SYNTHESIS AND LOCAL ANESTHETIC ACTIVITY OF ALKENYL-SUBSTITUTED AMINOACETANILIDES

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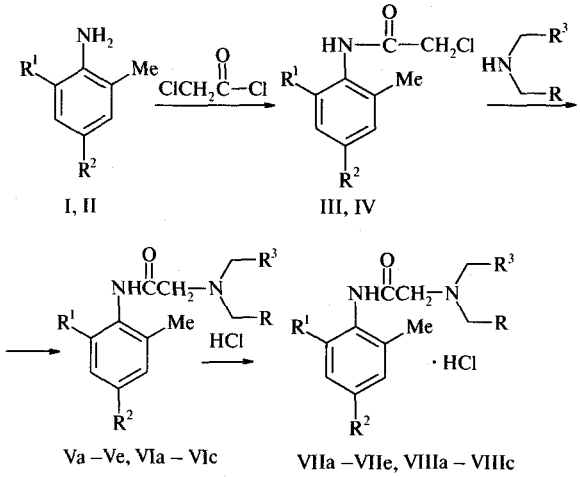
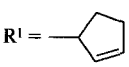
The well-known local anesthetics trimecaine and lidocaine are derivatives of 2,4,6-trimethyl- and 2,6-dimethylaniline, respectively [1]. However, the set of accessible 2,6-disubstituted aninine fragments is very restricted, which is related to general difficulties in the synthesis of *ortho-ortho* disubstituted arylamines. Recently, a new method was suggested for the synthesis of *ortho*-alkenylanilines, which can be used to obtain 2,6-disubstituted arylamines with more complicated structures [2].

In this work, we have synthesized a series of aminoacetyl derivatives of 2-methyl-6-(cyclopent-2′-en-1′-yl)aniline (I) and 2,4-dimethyl-6-(1′-methyl-2′-buten-1′-yl)aniline (II) and studied their local anesthetic properties.



I, II — III, IV — Va – Ve, VIa – VIc — VIIa – VIIe, VIIIa – VIIIc

I, III, V, VII: R^1 =  , R^2 = H;

II, IV, VI, VIII: R^1 = –CH(CH$_3$)CH=CHCH$_3$, R^2 = Me;
R + R^3 = $CH_2CH_2CH_2$ (a), CH_2OCH_2 (b), CH_2NHCH_2 (c), $CH_2N(CH_3)CH_2$ (d); R = R^3 = CH_3 (e).

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First, reactions of chloroacetyl chloride with amines (I) or (II) in toluene in the presence of K_2CO_3 led to N-(2-chloroacetyl)-2-methyl-6-(cyclopent-2′-en-1′-yl)aniline (III) and N-(2-chloroacetyl)-2,4-dimethyl-6-(1′-methyl-2′-buten-1′-yl)aniline (IV) with a yield of 80 – 86%.

Subsequent condensation of chloroacetanilide III with piperidine, morpholine, piperazine, N-methylpiperazine, and N,N′-diethylamine led to 2-[2′-(cyclopent-2″-en-1″-yl)-6′-methylphenylamino]-2-oxoethylpiperidine (Va), -morpholine (Vb), -piperazine (Vc), -N′-methylpiperazine (Vd), and N-(diethylaminoacetyl)-2-methyl-6-(cyclopent-2′-en-1′-yl)aniline (Ve). The reactions of anilide IV with piperidine, morpholine, and piperazine under similar conditions gave 2-[2′-(1″-methyl-2″-buten-1″-yl)-4′,6′-dimethylphenylamino]-2-oxoethylpiperidine (VIa), -morpholine (VIb), and -piperazine (VIc). Passing gaseous HCl through the solutions of amines V and VI in hexane led to precipitation of the corresponding hydrochlorides VIIa – VIIe and VIIIa – VIIc. The resulting hydrochlorides were tested for local anesthetic activity in the form of aqueous solutions.

EXPERIMENTAL CHEMICAL PART

The ^{1}H and ^{13}C NMR spectra were measured on a Bruker AM-300 spectrometer (Germany) operating at a working frequency of 300 and 75 MHz, respectively (solvent, $CDCl_3$; internal standard, TMS). The melting points were determined in a Boetius device. The purity of the initial reagents and the reaction products was checked by gas chromatography on a Chrom 5 instrument (Russia) and by TLC on Silufol UV-254 plates (Czech Republic) eluted in a CH_2Cl_2 – MeOH (95 : 5) mixture.

