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A hydrogen-bonded dimer in 6-(4-bromophenyl)-3-methyl-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine and a chain of rings built from N—H···N and C—H···π(pyridine) hydrogen bonds in 3-(4-nitrophenyl)-4-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine

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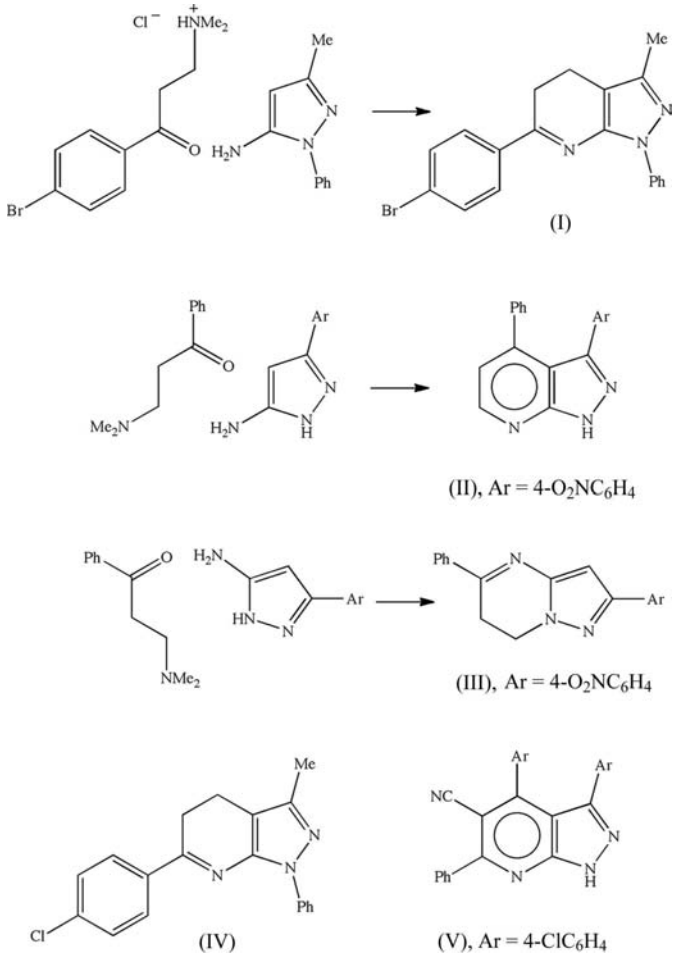
In 6-(4-bromophenyl)-3-methyl-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine, $C_{19}H_{16}BrN_3$, the reduced pyridine ring adopts a conformation that is close to a screw-boat form. Molecules are linked by pairs of symmetry-related C—H···π(arene) hydrogen bonds into cyclic centrosymmetric dimers. Molecules of 3-(4-nitrophenyl)-4-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine, $C_{18}H_{12}N_4O_2$, are linked into centrosymmetric $R_2^2(8)$ dimers by pairs of symmetry-related N—H···N hydrogen bonds, and these dimers are linked by pairs of C—H···π(pyridine) hydrogen bonds to form a chain of edge-fused rings, or a molecular ladder, along [100]. The molecular aggregation in this compound is completed by two weak C—H···O hydrogen bonds, one of which links the chains along [100] into sheets.

Comment

4,5-Dihydropyrazolo[3,4-*b*]pyridines and their derivatives are useful synthetic intermediates as position 5 is active in, for example, Vilsmeier formylation reactions (Quiroga *et al.*, 2008). The analogous 6,7-dihydropyrazolo[1,5-*a*]pyrimidines, which are purine analogues, are of potential pharmacological value (Novinson *et al.*, 1976; Senga *et al.*, 1981). We report here the molecular and supramolecular structures of two pyrazolo[3,4-*b*]pyridine derivatives, namely 6-(4-bromophenyl)-3-methyl-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine, (I), and 3-(4-nitrophenyl)-4-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine, (II) (Figs. 1 and 2), each of which was obtained from a cyclization reaction between a substituted 5-aminopyrazole and a 3-(dimethylamino)propiophenone derivative, but involving different regiochemistry in the two cases.



