Synthesis and Spectral Properties of the 1-Aryl-2-phenyl-4-oxo-4,5,6,7-tetrahydroindole Oximes and of Their Beckmann Rearrangement Products

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Under Beckmann conditions the oximes of the 1-aryl-2-phenyl-4-oxo-4,5,6,7-tetrahydroindoles **2a-k** are rearranged yielding as the sole product, 1-aryl-2-phenyl-4-oxo-1,4,5,6,7,8-hexahydropyrrolo[3,2-*c*]azepine **3a-k**. The spectral data (ir, uv, ms) of these two classes of compounds are also discussed.

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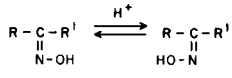
We reported recently on the synthesis and mass spectrometry of a series of 1-aryl-2-phenyl-4-oxo-4,5,6,7-tetrahydroindole derivatives **1a-k** possessing some interesting biological activity [1].

Keeping with this line of interest, we here report on the synthesis of the oximes **2a-k** of these ketones and their rearrangement under Beckmann conditions to the corresponding lactams **3a-k**. The spectral properties of these compounds (**2** and **3**) are investigated and discussed. We have found that these data could be used sucessfully to distinguish between these classes of compounds and to establish the structure of the lactams **3**.

Preparation of Oximes **2a-k**.

By heating at reflux temperature a methanolic solution of ketones **1a-k** and hydroxylamine hydrochloride in presence of sodium acetate [2], the oximes **2a-k** were obtained as a mixture of geometrical isomers **2** and **2'**. In some cases these mixtures were separated by preparative thin layer chromatography followed by recrystallization from a mixture of chloroform and methanol. Isomers **2a** and **2'a** were obtained in a ratio of two to one. The minor and low melting point isomer (200-205°) rearranged completely after it had melted to the more stable and high melting point isomer (245-250°). A similar but partial rearrangement was also observed during the recrystallization of the low melting isomer. Similar isomerization of oximes in acidic medium [3] (protonic acid) have been reported.



Structure **2a** (Scheme 1) was assigned to the high melting point isomer on the basis of the following sequence of events: low mp isomer (recrystallization or heat) → high mp isomer (Beckmann) → lactam **3a**. The Beckmann rearrangement has been the subject of several investigations [4]. The mechanism of this reaction is well documented and involves the migration of the bond anti to the leaving group. The lactam **3a** whose structure is discussed later was therefore generated from the oxime having the hydroxyl group oriented toward the heterocycle. Consequently structure **2a** is attributed to the major and high melting point oxime. Therefore the structure of

Table 1

Compound	Mp °C	Yield %	Molecular formula	Elemental Analysis Calcd. (Found) C		H	
2a	245-250	67	$C_{22}H_{22}ON_2$	79.9	(79.6)	6.7	(6.7)
2'a	200-205	32	$C_{22}H_{22}ON_2$	79.9	(79.7)	6.7	(6.7)
2b	210-215	95	$C_{23}H_{24}ON_2$	80.2	(79.9)	7.0	(7.2)
2c	224-227	97	$C_{23}H_{24}ON_2$	80.2	(80.0)	7.0	(7.2)
2d	243-247	95	$C_{23}H_{24}ON_2$	80.2	(79.9)	7.0	(6.9)
2e	255-259	95	$C_{22}H_{21}BrON_2$	64.5	(64.7)	5.1	(5.1)
2f	235-240	70	$C_{23}H_{24}O_2N_2$	76.6	(76.7)	6.7	(6.9)
2g	223-225	95	$C_{22}H_{21}O_3N_3$	70.3	(70.2)	5.6	(5.5)
2h	221-225	95	$C_{21}H_{20}ON_2$	79.7	(79.8)	6.4	(6.4)
2i	231-235	95	$C_{21}H_{20}ON_2$	79.7	(79.9)	6.4	(6.4)
2j	245-248	95	$C_{21}H_{20}ON_2$	79.7	(79.9)	6.4	(6.5)
2k	240-245	96	$C_{20}H_{17}BrON_2$	63.0	(62.8)	4.5	(4.4)

