NEW METHOD FOR SYNTHESIS OF THE AZA ANALOGS OF TETRABENZOPORPHIN

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The reaction of 1-hydroxy-1-methyl-1H-3-(1-oxo-6-tert-butylisoindolin-3-ylidenemethyl)-5-tert-butylisoindole, which is the product from the condensation of potassium 4-tert-butylphthalimide and malonic acid, with phthalonitrile or 3-iminophthalimide leads to the formation of a mixture of the tert-butyl-substituted mono-, di-, and triaza analogs of zinc tetrabenzoporphin. The mixture was separated by chromatography on aluminum oxide. The zinc complex of di(4-tert-butylbenzo)di-benzodiazaporphin is demetallated by the action of HCl in acetic acid. The characteristics of the synthesized compounds are given.

Tetrabenzoporphins (TBP) and their tetraaza analogs [the phthalocyanines (PC)] are symmetrical isoelectronic structures, and the aza analogs of TBP with a smaller degree of azasubstitution [monoazatetrabenzoporphin (MATBP), diazatetrabenzoporphin (DATBP), and triazatetrabenzoporphin (TATBP)] occupy an intermediate position between them. The development of convenient methods for the synthesis of the latter compounds is of interest both in theoretical respects, e.g., for the determination of the effect of the molecular symmetry on the electronic spectrum, and for the production of practically important compounds.

Traces of MATBP were obtained during investigation of the reaction of o-halogenoacetophenones with cuprous cyanide [1] and of o-cyanoacetophenone with cuprous chloride [2]. The reaction of phthalonitrile with methylmagnesium iodide leads to the production of a compound identified as magnesium TATBP [3]. More recently [4] it was shown that a mixture of ATBPs with various contents of bridging nitrogen atoms is formed in all cases. The magnesium complexes of MATBP, DATBP, and TATBP were isolated in the pure form by adsorption chromatography and characterized, but DATBP was only isolated as a mixture of the cis and trans forms. Thus, methods available at the present time for the synthesis of ATBPs give very low yields and are unsuitable for practical purposes. The obtained mixtures of ATBPs are difficult to separate on account of their poor solubility in organic solvents. All this restricts the study of their properties.

In order to develop suitable methods for the synthesis of ATBPs we used the method for construction of the macrocycle by building it up from the dimeric isoindologen with a fixed meso-methine bridge. In order to obtain high solubility in a wide range of organic solvents it was desirable to introduce tert-butyl groups into the macrocycle. On this basis as initial dimeric compound in the present work we used 1-hydroxy-1-methyl-1H-3-(1-oxo-6-tert-butylisoindolin-3-ylidenemethyl)-5-tert-butylisoindole (I), which is the product from the condensation of potassium 4-tert-butylphthalimide with malonic acid in the presence of zinc acetate at 260°C. The structure of (I) was established on the basis of the data from IR spectroscopy, mass spectrometry, and elemental analysis. In the electron impact mass spectrum of (I) we recorded a peak of average intensity for the molecular ion $M^{+\cdot}$ 402 (30.5%), corresponding to the molecular formula $C_{26}H_{30}N_2O_2$. The formation of ions with m/z 387 (100%) and 372 (6%) is evidently due to the successive elimination of two methyl groups from $M^{+\cdot}$. The appearance of a medium-intensity peak for an ion with m/z 201 (40%) was also observed, and this is formed during cleavage of the bond between the exocyclic carbon atom and the 1H-isoindole fragments of the molecule. The process is accompanied by migration of a hydrogen atom, probably, from the hydroxyl group to the exocyclic carbon atom. During further dissocation of the ion with m/z 201 fragments with m/z 186 (80.5%), 172 (15%), 160 (20.3%), and 158 (18%) are formed. This further confirms the structure of (I). In the IR spectrum of (I) there are bands at 1720 (C=O), 2875-2970 (C–H), 3260 (N–H), and 3445 cm^{-1} (bonded OH).