The synthesis of (I) involved a cyclization reaction between 5-amino-3-methyl-1-phenylpyrazole and bromo-substituted 3-(dimethylamino)propiophenone hydrochloride to give the

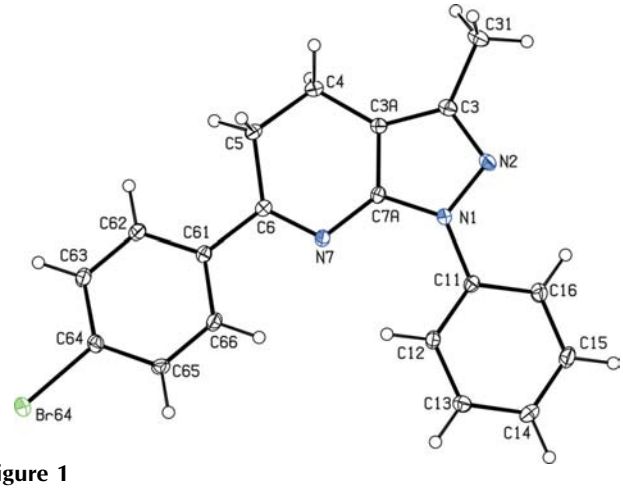


Figure 1
The molecular structure of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level.

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product (I) in 75% yield (see scheme). In this cyclization, the amine group of the pyrazole component reacts with the carbonyl group of the propiophenone component, while atom C4 of the pyrazole reacts at position 3 of the propiophenone. By contrast, in the corresponding reaction between 5-amino-3-(4-nitrophenyl)-1*H*-pyrazole and neutral 3-(dimethylamino)-propiophenone, the formation of (II) involves the opposite regiochemistry, with atom C4 of the pyrazole reacting with the carbonyl group and the amine group of the pyrazole attacking at position 3 of the propiophenone. Compound (II) was, in fact, formed as a very minor product, and the major product of this reaction resulted from a cyclization utilizing both the NH_2 and the NH functions of the pyrazole component to yield 2-(4-nitrophenyl)-5-phenyl-6,7-dihydropyrazolo[1,5-*a*]pyrimidine, (III), in 80% yield (see scheme). Compounds (I) and (II) thus differ in several respects: the oxidation level of the six-membered heterocyclic ring; the location of the aryl substituent in this ring; and the presence in (II), but not in (I), of an NH group available for hydrogen-bond formation. However, because of the very similar processes by which they are formed, differing primarily in the regiochemistry of the reaction rather than in the reactants themselves, it is appropriate to consider them at the same time. Compounds (IV) and (V) (see scheme), whose structures have been published, are close analogues of compounds (I) and (II), respectively, and (IV) and (V) are discussed following the discussion of compounds (I) and (II).

Within the molecule of (I), the reduced pyridine ring is nonplanar, with ring-puckering angles (Cremer & Pople, 1975) θ = 62.0 (5)° and φ = 161.7 (6)°; these values indicate a ring conformation that is close to the screw-boat form, where the idealized ring-puckering angles are θ = 67.5° and φ = (60*k* + 30)° (*k* represents an integer). The rest of the molecular conformation in (I) can be defined in terms of just two torsion angles (Table 1). The molecular conformation of compound (II) can be defined in terms of three torsion angles (Table 1) or, alternatively, in terms of three interplanar angles. The substituted and unsubstituted aryl rings in (II) make dihedral angles with their neighbouring heterocyclic rings of 46.1 (2) and 46.4 (2)°, respectively, while the nitro group makes a dihedral angle of 11.3 (2)° with the adjacent benzene ring. The molecules of (I) and (II) thus have no internal symmetry, and so they are conformationally chiral; however, the centrosymmetric space groups accommodate equal numbers of the two conformational enantiomers in each case. The bond distances in the fused heterocyclic systems (Table 1) are consistent with a modest degree of electronic delocalization in the pyrazole ring of (I) and with a delocalized pyridine system in (II).

