Synlett E. L. Watson et al. Letter

Synthetic Studies on Psychotrimine: Palladium-Catalysed Arylation of 2-(*N*-Indolyl) Amides

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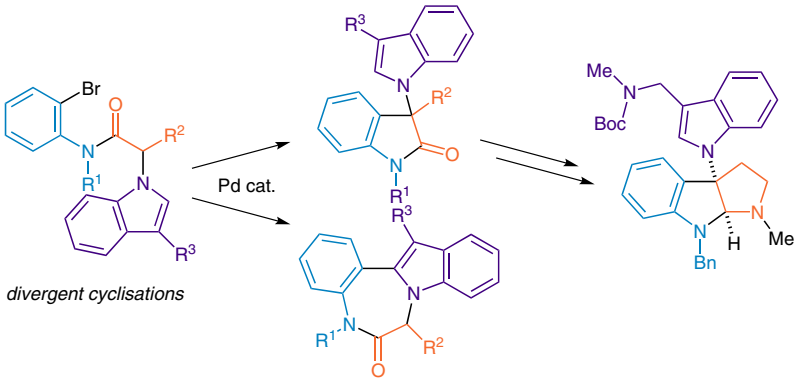
Dedicated to Professor Steve Ley FRS on the occasion of his 70th birthday



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Abstract Through careful choice of conditions, 2-(*N*-indolyl) amides can be directed to undergo selectively either enolate arylation to give oxindoles or direct arylation to give indolo-fused benzodiazepines. The former chemistry facilitates the synthesis of the hexahydropyrrolindole core of psychotrimine.

Key words alkaloids, arylation, cyclisation, polycycles, total synthesis

Psychotrimine (**1**) is an indole alkaloid first isolated in 2004 from the leaves of the plant *Psychotria rostrata* (Figure 1).[1] Psychotrimine is part of a wider family of cyclotryptamine natural products[2] but, along with the tetrameric product psychotetramine (**2**),[3] is structurally distinct from the majority of the family by virtue of the N1–C3a linkage of two tryptamine units. This structural novelty, along with reported biological activity against Gram-positive bacteria,[4] has prompted significant synthetic interest in psychotrimine. Takayama achieved the first racemic[5] and enantioselective[6] total syntheses of psychotrimine, creating the fully substituted C3a centre in an acyclic context, and then assembling the core hexahydropyrrolindole skeleton by copper-mediated imidation or amidation chemistry, respectively. Baran reported a remarkable gram-scale synthesis of racemic psychotrimine from commercial 7-bromotryptamine in just five synthetic operations, utilising a direct oxidative indole–aniline coupling.[7] This was subsequently adapted to an asymmetric synthesis using a diastereoselective variant of the coupling starting from a tryptophan derivative, with subsequent reductive removal of the vestigial carboxylate functionality; the key intermediate was also used in a total synthesis of psychotetramine.[3] Formal asymmetric syntheses based upon interception of Takayama's intermediates have also been reported.[8]

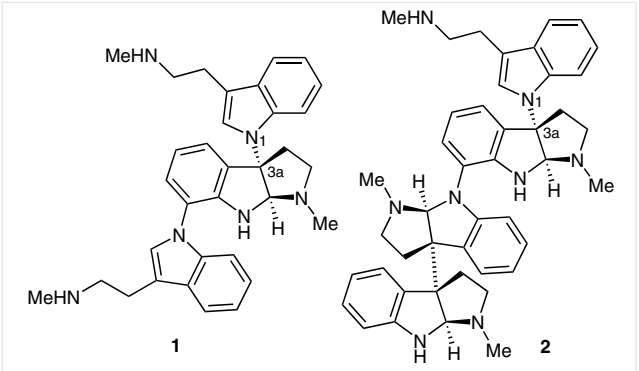
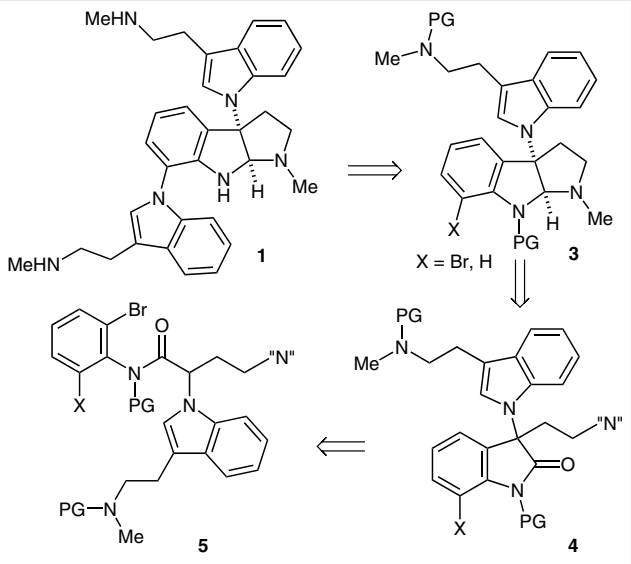