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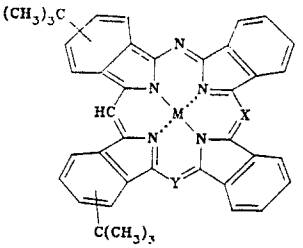
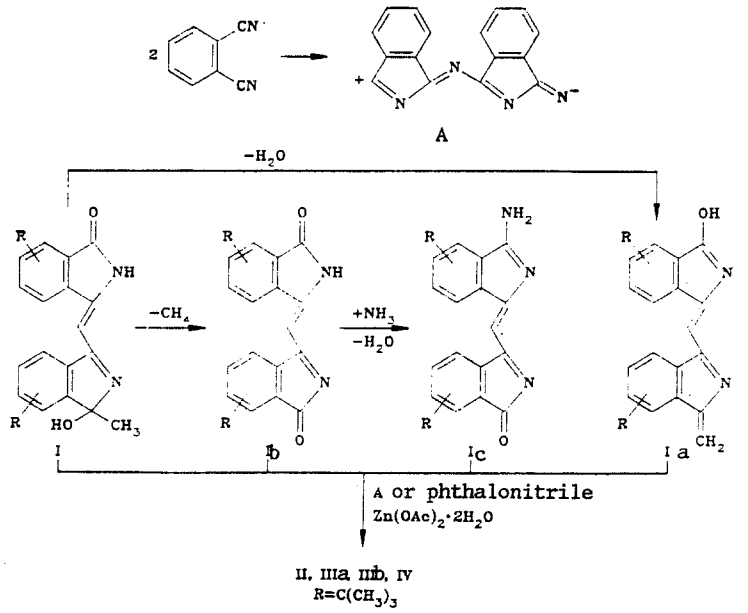
The reaction of the dimer (I) with phthalonitrile in the presence of zinc acetate in bromonaphthalene at 280°C in a stream of helium for 4 h, followed by chromatographic separation of the reaction mass, gave the zinc complexes of di(4-tert-butylbenzo)dibenzomonoazaporphin (II) (0.7%) and the corresponding diazaporphin (III) (2.9%) and triazaporphin (IV) (13.1%). The reaction of (I) with 3-iminophthalimide under the same conditions led to the formation of 1.2% of (II), 5.8% of (III), and 3.9% of (IV).



II–V

II, IIIa,b,IV M=Zn, Va,b M=HH; II X=Y=CH; IIIa,b X=N, CH, Y=CH, N; IV X=Y=N; Va X=N, Y=CH; Vb X=CH, Y=N

The compounds (II, IIIa, IV) are probably formed from the dimer (I) according to the following scheme:



A

I Ia Ib Ic

A or phthalonitrile

$Zn(OAc)_2 \cdot 2H_2O$

II, IIIa IIIb, IV

R=C(CH$_3$)$_3$

Under the reaction conditions at elevated temperatures the dimer (I) undergoes fragmentation in two directions with the elimination of the elements of H_2O and CH_4 and the formation of compounds (Ia) and (Ib), respectively. In reaction with ammonia, of which phthalonitrile is a donor, compound (Ib) forms the dimer (Ic). At the same time phthalonitrile undergoes dimerization with the formation of the bipolar ion A according to the scheme proposed earlier in the synthesis of phthalocyanine [5]. With (Ia) the bipolar ion A then forms the zinc complex (IIIa), and with (Ic) it forms the complex (IV). The higher yields of (IV) than of (IIIa) can probably be explained by the preferential fragmentation of the dimer (I) with the elimination of CH_4. The dimer (I) also reacts with 3-iminophthalimidine by a similar scheme. The formation of small amounts of the monoaza (II) and trans-diaza (IIIb) products in the reaction can be represented as the interaction of the above-mentioned dimers with phthalonitrile and with its transformation products under the reaction conditions.

In the PMR spectrum of (III) in pyridine-d_5 in the downfield region there are two signals for the protons of the methine bridges at δ 11.18 and 11.39 ppm. The aromatic protons have two regions of resonance at δ 9.50-10.18 (3-H and 6-H) and 8.10-8.46 ppm (4-H and 5-H), like unsubstituted zinc TBP [6]. The aliphatic protons of the tert-butyl group give an upfield