The supramolecular aggregation is very simple in (I) and more complex in (II). In (I), pairs of molecules related by inversion are linked by pairs of symmetry-related C—H···π(arene) hydrogen bonds (Table 2) to form a cyclic centrosymmetric dimers (Fig. 3), but there are no significant direction-specific interactions between the dimers.

The molecules of (II) are linked into a chain of edge-fused rings, or a molecular ladder, by a combination of N—H···N and C—H···π(pyridine) hydrogen bonds (Table 2). Pairs of molecules related by inversion are linked by pairs of symmetry-related nearly linear N—H···N hydrogen bonds to form cyclic dimers characterized by an $R_2^2(8)$ (Bernstein *et al.*, 1995) motif (Fig. 4). In addition, atom C45 of the benzene ring in the molecule at (*x*, *y*, *z*) acts as hydrogen-bond donor to the pyridine ring of the molecule at (*x* + 1, *y*, *z*), so linking cyclic dimers into a chain of edge-fused rings running parallel to the [100] direction. In this chain, the centrosymmetric $R_2^2(8)$ rings are centred at (*n*, 0, 1), where *n* represents an integer. These alternate with the larger centrosymmetric rings formed by the C—H···π(pyridine) hydrogen bonds and centred at ($n + \frac{1}{2}$, 0, 1), where *n* again represents an integer (Fig. 4).

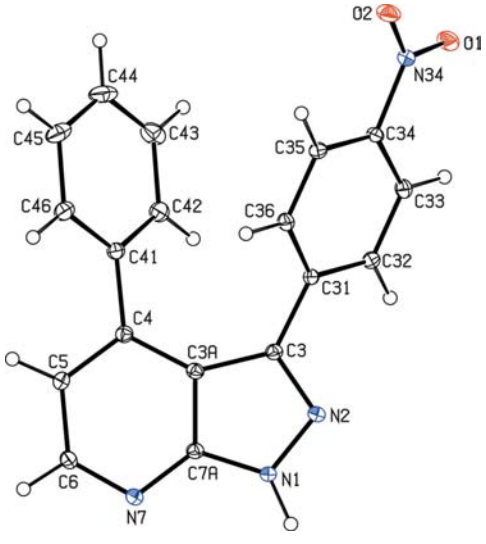

Figure 2
The molecular structure of (II), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level.

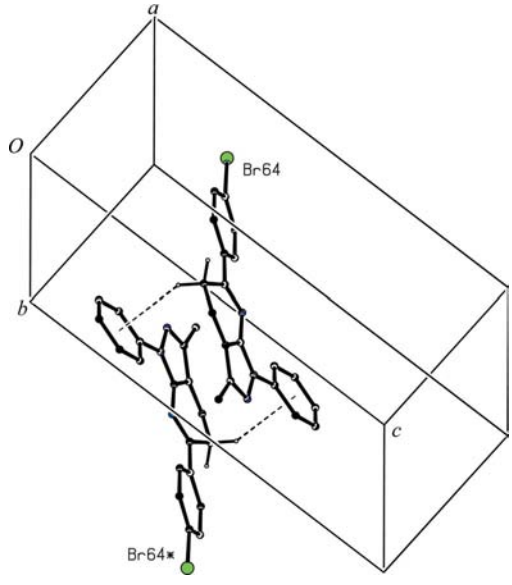

Figure 3
Part of the crystal structure of (I), showing the formation of a centrosymmetric hydrogen-bonded dimer. For the sake of clarity, H atoms not involved in the motif shown have been omitted. The atom marked with an asterisk (*) is at the symmetry position (−*x*, 1 − *y*, 1 − *z*).