Chloroacetylation of anilines I and II. To a mixture of 48 g K_2CO_3 (0.1 mole) alkenylaniline I or II, and 100 ml benzene or toluene in a three-neck flask equipped with mechanical stirrer, dropping funnel, and reflux cooler were gradually (dropwise) added with stirring 22.6 g (0.2 mole) of

freshly distilled chloroacetyl chloride. Upon accomplishing this procedure, the mixture was heated to boiling, treated at this temperature for 2 h, and filtered hot. Then the filtrate was evaporated to dryness at a reduced pressure and the residue was recrystallized from benzene to obtain compounds III and IV.

N-Chloroacetyl-2-methyl-6-(cyclopent-2′-en-1′-yl)aniline (III). Yield, 80%; m.p., 120 – 122°C; $C_{14}H_{16}ClNO$; ^1H NMR spectrum (δ, ppm): 1.60 – 2.60 (m, 4H, $2CH_2$), 2.25 (s, 3H, CH_3), 4.05 (m, 1H, CH), 4.21 (s, 2H, CH_2), 5.75 – 6.05 (m, 2H, HC=CH), 7.10 – 7.45 (m, 3H, ArH), 8.10 (s, 1H, NH); ^{13}C NMR spectrum (δ, ppm): 18.41 (CH_3), 32.45, 32.52 (C-4″, C-5″), 42.76 (C-Cl), 46.83 (C-1″), 136.02 (C-1′), 143.25 (C-2′), 128.25 (C-3′), 133.19 (C-4′), 128.43 (C-5′), 132.53 (C-6′), 133.51 (C-2″), 125.43 (C-3″).

N-Chloroacetyl-2,4-dimethyl-6-(1′-methyl-2′-buten-1′-yl)aniline (IV). Yield, 86%; m.p., 105°C; $C_{15}H_{20}ClNO$; ^1H NMR spectrum (δ, ppm): 1.33 (d, 3H, J 7.15 Hz, CH_3), 1.69 (d, 3H, J 5.05 Hz, CH_3), 2.20 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 3.50 (m, 1H, H-1′), 4.23 (s, 2H, CH_2), 5.50 (m, 2H, HC=CH), 6.95 (s, 1H, ArH), 6.97 (s, 1H, ArH), 7.95 (bs, 1H, NH); ^{13}C NMR spectrum (δ, ppm): 17.63, 18.39, 20.29, 21.25, 37.80 (C-1′), 42.76 (C-Cl), 164.51 (C=O), 137.75 (C-1), 141.79 (C-2), 125.48 (C-3), 124.41 (C-5), 129.53 (C-4), 135.79 (C-6), 135.50 (C-2′), 129.53 (C-3′).

Aminoacetic acid anilides Va – Ve and VIa – VIc. To 0.02 mole of compound III or IV in a round-bottom flask with reflux cooler was added 75 ml of toluene and the mixture was heated to 80°C. After that, the corresponding amine was added in excess (0.20 mole) and the reaction mixture was treated at this temperature for another 4 h and cooled. The precipitate of amine hydrochloride was separated by filtration. The filtrate was evaporated to dryness and the residue recrystallized from toluene.

2-[2′-Methyl-6′-(cyclopent-2″-en-1″-yl)phenylamino]-2-oxoethylpiperidine (Va). Yield, 76%; m.p., 90 – 92°C; $C_{19}H_{26}N_2O$; ^1H NMR spectrum (δ, ppm): 3.97 (m, 1H, H-1″), 5.70 – 5.89 (m, 1H, H-2″, H-3″), 2.30 (m, 3H, H-4″a, b, H-5″a), 1.56 (m, 1H, H-5″b), 2.15 (s, 1H, CH_3), 3.08 (s, 2H, H-1a, b), 1.40 – 2.52 (m, 10H, $5CH_2$), 7.00 (m, 3H, ArH), 8.77 (s, 1H, NH); ^{13}C NMR spectrum (δ, ppm): 18.73 (CH_3), 23.70, 26.41, 55.38 (C-piperidine), 62.67 (C-1), 169.39 (C-2), 135.76 (C-1′), 142.75 (C-2′), 127.37 (C-3′), 133.08 (C-4′), 128.39 (C-5′), 132.12 (C-6′), 46.95 (C-1″), 133.70 (C-2″), 125.02 (C-3″), 32.67 (C-4″), 32.38 (C-5″).

