 (6.4)	C ₂₂ H ₂₀ N ₂ O ₈ (440)
3c	122–123	1680, 1735		347	316	72.4 (72.6)	4.7 (4.9)	4.1 (4.0)	C ₂₁ H ₁₇ NO ₄ (347)
4c	160–163	1715, 1770	2230	516	472	64.9 (65.1)	4.6 (4.7)	5.4 (5.4)	C ₂₈ H ₂₄ N ₂ O ₈ (516)
3d	124–126	1715, 1740		333	302	72.0 (72.1)	4.5 (4.5)	4.5 (4.2)	C ₂₀ H ₁₅ NO ₄ (333)
4d	73–80 ^b	1725, 1770	2210	502	471	— (64.5)	— (4.4)	5.2 (5.6)	C ₂₇ H ₂₂ N ₂ O ₈ (502)
3e	88–91	1685, 1740		285	254	67.6 (67.4)	5.3 (5.3)	4.8 (4.9)	C ₁₆ H ₁₅ NO ₄ (285)
3f	165–167	1715, 1745	2210	282	251	63.7 (63.8)	3.5 (3.6)	9.7 (9.9)	C ₁₅ H ₁₀ N ₂ O ₄ (282)
2g	197–200	1710, 1745	2205	342	314	59.8 (59.7)	3.8 (4.1)	7.9 (8.2)	C ₁₇ H ₁₄ N ₂ O ₆ (342)
3g	150–151	1710, 1743		315	284	60.9 (61.0)	4.0 (4.2)	4.1 (4.4)	C ₁₆ H ₁₃ NO ₆ (315)
2h	82–84	1660, 1725	2190	334	276	— (68.3)	— (4.2)	7.9 (8.4)	C ₁₉ H ₁₄ N ₂ O ₄ (334)

^a Lit., ² 91–92 °C. ^b Crude.**Table 3** ¹H NMR spectra for the products 2, 3 and 4

Product	¹ H NMR spectra (δ)
3a	4.04, 4.08 (6 H, each s, OCH ₃ × 2), 7.43, 7.75 (2 H, ABq, J 5, 6, 7-H), 7.89 (1 H, d, J 7, 3-H), 7.9–8.1 (1 H, m, 4-H), 8.44 (1 H, dd, J 1 and 7, 5-H)
4a	3.77, 3.87, 3.91, 4.03 (12 H, each s, OCH ₃ × 4), 6.96, 6.72 (2 H, ABq, J 12, 1', 2'-H), 7.3–7.4 (3 H, m, 4'', 5'', 6''-H), 8.01 (1 H, s, 5-H)
3b	2.78 (3 H, s, CH ₃), 4.03, 4.06 (6 H, each s, OCH ₃ × 2), 7.31, 7.67 (2 H, ABq, J 5, 6, 7-H), 7.78 (1 H, br s, 3-H), 8.23 (1 H, br s, 5-H)
4b	2.25 (3 H, s, CH ₃), 3.75, 3.84, 3.86, 4.03 (12 H, each s, OCH ₃ × 4), 6.96, 6.72 (2 H, ABq, J 12, 1', 2'-H), 7.12, 7.63 (2 H, each br s, 4'', 6''-H), 7.99 (1 H, s, 5-H)
3c	4.05, 4.08 (6 H, each s, OCH ₃ × 2), 4.41 (2 H, s, CH ₂), 7.2–7.4 (5 H, m, C ₆ H ₅), 7.32, 7.70 (2 H, ABq, J 5, 6, 7-H), 7.80 (1 H, br s, 3-H), 8.35 (1 H, br s, 5-H)
4c	3.76, 3.87, 3.91, 4.04 (12 H, each s, OCH ₃ × 4), 3.86 (2 H, s, CH ₂), 6.65, 6.96 (2 H, ABq, J 11, 1', 2'-H), 6.9–7.3 (5 H, m, C ₆ H ₅), 7.70, 7.73 (2 H, each br s, 4'', 6''-H), 7.84 (1 H, s, 5-H)
3d	4.05, 4.08 (6 H, each s, OCH ₃), 7.4–7.8 (7 H, m, C ₆ H ₅ + 6, 7-H), 8.13 (1 H, br s, 3-H), 8.61 (1 H, br s, 5-H)
4d	3.77, 3.89, 3.91, 4.01 (12 H, each s, OCH ₃ × 4), 6.7–8.2 (10 H, m, 1', 2', 4'', 6'' and 5-H + C ₆ H ₅)
3e	2.74, 2.83 (6 H, each s, CH ₃ × 2), 4.02 (s, 6 H, OCH ₃ × 2), 7.29, 7.54 (2 H, ABq, J 5, 6, 7-H), 7.32 (1 H, br s, 4-H)
3f	4.09, 4.11 (6 H, each s, OCH ₃ × 2), 7.59, 7.91 (2 H, ABq, J 5, 6, 7-H), 8.27 (br s, 1 H, 3-H), 8.74 (1 H, br s, 5-H)
2g	4.10 (9 H, s, OCH ₃ × 3), 6.33 (1 H, br s, 2a-H), 7.55, 7.79 (2 H, ABq, J 5, 6, 7-H), 8.28 (1 H, br s, 3-H), 8.71 (1 H, s, 5-H)
3g	4.05 (9 H, s, OCH ₃ × 3), 7.42, 7.67 (2 H, ABq, J 4.5, 6, 7-H), 8.55 (1 H, s, 3-H), 8.94 (1 H, s, 5-H)