TABLE 1. The Electronic Absorption Spectra of Compounds (II-V) in Benzene

Compound	λ_{max}, nm (lg ε) [I_{rel}, %]
II	672 (4,13), 646 (5,15), 628 (4,84), 586 (4,17), 420 (5,00), 402 (4,78), 390 sh (4,61)
III	672 (4,62), 646 (5,23), 584 (4,26), 422 (4,85), 416 (4,79), 404 (4,72), 384 (4,69)
	672 [0,27], 646 [1,0], 574 [0,14], 416 [0,54], 386 [0,42]*
IV	670 (5,32), 648 (5,16), 614 (4,43), 590 (4,47), 380 (4,78)
	672 [1,0], 650 [0,65], 618 [0,18], 592 [0,12], 390 [0,29], 380 [0,29]*
Va	670 (4,96), 634 (4,91), 580 (4,21), 400 (4,75), 378 (4,77)
Vb	690 [2,10], 670 [1,00], 646 [1,75], 634 [1,29], 586 [0,45], 378 [1,56]
t-Bu$_4$-4TBPZn	626 [1,0], 575 [0,16], 454 [0,50], 424 [2,50], 400 [0,3]**
t-Bu$_4$-4PCZn	678 (5,30), 648 (4,41), 610 (4,48), 584 sh, (3,73), 567 sh (3,57), 349 (4,76)***

*In pyridine.
**According to published data [7].
***According to published data [8].

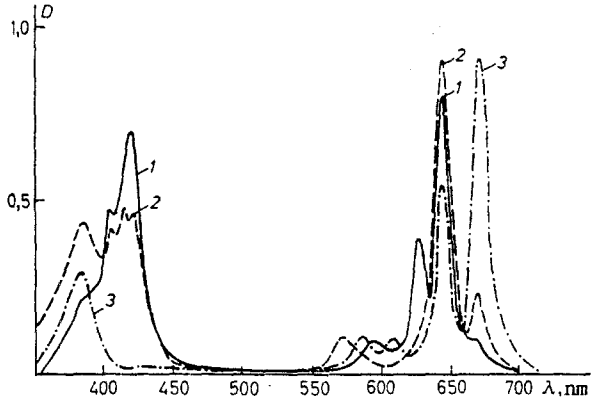


Fig. 1. The electronic absorption spectra of compounds (II) (1), (III) (2), and (IV) (3) in benzene.

signal at 1.73 ppm. The integral intensity ratios of the signals for the protons of the methine bridges, the benzene rings at positions 3,6 and 4,5, and the tert-butyl groups correspond fairly well to the structure of (III).

The zinc complexes (III) and (IV) exhibit increased stability to demetallation in an acidic medium compared with zinc TBP. Thus, cis- and trans-di(4-tert-butylbenzo)dibenzodiazaporphins (Va, b) were obtained with a yield of 81% by treatment of an acetic acid solution of (IIIa, b) with gaseous hydrogen chloride at 20°C. Under the same conditions compound (IV) forms the metal-free compound with only a small yield, i.e., it is similar to zinc PC in behavior. In contrast to the zinc complex (IIIa, b), in the case of the metal-free compound (Va, b) it was possible to isolate the cis (Va) and trans (Vb) isomers with the adjacent and opposite arrangements of the bridging nitrogen atoms by chromatography.

In the electron impact mass spectrum of (Va) there is a maximum-intensity peak for the molecular ion $M^{+\cdot}$ 624 (100%), corresponding to the molecular formula $C_{42}H_{36}N_6$. The formation of the fragments with 609 (12%) and 594 (13%) is probably due to the elimination of the methyl groups from the $M^{+\cdot}$ ion. The formation of the strong peak at 312 (36%, $M/2^+$) must be attributed to features of the fragmentation of (Va). As during the dissociation of the molecular ion, the elimination of methyl groups [ions 297 (26%), 282 (14%)] is observed during the fragmentation of the 312 ion.

The synthesized compounds (II-V) were green crystalline substances readily soluble in a wide range of organic solvents (benzene, chloroform, etc.).