Within this chain of rings, pairs of pyrazolopyridine rings related by inversion across ($n + \frac{1}{2}$, 0, 1) have an interplanar spacing of 3.663 (2) Å between the pyridine rings, whose ring-centroid separation is 3.827 (2) Å, corresponding to a ring-centroid offset of 1.106 (2)°. The interplanar spacing and the ring-centroid separation are both quite large, and it is possible that this contact is an adventitious consequence of the hydrogen bonding, rather than being of structural significance in itself. Nonetheless, any attractive interaction associated with this contact will reinforce, albeit weakly, the formation of the chain of rings parallel to [100].

There are also two short intermolecular C—H···O contacts in the crystal structure of (II), both involving nitro atom O2 (Table 2). One of these contacts, involving atom C32, is between molecules related by translation along the [100] direction so that, if this contact is regarded as a weak hydrogen bond, its role is to reinforce the chain along [100]. The second contact, involving atom C6, is between molecules related by translation along [10$\bar{1}$]; if this contact is regarded as a weak hydrogen bond, then its role is to link the chains along [100] into a sheet parallel to (010).

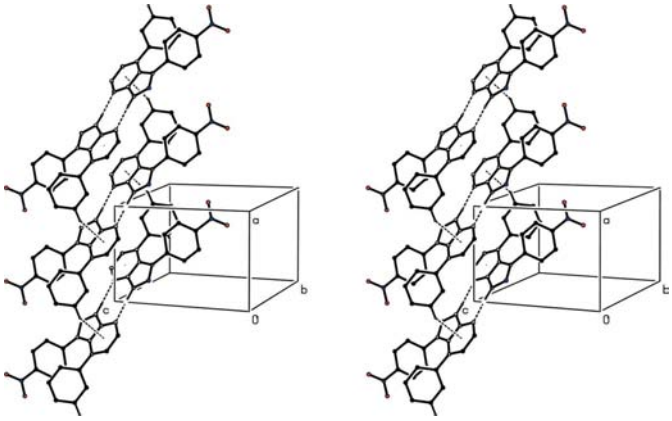

Figure 4
A stereoview of part of the crystal structure of (II), showing the formation of a chain of hydrogen-bonded rings along [100] built from N—H···N and C—H···π(pyridine) interactions. For the sake of clarity, H atoms not involved in the motif shown have been omitted.

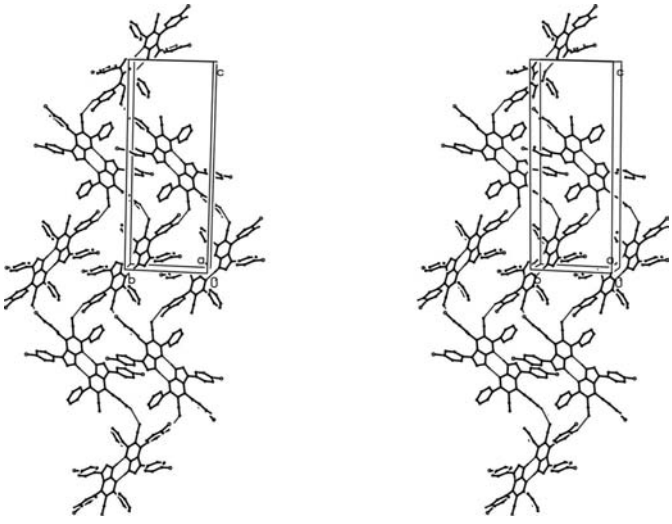

Figure 5
A stereoview of part of the crystal structure of (V), showing the formation of a hydrogen-bonded sheet parallel to (10$\bar{1}$). The original atomic coordinates (Quiroga *et al.*, 1999) have been used and, for the sake of clarity, H atoms not involved in the motifs shown have been omitted.