benzene–ethyl acetate as eluent to give the cyclazines 3 or the 1:1 adducts 2 and/or the 1:2 adducts 4. The analytical samples were obtained by recrystallization either from ethanol or hexane–benzene. The results are presented in Tables 1–3.

(b) *In the absence of Pd–C.* A mixture of the indolizine-3-

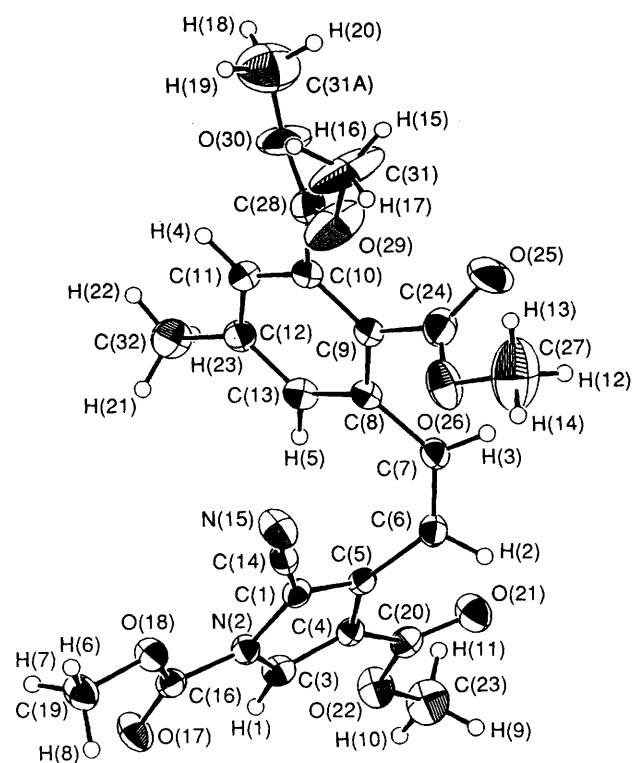
carbonitrile 1 (1.76 mmol) and DMAD (see Table 1) in dry toluene (30 cm³) was heated under reflux for the stated time (Table 1). Chromatography of the residue obtained upon work-up using benzene–ethyl acetate as eluent afforded the pure pyrroles 4 after recrystallization from hexane–benzene.