Figure 1 The cyclotryptamine natural products psychotrimine (**1**) and psychotetramine (**2**)

Our interest in investigating the synthesis of psychotrimine was based upon our construction of 3-amino-[9] and 3-alkoxyoxindoles[9b,10] by palladium-catalysed intramolecular arylation[11] of protected α-amino and α-hydroxy acid enolates.

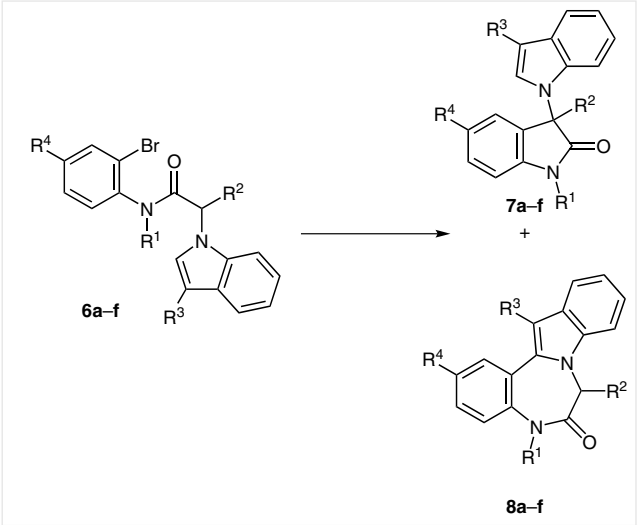
Specifically, we envisaged that the hexahydropyrrolindole core **3** of psychotrimine might be accessed by reductive cyclisation of a 3,3-disubstituted oxindole **4** bearing both the N-linked tryptamine unit and a suitably functionalised synthetic equivalent of a 2-aminoethyl side chain (Scheme 1). The oxindole **4** itself would be accessed using our enolate arylation methodology from a suitable acyclic precursor **5**. Attachment of the N-linked tryptamine to the C7 carbon of hexahydropyrrolindole **3** would be achieved by copper- or palladium-mediated arylation of the indole nitrogen of a suitably protected tryptamine, as in the previous syntheses by Takayama[5,6] and Baran.[3,7] The C7 halide required for such a coupling would either be carried through the synthesis, exploiting a selective monoarylation of a suitable 2,6-dibromoanilide (**5**, X = Br), or else installed

by late-stage C7 lithiation directed by a N8 carbamate, a strategy employed by Takayama[5,6] and inspired by earlier work on C-linked cyclotryptamines by Overman.[12] In this Letter, we describe our investigations into this synthetic strategy, culminating in the successful preparation of the fully protected hexahydropyrroloindole core of psychotrimine.



Scheme 1 Retrosynthetic analysis for psychotrimine based upon palladium-catalysed enolate arylation of 2-(*N*-indolyl) amides **5**