The structure of the 4-chlorophenyl analogue of (I), compound (IV) (see scheme) was reported some years ago on a proof of constitution basis, without discussion [Cambridge Structural Database (CSD; Allen, 2002) refcode LABDAT (Quiroga *et al.*, 1998)]. It is clear from the unit-cell dimensions for (IV) [a = 8.113 (1) Å, b = 17.315 (1) Å, c = 11.789 (1) Å, β = 104.77 (1)° in space group $P2_1/n$ (incorrectly reported as $P2_1/c$)] that (I) and (IV) are by no means isomorphous, as might possibly have been expected. However, since no H-atom coordinates for (IV) have been deposited, very little can be deduced about any supramolecular aggregation in the structure of (IV). Somewhat similar to (II), and obtained in a somewhat similar way, is compound (V), which was also reported on a proof of constitution basis without discussion (CSD refcode DEZQII; Quiroga *et al.*, 1999), although this appears to be the only previously reported example of a 1*H*-pyrazolo[3,4-*b*]pyridine carrying two aryl substituents at the 3- and 4-positions. Examination of the crystal structure of (V) using the deposited atomic coordinates shows the presence of two hydrogen bonds, one each of N—H···N and C—H···N types, where the acceptors are, respectively, the pyridine ring N atom and the nitrile N atom. Inversion-related pairs of molecules are linked by pairs of N—H···N hydrogen bonds to form centrosymmetric $R_2^2(8)$ dimers, just as in (II). However, in (V) these dimers are linked by the C—H···N hydrogen bond to form a sheet lying parallel to (10$\bar{1}$) and built from centrosymmetric $R_2^2(8)$ and centrosymmetric $R_6^6(44)$ rings arranged in a chessboard fashion (Fig. 5). Unlike the structure of (II), that of (V) contains no C—H···π(arene) hydrogen bonds.

Experimental

For the synthesis of (I), a solution of 5-amino-1-phenyl-3-methylpyrazole (0.5 mmol) and 1-(4-bromophenyl)-3-(dimethylamino)propan-1-one hydrochloride (0.5 mmol) in pyridine (2 ml) was heated under reflux for 20 min. The mixture was cooled to ambient temperature and the product was isolated by filtration, washed with ethanol and dried prior to purification by column chromatography on silica gel using chloroform as eluant (yield 75%, m.p. 420–422 K). MS (70 eV) m/z (%): 365 (M^+, 100), 364 (41), 183 (31), 143 (18), 102 (50), 77 (79), 51 (48); HRMS found 365.0535, $C_{19}H_{16}BrN_3$ requires 365.0528. Yellow crystals suitable for single-crystal X-ray diffraction were obtained by slow evaporation, at ambient temperature and in air, of a solution in dimethylformamide.

For the synthesis of (II), a solution of 5-amino-3-(4-nitrophenyl)-1*H*-pyrazole (1.9 mmol) and 3-(dimethylamino)propiophenone (1.9 mmol) in pyridine (0.5 ml) was heated under reflux for 20 min. The solution was cooled to ambient temperature and the product mixture was collected by filtration, washed with ethanol and dried in air. The two components were separated by column chromatography on alumina using chloroform as the eluant. The main product 2-(4-nitrophenyl)-5-phenyl-6,7-dihydropyrazolo[1,5-*a*]pyrimidine, (III),

was isolated as a yellow solid (yield 80%, m.p. 552–544 K). HRMS found 318.0959, $C_{18}H_{14}N_4O_2$ requires 318.0960. Crystallization from ethanol–dimethylformamide (1:1 *v*/*v*) of the impure column fractions gave just a few crystals of compound (II) that proved to be suitable for single-crystal X-ray diffraction.

Compound (I)

Crystal data

$C_{19}H_{16}BrN_3$
M_r = 366.26
Monoclinic, $P2_1/c$
a = 7.5165 (1) Å
b = 11.6572 (3) Å
c = 17.6917 (5) Å
β = 92.701 (2)°
V = 1548.45 (6) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 2.66 mm^{-1}
T = 120 K
0.20 × 0.06 × 0.04 mm

Data collection

Bruker–Nonius KappaCCD diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.685, T_{max} = 0.901
21038 measured reflections
3058 independent reflections
2597 reflections with $I > 2\sigma(I)$
R_{int} = 0.048