The electronic absorption spectra of solutions of the synthesized ATPBs (II-V) were measured in the region of 220-800 nm. In the transition from zinc TBP to the aza analogs (II-V)

there are qualitative changes in the spectrum, i.e., a bathochromic shift and splitting of the long-wave band. This can be explained by a decrease in the symmetry of zinc TBP (D_{4h}) on account of aza substitution. Thus, in the spectrum of (II) (Table 1, Fig. 1) there is a doublet at 646 and 628 nm, and the long-wave component coincides with the absorption band of zinc TBP. The position of the doublet in (III) and (IV) is almost identical, but the intensity ratio differs. In the case of (III) the short-wave component is stronger, while in the zinc complex (IV) the long-wave component, which coincides in position with the absorption band of zinc PC, is stronger. Similar agreement in the positions of the bands was observed earlier [4] in the magnesium and cadmium complexes of ATBP.

Aza substitution is also accompanied by a significant hypsochromic shift of the strongest Soret band in TBP toward the UV region of the spectrum and by its broadening. The Soret band of (II) appears in the form of a doublet at 420 and 402 nm in benzene, while that of (III) appears at 416 and 386 nm in a mixture of chloroform and pyridine. In benzene the long-wave component at 416 nm is resolved in the spectrum of (III) into a triplet with approximately equal intensities at 422, 416, and 404 nm. In compound (IV), on the other hand, the broad low-intensity Soret band at 380 nm in benzene is represented by a doublet at 390 and 380 nm in a mixture of chloroform and pyridine or in pure pyridine. According to [4], the metal derivatives of the trans form of the diaza compound should contain two strong bands in the visible region, while the cis form should contain one somewhat broadened band. From the analysis of the spectrum of (III) it follows that it is a mixture of two isomers.

In the transition from the zinc complex (III) to the metal-free compound there is further complication in the spectral pattern. Thus, in the spectrum of (Vb) in the visible region there is a partially resolved quartet at 690, 670, 646, and 634 nm (Fig. 2b), while in the spectrum of (Va) in the same region there is a triplet at 670 and 634 nm (Fig. 2a). The four-band spectrum of the metal-free compound (Vb) is transformed in an alkaline medium into the two-band spectrum of the dianion of (Vb) (L^{2-}). The dianion of (Va) only has a single band in the spectrum at 646 nm. Since the electronic absorption spectrum of the dianionic form becomes analogous with the spectrum of the metal complex as a result of the increased symmetry, it is possible on the basis of analysis of the spectra of the dianions to assign the trans-di(4-tert-butylbenzo)dibenzodiazaporphin structure to (Vb) and the cis structure to (Va).

EXPERIMENTAL

The electronic absorption spectra were measured on a Hitachi 356 spectrophotometer for solutions at concentrations of ~10^{-5} M. The mass spectra of (Va) were obtained on an MS-30 instrument with direct injection of the sample into the ion source at 70 eV with an inlet temperature of 430°C. The mass spectrum of (I) was obtained on an MX-1320 mass spectrometer at 180°C. The PMR spectrum of (III) was recorded on a Bruker WM-360 spectrometer at 360 MHz in C_5D_5N with TMS as internal standard.

The data from elemental analyses for C, H, and N agreed with the calculated values.

1-Hydroxy-1-methyl-1H-3-(1-oxo-6-tert-butylisoindolin-3-ylidenemethyl)-5-tert-butylisoindole (I) ($C_{26}H_{30}N_2O_2$). A mixture of 3.0 g (12 mmole) of potassium 4-tert-butylphthalimide [8], 1.8 g (17 mmole) of malonic acid, and 2.0 g (9 mmole) of zinc acetate dihydrate was heated in a stream of helium at 260°C for 1 h. The mixture was then cooled and dissolved in 20 ml of chloroform. The solution was transferred to a column of silica gel (4 × 25 cm) and eluted with a 1:1 mixture of chloroform and ethyl acetate. We obtained 0.9 g (30%) of (I); mp 246-247°C (from benzene), R_f 0.48 (silica gel, 1:1 chloroform–ethyl acetate). IR spectrum: 1720 (C=O), 2875-2970 (C–H), 3280 (N–H), 3445 cm^{-1} (bonded OH). M^+ 402.