We commenced our study with an investigation of the intramolecular arylation of simple model 2-(*N*-indolyl)alkanamides **6** (Scheme 2). In our initial investigations,[9a] we had shown that substrate **6a** could be successfully cyclised to the 3-(*N*-indolyl)oxindole **7a** in 65% yield under our standard conditions using a catalyst derived from a 1:1 mixture of palladium(II) acetate and tricyclohexylphosphine (added as its phosphonium salt) with sodium *tert*-butoxide as base in toluene under microwave irradiation (Table 1, entry 1). The desired oxindole was also accompanied by a small amount of the indolo-fused benzodiazepinone **8a**, which arises from direct C2 arylation of the indole by the aryl halide in competition with the base-mediated enolate arylation.[13,14] The indolo-fused benzodiazepine skeleton is found in bioactive compounds including hepatitis C virus inhibitors such as beclabuvir,[15] and as a diversion we sought to identify conditions which would promote selective formation of this motif. Clearly the use of a weaker base would disfavour or shut down the enolate arylation pathway, and after some optimisation we found that the use of potassium acetate along with tetrabutylammonium bromide led to an 87% yield of the desired benzodiazepinone **8a**, further exemplified by the successful cyclisation of analogues **8b–d** (Table 1, entries 2–5).[16]



Scheme 2 Competing enolate arylation and direct C–H arylation reactions. *Reagents and conditions*: A: $Pd(OAc)_2$ (10 mol%), $HPCy_3{\cdot}BF_4$ (10 mol%), NaO*t*-Bu (3 equiv), toluene, 110 °C, microwave; B: $Pd(OAc)_2$ (10 mol%), Ph_3P (10 mol%), TBAB, KOAc, toluene, 120 °C, microwave.

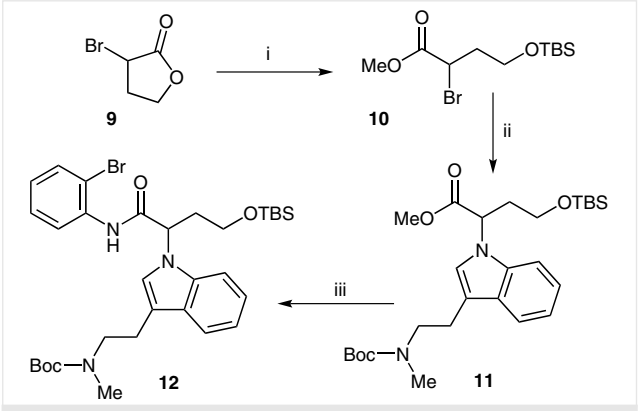
Returning to the approach to psychotrimine, we were dismayed to find that, in contrast to the successful oxindole formation from the simple substrate **6a**, variation of the N-protecting group (Table 1, entry 6) or incorporation of a

Table 1 Competing Enolate Arylation and Direct C–H Arylation Reactions

Entry	Substrate	R^1	R^2	R^3	R^4	Conditions	Yield of **7** (%)	Yield of **8** (%)
1	**6a**	Me	Et	H	H	A	**7a** 65	**8a** 3
2	**6a**	Me	Et	H	H	B	**7a** 0	**8a** 87
3	**6b**	Me	H	H	F	B	**7b** 0	**8b** 71
4	**6c**	SEM	Et	H	H	B	**7c** 0	**8c** 43
5	**6d**	SEM	H	H	H	B	**7d** 0	**8d** 36
6	**6e**	Bn	Et	H	H	A	**7e** 0	**8e** 60
7	**6f**	Me	$(CH_2)_2OTBS$	H	H	A	**7f** 0	**8f** 57
8	**6g**	Me	$(CH_2)_2OTBS$	$(CH_2)_2NMe(Boc)$	H	A	**7g** 41	**8g** 0

more highly functionalised alkyl substituent (Table 1, entry 7) under the standard enolate arylation conditions returned only the indolobenzodiazepinone products of direct C–H arylation, with no oxindole being formed. Thankfully, however, the use of tryptamine-derived substrate **6g** gave clean conversion to the desired oxindole with none of the direct arylation product observed (Table 1, entry 8). It appears that incorporation of a C3 substituent on the indole disfavours C2 arylation, presumably on steric grounds.