2-[2′-Methyl-6′-(cyclopent-2″-en-1″-yl)phenylamino]-2-oxoethylmorpholine (Vb). Yield, 69%; m.p., 85 – 87°C; $C_{18}H_{24}N_2O_2$; ^1H NMR spectrum (δ, ppm): 1.65 – 2.40 (m, 4H, $4CH_2$), 2.20 (s, 3H, CH_3), 2.70 (m, 4H, $2CH_2$), 3.75 (m, 4H, $2CH_2$), 3.20 (s, 2H, CH_2), 3.99 (m, 1H, CH), 5.70 – 5.97 (m, 2H, HC=CH), 7.10 (m, 3H, ArH), 8.69 (s, 1H, NH); ^{13}C NMR spectrum (δ, ppm): 18.84 (CH_3), 62.23 (C-1), 168.59 (C-2), 46.90 (C-1″), 133.52 (C-2″), 127.64 (C-3″), 32.62 (C-4″), 32.40 (C-5″), 135.73 (C-1′), 142.69 (C-2′), 127.64 (C-3′), 123.70 (C-4′), 128.71 (C-5′), 132.35 (C-6′), 54.22, 67.11 (C-morpholine).

2-[2′-Methyl-6′-(cyclopent-2″-en-1″-yl)phenylamino]-2-oxoethylpiperazine (Vc). Yield, 72%; m.p., 85°C; $C_{18}H_{25}N_3O$; ^1H NMR spectrum (δ, ppm): 1.60 – 2.80 (m, 12H, $6CH_2$), 2.23 (s, 3H, CH_3), 2.65 (s, 1H, NH), 3.20 (s, 2H, CH_2), 3.97 (m, 1H, CH), 5.70 – 5.95 (m, 2H, HC=CH), 7.00 – 7.15 (m, 3H, ArH), 8.70 (s, 1H, NH); ^{13}C NMR spectrum (δ, ppm): 18.81 (CH_3), 61.56 (C-1), 186.92 (C-1″), 133.48 (C-2″), 132.30 (C-3″), 32.59 (C-4″), 32.36 (C-5″), 135.71 (C-1′), 142.69 (C-2′), 127.54 (C-3′), 125.07 (C-4′), 128.63 (C-5′), 132.70 (C-6′).

2-[2′-Methyl-6′-(cyclopent-2″-en-1″-yl)phenylamino]-2-oxoethyl-N-methylpiperazine (Vd). Yield, 56%; m.p., 55°C; $C_{19}H_{27}N_3O$; ^1H NMR spectrum (δ, ppm): 1.60 – 2.70 (m, 12H, $6CH_2$), 2.25 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.20 (s, 2H, CH_2), 4.00 (m, 1H, CH), 5.70 – 5.95 (m, 2H, HC=CH), 7.00 – 7.15 (m, 3H, ArH), 8.72 (s, 1H, NH); ^{13}C NMR spectrum (δ, ppm): 47.16 (CH_3), 18.81 (CH_3), 61.56 (C-1), 168.92 (C-2), 46.77 (C-1″), 133.48 (C-2″), 132.30 (C-3″), 32.59 (C-4″), 32.36 (C-5″), 135.71 (C-1′), 142.70 (C-2′), 127.64 (C-3′), 125.98 (C-4′), 128.63 (C-5′), 132.70 (C-6′).