Reaction of Dimer (I) with Phthalonitrile and Zinc Acetate. A mixture of 0.4 g (1 mmole) of the dimer (I), 0.26 g (2 mmole) of phthalonitrile, and 0.22 g (1 mmole) of zinc acetate dihydrate in 1 ml of 1-bromonaphthalene was stirred at 280°C in a stream of helium for 4 h, cooled, and diluted with 50 ml of hexane. The precipitate was filtered off and washed on the filter with 50 ml of hexane. The residue was dissolved in 30 ml of chloroform, and the chloroform solution was filtered from the insoluble phthalocyanine, transferred to a column of aluminum oxide (4 × 40 cm), and eluted with chloroform and then with a 1:50 mixture of pyridine and benzene. In both cases the green fraction was collected. After distillation of the solvent we obtained 0.12 g of a mixture of the zinc complexes of the aza-substituted TBPs, which were then separated by chromatography on aluminum oxide (4 × 50 cm) in a 10:10:1 mixture of ethyl acetate, chloroform, and hexane into three fractions. From the first fraction

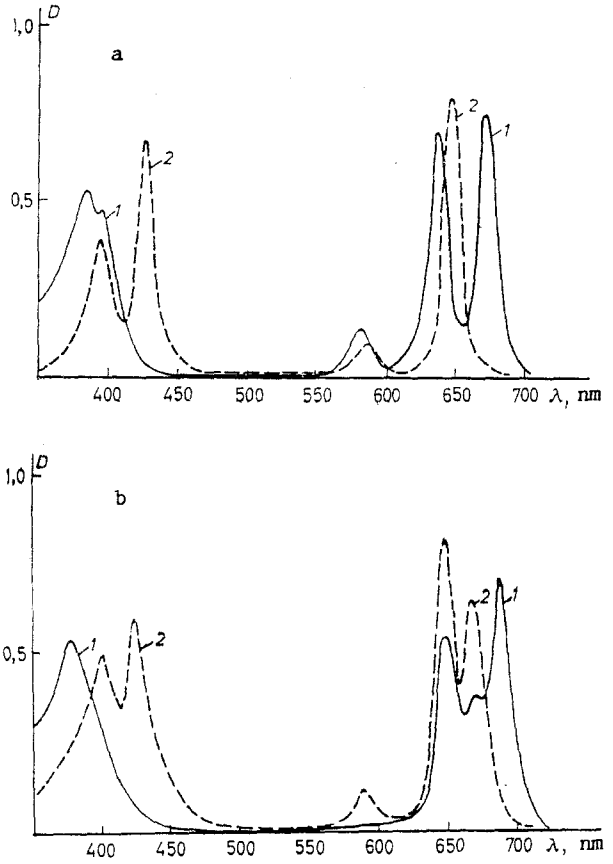


Fig. 2. The electronic absorption spectra of compounds (Va) (a) and (Vb) (b): 1) in benzene 2) in DMFA in the presence of NaOH.

with R_f 0.76 (aluminum oxide, L 40/250, 10:10:1 ethyl acetate–chloroform–hexane) we isolated 5 mg (0.7%) of zinc di(4-tert-butylbenzo)dibenzomonoazaporphin (II) ($C_{43}H_{35}N_5Zn$). From the second fraction with R_f 0.48 (aluminum oxide, L40/250, 10:10:1 ethyl acetate–chloroform–hexane) we isolated 20 mg (2.9%) of zinc di(4-tert-butylbenzo)dibenzodiazaporphin (IIIa,b) ($C_{42}H_{34}N_6Zn$). The third fraction contained 90 mg (13.1%) of zinc di(4-tert-butylbenzo)dibenzodiazaporphin (IV) ($C_{41}H_{33}N_7Zn$); R_f 0.28 (aluminum oxide, L40/250, 10:10:1 ethyl acetate–chloroform–hexane).

Reaction of Dimer (I) with 3-Iminophthalimide. A mixture of 0.4 g (1 mmole) of the dimer (I), 0.29 g (2 mmole) of 3-iminophthalimidine [9], and 0.44 g (2 mmole) of zinc acetate dihydrate in 2 ml of 1-bromonaphthalene was boiled in a stream of helium for 2 h, a further 0.29 g of 3-iminophthalimidine was added to the reaction mass, and the mixture was heated for 2 h. The product was isolated and purified as in the previous experiment. We obtained 8 mg (1.2%) of (II), 40 mg (5.8%) of (IIIa, b), and 27 mg (3.9%) of (IV).