Table 4 ^{13}C NMR spectra of the products 3

Product	^{13}C NMR spectra (δ)												Substituents
	CH_3O	$\text{C}=\text{O}$	C-1	C-2	C-2a	C-3	C-4	C-5	C-5a	C-6	C-7	C-7a	
3a	51.8, 52.6	164.2, 164.6	127.2	121.6	129.7	115.8	120.6	124.8	132.0	115.5	117.5	112.4	
3b	51.7, 52.5	164.3, 164.8	127.0	121.5	130.9	117.9	129.7	120.9	136.4	115.4	116.5	112.2	22.6 (Me)
3c	51.8, 52.6	164.4, 164.6	126.9	121.5	129.6	116.3	132.0	121.1	139.6	115.7	117.9	111.7	42.7 (CH_2), 140.3 (<i>ipso</i> -Ph), 128.7 (<i>o</i> -Ph), 128.9 (<i>m</i> -Ph), 126.5 (<i>p</i> -Ph)
3d	52.6, 52.8	164.2, 164.6	127.0	122.2	129.7	116.4	139.5	121.3	132.1	114.8	116.3	112.7	140.6 (<i>ipso</i> -Ph), 128.2 (<i>o</i> -Ph), 129.1 (<i>m</i> -Ph), 128.1 (<i>p</i> -Ph)
3e	52.2, 52.4	164.2, 164.8	126.7	117.6	128.6	125.5	128.0	126.9	129.4	113.2	117.6	115.5	17.2 (Me), 18.6 (Me)
3f	52.1, 52.8	162.9, 163.5	128.3	124.8	128.8	121.0	107.4	123.0	131.2	117.3	117.6	112.1	118.5 (CN)
3g	52.6, 52.8	163.5, 164.0	126.5	123.4	128.3	118.7	128.7	122.5	131.1	115.9	117.6	115.7	52.0 (MeO), 166.5 ($\text{C}=\text{O}$)

Table 5 ^{13}C NMR spectra of the products 4

Product	^{13}C NMR spectra (δ)															
	$\text{O}=\text{COCH}_3$	$\text{O}=\text{COCH}_3$	CN	C-2	C-3	C-4	C-5	C-1'	C-2'	C-1''	C-2''	C-3''	C-4''	C-5''	C-6''	
4a	51.9, 52.6, ^a 55.6	162.4, ^a 166.9, 168.6	110.5	103.4	129.9	118.4	129.5	121.0	132.5	148.1	134.5	135.5	134.5	128.9	132.1	
4b	51.9, 52.6, ^a 55.6	162.5, ^a 166.6, 168.9	110.8	105.6	129.2	118.6	129.8	120.8	132.6	148.3	134.8	135.6	135.2	139.3	131.6	
4c	51.9, 52.6, ^a 55.6	162.3, ^a 166.3, 168.7	110.5	103.2	129.9	118.0	129.5	120.9	103.2	148.1	132.8	135.5	134.9	139.4	129.6	other carbons: 41.1 (CH_2), 126.2 (<i>p</i> -Ph), 128.4 (<i>m</i> -Ph), 128.9 (<i>o</i> -Ph), 142.3 (<i>ipso</i> -Ph)

^a The intensity is about two times that of the other similar signals.**Fig. 1** X-Ray crystal structure of **4b**. Selected distances ($\text{\AA}$): C(1)–N(2), 1.404(6); N(2)–C(3), 1.367(6); C(3)–C(4), 1.359(7); C(4)–C(5), 1.427(7); C(1)–C(5), 1.368(7)

Crystal Structure Determination.—A summary of the crystal data and structure refinement details are given in Table 6. The structure was solved by a direct method,¹⁴ and refined by full matrix least-squares. The atoms other than hydrogen were refined anisotropically.

The atomic scattering factors for all atoms and the anomalous dispersion correction factors for atoms other than hydrogen were taken from the literature.^{15–17} All calculations