N-(Diethylaminoacetyl)-2-methyl-6-(cyclopent-2′-en-1′-yl) aniline (Ve). Yield, 48%; m.p., 54°C; $C_{18}H_{26}N_2O$; ^1H NMR spectrum (δ, ppm): 1.12 (t, 6H, $2CH_3$), 2.71 (q, 4H, $2CH_2$), 1.65 – 2.40 (m, 4H, $2CH_2$), 2.24 (s, 3H, CH_3), 2.91 (s, 2H, CH_2), 4.00 (m, 1H, CH), 5.72 – 5.97 (m, 2H, HC=CH), 7.10 (m, 3H, ArH), 9.00 (s, 1H, NH); ^{13}C NMR spectrum (δ, ppm): 12.40 – 48.69 (CH_2), 18.55 (CH_3), 57.37 (CH_2), 170.45 (C=O), 134.73 (C-1′), 133.48 (C-2′), 124.70 (C-3′), 32.65 (C-4′), 32.16 (C-5′), 135.56 (C-1), 145.81 (C-2), 127.33 (C-3), 132.89 (C-4), 128.34 (C-5), 132.04 (C-6).

2-[2′,4′-Dimethyl-6′-(1″-methyl-2″-buten-1″-yl)phenyl amino]-2-oxoethylpiperidine (VIa). Yield, 82%; m.p., 55°C; $C_{20}H_{30}N_2O$; ^1H NMR spectrum (δ, ppm): 1.36 (d, 3H, J 7.11 Hz, CH_3), 1.70 (d, 3H, J 5.05 Hz, CH_3), 1.50 (m, 2H, CH_2), 1.65 (m, 4H, $2CH_2$), 2.61 (m, 4H, $2CH_2$), 2.19 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.12 (s, 2H, CH_2), 3.50 (m, 1H, H-1′), 5.50 (m, 2H, HC=CH), 6.93 (s, 1H, ArH), 6.95 (s, 1H, ArH), 8.75 (bs, 1H, NH); ^{13}C NMR spectrum (δ, ppm): 17.97, 18.76, 20.52, 21.21 (CH_3), 23.73, 26.35, 55.41 (C-piperidine), 169.50 (C-2), 62.71 (C-1), 136.90 (C-1′), 41.91 (C-2′), 125.25 (C-3′), 123.66 (C-5′), 129.37 (C-4′), 130.44 (C-6′), 135.88 (C-3″), 135.59 (C-4″).

2-[2′,4′-Dimethyl-6′-(1″-methyl-2″-buten-1″-yl)phenyl amino]-2-oxoethylmorpholine (VIb). Yield, 83%; m.p., 62 – 64°C; $C_{19}H_{28}N_2O_2$; ^1H NMR spectrum (δ, ppm): 1.28 (d, 3H, J 7.03 Hz, CH_3), 1.69 (d, 3H, J 5.02 Hz, CH_3), 2.17

(s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.65 (m, 4H, $2CH_2$), 3.15 (s, 2H, CH_2), 3.75 (m, 4H, $2CH_2$), 5.45 (m, 2H, HC=CH), 6.90 (s, 1H, ArH), 6.93 (s, 1H, ArH), 8.55 (s, 1H, NH); ^{13}C NMR spectrum (δ, ppm): 17.94, 18.59, 20.25, 21.12 (CH_3), 37.27 (C-1″), 54.07, 67.94 (C-morpholine), 62.09 (C-1), 137.03 (C-1′), 141.43 (C-2′), 123.58 (C-3′), 129.39 (C-4′), 125.16 (C-5′), 135.38 (C-6′), 135.64 (C-2″), 129.32 (C-3″).

2-[2′,4′-Dimethyl-6′-(1″-methyl-2″-buten-1″-yl)phenyl amino]-2-oxoethylpiperazine (VIc). Yield, 82%; m.p., 64 – 66°C; $C_{19}H_{29}N_3O$; ^1H NMR spectrum (δ, ppm): 1.24 (d, 3H, J 6.71 Hz, CH_3), 1.63 (d, 3H, J 5.13 Hz, CH_3), 2.13 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.00 (bs, 1H, NH), 2.58 – 2.89 (m, 8H, $4CH_2$), 3.11 (s, 2H, CH_2), 3.45 (m, 1H, H-1′), 5.40 (m, 2H, HC=CH), 6.86 (s, 1H, ArH), 6.88 (s, 1H, ArH), 8.59 (s, 1H, NH); ^{13}C NMR spectrum (δ, ppm): 17.89, 18.67, 20.29, 21.10 (CH_3), 46.14, 55.06 (C-piperazine), 62.32 (C-1), 168.71 (C-2), 37.24 (C-1″), 129.25 (C-2″), 135.64 (C-3″), 136.92 (C-1′), 141.60 (C-2′), 123.58 (C-3′), 130.08 (C-4′), 125.11 (C-5′), 135.42 (C-6′).