Di(4-tert-butylbenzo)dibenzodiazaporphin (Va, b). A stream of gaseous hydrogen chloride was passed into a solution of 50 mg (0.073 mmole) of the zinc complex (IIIa, b) in 50 ml of acetic acid at 20°C for 3 h. The reaction mass was poured into 100 ml of cold water. The precipitate was filtered off, washed on the filter with 250 ml of water, 100 ml of 5% ammonium hydroxide, and 250 ml of water, dried in air, and dissolved in 10 ml of chloroform. The solution was transfered to a column of aluminum oxide (4 × 30 cm) and eluted with chloroform. We obtained 37 mg (81%) of (Va, b) [R_f 0.63 (aluminum oxide, L40/250, chloroform)] and 8 mg of the initial compound (III) [R_f 0.18 (aluminum oxide, L 40/250, chloroform)]. The first fraction was then dissolved in 10 ml of a 1:1 mixture of benzene and methylene chloride. The solution was transferred to a column (4 × 30 cm) and eluted with the same mixture. We obtained 9 mg of the trans isomer (Vb) [R_f 0.56 (aluminum oxide, L 40/250, 1:1 benzene–methylene chloride)] and 25 mg of the cis isomer (Va) [R_f 0.28 (aluminum oxide), L 40/250, 1:1 benzene–methylene chloride)].

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SYNTHESIS AND REACTIONS OF 5-HYDROXY-4-OXO-3-ARYLPYRROLIDINO[1,2-b]PYRAZOLES

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Successive treatment of epoxypropionylpyrazolines with N-bromosuccinimide in chloroform and triethylamine in acetone affords 5-hydroxy-4-oxo-3-arylpyrrolidino[1,2-b]-pyrazoles, which are oxygenated derivatives of the alkaloid withasomnine. The reaction proceeds via the cyclization of the intermediate pyrazole bromohydrins. Some reactions of the pyrrolidino[1,2-b]pyrazoles obtained have been examined.

In a study of the heterocyclization of compounds containing two reactive heterocycles, one of which is oxirane, we have developed a convenient synthesis of 5-hydroxy-4-oxo-3-arylpyrrolidino[1,2-b]pyrazoles, by cyclization of epoxypropionylpyrazolines. 5-Hydroxy-4-oxo-3-arylpyrrolidino[1,2-b]pyrazoles are functional derivatives of the alkaloid withasomnine, isolated from the roots of Withania somnifera Dunal [1-6].

We have shown that successive treatment of the readily accessible epoxypropionylpyrazolines (Ia-d) [7] with N-bromosuccinimide in chloroform and triethylamine in acetone gives 5-hydroxy-4-oxo-3-arylpyrrolidino[1,2-b]pyrazoles (Ia-d) in 70-86% yield. Reaction of the epoxypropionylpyrazoline (Ic) with N-bromosuccinimide gave the intermediate epoxypropionylpyrazole (IIIc) and the pyrazole bromohydrin (IVc), the pyrazole bromohydrins (IVa, c) cyclizing to the pyrrolidino[1,2-b]pyrazoles (IIa, c) on boiling in toluene, or treatment with triethylamine in acetone. It follows from these observations that the reaction of epoxypropionylpyrazolines with N-bromosuccinimide and triethylamine involves the intermediate formation of the pyrazole bromohydrins formed by cleavage of the epoxide ring during the aromatization of the pyrazoline ring in the presence of N-bromosuccinimide. The function of the triethylamine is solely to bind the acidic proton of the pyrazole ring in the intermediate pyrazole halohydrin, which facilitates intramolecular cyclization.

The cyclization of pyrazole bromohydrins to pyrrolidino[1, 2-b]pyrazoles has been found to be a general reaction. For example, reaction of the epoxypropionylpyrazole (IIIe) with hydrobromic acid gave the bicyclic ketone (IIe). The structures of products (IIa-e) were confirmed spectrally (Table 1) and by their chemical properties.

The IR spectra of (IIa-e) showed absorption at 3620 (OH) and 1730 cm^{-1} (C=O).

Treatment of (IIa) and (IIe) with acetic anhydride converted them into the acetates (Va, e). Reduction of the carbonyl group in the bicyclic ketones (IIa, e) with sodium borohydride gave a mixture of stereoisomeric diols (VIa, e) and (VIIa, e) with trans- and cis-orientation

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