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.029
$wR(F^2)$ = 0.069
S = 1.05
3058 reflections
209 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.26 e Å^{-3}
$\Delta\rho_{min}$ = −0.51 e Å^{-3}

Compound (II)

Crystal data

$C_{18}H_{12}N_4O_2$
M_r = 316.32
Triclinic, $P\overline{1}$
a = 7.0408 (1) Å
b = 9.6360 (3) Å
c = 11.1961 (3) Å
α = 84.906 (1)°
β = 89.177 (2)°
γ = 81.012 (2)°
V = 747.31 (3) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.10 mm^{-1}
T = 120 K
0.24 × 0.20 × 0.06 mm

Data collection

Bruker–Nonius KappaCCD diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.974, T_{max} = 0.994
13461 measured reflections
2938 independent reflections
2447 reflections with $I > 2\sigma(I)$
R_{int} = 0.038

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.038
$wR(F^2)$ = 0.101
S = 1.06
2938 reflections
217 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.20 e Å^{-3}
$\Delta\rho_{min}$ = −0.34 e Å^{-3}

All H atoms were located in difference maps and then treated as riding atoms in geometrically idealized positions, with C—H distances of 0.95 (aromatic or pyridyl), 0.98 (CH_3) or 0.99 Å (CH_2) and N—H distances of 0.88 Å, and with U_{iso}(H) = kU_{eq}(carrier), where k = 1.5 for the methyl group in (I), which was permitted to rotate but not to tilt, and k = 1.2 for all other H atoms.

For both compounds, data collection: *COLLECT* (Hooft, 1999); cell refinement: *DIRAX*/*LSQ* (Duisenberg *et al.*, 2000); data reduction: *EVALCCD* (Duisenberg *et al.*, 2003); program(s) used to solve structure: *SIR2004* (Burla *et al.*, 2005); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *PLATON* (Spek, 2009); software used to prepare material for publication: *SHELXL97* and *PLATON*.

Table 1
Selected geometric parameters (Å, °) for compounds (I) and (II).

	(I)	(II)
N1—N2	1.373 (2)	1.3599 (15)
N2—C3	1.336 (3)	1.3316 (17)
C3—C3*A*	1.409 (3)	1.4354 (19)
C3*A*—C4	1.492 (3)	1.4135 (19)
C4—C5	1.534 (3)	1.3868 (19)
C5—C6	1.516 (3)	1.4034 (19)
C6—N7	1.300 (3)	1.3350 (18)
N7—C7*A*	1.388 (3)	1.3463 (17)
C7*A*—N1	1.373 (3)	1.3543 (17)
C3*A*—C7*A*	1.366 (3)	1.4116 (18)
N2—N1—C11—C12	162.54 (18)	–
N2—C3—C31—C32	–	46.95 (18)
N7—C6—C61—C62	−165.64 (19)	–
C3*A*—C4—C41—C42	–	45.51 (19)
C33—C34—N34—O1	–	10.69 (18)

Table 2
Hydrogen bonds and short intermolecular contacts (Å, °) for compounds (I) and (II).

*Cg*1 and *Cg*2 represent the centroids of the C11–C16 and C3*A*/C4–C6/N7/C7*A* rings, respectively.

Compound	D—H···A	D—H	H···A	D···A	D—H···A
(I)	C5—H5*A*···*Cg*1^{i}	0.99	2.80	3.662 (2)	146
(II)	N1—H1···N7^{ii}	0.88	2.04	2.9164 (16)	171
	C6—H6···O2^{iii}	0.95	2.55	3.3971 (17)	149
	C32—H32···O2^{iv}	0.95	2.53	3.3354 (17)	142
	C45—H45···*Cg*2^{v}	0.95	2.79	3.4715 (16)	129

Symmetry codes: (i) $-x, -y+1, -z+1$; (ii) $-x, -y, -z+2$; (iii) $x-1, y, z+1$; (iv) $x-1, y, z$; (v) $x+1, y, z$.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: EG3040). Services for accessing these data are described at the back of the journal.

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