Table 2

Compound	Mp °C	Yield %	Molecular formula	Elemental Analysis Calcd. (Found) C		H	
3a	300-303	67	$C_{22}H_{22}O_2N$	79.9	(79.8)	6.7	(6.6)
3b	210-213	80	$C_{23}H_{24}ON_2$	80.2	(80.0)	7.0	(7.2)
3c	270-273	73	$C_{23}H_{24}ON_2$	80.2	(79.7)	7.0	(7.2)
3d	251-253	90	$C_{23}H_{24}ON_2$	80.2	(79.7)	7.0	(7.2)
3e	293-295	73	$C_{22}H_{21}BrON_2$	64.5	(64.4)	5.1	(5.2)
3f	220-223	85	$C_{23}H_{24}O_2N_2$	76.6	(76.3)	6.7	(6.4)
3g	241-245	40	$C_{22}H_{21}O_3N_3$	70.3	(70.2)	5.6	(5.6)
3h	216-219	84	$C_{21}H_{20}ON_2$	79.7	(79.8)	6.4	(6.4)
3i	250-252	78	$C_{21}H_{20}ON_2$	79.7	(79.8)	6.4	(6.5)
3j	211-215	85	$C_{21}H_{20}ON_2$	79.7	(79.6)	6.4	(6.4)
3k	277-280	76	$C_{20}H_{17}BrON_2$	63.0	(62.8)	4.5	(4.6)

Table 3

Compound	UV (a) λ max (log ε)	IR ν cm^{-1}
2a	253 (3.3), 290 (3.2)	3240-3220, 1650,
2'a	sh 243 (2.9), 285 (2.8)	3470-3450, 1655
2b	245 (4.4), 278 (4.3)	3200-3100, 1640
2c	250 (4.5), 277 (4.5)	3200-3100, 1640
2d	250 (4.5), 270 (4.3)	3200-3100, 1640
2e	253 (4.6), 280 (4.8)	3200-3100, 1640, 1630
2f	246 (4.5), 274 (4.4)	3300-3100, 1650
2g	253 (4.6), 285 (4.4)	3300-3100, 1680
2i	246 (4.2), 270 (4.0)	3300-3200, 1640
2j	250 (4.3), 270 (4.3)	3400-3200, 1640
2k	253 (4.5), 287 (4.2)	3200-3100, 1640, 1630

(a) The ir spectra of these oximes were measured in nujol. Shoulder shown by sh.

Table 4

Compound	UV (a) λ max (log ε)	IR ν cm^{-1}
3a	sh 240 (3.3), 284 (3.2)	3480, 1625
3b	227 (4.5), 281 (4.4)	3420, 1625
3c	228 (4.4), 281 (4.3)	3420, 1625
3d	227 (4.2), 281 (4.0)	3420, 1625
3e	245 (4.4), 277 (4.2)	3420, 1625
3f	231 (4.5), 282 (4.3)	3420, 1630
3g	245 (4.5), sh 274 (4.4)	3420, 1660
3h	231 (4.3), 281 (4.2)	3420, 1625
3i	228 (4.4), 281 (4.3)	3420, 1625
3j	220 (4.2), 281 (4.2)	3420, 1625
3k	246 (4.5), 282 (4.3)	3420, 1625

(a) Shoulder shown by sh.

the minor isomer **2'a** has the hydroxyl group oriented in the opposite direction toward the saturated ring.

Beckmann Rearrangement of the Oximes **2a-k**.

When the two isomeric oximes **2a** and **2'a** were separately heated for 20 minutes at 150° with polyphosphoric acid according to the procedure of Lansbury [5-6], only one lactam **3a** was obtained in high yield. This result demonstrates [i] that the rate of isomerization of the oxime (**2'a** → **2a**) is faster than the rate of Beckmann rearrangement (**2a** → **3a**) and [ii] that the mixture of isomeric oximes need not be separated prior to rearrangement. After purification the lactams were obtained as nice crystals whose melting points are generally higher than the melting points of the corresponding mixture of isomeric oximes **2** and **2'**. Yields, melting points and elemental analysis of compounds **2** and **3** are reported in Tables 1 and 2.