Table 6 Crystal data for **4b**

Formula	$\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_8$
M (a.m.u.)	440.41
Triclinic	
Space group	$P1$ (#2)
$a/\text{\AA}$	10.8661(9)
$b/\text{\AA}$	15.452(2)
$c/\text{\AA}$	6.4817(2)
$\alpha/^\circ$	91.077(5)
$\beta/^\circ$	99.344(5)
$\gamma/^\circ$	86.287(8)
$U/\text{\AA}^3$	1071.6(2)
Z	2
$D_s/\text{g cm}^{-3}$	1.365
μ/cm^{-1}	8.47
$F(000)$	460
Radiation Cu-K α graphite monochromator	$\lambda = 1.54178 \text{ \AA}$
Diffractometer	Rigaku AFC-5R
Orienting reflections, range	$2\theta, 71.5 < 2\theta < 79.7^\circ$
$T/^\circ\text{C}$	23
Scan method	ω -2 θ
Data collection range	$3.0 < 2\theta < 110.0^\circ$
No. unique data	2700
Total $I > 3\sigma I$	1915
No. of parameters fitted	299
R^a	6.6%
R_w^b	9.5%
Largest shift/esd, final cycle	0.25
Largest positive peak ($\text{e}/\text{\AA}^3$)	0.69
Largest negative peak ($\text{e}/\text{\AA}^3$)	–0.44

^a $R = [\sum |F_o| - |F_c|] / \sum |F_o|$. ^b $R_w = \{[\sum w(|F_o| - |F_c|)^2] / [\sum w(|F_o|)^2]\}^{1/2}$; $w = 1/[\sigma^2(F_o)]$.

were performed using the TEXSAN¹⁸ crystallographic software package of the Molecular Structure Corporation. Fractional atomic coordinates are given in Table 7. Bond lengths, bond angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.*

* For details of the CCDC deposition scheme see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 1*, 1992, issue 1.

Table 7 Fractional atomic coordinates for **4b**

Atom	x	y	z
O(17)	0.3625(3)	0.4883(3)	0.3520(6)
O(18)	0.1586(3)	0.5157(2)	0.2427(5)
O(21)	0.3297(4)	0.6968(3)	1.1987(6)
O(22)	0.4939(3)	0.6398(3)	1.0675(6)
O(25)	-0.2966(6)	0.8937(3)	0.765(1)
O(26)	-0.2793(4)	0.7588(3)	0.6687(7)
O(29)	-0.3744(5)	0.8925(5)	0.297(1)
O(30)	-0.2952(6)	1.0108(4)	0.211(1)
N(2)	0.2467(4)	0.5728(3)	0.5483(6)
N(15)	-0.0822(4)	0.6154(3)	0.3898(8)
C(1)	0.1385(4)	0.6165(3)	0.6009(7)
C(3)	0.3432(4)	0.5872(3)	0.7062(8)
C(4)	0.2996(4)	0.6361(3)	0.8585(7)
C(5)	0.1693(4)	0.6558(3)	0.7915(7)
C(6)	0.0820(5)	0.7038(3)	0.9099(8)
C(7)	-0.0021(5)	0.7687(3)	0.8459(8)
C(8)	-0.0213(5)	0.8156(3)	0.6474(8)
C(9)	-0.1417(5)	0.8498(3)	0.5620(8)
C(10)	-0.1580(5)	0.9005(3)	0.3841(8)
C(11)	-0.0567(6)	0.9171(3)	0.2907(8)
C(12)	0.0626(5)	0.8841(3)	0.3686(9)
C(13)	0.0777(5)	0.8343(3)	0.5464(9)
C(14)	0.0173(5)	0.6139(3)	0.4785(8)
C(16)	0.2640(5)	0.5214(3)	0.3712(8)
C(19)	0.1636(5)	0.4560(4)	0.0689(9)
C(20)	0.3739(5)	0.6615(3)	1.0578(9)
C(23)	0.5732(6)	0.6609(5)	1.260(1)
C(24)	-0.2452(6)	0.8372(5)	0.675(1)
C(27)	-0.384(1)	0.7521(8)	0.780(2)
C(28)	-0.2840(6)	0.9402(5)	0.289(1)
C(31) ^a	-0.504(1)	0.918(1)	0.232(3)
C(31A) ^a	-0.376(2)	1.067(2)	0.105(5)
C(32)	0.1718(6)	0.9015(4)	0.267(1)

^a The ester group at the C(10) position is disordered at the two sites, C(28)–O(30)–O(29)–C(31) and C(28)–O(29)–O(30)–C(31A), for which the occupancy ratio (0.6 and 0.4) was adjusted to equalize the temperature factors of C(31) and C(31A) at the last stage of refinement.

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