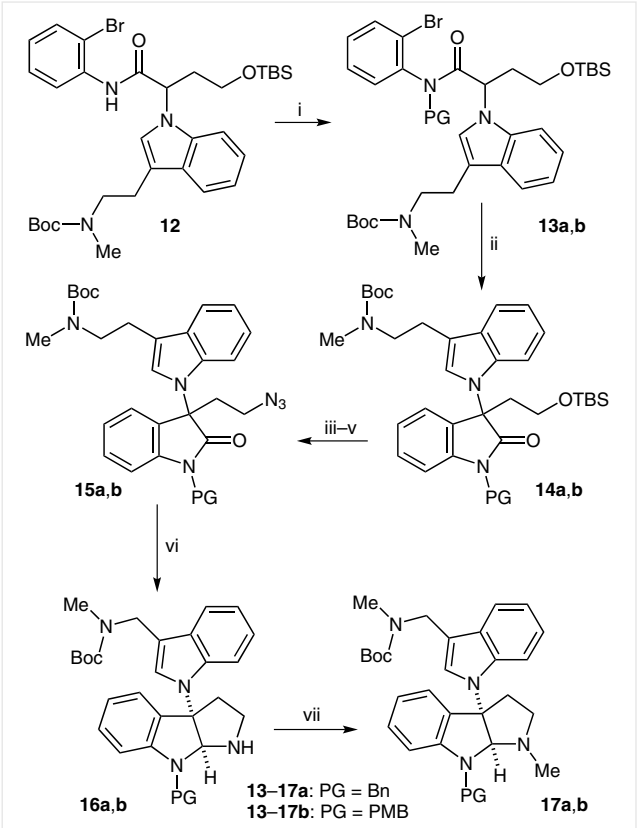
A successful approach to psychotrimine would require elaboration of the hexahydropyrrolindole structure by reductive cyclisation of a nitrogen nucleophile to the oxindole, and also deprotection of the oxindole-derived nitrogen atom. We therefore developed a route to the cyclisation precursors which would allow for late-stage incorporation of different N-protecting groups to give maximum synthetic flexibility (Scheme 3). Thus, methanolytic ring opening of commercial 2-bromobutyrolactone (**9**) followed by TBS protection of the liberated hydroxyl group gave bromoester **10**, which underwent nucleophilic substitution by Boc-protected tryptamine under basic conditions to give the 2-*N*-indolyl ester **11**. Finally, trimethylaluminium-mediated amidation of the ester with 2-bromoaniline gave the anilide **12**, ready for appropriate N-protection.



Scheme 3 Preparation of tryptamine-derived arylation precursor **12**. *Reagents and conditions*: i) K_2CO_3, MeOH, r.t., 35 min then TBSCl, imidazole, DMAP, DMF, r.t., 1 h (68% over 2 steps); ii) *N*-Boc tryptamine, NaH, MeCN, 0 °C to r.t., 4 h (61%); iii) 2-bromoaniline, $AlMe_3$, toluene, 60 °C, 4 h (77%).

We progressed intermediate **12** with both benzyl and 4-methoxybenzyl protection in parallel, to facilitate different options for deprotection towards the end-game of the synthesis. Thus, N-alkylation of anilide **12** with the appropriate benzylic halide proceeded without incident to give cyclisation precursors **13a**,**b** (Scheme 4). Pleasingly, both substrates cyclised efficiently under conditions we have previously described for arylation under simple (non-microwave) heating conditions, using a palladium(0) precatalyst and the N-heterocyclic carbene SIPr as the ligand, giving oxindoles **14a**,**b** in 73% and 58% yields, respectively.[9c,17]

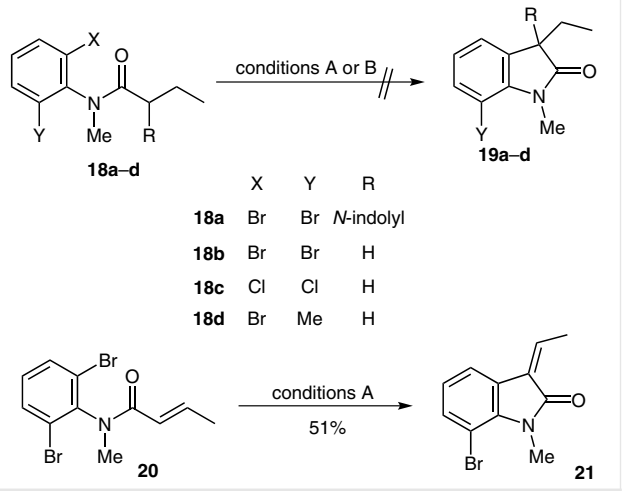
Attention then turned to the construction of the hexahydropyrrolindole skeleton. After some experimentation, we found that the most effective method was based on the two-step reductive cyclisation of azidolactams described by Porter.[18] Thus, azides **15a**,**b**, prepared in three simple steps from **14a**,**b**, were exposed first to tributylphosphine then lithium aluminium hydride to give the N-unsubstituted hexahydropyrrolindoles **16a**,**b** in moderate yield. Reductive methylation was efficiently achieved using formaldehyde and sodium triacetoxyborohydride, giving compounds **17a**,**b** as the fully protected core of psychotrimine.