Scheme 1

3a-k

a, R = CH_3, Ar = C_6H_5- **b**, R = CH_3, Ar = 2-$CH_3C_6H_4$-
c, R = CH_3, Ar = 3-$CH_3C_6H_4$- **d**, R = CH_3, Ar = 4-$CH_3C_6H_4$-
e, R = CH_3, Ar = 4-BrC_6H_4- **f**, R = CH_3, Ar = 4-$CH_3OC_6H_4$-
g, R = CH_3, Ar = 3-$ON_2C_6H_4$- **h**, R = H, Ar = 2-$CH_3C_6H_4$-
i, R = H, Ar = 3-$CH_3C_6H_4$- **j**, R = H, Ar = 4-$CH_3C_6H_4$-
k, R = H, Ar = 4-BrC_6H_4-

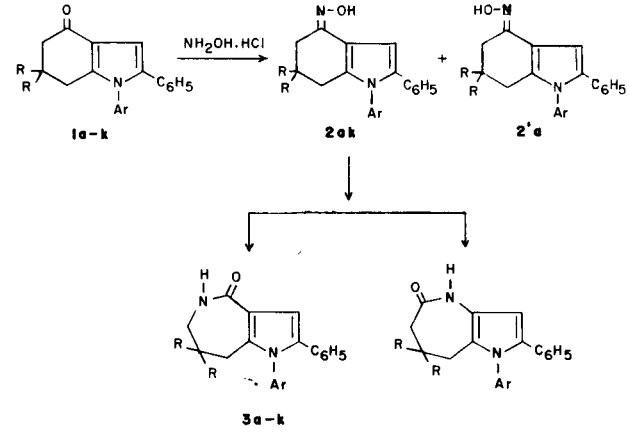


Table 5

Compound	Mass Spectra (a) m/z (relative intensity)
2a	330 (100), 313 (6.4), 270 (7.4), 258 (7.4), 257 (24.0), 77 (13.2), 69 (9.3), 57 (16.1), 55 (10.9), 43 (22.5), 41 (13.7).
2b	344 (100), 329 (11.4), 328 (19.0), 327 (16.1), 313 (9.5), 285 (22.8), 272 (10.4), 271 (29.5), 256 (11.4), 255 (9.5), 244 (9.5).
2c	344 (100), 328 (23.1), 327 (29.5), 326 (18.1), 285 (27.2), 272 (17.7), 271 (40.9), 244 (12.7), 148 (13.6), 91 (15.4), 44 (54.5).
2d	344 (100), 329 (8.8), 328 (7.3), 327 (10.7), 286 (7.8), 285 (18.5), 272 (10.4), 271 (26.4), 256 (8.3), 244 (8.5), 91 (7.6).
2e	410 (100), 408 (90.3), 256 (96.8), 255 (61.8), 230 (64.5), 155 (35.4), 128 (32.2), 127 (37.0), 77 (32.2), 44 (67.7).
2h	316 (100), 315 (12.3), 300 (1.6), 299 (23.3), 271 (9.6), 255 (9.6), 143 (11), 65 (12.3), 57 (16.6), 55 (13), 43 (13).
2i	316 (100), 315 (15.0), 300 (7.5), 299 (16.2), 298 (7.5), 287 (8.7), 271 (7.5), 270 (7.5), 269 (8.7), 91 (6.1), 44 (37.5).
2j	316 (100), 315 (12.0), 301 (8.0), 299 (19.0), 287 (7.0), 272 (7.0), 271 (9.0), 269 (7.0), 255 (6.0), 44 (20), 40 (16).
2k	382 (100), 381 (35.7), 380 (80.9), 379 (16.6), 363 (16.6), 300 (19.0), 256 (23.8), 255 (28.5), 230 (16.6), 65 (15.4), 44 (19.0).

(a) Reported in this table are the parent ion and the 10 most intense ions.