Synthesis of hydrochlorides VIIa – VIIe and VIIIa – VIIIc. A solution of the corresponding anilide (Va – Ve, VIa – VIc) in hexane was bubbled with dry hydrogen chloride until the reaction product ceased to precipitate. The precipitated crystals were filtered, washed with hexane, and dried in vacuum.

EXPERIMENTAL PHARMACOLOGICAL PART

The experiments were performed on white mongrel mice weighing 20 – 25 g and white rats (180 – 200 g). The infiltration anesthetic activity was studied by injecting the synthesized compounds into the hind foot aponeurosis (on the plantar side) in the region of distal branches of the tibial and peroneal nerves [3]. The substances were used in the form of 0.5 and 1% solutions and injected in a volume of 0.05 and 0.1 ml to mice and rats, respectively. The local anesthetic activity was assessed by determining the onset time of the anesthetic effect, the degree of anesthesia (a change in the sensitivity threshold 10 min upon drug injection), and the duration of drug action.

The depth of the local anesthesia was evaluated as the percentage change in the latent period of the pain reaction relative to the initial value. The analgesic effect was studied using the hot-plate test [4 – 6], by measuring the time to first defensive drawing back of the hind paws in response to electrical skin irritation (a.c. current strength, 5.0 mA; frequency, 50 Hz), or by measuring the response delay time for nociceptive irritation of the tail via subcutaneous needle electrodes (spaced by 1.5 cm) with single 5-sec rectangular current pulses generated by an SIF-3M electric stimulator. The irritation pulse repetition period was not less than 30 sec, the total duration of one experiment not exceeding 2 – 3 h.

The conduction anesthesia was studied on urethane-narcotized rats with exposed sciatic nerves. The test compounds were applied onto the exposed area using cotton

TABLE 1. Infiltration Anesthetic Activity of Alkenyl-Substituted Acetanilides

Compound	Solution concentration, %	Anesthesia onset time, min	Percentage increase in latent period to first pain reaction (relative to initial level, 30 min after injection)			Anesthesia duration, min
			hot plate	skin irritation	tail irritation	
VIIa′	0.5	12.3 ± 1.0	500.7 ± 25.1	280 ± 32.2	200.0 ± 11.7	90.4 ± 9.2*
VIIa′	1	11.5 ± 1.2	568.0 ± 31.7*	320 ± 30*	220.0 ± 17.0	95.8 ± 8.2*
VIIb′	0.5	15.4 ± 1.2	428.3 ± 30.5	220 ± 20.8	140.0 ± 11.0	80.0 ± 7.5
VIIb′	1	13.8 ± 1.0	475.0 ± 32.8	240 ± 32.0	160.0 ± 13.0	80.8 ± 8.2
VIIc′	0.5	11.2 ± 1.0	410 ± 31.5	240 ± 30	160 ± 15.5	85.8 ± 8.8
VIIc′	1	11.0 ± 1.0	458 ± 40.5	280 ± 23	180 ± 17	80 ± 7.5
VIId′	0.5	13.7 ± 1.0	450.0 ± 39.7	200 ± 20.8	160 ± 11.9	80.6 ± 9.2
VIIe′	1	13.0 ± 1.2	468.0 ± 42.0	220 ± 30.2	184.0 ± 17	85.8 ± 8.8
VIIe′	0.5	13.5 ± 1.0	360.5 ± 20.8	140 ± 8.5	130 ± 10.2	80.0 ± 9
VIIe′	1	13.0 ± 1.0	395.8 ± 20.0	150 ± 8.5	140 ± 12.4	80.8 ± 8.8
VIIIa′	0.5	12.5 ± 1.2	442.13 ± 23.7	241.0 ± 19.1*	240 ± 18.8	70.9 ± 6.8
VIIIb′	0.5	15.0 ± 1.7	285.2 ± 19.4	208.4 ± 14.4	264 ± 28.0	68.1 ± 5.1
VIIIc′	0.5	15.8 ± 1.7	264.6 ± 24.2	182.1 ± 27.6	172 ± 17.0	55.3 ± 4.7
Novocaine′	0.5	11.3 ± 1.2	428.3 ± 24.8	240.0 ± 20.4	200 ± 17.0	60.9 ± 5.7
Lidocaine′	1	9.7 ± 0.8	785.7 ± 50.3	560 ± 41.0	360 ± 32.2	110.3 ± 9.5