Scheme 4 *Reagents and conditions*: i) NaH, BnCl or PMBCl, MeCN, 0 °C to r.t., 4 h (PG = Bn, 84%; PG = PMB, 59%); ii) 5% $Pd_2(dba)_3$, 10% SIPr·HCl, NaO*t*-Bu, toluene, reflux, 8 h (PG = Bn, 73%; PG = PMB, 58%); iii) TBAF, THF, r.t., 2 h (PG = Bn, 85%; PG = PMB, 63%); iv) MsCl, pyridine, CH_2Cl_2, r.t., 18 h (PG = Bn, 75%; PG = PMB, 98%); v) NaN_3, DMSO, 60 °C, 5 h (PG = Bn, 64%; PG = PMB, 77%); vi) PBu_3, THF, r.t., 1 h, then $LiAlH_4$, r.t., 1 h (PG = Bn, 51%; PG = PMB, 49%); vii) H_2C=O (38% aq solution), $NaBH(OAc)_3$, MeOH, 0.5 h (PG = Bn, 99%; PG = PMB, 98%).

Further progress towards psychotrimine would require installation of an additional tryptamine unit linked through the indolic nitrogen to C7 of the hexahydropyrrolindole, which we envisaged achieving by metal-mediated C–N coupling. We were attracted by the potential to directly incorporate a C7 bromide by the selective enolate arylation of a 2,6-dibromoanilide. To our knowledge, such substrates have not previously been investigated in enolate arylation reac-

tions, although they have been successfully employed in intramolecular Heck cyclisations.[19] We therefore prepared the model dibromide **18a**, but were disappointed to find that this did not undergo cyclisation under either our microwave-based [Pd(II) precatalyst] or conventional thermal [Pd(0) precatalyst] conditions (Scheme 5).



Scheme 5 Behaviour of 2,6-dihalogenated *N*-methyl anilides under enolate arylation and Heck conditions. *Reagents and conditions*: A: 10% $Pd(OAc)_2$, 10% $HPCy_3{\cdot}BF_4$, NaO*t*-Bu, toluene, 110 °C, microwave. B: 5% $Pd_2(dba)_3$, 10% SIPr·HCl, NaO*t*-Bu, toluene, reflux.

The reactions gave largely recovered starting material, suggesting the catalytic reaction had not initiated or had stalled. The simpler anilide **18b** was also examined, but similarly returned starting material. Concerned that the relatively large bromide substituent might be inducing unfavourable conformations that were preventing reaction, we examined the corresponding dichloride **18c**, again with no success. Finally, we ruled out electronic influences of the additional halide by examining the almost isosteric 2-bromo-6-methyl anilide **18d**, again recovering starting materials. The successful Heck cyclisation in our hands of crotonamide **20** under the standard reaction conditions in an unoptimised 51% yield confirmed that the dibrominated aniline function is capable of entering palladium-catalysed pathways. The contrast between the Heck and enolate chemistry is stark; at this stage we tentatively propose that the Heck pathway is facilitated by a favourable coordination of the palladium(0) to the electron-deficient alkene prior to C–Br insertion, a pathway which is not available in the enolate arylation manifold. Future work towards psychotrimine through intermediates **17a**,**b** will therefore focus on directed metallation strategies for functionalization of the C7 position.

In summary, we have examined the behaviour of 2-(*N*-indolyl)amides under various palladium-catalysed arylation conditions. Through judicious choice of catalysts and reagents, the substrates can be directed to selectively undergo either enolate arylation to oxindoles or direct C–H functionalization of the indole to give indolo-fused benzodiazepines. The former chemistry has facilitated the synthesis of the fully protected hexahydropyrrolindole core of psychotrimine.