Table 6

Compound	Mass Spectra (a) m/z (relative intensity)
3a	330 (100), 272 (11.3), 232 (10.0), 230 (12.5), 180 (13.8), 109 (11.3), 97 (20.8), 95 (14.2), 85 (17.5), 83 (25.3), 77 (21.7).
3b	344 (100), 329 (40.0), 300 (13.3), 286 (16.6), 274 (38.3), 258 (26.6), 246 (14.0), 245 (13.3).
3c	344 (100), 329 (21.8), 301 (12.5), 287 (12.5), 286 (18.7), 274 (55.4), 246 (19.5), 245 (15.6), 244 (14.0), 91 (23.4), 44 (21.8).
3d	344 (100), 329 (23.6), 287 (19.0), 286 (23.6), 273 (15.9), 246 (19.0), 244 (14.6), 194 (14.0), 91 (31.8), 65 (16.8), 44 (63.1).
3h	316 (100), 299 (15.7), 287 (18.4), 286 (42.1), 273 (14.4), 246 (13.1), 244 (14.4), 243 (10.5), 91 (11.8), 44 (27.6).
3e	410 (100), 409 (31.3), 408 (98.0), 395 (31.3), 393 (35.2), 340 (47.0), 338 (43.1), 230 (78.4), 128 (25.4), 115 (27.4), 44 (58.8).
3k	382 (100), 381 (35.3), 380 (92.3), 364 (38.4), 362 (33.8), 352 (32.3), 350 (30.7), 243 (27.6), 230 (36.9), 116 (27.6), 77 (29.2).

(a) See Table 5.

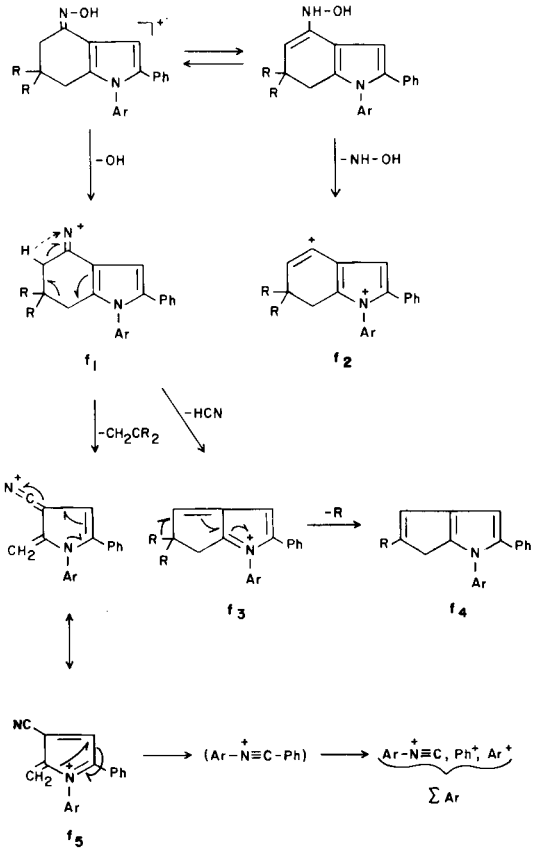
Discussion of Spectral Data.

[a] IR and UV Spectra. Tables 3 and 4.

A common feature of the ir spectra of the oximes **2a-k** is the presence [i] of a large absorption band between 3200-3100 cm^{-1} attributed to the stretching vibration of the hydroxyl group and [ii] another absorption band between 1640-1650 cm^{-1} corresponding to the stretching vibration of the C=N group. Similarly two absorption bands are also observed in the ir spectra of the lactams **3a-k**. The high (3420-3480 cm^{-1}) and low (1625-1640 cm^{-1}) wave number absorption bands are characteristic of the NH and amide group, respectively. The absorption peak at 1625-1640 cm^{-1} indicates that the carbonyl group of the lactam is conjugated with the aromatic heterocycle.

The uv spectra of the oximes **2a-k** and of their corresponding lactams **3a-k** show two absorption bands. The main difference between these two classes of compounds is the hypsochromic shift (10-20 nm) suffered by the short wave length absorption band of the lactams **3a-k**.