Note. Each compound was tested on six animals.
* Reliable difference relative to the novocaine test ($p < 0.05$).

TABLE 2. Conduction Anesthetic Activity of Alkenyl-Substituted Acetanilides

Compound	Solution concentration, %	Anesthesia onset time, min	Percentage increase in latent period to first pain reaction (relative to initial level, 30 min after injection)	Anesthesia duration, min
VIIa′	0.5	15.0 ± 1.2	80.3 ± 7.3	90.0 ± 7.8*
VIIa′	1	12.8 ± 0.9	99.1 ± 4.0*	95.5 ± 8.0
VIIb′	0.5	16.4 ± 0.8	70.5 ± 10.5	75.0 ± 6.5
VIIb′	1	14.5 ± 1.0	85.0 ± 3.7	78.3 ± 5.8
VIIc′	0.5	16.9 ± 1.2	50.9 ± 4.6	83.5 ± 5.8*
VIIc′	1	12.5 ± 1.0	83.7 ± 4.5	75.7 ± 5.4
VIId′	0.5	17.0 ± 1.3	60.2 ± 5.3	85.1 ± 7.5*
VIId′	1	14.9 ± 1.3	65.7 ± 5.2	65.3 ± 5.5
VIId′	0.5	20.0 ± 1.7	58.3 ± 5.0	68.0 ± 5.3
VIId′	1	15.5 ± 1.2	77.3 ± 6.5	60.8 ± 6.0
VIIIa″	0.5	12.5 ± 1.2	89.8 ± 10.2	70.9 ± 6.8
VIIIb″	0.5	15.0 ± 1.7	75.6 ± 6.8	68.1 ± 5.1
VIIIc″	0.5	15.8 ± 1.7	65.5 ± 6.8	60.5 ± 5.1
Novocaine	0.5	12.5 ± 0.8	70.8 ± 6.3	70.3 ± 6.1
Novocaine	1	13.0 ± 1.2	95.3 ± 9.7	85.0 ± 6.3
Lidocaine	1	10.0 ± 0.6	100.3 ± 8.9	90.5 ± 8.5

Note. Each compound was tested on eight (VII) and six (VIII) animals.

* Reliable difference relative to the novocaine test ($p < 0.05$).

impregnated with solutions of various concentrations. The nerve was irritated every 10 min with electric current pulses at a point shifted from the test site to the periphery. The anesthetic effect was evaluated by measuring the latent period of the pain reaction and the anesthesia extent and duration. The reference drugs were novocaine and lidocaine.

The experimental data were statistically processed to determine the arithmetic mean (M) and its confidence interval (m). The reliability of differences was characterized in terms of the Student t-criterion ($P < 0.05$).

RESULTS AND DISCUSSION

It was found that all the synthesized compounds are capable of increasing the pain reaction threshold. The anesthetic effect depends on the solution concentration and the type of irritation.

In the hot-plate test and the electrical skin irritation experiment, the most active compound VIIa at a 1% solution concentration was reliably superior to 0.5% novocaine solution (Table 1) but inferior to lidocaine. In the tail irritation experiment, the activity of compounds VIIa and VIIIa (at 0.5% concentration) was similar to that of novocaine. As for the anesthesia duration, compounds VIIa – VIIe were superior to novocaine and inferior to lidocaine.

Compounds VIIb and VIIIb were most active with respect to the conduction anesthesia, their 0.5% solutions being comparable with novocaine in the extent of anesthesia. The action of compound VIIa also exceeded that of novocaine, but only at a 1% concentration (Table 2). As for the conduction anesthesia duration, 0.5% solutions of compounds VIIa, VIIc, and VIId were superior to novocaine at the same concentration.

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