Acknowledgment

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(16) **General Procedure for the Synthesis of Indolo-Fused Benzodiazepinones 8**

To a mixture of $Pd(OAc)_2$ (0.1 equiv), Ph_3P (0.1 equiv), TBAB (1 equiv), and KOAc (2 equiv) in a microwave vial was added toluene (1 mL) and the mixture stirred at r.t. for 30 min. A solution of the substrate (0.5 mmol) dissolved in toluene (1 mL) was added, the vial sealed under nitrogen, and the mixture subjected to microwave irradiation [CEM Discover, variable power mode (max 300 W), constant temperature of 120 °C] for 15 min. The reaction mixture was cooled and filtered. The filtrate was diluted with EtOAc and H_2O. The layers were separated and the organic layer dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product, which was purified by chromatography. By this general procedure, compound **6a** (200 mg, 0.54 mmol) gave the known product **8a** (134 mg, 87% yield), whose spectral data were identical to those reported in ref. 9a.

(17) **General Procedure for the Synthesis of Oxindoles 14**

To a mixture of $Pd_2(dba)_3$ (0.05 equiv), 1,3-bis-(2,6-diisopropylphenyl)imidazolinium chloride (0.01 equiv), and NaO*t*-Bu (3.0 equiv) was added toluene (ca. 0.10 M). A solution of the substrate (1.0 equiv) in the minimum volume of toluene was added, and the mixture was stirred and heated to 80 °C for 8 h. After cooling to r.t., the reaction mixture was concentrated under reduced pressure to leave a dark brown powdery residue. This was dry-loaded onto a silica gel column and purified by chromatography. By this procedure, amide **13a** (0.10 g, 0.14 mmol) gave, after chromatography (eluent EtOAc–PE, 1:5), oxindole **14a** (66.8 mg, 73%) as a yellow oil; R_f = 0.31 (solvent Et_2O–PE, 1:1). IR (film): ν_{max} = 2928, 1730, 1693, 1612, 1459, 1364, 1171, 1098 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.58–7.24 (9 H, m, ArH), 7.10 (1 H, d, *J* = 7.2 Hz, ArH), 7.00 (1 H, t, *J* = 7.5 Hz, ArH), 6.91 (1 H, d, *J* = 7.8 Hz, ArH), 6.77 (1 H, t, *J* = 7.7 Hz, ArH), 6.29 (1 H, d, *J* = 8.4 Hz, ArH), 5.04 (1 H, d, *J* = 15.4 Hz, NCH_AH_BPh), 4.87 (1 H, d, *J* = 15.4 Hz, NCH_AH_BPH), 3.74–3.46 (4 H, m, OCH_2, NCH_2), 3.18–2.66 (7 H, m, NCH_3, $CqCH_2$, $ArCH_2$), 1.43 [9 H, br s, $OC(CH_3)_3$], 0.82 [9 H, s, $SiC(CH_3)_3$], –0.01 (3 H, s, $SiCH_3$), –0.06 (3 H, s, $SiCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.9 (oxindole C=O), 155.8 (Boc C=O), 142.4 (ArCq), 135.6 (ArCq), 129.8 (ArCH), 129.5 (ArCq), 128.9 (2 × ArCH), 128.7 (ArCq), 128.4 (ArCq), 128.3 (ArCH), 128.0 (ArCH), 127.5 (ArCH), 124.4 (ArCH), 123.4 (ArCH), 121.8 (ArCH), 119.5 (ArCH), 118.9 (ArCH), 113.1 (ArCq), 111.5 (ArCH), 109.7 (ArCH), 79.3 [$OC(CH_3)_3$], 64.9 (Cq), 58.2 (OCH_2), 49.8 (NCH_2), 44.4 (NCH_2Ph), 40.1 ($CqCH_2$), 34.4 (NCH_3), 28.5 [$OC(CH_3)_3$], 25.9 [$SiC(CH_3)_3$], 23.8 ($ArCH_2$), 18.2 [$SiC(CH_3)_3$], –5.4 [$Si(CH_3)_2$]. HRMS: *m/z* calcd for $C_{39}H_{52}N_3O_4Si$ [MH^+]: 654.3722; found: 654.3720.

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