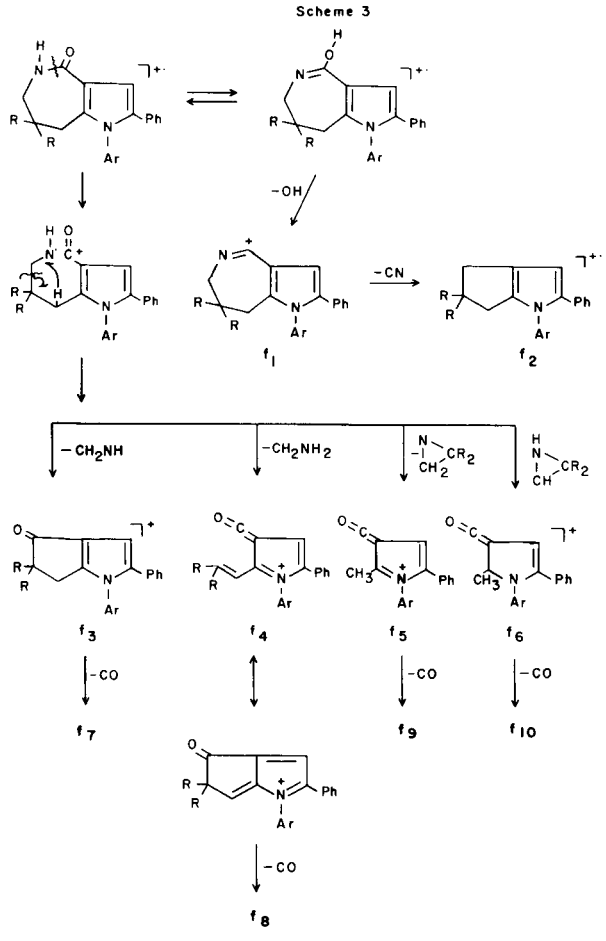
Scheme 2



[b] Mass Spectra.

Further evidence in favour of structure **3a-k** of the lactams was gained from the comparison of their mass spectra with the mass spectra of the corresponding oximes **2a-k**. The parent ion of compounds **2** and **3** is the base peak. The positive charge in the molecular ion is probably localized in the region of the oximino group, since the intense ions usually formed during the first steps of the fragmentation and which are characteristic of the arylpyrrole and the arylindole (M-H), (M-HCN) and M-H_2CN) are not observed [7-9]. Beside this common feature, the mass spectra of compounds **2** and **3** show striking differences. The molecular ion of the oximes **2** eliminates first of all a hydroxyl or a hydroxylamine group yielding ions **f1** and **f2** (Scheme 2). Oximes are usually characterized by this type of fragmentation and especially the oximes of cyclic ketones [10-12]. Ion **f1** can eliminate a molecule of HCN or an

Scheme 3



olefin (CH_2=CR_2) giving rise to ions **f3** and **f5**. This ion **f5** retains carbon atoms C_5 and C_6 of the heterocycle. The intensy of ion **f5** is generally greater than that of other ions (Table 7). In the mass spectra of compounds **3** ion **f1** resulting from the elimination of a hydroxyl group is present but it has a low relative intensy. Upon elimination of CN it yields ion **f2**. Fragments resulting from the elimination of NHOH, (M-NHOH) are not observed. The formation of the important ions **f3**, **f4**, **f5** and **f6** is accounted for from a common intermediate (obtained by α cleavage of the molecular ion) through the elimination of methyleneimine, methylamine or the loss of the nitrogen atom and carbon atoms C_6 and C_7 of the saturated ring. These ions yielded fragments **f7**, **f8**, **f9** and **f10** upon elimination of a molecule of carbon monoxide. This result demonstrates that the carbonyl group is conjugated with the heterocycle. The type of fragmentation discussed is characteristic of lactams and especially caprolactam [13]. It is interesting to point out that the aromatic ions and the fragments generated from them are only observed in the last steps of the fragmentation of oximes and lactams. The differences observed between the mass spectra of compounds **2** and **3** lead to the following conclusion: rearrangement of the oximes **2** to the corresponding lactams **3** does not take place in the gaseous phase in the mass spectrometer prior to or after ionization. Similar behaviour was reported for other compounds [14-15]. Consequently mass spectrometry can be successfully used for the investigation of this class of compounds.

EXPERIMENTAL

Unless otherwise specified uv and ir spectra were measured in ethanol and chloroform solutions, respectively, with Perkin-Elmer 292 and 472 spectrophotometers. The mass spectra were obtained by using a Varian Mat 112S and MX-1303 spectrometers at 80 and 50 eV respectively. All melting points were taken on a Reichert Thermovar apparatus and are uncorrected.

Synthesis of Oximes **2a-k**. General Procedure.

A mixture of **1** (3 mmoles) methanol (45 ml) and hydroxylamine hydrochloride (15 mmoles dissolved in the minimum amount of water) was heated in the presence of sodium acetate for 2 hours at the reflux temperature. At the end of this period, cold water was added and the resulting precipitate was filtered off, washed with water and dissolved in chloroform. The chloroform solution was dried over anhydrous sodium sulfate and then concentrated on the water bath. The oxime was recrystallized from a mixture of chloroform and methanol. In one case (series a)

Table 7

Intensities of the Characteristic Ions in the Mass Spectra of Compounds **2**. $\%\Sigma_{40}$

Compound	W_m (a)	f_1 (m/z)	f_2 (m/z)	f_3 (m/z)	f_4 (m/z)	f_5 (m/z)	Σ_{Ar} (b)
a	30.3	1.8 (313)	0.4 (218)	———	0.4 (271)	6.7 (274)	5.2
b	17.8	2.8 (327)	0.7 (312)	0.7 (300)	3.9 (285)	5.2 (288)	5.4
c	11.5	3.4 (327)	1.1 (312)	0.5 (300)	3.1 (285)	4.7 (288)	6.0
d	16.1	1.7 (327)	0.5 (312)	0.8 (300)	2.9 (285)	4.2 (288)	5.4
e	3.8	0.8 (393)	0.2 (378)	0.2 (366)	1.1 (351)	1.1 (354)	11.3
h	14.0	3.2 (299)	0.6 (284)	0.6 (272)	1.3 (271)	1.3 (271)	5.2
i	14.0	2.2 (299)	0.7 (284)	0.6 (272)	10.5 (271)	10.5 (271)	4.2
j	17.5	3.3 (299)	0.7 (284)	1.2 (272)	1.5 (271)	1.5 (271)	4.1
k	6.6	0.9 (365)	0.3 (350)	0.4 (338)	0.6 (337)	0.6 (337)	8.0

(a) $W_m = (\Sigma Im/\Sigma_{40}I)100$, W_m refers to molecular ion; the units are percentage of total ion current. (b) Σ_{Ar} Sum of the intensities of ions $AR\text{-}N^+{\equiv}CPh$ and of fragments generated from them.

Table 8

Intensities of the Characteristic Ions in the Mass Spectra of Compounds **3**. $\%\Sigma_{40}$

Compound	W_m (a)	f_1 (m/z)	f_2 (m/z)	f_3 (m/z)	f_4 (m/z)	f_5 (m/z)	f_6 (m/z)	$\Sigma_{f_7\text{-}f_{10}}$	Σ_{A_r} (b)
a	26.1	0.7 (313)	1.1 (287)	———	———	10.1 (260)	0.8 (259)	8.1	9.7
b	11.8	0.7 (327)	0.7 (301)	0.5 (315)	0.7 (314)	4.5 (274)	1.0 (273)	6.2	8.6
c	15.6	1.2 (327)	1.9 (301)	0.8 (315)	0.7 (314)	8.6 (274)	1.1 (273)	10.3	7.6
d	10.8	1.0 (327)	1.4 (301)	0.7 (315)	0.6 (314)	5.4 (274)	1.7 (273)	7.9	9.5
e	5.5	1.9 (393)	0.8 (367)	0.4 (381)	0.7 (380)	2.6 (340)	1.3 (339)	3.5	9.5
h	16.7	2.6 (299)	2.4 (273)	3.0 (287)	7.0 (286)	1.2 (274)	2.4 (273)	6.9	5.3
k	9.7	———	2.0 (339)	1.8 (353)	3.1 (352)	———	2.0 (311)	———	17.2

For (a) and (b) see Table 7.

the mixture of isomeric oximes was separated by preparative thin layer chromatography (eluent light petroleum-ethyl acetate 60:40) followed by recrystallization from a mixture of chloroform and methanol. The less polar isomer (32%) had the low melting point.

Rearrangement of the Oxime **2** Into the Lactam **3**. General Procedure.

A mixture of the oxime **2** (1 mmole) and polyphosphoric acid 6.3 g (15-20 times the mass of the oxime) was heated at 140-150° for 15-20 minutes. At the end of this period ice and water were added to the dark brown mixture and the acid was neutralized by careful addition of 10% sodium hydroxide solution. The precipitate was filtered off, thoroughly washed with water and dissolved in dichloromethane. After drying over anhydrous sodium sulfate the organic solution was concentrated on the water bath. the analytical sample was obtained by recrystallization from a mixture of dichloromethane and methanol.

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